19 September 2024
EMA/CHMP/196327/2025 Corr[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Syfovre

International non-proprietary name: pegcetacoplan

Procedure No. EMEA/H/C/005954/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] The title of the CHMP assessment report for Syfovre was corrected on 10 October 2025 from 'Withdrawal Assessment Report' to 'Assessment Report'

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of an ASMF
RP	Restricted Part (or Closed Part) of an ASMF
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
BCVA	Best-corrected visual acuity
CEP	Certificate of Suitability of the Ph. Eur.
BLQ	Below Limit of Quantification
CFU	Colony Forming Units
CNS	Central Nervous System
CMS	Concerned Member State
CoA	Certificate of Analysis
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRS	Chemical Reference Substance (official standard)
CV	Coefficient of Variation
DS	Drug Substance
DSM	Drug Substance Manufacturer
DP	Drug Product
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
FP	Finished Product
FPM	Finished Product Manufacturer
FRI	Functional Reading
(HS-)GC	(Headspace-) Gas Chromatography
(HP)LC	(High-Performance) Liquid Chromatography
GA	Geographic Atrophy
ICP	Inductively Coupled Plasma
IPC	In-Process Control
IR	Infrared (spectroscopy)
IU	International Units
LLD	Low-Luminance Deficit
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LT	Less Than
MAH	Marketing Authorisation Holder
MS	Mass Spectrometry
MDD	Maximum Daily Dose
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
OES	Optical Emission Spectrometry
OOS	Out of Specification
PDE	Permitted Daily Exposure
PES	Polyethersulfone
(LD/HD)PE	(Low Density / High Density) Polyethylene
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PP	Polypropylene
PVC	Polyvinylchloride
XR(P)D	X-Ray (Powder) Diffraction
QP	Qualified Person
PVDF	Polyvinylidene fluoride
RH	Relative Humidity
RMS	Reference Member State
(R)RT	(Relative) Retention time
RSD	Relative Standard Deviation
SM	Starting Material (of drug substance synthesis)

S(m)PC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
TLC	Thin-Layer Chromatography
TTC	Threshold of Toxicological Concern (acc. to ICH M7)
UV	Ultraviolet (spectroscopy)
USP	U.S. Pharmacopeia
w.r.t.	With respect to

Background information on the procedure

1.1. Submission of the dossier

The applicant Apellis Netherlands B.V. submitted on 16 December 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Syfovre, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 June 2021.

The applicant applied for the following indication: "*Syfovre is indicated in adults for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)*".

The applicant was changed during the assessment procedure to Apellis Europe B.V.

Additional background information

Following the appellate judgment of the European Court of Justice in Case C-291/22 P of 14 March 2024, the EC returned the opinion of 25 January 2024 so that EMA can take the necessary steps to ensure the compliance of this opinion with the principle of objective impartiality.

As the composition of the AHEG held conducted on 4 December 2023 during the first initial assessment of Syfovre was considered to be incompatible with the principle of objective impartiality as interpreted in the judgement in Case C-291/22 P, the CHMP agreed that the Syfovre AHEG should be reconvened, and the procedure restarted from the assessment point before the conduct of AHEG.

Accordingly, the procedural step of the AHEG conducted on 4 December 2023 and the subsequent procedural steps (i.e. the negative CHMP opinion adopted on 25 January 2024 and re-examination request dated 2 April 2024) were annulled. A List of Outstanding Issues to be addressed in writing and/or in an oral explanation was adopted on 25 April 2024 and a new AHEG convened on 18 June 2024.

1.2. The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance pegcetacoplan contained in the above medicinal product to be considered as a new active substance in comparison to pegcetacoplan previously authorised in the European Union as Aspaveli, as the applicant claimed that pegcetacoplan contained in Syfovre differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 March 2018	EMEA/H/SA/3633/2/2018/SME/II	*Nicolas Beix and Kerstin Wickström*
25 February 2021	EMA/SA/0000050229	*Nicolas Beix and Brigitte Schwarzer-Daum*

The scientific advice pertained to the following *clinical* aspects:

- Proposed phase III studies: The choice of primary and secondary endpoints in the proposed phase III studies, assessment of lesion size change with fundus autofluorescence (FAF), the proposed study population is representative of the indication for the treatment of patients with GA secondary to AMD, the proposed masking of the study, the submission strategy, doses and treatment posologies proposed for the phase III studies, the proposed statistical analysis of the two phase III studies, the proposed safety database:

The applicant received Scientific Advice on the development of pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration from the CHMP on 25/02/2021 (EMA/SA/0000050229). The Scientific Advice pertained to the following clinical aspects:

- The strategy for analysis of the Phase 3 studies considering the potential impact of the Covid-19 pandemic.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christian Gartner   Co-Rapporteur: Maria Concepcion Prieto Yerro (up to 5 April 2024), Antonio Gomez-Outes (from 6 April 2024 onwards)

The application was received by the EMA on	16 December 2022
The procedure started on	26 January 2023
The CHMP Rapporteur's first Assessment Report was circulated to all	17 April 2023

CHMP and PRAC members on	
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 April 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	2 May 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 May 2023
The applicant submitted the responses to the CHMP List of Questions on	11 August 2023
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	25 September 2023
The CHMP agreed on a List of Outstanding Issues in writing and/or in an oral explanation to be sent to the applicant on[1]	12 October 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 November 2023
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	29 November 2023
An Ad-Hoc Expert Group (AHEG) was convened to address questions raised by the CHMP on[1] The CHMP considered the views of the AHEG as presented in the minutes of this meeting. [1]	4 December 2023
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on[1]	13 December 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Syfovre on[1]	25 January 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS) [1]	25 January 2023
Following the appellate judgement of the Court of Justice of the European Union in Case C-291/22 the CHMP decided to convene a new AHEG and restart the procedure from the point in time when the previous AHEG was convened. The CHMP agreed on a List of Outstanding Issues in writing and/or in an oral explanation to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 May 2024
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 June 2024
An Ad-Hoc Expert Group (AHEG) was convened to address questions raised by the CHMP on	18 June 2024

The CHMP considered the views of the AHEG as presented in the minutes of this meeting.	
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	25 June 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Syfovre on	27 June 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS) on	27 June 2024

[1]Procedural steps annulled. Following the appellate judgment of the Court of Justice of the European Union in Case C-291/22 P, CHMP decided to convene a new AHEG for Syfovre and restart the procedure from the point in time when the previous AHEG was convened. The procedure step of the AHEG convened on 04 December 2023 was annulled and all subsequent procedural steps were considered invalid.

1.8. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise (subsequently Janet Koenig) Co-Rapporteur: Larisa Gorobets

The appointed CHMP co-rapporteur had no such prominent role in Scientific advice relevant for the indication subject to the present application.

The Applicant submitted written notice to the EMA, to request a re-examination of Syfovre CHMP opinion of 27 June 2024., on	08 July 2024
The CHMP appointed as Rapporteur and as Co-Rapporteur on	16 July 2024
The Applicant submitted the detailed grounds for the re-examination (Appendix X of Final Opinion) on	22 July 2024
The re-examination procedure started on	23 July 2024
The CHMP Rapporteur's re-examination assessment report was circulated to all CHMP members on	30 August 2024
The CHMP Co-Rapporteur's assessment report was circulated to all CHMP members on	02 September 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the detailed grounds for re-examination to all CHMP members on	13 September 2024
The detailed grounds for re-examination were presented by the applicant during an oral explanation before the CHMP on	18 September 2024
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the conditional	19 September 2024

marketing authorisation on	

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Syfovre (pegcetacoplan) is intended to be indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) in adults.

GA is an advanced form of AMD and is characterised by thinning and loss of the retinal pigment epithelium (RPE) and concurrent atrophy of photoreceptors and the choriocapillaris that leads to progressive and irreversible loss of visual function.

2.1.2. Epidemiology

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in people over the age of 65 in the US and other Western countries (Rein et al. 2009). The prevalence of late AMD by 2040 is estimated to be >18 million globally (Wong et al. 2014) and between 3.9 and 4.8 million in Europe (Colijn et al. 2017). Approximately 67 million people in the European Union are currently affected by any AMD, and this number is expected to increase by 15% by 2050. Several genetic and environmental risk factors were associated with AMD, such as age, cigarette smoking, blood hypertension, high lipid levels, abdominal obesity, dietary fat and low physical activity (Sacconi et al. 2017).

2.1.3. Biologic features

Genetic susceptibility has become increasingly recognised as a risk factor and important contributor to AMD. More than 19 genetic polymorphisms have been demonstrated to influence AMD risk, with as many as 5 of these encoded by genes that modulate the complement system (Fritsche et al. 2016; Fritsche et al. 2013). Overactivation of the complement system is strongly associated with GA progression, and increased levels of complement activity have been found in patients with GA, including atrophic lesions and surrounding areas (Anderson et al. 2010; Heesterbeek et al. 2020; Katschke et al. 2018). The complement component C3 plays a central role in driving downstream damaging effects of complement overactivation in the progression of GA, including uncontrolled inflammation, opsonisation, and retinal cell death (Boyer et al. 2017; Park et al. 2019). In summary, pathogenesis of GA is related to overactivation of the complement system that leads to phagocytosis of the retina cells and subsequent growth of atrophic lesions.

2.1.4. Clinical presentation, diagnosis

GA lesions grow at a rate of approximately 2 mm^2 per year on average (~0.53 to 2.6 mm^2 per year) (Holekamp et al. 2020; Fleckenstein et al. 2018; Holz et al. 2018; Heier 2020). GA patients present with diverse spectrum of disease characteristics (Biarnés et al. 2020; Fleckenstein et al. 2018; Keenan et al. 2018; Schmitz-Valckenberg et al. 2011; Steinle et al. 2021) which contribute to the heterogeneity of disease progression (growth rate) as well as visual function changes over time

(Fleckenstein et al. 2018). These characteristics include lesion size, focality, and location. For example, nonsubfoveal lesions have a faster growth rate than subfoveal lesions, multifocal lesions grow faster than unifocal lesions, and larger lesions grow faster than smaller lesions (Fleckenstein et al. 2018). GA lesions typically appear first in the perifoveal macula, initially sparing the central fovea, and over time often expand and coalesce to include the fovea (Fleckenstein et al. 2018). GA patients experience symptoms of functional vision loss such as decreased contrast sensitivity, poor dark adaptation, visual disturbances, increased risk of falls, difficulty in reading, driving, and night vision. Once the atrophy progresses to the central fovea, severe central vision loss, and legal blindness can occur.

The diagnosis of geographic atrophy is clinical and is based on ophthalmoscopy or on fundus photography.

2.1.5. Management

There are currently no medicinal products licensed in Europe for the use in GA and no standard of care treatment (medical or surgical) is available that can halt or reverse the progression of geographic atrophy. Currently, the management of dry AMD consists of observation, regular follow-up evaluations and documentation, for timely recognition of visual function deterioration with appropriate rehabilitation and early choroidal neovascularisation (CNV) detection.

Natural disease progression appears devastating for the individual and the progressing GA manifests a major threat to a patient´s eyesight as well as general well-being. Findings from the MOSAIC Burden-of-Illness Study (MOSAIC study: A clinical, humanistic, and economic burden of illness survey among patients with geographic atrophy and their caregivers – European results. Prepared by Modus Outcomes for Apellis Pharmaceuticals. 21 November 2022) and the Retina International Study (Retina International. The socio-economic impact of age-related macular degeneration (AMD) in Bulgaria, Germany and USA - A disease burden assessment of GA and nAMD. 06 October 2022) reveal there is a significant unmet need for people living with GA (patients and caregivers), not only for a treatment, but also support in various daily life activities, and social and mental health support. Thus, GA represents a significant unmet medical need. Medical care is required in order to ultimately prevent or delay severe irreversible vision loss.

<u>CHMP early contact with patient and consumer organisations</u>

In February 2023 the CHMP initiated an early contact with patient and consumer organisations. Feedback from Retina International was provided. In summary, it was underlined that *the community affected by GA live with specific challenges and a significant unmet need brought about by a progressive form of severe vision loss. The terms used to describe the impact of the condition was consistent across regions and countries. The most frequently cited concerns were: fear/anxiety, becoming a burden, erosion of independence and isolation. When asked what patients would expect from treatment, those living with the condition stated that they want to have their sight restored, further degeneration stopped or slowed down. If a treatment could slow down the degeneration to the point that it would give them 'time' they would be willing to access therapy. In discussion with caregivers the same was true. There is an understanding that if treatment slows down or arrests the condition the quality of life of the patient would be radically improved as well as their mental health. Injections into the eye were not viewed as a reason not to take the medication. The regularity of the injections were not considered off putting. The potential of a treatment slowing or arresting GA to the point that the patient would not notice a difference was also considered by individuals with caregivers seeing the benefit. However, it is the opinion of Retina International that clarity would be required in discussions with treating eye doctors to explain what the expected outcome is.*

2.2. About the product

Syfovre contains the active substance pegcetacoplan. The Anatomic Therapeutic Class (ATC) code for the product is S01XA. Pegcetacoplan is a symmetrical molecule comprised of 2 identical pentadecapeptides covalently bound to the ends of a linear 40-kDa polyethylene glycol (PEG) molecule. The peptide moieties bind to C3 and exert a broad inhibition of the complement cascade, a biological process that is part of the innate immunity and is involved in multiple inflammatory processes. Inhibition of C3, with subsequent reduction in inflammation and cell death, is a therapeutic strategy for GA with a justification that is found in the literature (Park et al. 2019; Merle 2015; Katschke et al. 2018).

Syfovre (pegcetacoplan) is being developed for the treatment of adult patients with GA secondary to AMD, applied as a solution for injection for intravitreal (IVT) use. The proposed dose regimen for Syfovre is 15 mg (0.1 mL solution) administered by a single intravitreal injection to the affected eye once every other month (60 days). Based on HCP discretion Syfovre could also be administered every month (30 days).

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a solution for injection containing 60 mg of pegcetacoplan as active substance. Each vial contains 0.4 mL solution corresponding to an active substance concentration of 150 mg/mL. This allows for the delivery of a single dose of 0.1 mL solution containing 15 mg of pegcetacoplan.

Other ingredients are: trehalose dihydrate, glacial acetic acid, sodium acetate trihydrate, sodium hydroxide (for pH adjustment), and water for injections.

The product packaging is vial (2R clear Type 1 glass) with a stopper (13- mm ethylene tetrafluoroethylene coated chlorobutyl) and sealed with 13- mm aluminium/polypropylene flip-off type seal.

2.3.2. Active Substance

2.3.2.1. General information

Pegcetacoplan is a synthetic molecule comprised of two identical peptides covalently linked to both ends of a linear 40 kDa polyethylene glycol (PEG) in a site-specific manner.

The chemical name of pegcetacoplan is *N*6,15,*N*6,15′-[poly(oxyethylene), oxy-ɑ-carbonyl, ω-carbonyl]-bis[*N*-acetyl-L-isoleucyl-L-cysteinyl–L-valyl–1-methyl-L-tryptophyl-L-glutaminyl–L-aspartyl–L-tryptophylglycyl-L-alanyl-L-histidyl–L-arginyl–L-cysteinyl–L-threonyl–2-[2-(2-aminoethoxy)ethoxy]acetyl-L-lysinamide, cyclic (2-12)-disulfide] corresponding to the molecular formula $C_{1970}H_{3848}N_{50}O_{947}S_4$. It has a relative molecular mass 43.5 kDa and the following structure:

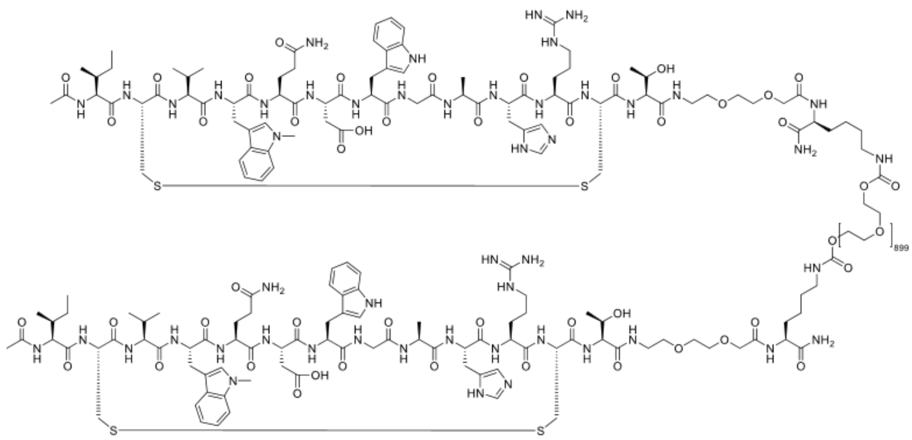


Figure 1: active substance structure

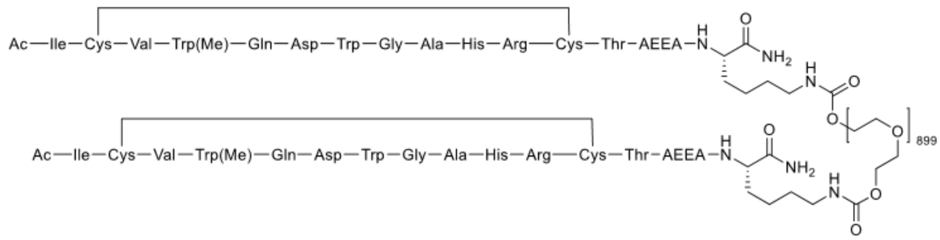


Figure 2: active substance structure using peptide abbreviations

A broad set of analytical methods have been used to elucidate the structure of the active substance and characterise it. This includes i) structural studies, including route of synthesis analysis, sequencing, peptide mapping, circular dichroism, molecular weight determination by MALDI-TOF-MS, molecular weight/polydispersity/molecular weight distribution by SEC-MALS, amino acid analysis, ^{1}H-NMR, FT-IR, UV/Vis spectroscopy, combustion analysis, chiral amino acid analysis, and disulphide bonding; ii) physicochemical characteristics, including appearance, solubility profile, optical rotation, analysis of thermal properties by differential scanning calorimetry, thermogravimetric analysis, isoelectric point, pH in solution, molar extinction coefficient, solid-state properties by X-ray powder diffraction, hygroscopicity, and residue on ignition; iii) purity and impurity tests, including three orthogonal HPLC methods (reversed phase (RP)-, size exclusion (SE)-, and strong cation exchange (SCX)-HPLC), analytical ultracentrifugation, acetate content, and free-PEG content; iv) biophysical and biological attributes, including biopotency by ELISA and thermodynamic properties by isothermal calorimetry.

The active substance is a white to off-white solid, very soluble in both water and buffer (buffer, at the target pH containing sorbitol). At 25°C, pegcetacoplan displays negligible adsorption.

All the chiral amino acids contain the L configuration. The peptide portions contain two unnatural amino acids: 1-methyl-L-tryptophan (Trp(Me)) in position 4 and amino(ethoxyethoxy)acetic acid (AEEA) in position 14. The polyethylene glycol bridging the two peptides consists of 900 repeating units representing a nominal mass of 40 kDa and is covalently linked to the side chains of each lysine residue of each peptide.

The crystallinity of the active substance is not critical to the bioavailability of the finished product since the product is administered as a solution for injection. Hence the absence of polymorphism discussion in the dossier is acceptable.

The applicant requested the active substance Pegcetacoplan to be considered as a new active substance. Pegcetacoplan in the present Marketing Authorisation Application (MAA) has the same structural formula and molecular mass as the active substance in the authorised medicinal product Aspaveli. The applicant acknowledges that the active substance pegcetacoplan in this MAA is the same as previously authorised in the medicinal product Aspaveli. The applicant presented differences in quality aspects between finished products containing pegcetacoplan for GA (Syfovre) and PNH (Aspaveli). However, these differences are not related to the active substance itself. No quality differences have been identified between the active substance in this MAA and the active substance in Aspaveli. Therefore, the quality data is not considered to support a NAS claim. (see Appendix for further details).

2.3.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site, with a further site involved in the manufacture of an intermediate.

The manufacture of the active substance consists of eight specific stages.

The starting materials are considered acceptable with acceptable specifications. The starting materials are commercially available.

A detailed description of each stage of the manufacturing process is provided. Critical process parameters (CPP) and their proven acceptable ranges are described. In-process tests are listed for each stage of the manufacturing process.

The process description provided by the applicant is very detailed and consistent with standard chemistry and controls for SPPS. This high level of detail provides a large degree of assurance that the process will be under sufficient control. Critical steps and controls have been identified and the designation of them as critical/non-critical is acceptable based on the multiple chromatographic purification steps used in the process. Holding times and storage conditions for process intermediates were established based on data generated during development, stability studies, and/or manufacturing experience and are acceptable.

In-process controls applied during the synthesis are described. The specifications and control methods for critical steps, intermediate products, starting materials and reagents have been presented.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes introduced have been presented in sufficient detail and have been justified.

Potential and actual impurities are described in detail. A detailed summary of the genotoxic assessment performed for each pegcetacoplan manufacturing process reagent, solvent, and potential by-products, raw materials and intermediates produced during manufacturing is provided. All compounds were classified either as ICH M7 class 5 or as ICHQ3C class 2 except for acetamide for which a PDE is established. Acetamide is not used in the manufacturing process. It is a potential impurity that could derive from hydrolysis of acetonitrile, which is used in the final purification. The proposed limit for acetamide is acceptable and omission of testing for acetamide in the final active substance is justified based on batch data.

The active substance is packaged in compliance with the European Union Regulations EU/10/2011, and EC/1935/2004.

2.3.2.3. Specification

The active substance specification includes tests for appearance (visual), identification (MALDI-TOF-MS and RP-HPLC), assay (RP-HPLC), purity (RP-HPLC), related substances (RP-HPLC, SE-HPLC, SCX-HPLC), water content (KF), residual organic solvents (HS GC-FID), acetate content (IC), bioassay (ELISA), bacterial endotoxins (Ph. Eur.) and microbial enumeration (Ph. Eur.).

The applicant has provided a detailed and sound justification of the proposed limits in line with ICH Q6A. An acceptable toxicological justification has been provided for those impurities where the respective limit is above the Ph. Eur. qualification threshold (1.0%).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for 11 process validation and post process validation batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

2.3.2.4. Stability

Stability data from three batches of active substance from three registration batches from the proposed active substance manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (- 20°C ± 5°C) and for up to 6 months under accelerated conditions (5 ± 3°C) according to the ICH guidelines were provided. Two of these batches were manufactured at the proposed commercial size while one batch was approximately one half of the commercial size. For these three batches, the activated PEG intermediate used to produce the active substance was manufactured at pilot scale by the site of manufacture for this intermediate used during development. The use of batches with intermediate from this site is acceptable based on the comparability data provided.

The analytical methods used were stability indicating. All tested parameters were within the specifications.

The intermediate manufacturing process was scaled up at the site proposed for commercial manufacturing. Stability data are available for four additional active substance lots using intermediate from this site. To date, stability data through 24 months at the long-term and 6-months under the accelerated condition are available. No significant trends were observed, and the tested samples met the proposed commercial active substance specification. The results from these studies support the comparability assessment.

Forced degradation studies were conducted. No significant change in purity and related impurities was observed in pegcetacoplan samples exposed to thermal stress conditions.

Photostability testing following ICH guideline Q1B was performed on one batch.

The proposed 36-month retest period for pegcetacoplan stored at -20 ± 5°C (-20°C) protected from light is considered acceptable. The available accelerated stability data (6 months at 5°C) support short-term excursions outside the proposed label storage condition of -20°C during handling.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Syfovre solution for injection is a sterile, aqueous, acetate-buffered trehalose solution for intravitreal administration. The appearance of the solution is clear and colourless to light yellow. Each single-use vial contains pegcetacoplan in solution (concentration 150 mg/mL). Each vial delivers a single dose of 0.1 mL solution containing 15 mg of pegcetacoplan.

No overages are used in the pegcetacoplan finished product formulation.

The active substance concentration was set to deliver the required amount (15 mg) in a solution for injection. The active substance pegcetacoplan is a symmetrical molecule comprised of two pentadecapeptides covalently bound to the ends of a linear 40 kDa polyethylene glycol molecule and is a lyophilised amorphous solid of low bulk density which is freely soluble to very soluble in aqueous solutions such as water and buffer up to at least 250 mg/mL. Consequently, there are no risks to achieve complete dissolution to a final concentration of 150 mg/mL during finished product manufacturing.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in paragraph 2.3.1 of this report. The function of each excipient was adequately described, and the concentration of the chosen excipients has been satisfactorily justified. Trehalose dihydrate is used as a tonicity agent and was selected due to its common use and protecting properties (i.e., protein stabiliser, radical scavenger, and cryoprotectant). Glacial acetic acid is used as a buffering agent and for pH adjustment. Sodium acetate trihydrate is used as a buffering agent. Sodium hydroxide is used for pH adjustment and water is used as solvent. Excipients were selected based on the route of administration and the need to stabilise the active substance in solution. Acetate buffer was selected based on the pH of optimal stability of the active substance.

The compatibility of the active substances with the excipients has been adequately investigated.

Detailed information on formulation development has been presented.

The development of the manufacturing process is described in detail. The proposed commercial manufacturing process was developed in parallel to the different phases of clinical studies. Adequate information has been provided and the optimisation of the manufacturing process is described and acceptable. The intended commercial manufacturing process, product compatibility with manufacturing components, manufacturing process characterisation, justification for critical/non-critical process parameters and in-process controls, risk assessment of the finished product manufacturing process and intended control strategy for the manufacturing process were described.

The choice of the sterilisation method was explained. The chosen sterilisation method is acceptable.

The primary packaging is a 2R Type 1 clear glass vial closed with chlorobutyl rubber stopper and sealed with aluminium seal. The material complies with Ph. Eur. 3.2.1 (glass vials) and Ph. Eur. 3.2.9 (rubber stoppers) requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The manufacturing process consists of nine main steps. The manufacturing process has been adequately described.

During the procedure, a major objection was raised due to the initial lack of data on process validation from production-scale batches. In response, process validation data on four production-scale batches were provided. The data confirms the validation of the manufacturing process. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.3.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual, Ph. Eur.), degree of colouration (Ph. Eur.), pH (Ph. Eur.), identity (RP-HPLC, SE-HPLC), assay (RP-HPLC), degradation products (RP-HPLC, SE-HPLC, SCX-HPLC), isoaspartic acid content (RP-HPLC), bioassay (ELISA), particulate matter (Ph. Eur.), minimum fill (compendial – USP), osmolality (vapor pressure, Ph. Eur.), viscosity (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

The finished product specification includes all relevant test parameters for a sterile solution for intravitreal administration and complies with Ph. Eur. and EU/ICH guidelines. Sterility is confirmed according to Ph. Eur. 2.6.1 at release and in addition the finished product is tested for bacterial endotoxins.

All proposed acceptance criteria have been sufficiently justified. Limits established for impurities are set in line with ICH Q3B (R2). The control strategy for organic impurities, elemental impurities and residual solvents has been sufficiently justified. The finished product manufacturing process does not include the use of organic solvents. The observed and potential impurities and degradation products have been adequately discussed. The proposed limits for each unspecified finished product degradant are the same as in the active substance. The finished product meets both the requirements for minimum fill (as per USP <755>) and extractable volume (as per Ph. Eur. 2.9.17).

The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Testing for elemental impurities in the finished product has been conducted in accordance with ICH Q3D (R1) Elemental Impurities for parenteral products. The assessment included Class 1, Class 2A (including Ni) and selective Class 3 elements (Li, Sb, Cu, and Cr). While no elemental impurities are intentionally added in the manufacturing process, a low risk of presence of Nickel and Chromium was identified due to the use of stainless-steel equipment. Batch analysis data on five batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

During the procedure, a major objection was raised in relation to the provided risk assessment concerning the presence of nitrosamine impurities in the finished product. The risk assessment did not initially adequately consider all risk factors such as the presence of secondary and tertiary amine moieties in the active substance and the presence of nitrites in excipients. In response, an updated risk assessment was provided. This resolved the major objection. The risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No

726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product.

Batch analysis results were provided for four production scale batches of the finished product. Additional batch analysis results were also provided for pegcetacoplan finished product batches used in clinical studies and in registration stability studies. The results provided confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.3.3.4. Stability of the product

Stability data from four commercial-scale batches of finished product stored for up to 18 months under long term conditions (5°C) according to the ICH guidelines were provided. In addition, data from four additional commercial-scale batches stored for six months under long term conditions (as before) and under accelerated conditions (25ºC / 60% RH) according to the ICH guidelines were provided.

Forced degradation studies were conducted to assess the stability indicating capability of the analytical methods and also to determine the degradation pathway of the active substance pegcetacoplan in the finished product matrix.

The photostability of the finished product was evaluated in light conditions that meet or exceed the conditions for confirmatory studies specified in ICH Q1B.

An in-use stability study at ambient temperature was also conducted.

Based on available stability data, the proposed shelf-life of 18 months when stored in the carton to protect from light and when stored in a refrigerator (2°C – 8°C) is acceptable.

2.3.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The active substance is a symmetric polypeptide covalently linked to polyethylene glycol and is manufactured via solid-phase peptide synthesis.

During the procedure major objections were raised in relation to the finished product regarding the lack of commercial scale process validation data and regarding the nitrosamine risk evaluation. On both questions, satisfactory responses were received to resolve the major objections.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

Age-related macular degeneration (AMD) is a chronic inflammatory disease of the retina with strong metabolic and hereditary components (Owsley, et al., 2016). Clinical signs of retinal injury are drusen depositions and atrophic changes in the retinal pigment epithelium. The number and character of drusen determines the stage of the disease, but not vision impairment (Pinelli et al. 2020). The late stage of this degeneration may lead to geographic atrophy (GA), which is the indication concerned in this application, or an exudative form with neovascularisation.

Throughout the non-clinical programme pegcetacoplan was termed aPi1514, APL-2 and formulated in different galenics. Pegcetacoplan is proposed for the treatment of geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD). The formulation is a 150 mg/mL solution in 18 mM acetate buffer, pH 5, containing 5.38% w/v trehalose. The intended clinical therapeutic dose is 15 mg/eye administered once monthly, or every other month, via intravitreal (IVT) injection.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The preclinical pharmacology study programme covers in vitro and in vivo assessment of pegcetacoplan, but no intravitreal administrations or pegcetacoplan in the final formulation, except study 22CAPH-001 in five healthy cynomolgus monkeys.

The stoichiometry and binding affinity of aPi1514 (APL-2, pegcetacoplan) to C3 and C3b proteins were determined in vitro by isothermal titration calorimetry in a buffer containing 10 mM phosphate buffer with 150 mM NaCl (pH 7.4) (study 18xtph-001). Hence, pegcetacoplan targets were not tested in formulations containing 5% dextrose or 18mM acetate buffer (pH 5.0) and 5.38% (w/v) trehalose used in the following in vivo studies.

APL-2 inhibited the alternative and classical pathway of the complement system and preventing the membrane attack complex (MAC; C5b-9) formation in cynomolgus and human serum (Study-19CFPH-001). These effects were specific in these species, since MAC formation in rabbit or rat serum was not inhibited by APL-2. APL-2 (pegcetacoplan) revealed an IC50 value of the classical and alternative pathway of 136 nM and 64 nM, respectively. Thus, a more potent inhibition of the alternative pathway is assumed.

These results are corroborated by study 16CATX-003 in six female cynomolgus monkeys receiving two daily 60-minute intravenous 84 mg/kg infusions of pegcetacoplan (in 5% dextrose-group 1 or in 100mM sodium acetate, 0.9%NaCl (pH 5.0)-group 2). PK and PD data were generated over 15 days. The peak plasma concentration of pegcetacoplan (within the two day of drug application) were accompanied by a reduction of the C3a concentration and complete inhibition of the alternative pathway and a partial inhibition (35-37%) of the classical pathway of the complement system. The inhibition started to reverse within 5 days and reached pre-exposure values after ten days and turned into an overshoot thereafter. Hence, it is not clear if intravenous pegcetacoplan-induced inhibition of the complement system triggers a rebound phenomenon with increases production of C3 and C3a (3b not shown) and enhanced CH50 and AH50 activities. These overshoots were seen with both galenics and may be indicative for possible inflammatory processes. The applicant argued that increased C3 levels may be explained by target mediated drug disposition (TMDD) predicted from PK modelling a decreased clearance rate of C3 bound to pegcetacoplan.

No effect has been specifically reported on the lectin (MBL) pathway.

2.4.2.2. Secondary pharmacodynamic studies

The secondary pharmacology was not investigated, but with the exception of an in silico genome wide query running with the 13 amino acid sequence of APL-2 to identify similar sequences (study 21AWPH-001).

2.4.2.3. Safety pharmacology programme

Cardiovascular and respiratory safety pharmacology was assessed with APL-2 given by subcutaneous injection to telemetered cynomolgus monkeys (study 13CATX-005). There were no changes in hemodynamic or respiratory parameters. No effects were found on body weight, heart rate, blood pressure, ECG parameters, including QT intervals, respiratory rate, tidal volume, minute volume and body temperature by the administration of APL-2.

In addition, the hERG ion channel-blocking profile of APL-2 and PEG40, was investigated in a stably transfected human embryonic kidney (HEK 293) cell line expressing with no significant effects for APL-2 or PEG40 (study 13ztx-001).

As for the potential effects of pegcetacoplan on CNS, the applicant reported no levels (BLQ) of pegcetacoplan in brain after IVT administration, so no assessment of the CNS function has been conducted.

2.4.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted since pegcetacoplan IVT administration is intended as a monotherapy.

2.4.3. Pharmacokinetics

The applicant provided a number of studies on the pharmacokinetics of pegcetacoplan either specifically conducted as PK studies or PK/TK evaluation was included in PD or toxicology studies. These studies include evaluation of absorption, distribution, metabolism and elimination of pegcetacoplan administered via the IVT or subcutaneous route. In addition, alternative formulations as well as routes of administration were investigated regarding PK. Also, transfer via the placenta and milk was addressed in the scope of developmental and reproductive toxicology studies. Three in vitro studies on the interaction with P450 cytochromes and transporter proteins were included in order to evaluate the potential for drug-drug interaction of pegcetacoplan.

Methods

Several bioanalytical methods for the determination of pegcetacoplan in serum, vitreous humour, aqueous humour, retina and retinal pigmented epithelium(RPE)/choroid of rabbits and monkey using liquid chromatography tandem mass spectrometry (LC-MS/MS) were established.

The overall calibration range for serum was 0.500 µg/mL or 1.00 µg/mL for monkey serum, respectively, to 50.0 µg/mL, for vitreous humour 0.500 – 500 µg/mL (monkey) and 5.00 – 1600 µg/mL (rabbit), for rabbit aqueous humour 0.500 – 100 µg/mL, 0.0100 – 2.50 µg for monkey retina, 0.0300 – 12.0 µg for rabbit retina and iris ciliary body/choroid/RPE as well as 5.00 – 1000 ng/mL for monkey breast milk.

Tissue distribution and excretion was addressed after IVT injection of [^{3}H]APL-2 to rabbits and monkeys. For whole body autoradiography bodies were processed and sectioned. Radioactive concentrations were determined by image densiometry. The LLOQ was determined to range between <153 ng-eq/g and <147 ng-eq/g. Serum and urine samples were analysed by liquid scintillation counting.

Absorption

Toxicokinetic evaluation after IVT administration of a single dose (10 mg) to monkeys revealed serum peak concentrations of 13.4 to 62.0 µg/mL after 7 to 10 days (Study 13CTX-002). Low amounts were still detectable on day 28. Peak levels in the vitreous humour reached values of 706 to 3060 µg/mL at day 2. Concentrations declined thereafter in a linear manner and were below the level of quantification on day 28. Mean AUC_{0-t} and AUC_{0-inf} were 16,800 and 19,900 h × µg/mL for serum and 278,000 and 279,000 h × µg/mL for vitreous humour.

In animals dosed once IVT with 12 mg [^{3}H]pegcetacoplan per eye a serum C_{max} of 20,215.47 ± 4,052.63 ng-eq/g was measured after 5 days (Study 17MTX-001). The final serum concentration after 21 days was 6,335.64 ± 577.63 ng-eq/g.

Further, toxicokinetic parameters were evaluated after repeated IVT administration of monthly doses (10 doses in total) of pegcetacoplan (3.1, 12.4, or 24.8 mg/eye/dose), PEG40 or vehicle (Study 14CTX-001). Serum levels of pegcetacoplan were analysed through four weeks after the first and last administration, respectively. Serum levels were roughly dose-proportional and peak concentrations were reached between 144 and 180 h after administration. $T_{1/2}$ was 224 h after the first administration and slightly decreased to 192 h after the last administration. Vitreous samples were taken pre-dose through week 13. PEG levels appear very heterogenous through all time points evaluated and range from BLQ to 199 µg/mL. No indication for accumulation of PEG in the vitreous humour can be derived from the data provided, however, data are considered too limited to draw a definite conclusion (observation period too short, no comparison to other dosing groups).

After s.c. or i.v. administration of a single dose of 7 mg/kg [^{3}H]pegcetacoplan to monkeys a serum C_{max} of 41,700.00 ± 5,759.26 ng-eq/g was observed after 48 h (T_{max}) (Study 13APK-001). After 21 days the serum concentration declined to 6,572.92 ± 699.53 ng-eq/g.

Toxicokinetic parameters were evaluated after repeated s.c. administration of monthly doses of pegcetacoplan (1, 7 or 28 mg/kg/day), PEG40 or vehicle (Study 15CATX-004) in cynomolgus monkeys. C_{max} appeared to be dose-dependent and remained constant from day 28 to the end of the study period. Similarly, AUC increased in a dose-dependent manner and was roughly comparable through all time points starting from day 28. T_{max} was reached 0-24 h post-dose.

Distribution

A single s.c. administration of 7 mg/kg [^{3}H]pegcetacoplan to monkeys (Study 17MTX-001) led to a wide distribution to a large number of organs with the exception of, e.g. the central nervous system, bone, fat, eye and optic nerve. Similarly, after single bilateral IVT administration of 12.4 mg/eye, [^{3}H]pegcetacoplan was widely distributed including the optic nerve, but not the central nervous system.

The PK of IVT and suprachoroidal administration were comparatively assessed after single doses of 12 mg pegcetacoplan/eye in rabbits (Study 20PPK-004). Suprachoroidal administration did not result in distribution to vitreous humour or anterior chamber. Analysis of ocular compartments revealed that distribution to RPE/choroid was 100-times higher after IVT administration than after suprachoroidal administration. In addition, pegcetacoplan was no longer detected in the choroid after 4 days. Overall, distribution of pegcetacoplan after IVT administration appears to occur substantially to the RPE/choroid where the pharmacological interaction with C3 and C3b is expected to take place.

Metabolism

No studies on the metabolism of pegcetacoplan have been conducted, but the applicant provided a literature-based discussion on the metabolism of PEGylated peptides. The described mechanism of peptide degradation to amino acids by endogenous peptidases is acknowledged. For the metabolism of PEG the applicant referred to a publication that mainly describes PEG clearance via macrophages that may exhibit vacuolation upon PEG-uptake. In the specific case of pegcetacoplan, a distribution study after a single IVT administration of [^{3}H]pegcetacoplan to monkeys revealed distribution to the optic nerve which was still detectable after 21 days and raises concerns regarding accumulation in the optic nerve, which is regarded the most sensitive tissue of those to which pegcetacoplan distributed.

Moreover, the unlikeliness of dissociation of the PEG moiety from the peptide in the eye was discussed on the basis that harsh conditions were necessary to achieve cleavage of the respective carbamate bond under an experimental setting. It was further argued that despite the presence of proteases in the vitreous humour pegcetacoplan is unlikely to be degraded in the eye. Proteins resulting from theoretical degradation would be only present and traces and would be pharmacologically inactive or of similar activity as pegcetacoplan.

Excretion

Single IVT or SC administration of [^{3}H]pegcetacoplan to monkeys revealed that for both routes of administration the major route of elimination was urinary excretion (Study 17MTX-001).

Excretion of pegcetacoplan via milk was evaluated in the scope of the enhanced pre- and postnatal toxicity study in cynomolgus monkeys after s.c. administration (Study 18CATX-001). Pegcetacoplan was quantified in milk on PPD 7 and 14. On PPD 14 the concentration in milk was < 1% the concentration in maternal serum. No quantifiable levels were observed in the offspring between 14 and 182 days of age.

Pharmacokinetic drug interactions

In order to evaluate the potential of pegcetacoplan to induce or inhibit cytochrome P450 or to serve as a substrate or inhibitor for human drug transporters three in vitro studies were performed.

Induction of CYP1A2, CYP2B6, and CYP3A4 mRNA levels or activities were evaluated in human hepatocytes from three male donors that were incubated with 1, 2.5, 4, 5 and 6 mg/mL APL-2 for up to 72 hours in comparison to adequate positive controls (Study 17COTX-001). No cytotoxicity or CYP-induction was observed.

The inhibitory potential of APL-2 on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 in pooled human liver microsomes from 150 individual donors was evaluated at concentrations of 0.01, 0.0249, 0.0622, 0.155, 0.387, 0.965, 2.41, and 6 mg/mL and compared to adequate positive controls. Direct as well as metabolism-dependent (APL-2 incubation with 1 mM NADPH and a 10-fold concentrated microsome suspension at 37°C for 1 h) inhibition was investigated. No inhibitory activity on the selected CYP enzymes was attributable to APL-2.

Potential drug transporter interaction of APL-2 at concentrations of 60, 600 or 6000 µg/mL was evaluated in HEK293 cells for human uptake transporters (OAT1, OAT3, OCT2, OATP1B1, OATP1B3) or Caco-2 cells for human efflux transporters (P-gp and BCRP) that were transiently transfected with the respective transporter genes. APL-2 was not identified as a substrate for the investigated transporters, transporter inhibition by APL-2 in the range of negative control regarding uptake of probe substrates.

Other pharmacokinetic studies

Subcutaneous administration of a single 7 mg/kg dose pegcetacoplan with (40.8 kDa), mid (43.8 kDa) or high (48.8 kDa) molecular weight demonstrated that different lengths of the PEG linker do not significantly impact the PK parameters of pegcetacoplan (Study 19CAPK-001).

Pharmacokinetic analysis of comparatively IVT administered APL-2, APL-2 formulated in microparticle controls revealed that APL-2 concentration was not increased in animals treated with the microparticle formulation as compared to APL-2 alone (Study 19PPK-003). The applicant related this finding with degradation of APL-2 in the microparticles observed during stability studies. In addition, the applicant encountered issues in the LC-MS/MS method development testing for APL-2.Placental transfer was assessed in the scope of the pilot embryo-fetal development study in which female cynomolgus monkeys were S.C. administered daily doses of 28 mg/kg/day pegcetacoplan from organogenesis through the second trimester of pregnancy. On GD 141 fetal serum contained < 1% of the mean maternal concentration (1770 µg/mL).

Neither plasma protein binding nor distribution in red blood cells were specifically assessed for pegcetacoplan. The applicant explains that pegcetacoplan is expected to form 1:1 and 1:2 complexes with plasma C3. Distribution in red blood cells is considered unlikely due the structure of pegcetacoplan.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

A single dose of 10 mg pegcetacoplan formulated in 5% dextrose was administered intravitreally to cynomolgus monkeys. No treatment related changes were observed (Study 13CTX-002).

In order to investigate the cause for ocular inflammation that occurred in patients enrolled in studies APL2-304, APL2-303 and APL2-203, five acute tolerability studies were conducted in monkeys (18BPK-001, 18APK-001, 18BPK-002, 19BPK-001, 19BPK-002) and rabbits (18PPK-001, 18PPK-002, 18PPK-003, 19PPK-001, 19PPK-002). Six drug product batches and Lucentis as a control were tested. Transient inflammation with variable incidence and severity was observed in all treatment groups. Batch #040-001-001 was comparatively less tolerated. Finally, an impurity in one starting material was identified to be causative for the clinical findings. Consequently, a change in the manufacturing process and control of the impurity were introduced to resolve the issue.

The tolerability of APL-2 and APL-2 formulated in microparticles was comparatively evaluated in a single-dose study in rabbits (Study 19PPK-003). Microparticle-APL-2 and, to a lesser extent the microparticle control caused more severe ocular findings including chemosis, redness and congestion as compared to APL-2 alone.

Tolerability of IVT and suprachoroidal administration were comparatively assessed after single doses of 12 mg pegcetacoplan/eye in rabbits. Ocular examination did not reveal notable differences regarding the safety of either route of administration.

2.4.4.2. Repeat dose toxicity

The applicant submitted fourteen repeat-dose toxicity studies, five of them conducted in New Zealand White Rabbits and nine of them in cynomolgus monkeys.

Rabbits

Seven-days subcutaneous administration of pegcetacoplan at 20mg/kg/day or control article (PEG40) at 16mg/kg/day was investigated in rabbits (3/sex/group) in a non-GLP pilot study (study 13CATX-001), followed by a GLP-compliant 28-day RDT study including a 28-day recovery period (study 13CATX-003) where rabbits received subcutaneous injections of APL-2 at 7, 28 or 140 mg/kg/day, control article (PEG40) at 112 mg/kg/day or the diluent alone (5% dextrose) in the main study (6/sex/group) and 140 mg/kg/day (3/sex), control article (2/sex) or diluent alone (2/sex) in the recovery arm. A second GLP-compliant 28-day repeat-dose toxicity study in rabbits (6/sex/group) was conducted (study 14CATX-001), investigating lower subcutaneous APL-2 doses at 0 (5% dextrose only), 0.25, 1 or 3mg/kg/day and a high intravenous (IV) dose of 42mg/kg administered twice in total, once every 14 days. In the 6-month GLP-compliant study (study 15CATX-003), New Zealand White Rabbits received doses of APL-2 at 1, 7 or 28mg/kg/day, control article (PEG40) at 26mg/kg/day or diluent control subcutaneously. Intravitreally, on both eyes on day 1 and 30, administered APL-2 trehalose drug product formulation buffer, APL-2 (15mg/eye) or heat-degraded APL-2 (15mg/eye) was investigated in rabbits to qualify specific degradants in heat-degraded pegcetacoplan (study 21CATX-002).

In the 7-day pilot RDT study in rabbits (13CATX-001), no APL-2 related findings were observed.

In the 28-day RDT study including recovery animals (13CATX-003), pegcetacoplan-related changes occurred at high APL-2-doses of 28 and 140mg/kg/day in regard to haematology parameters, as an increase in red blood cell counts, haemoglobin and haematocrit, an increase in reticulocyte counts and a decrease in platelet counts (the latter also occurring in PEG40 control females, but due the apparent dose response considered APL-2 related as well) was observed. At the same doses of 28 and 140mg/kg/day, a significant reduction in white blood cell counts was noticed but was considered to be related to PEG40, as this finding was observed in control animals as well. The same for APL-2 at 140mg/kg/day, where a significant increase in prothrombin time (PT), activated partial thromboplastin-time and significant decrease in fibrinogen was noticed to a similar extend in PEG40 control animals. Further APL-2 related changes were observed for clinical chemistry parameters, including a decrease in glucose and potassium, again at 28 and 140mg/kg/day. All findings returned to diluent control or baseline levels at the end of the 28-day recovery period, except for the increase in red blood cell count, haemoglobin and haematocrit and the decrease in platelet counts. APL-2 related organ weight changes at 140mg/kg/day (spleen weights and kidney weights, the latter with uncertain relationship to the test substance and only in male animals) were not observed in animals of the recovery arm. Furthermore, again at the high dose of 140mg/kg/day in males, an APL-2-related increase in focus/discoloration at the administration site with increased incidence and severity of fibrosis and haemorrhage was observed, whereas gross findings were not noticed at the end of the recovery period. Microscopic changes in the spleen and at the administration site were still present in recovery animals. Microscopic findings related to PEG40 were observed in several tissues [synovium of the femur, bone marrow (sternum and femur), choroid plexus of the brain, cervix, ciliary body of the eye, adrenal gland, pituitary gland, salivary gland, kidney, liver sinusoids, mandibular lymph node, ovary, pancreas, skin (inguinal), stomach, thymus, and uterus], with infiltrates of histiocytes (macrophages) or resident macrophages having abundant vacuolated cytoplasm with occasional flocculent material in the vacuoles. Vacuolation of epithelial cells was seen in the choroid plexus of the brain, kidney tubules, and synovium in the femur. For some of these findings a slight increase in severity and/or incidence was noticed at 140mg/kg/day APL-2 compared to PEG40, suggesting a possible APL-2-related effect as well. One high dose male (recovery animal) and female exhibited minimal tubular degeneration, which was considered APL-2 related. A dose-proportional increase in APL-2 exposure (C_{max} and $AUC_{(0-24)}$) was noticed between 7 and 28mg/kg and less than dose-proportional between the high dose groups. Additional, exposure increased with repeat dosing with no apparent sex differences. ADAs were observed in all APL-2 dose groups as well as in PEG40 treated animals.

In the second 28-day RDT study in rabbits with subcutaneous and intravenous APL-2 administration (study 14CATX-001), macrophage vacuolation was only observed in the kidneys [minimal vacuolation in cortical tubules at ≥ 1 mg/kg/day (SC) and at 45mg/kg/day (IV), both in males and females] and considered to be related to PEG40. Peak APL-2 concentrations were observed at 8 or 24 hours postdose on Day 28. Again, for the low doses of 0.25 mg/kg and 3 mg/kg (SC), C_{max} and $AUC_{(0-t)}$ increased with increasing dose levels in a dose-proportional manner and APL-2 exposure increased with repeat subcutaneous dosing, with no gender differences observed. APL-2 (SC) was found to be weakly to moderately antigenic. NOAELs for pegcetacoplan were determined to be 3mg/kg for SC and 42mg/kg for IV dosing.

In the 6-month SC RDT study in rabbits (15CATX-003), haematology parameters were observed to be minimally reduced (e.g. red blood cell counts, haematocrit and haemoglobin) in females at 26mg/kg/day PEG40 and in the 28mg/kg/day APL-2 high dose groups but not regarded biologically significant and considered related to PEG40. As already reported in previous studies (e.g. 13CATX-003), microscopic findings as infiltrates of vacuolated macrophages in several tissues were seen in control PEG40 and high dose 28mg/kg/day APL-2 treated animals, regarded to be related to PEG40 due to its dose-dependent occurrence in the 1 and 7mg/kg/day APL-2 treatment groups. Minimal tubular degeneration in the kidney was observed in all groups (including diluent group). T_{max}) ranged between 0 and 24 h post-dose, $AUC_{(0-t)}$ increased in a slightly less than dose-proportional manner between 1 and 28 mg/kg dose levels and APL-2 exposure increased with repeat dosing with no gender differences observed. ADAs were detected in almost all samples and were likely related to PEG40. A NOAEL could not be determined because renal tubular degeneration (considered adverse) was found in all treatment groups.

In rabbits, pegcetacoplan was administered intravitreally in study 21CATX-002, comparing APL-2 with heat-degraded APL-2 and vehicle control (APL-2 trehalose drug formulation buffer). Animals were only dosed twice (15mg/eye) four weeks apart. A minimal decrease in reticulocyte count (0.84x group mean compared to control) was observed in heat-degraded APL-2 treated rabbits but considered within the background range of New Zealand White Rabbits. Slight anterior vitreous cells in the eyes, correlating to vitreous infiltrates (vacuolated foamy macrophages) in the vitreous body were observed to a similar extend in APL-2 and heat-degraded APL-2 dosed animals. Vacuolated macrophages were also seen in the optic disc in both APL-2 groups, indicating ongoing clearance of these cells. One APL-2 treated rabbit developed a moderate inflammation in one eye following the second dose (anterior uveitis, cell-like opacities on anterior lens capsule, iris swelling and hyperaemia, incomplete pupil dilation, fundus hazy or limited view, vitreous opacities and cells, retinal elevation and haemorrhage, posterior lens capsule rupture). In this eye, moderate mononuclear cell infiltrates in the vitreous, moderate vacuolated macrophage infiltration in the optic disc and moderate choroid mononuclear cell infiltrates were noticed with additional changes as fibroplasia and choroid moderate infiltration, which might indicate a possible direct effect of the test-substance. As indicated by the applicant, ocular macrophage infiltrates in the vitreous have been reported in rabbits following IVT administration with another pegylated ocular product (Macugen EPAR Scientific Discussion 2006) and, as also seen in various tissues with other PEGylated drugs, the presence of these cells is typically considered a non-adverse adaptation to the PEG moiety. An increase in adrenal gland weight, correlating to minimal to mild cortical hypertrophy was noticed in rabbits dosed with heat-degraded APL-2 and one APL-2 treated rabbit and was considered to be related as a response to stress.

Monkeys

A 7-day non-GLP-compliant pilot study (study 13CATX-002) was conducted in cynomolgus monkeys (1/sex/group), which received either control article PEG40 at 16mg/kg/day or APL-2 at 20mg/kg/day subcutaneously. In the GLP-compliant study 13CATX-004, subcutaneous injections of diluent (5% dextrose), APL-2 at 7, 28 or 140mg/kg or control article PEG40 at 112mg/kg were administered daily to cynomolgus monkeys (3/sex/group) for 28 days, with additional animals for APL-2 at 140 mg/kg/day (2/sex), control article (2/sex) or diluent (1/sex) entering the 28 day recovery period. A further GLP-compliant 28-days subcutaneous RDT study (study 14CATX-005) was performed, comparing 28 mg/kg/day APL-2 (3/sex) and the control article PEG40 (from a different manufacturer)) at 25.6 mg/kg/day (2/sex). Heat-degraded APL-2 (28 mg/kg/day) was compared to non-degraded APL-2 (28 mg/kg/day) and vehicle control (acetate-buffered 4.1% sorbitol) within the course of the GLP-compliant 28-days subcutaneous injection toxicity study (study 19CATX-003) in cynomolgus monkeys (3/sex/group). The GLP-compliant study 14CATX-002 compared diluent control (5% dextrose) with low doses of APL-2 at 0.25, 1 or 3 mg/kg/day, administered daily by SC injections for 28 days and APL-2 at 42mg/kg given by intravenous injections on day 1 and 15 in cynomolgus monkeys (3/sex/group). A GLP-compliant 9 month repeat-dose toxicity study (SC) in cynomolgus monkeys (study 15CATX-004) of APL-2 at 1, 7 or 28 mg/kg/day, using control article (PEG40) at 26 mg/kg/day and the diluent control (5% dextrose), was conducted, including a 13-week interim necropsy group (additional 3/sex/group). Ocular safety of APL-2 was investigated in the GLP-compliant toxicity studies in cynomolgus monkeys after intravitreal injections of APL-2 in study 14CATX-004, 17CATX-002 and 14CTX-001. In study 14CATX-004, APL-2 (new formulation) at 12.4mg/eye/dose every 4 weeks for 2 months (2 doses in total) was administered (IVI) to three cynomolgus monkeys (no control groups included), whereas in the 2-month toxicity study (17CATX-002) three males/group received three different formulations of APL-2 (dextrose, sorbitol-, trehalose- and sodium chloride-based) at 12.4 mg/eye/dose (again 2 total doses) and were compared to control formulation (sorbitol-based). In the 9-month ocular toxicity study (study 14CTX-001), cynomolgus monkeys (3/sex/group) received either APL-2 at 3.1, 12.4 or 24.8mg/eye, PEG40 at 22.64mg/eye (Sunbright DKH-40%) or vehicle (5% Dextrose) by intravitreal injection into each eye once every four weeks for 9-month (10 total doses).

No APL-2-related changes were observed in the 7-day pilot repeat-dose toxicity study in cynomolgus monkeys (study 13CATX-002) after subcutaneous administration.

In study 13CATX-004 (28-day RDT in monkeys), a dose dependent reduction of CH50 was noticed at 7, 28, and 140 mg/kg/day of APL-2 (SC) as expected, since complement 3 inhibition is pegcetacoplan's mode of action. Further APL-2-related changes were seen in the high dose group at 140mg/kg/day, e.g. minimal vacuolation of the epithelium in tubules of the kidney and minimal to mild degeneration of the same, subcutaneous inflammatory cell infiltrates at the injections sites (vacuolated macrophages/histiocytes with lymphocytes, plasma cells and granulocytes) as well as frequent multinucleated cells. Control-article PEG40 associated microscopic findings were seen in all APL-2 treatment groups as well (most evident at 28 and only occasionally at 7mg/kg/day) and included infiltrates of histiocytes (macrophages) or resident macrophages with vacuolated cytoplasm and occasional flocculent material in the vacuoles in several tissues (e.g. bone marrow (sternum), choroid plexus of the brain, adrenal gland, pituitary gland, liver sinusoids, mandibular and mesenteric lymph node sinuses, ovary, the red pulp of the spleen, stomach, and urinary bladder) and vacuolation of epithelial cells in the choroid plexus of the brain. Microscopic findings were also noticed in recovery animals after a 28-day treatment fee period. No ADAs were detected in APL-2 treated animals, whereas in 2 animals of the PEG40 control article group (but one of them pre-dose) minimal antibody titres of 1:20 were detected. T_{max} was 24 hours post-dose on day 1 and pre-dose or 8 hours post dose on day 28, with a mono-exponential decline in the high dose recovery group. $t_{½}$ ranged from 6.3 to 8.25 days, C_{max} and $AUC_{(0-24)}$ values increased with increasing dose levels in a less than dose proportional manner and APL-2 exposure increased with repeat dosing, whereas accumulation ratios decreased with dose. A NOAEL was determined to be 7mg/kg/day due to observed renal tubular degeneration at higher doses.

In the second 28-day subcutaneous RDT study in cynomolgus monkeys (study 14CATX-005) APL-2-related tubular vacuolation and degeneration in the kidney was observed at 28mg/kg/day. Considered PEG40-related microscopic findings, as already reported in study 13CATX-004, precisely infiltrates of histiocytes (macrophages) or resident macrophages with small, clear vacuoles in the cytoplasm in several tissues (e.g. brain, adrenal gland, pituitary gland, liver, mandibular and mesenteric lymph nodes, ovary, spleen, and administration site), were seen again. APL-2 concentrations increased with time, dramatically within the first two weeks and then slightly, with no gender differences observed. APL-2 was not found to be antigenic.

In study 19CATX-003, subcutaneously administered heat-degraded and non-heat-degraded pegcetacoplan showed similar toxicological profiles at 28mg/kg/day (for 28days). As reported in previous studies, minimal tubular degeneration in the kidney (considered adverse) and non-adverse minimal to mild microscopic findings in the subcutaneous and dermal tissue at the administration site, lymph nodes, spleen, brain, and kidneys (considered non-adverse) were observed. In addition, minimal to mild changes in haematology and clinical chemistry parameters were noticed and considered APL-2 related, e.g. decrease in red blood cell count, haemoglobin concentration, and haematocrit, decrease in cholesterol and minimal decrease in potassium, all minimally more pronounced in heat-degraded APL-2 treated animals, with the latter only observed in heat-degraded APL-2 treated males. Considering the minor magnitude of difference between both APL-2 treatment groups, these findings were generally regarded as similar. No notable changes in pegcetacoplan serum concentrations were detected between heat-degraded and non-heat-degraded pegcetacoplan and sexes.

In study 14CATX-002, and in contrast to other studies, control article PEG40-related vacuolation of macrophages was only seen at the highest subcutaneously administered dose at 3mg/kg/day in a single mesenteric lymph node of a single male cynomolgus monkey. A clear inhibition of complement activity was reported for animals treated with 42mg/kg intravenously injected APL-2, whereas no haemolytic potential of the complement system was observed following dosing with 0.25, 1 and 3 mg/kg/day of APL-2 by daily subcutaneous injection. Peak APL-2 serum concentrations after SC administration were observed 24 hours post-dose on day 1 and 8 hours post-dose on day 28 and increased with dose and dose-proportionally from 1 to 3mg/kg/day. APL-2 exposure marginally increased following IV dosing. There were no gender-related difference in APL-2. No ADAs were detected.

In the 9-month repeat dose-toxicity study (SC) in cynomolgus monkeys (study 15CATX-004) APL-2 related changes were observed at 28mg/kg/day in haematology parameters (minimally reduced red blood cell counts, haematocrit and haemoglobin in males and females) and significantly reduced fibrinogen levels in females, both not considered biologically significant and the latter recovering to pre-study levels during the dosing period. There was no sign of complement activation at any dose for either sex (no notable changes in CH50 and C3a). At 7mg/kg/day and 28mg/kg/day APL-2, there was a measurable increase in C3 levels between day 1 and 28 but not between pre-dose and 8 hours post-dose, which was supposed to be indicative of a reduction in C3 catabolism and not related to an acute phase response. APL-2-related minimal tubular degeneration in the kidney (minimal vacuolation of the epithelium with minimal degeneration of tubules lined by attenuated epithelium) was noticed at 28mg/kg/day in both genders. Microscopic findings, as already reported for PEG40 in previous studies, were observed again, precisely, infiltrates of histiocytes (macrophages) or resident macrophages with abundant vacuolated cytoplasm (small and large vacuoles) and occasional flocculent material in the vacuoles in many tissues (choroid plexus of the brain, cervix, administration sites, adrenal gland, pituitary gland, liver sinusoids, mandibular and mesenteric lymph node sinuses, ovary, the red pulp of the spleen, and urinary bladder). In the choroid plexus of the brain and synovium of the femur, vacuolation of epithelial cells was seen as well. These findings were comparable in severity and incidence between PEG40 and 28mg/kg/day APL-2 treated animals, whereas in females the severity was greater in many of the tissues. Peak APL-2 concentrations occurred between 8.27 and 24 hours postdose on Day 1 and between the pre-dose and 24 hours post-dose on Days 28, 91, 180 and 273. C_{max} increased with increasing dose levels and APL-2 exposure increased following repeated administration of APL-2, until steady-state was supposed to be reached by day 28. No gender differences were observed. Several samples had titres greater than 20, only 5 of them reactive with the test article (samples of 1 PEG40, 1 APL-2 at 28mg/kg and 3 APL-2 at 1mg/kg animals), but the ELISA showed assay interference at levels of 100-250 µg/mL and was therefore considered unreliable.

Intravitreal administration of APL-2 in cynomolgus monkeys was investigated within the course of the two 2-month ocular safety study 14CATX-004 and 17CATX-002, and the 9-month ocular toxicity study 14CTX-001. In the 2-month safety studies, no APL-2 related changes were observed for all parameters evaluated [e.g. clinical signs, body weights, food evaluation, ophthalmology (Slit lamp biomicroscopy and indirect ophthalmoscopy), electroretinography, tonometry, spectral domain optical coherence tomography (SD-OCT), gross necropsy, and histopathologic examinations (eyes and optic nerve)], whereat ophthalmologic and tonometry findings were limited to inflammation and associated changes in intraocular pressure (IOP) that were considered procedure-related, with no differences noted between various formulations used.

In the 9-month ocular toxicity study in cynomolgus monkeys (study 14CTX-001), no APL-2 or PEG40 related changes were observed for most parameters investigated e.g. clinical signs, body weights, food consumption, slit-lamp bio-microscopy and indirect ophthalmoscopy, electroretinography (ERG), tonometry [intraocular pressure (IOP)], clinical pathology (haematology, coagulation, and clinical chemistry), bioanalysis (serum bioanalysis, anti-drug antibody and CH50), organ weights and macro- and microscopic pathology (eyes with optic nerves and a full range of extra-ocular tissues) and intraocular inflammation (assessed by a modified ophthalmoscopy-based scoring system, Hackett and McDonald 1996)]. Ocular clinical signs, slit-lamp biomicroscopy and tonometry findings were limited to inflammation (varying in severity and incidence in treatment groups with no pattern pointing out to a test-article related-effect) and associated changes in intraocular pressure (IOP) that were considered procedure-related, and, as inflammation of eyes in monkeys is occasionally noted in IVI studies, related to animals rubbing their eyes after injections. Findings based on optical coherence tomography (SD-OCT) were noted in the retina. Central retinal thickness in both eyes of one animal (APL-2, 12.4 mg/eye) were detected at week 13. At week 39 elevated central retinal thickness (between >20 but ≤40 µm or >40 µm) was never seen in group 1 (vehicle, 5% dextrose, no PEG40) or group 3 (3.1mg APL-2/eye/dose). Conversely, central retinal thickness was observed in 2/12 eyes from group 2 (PEG40 control in 5% dextrose), 3/12 eyes from group 4 (12,4mg APL-2/eye/dose) and 4/12 eyes from group 5 (24.8mg APL-2/eye/dose). After revision of data and correction of the range of increase (20 to ≤40 µm instead of >20 to ≤40 µm) by the applicant, comparative statistics for groupwise incidences of eyes with increases in central retinal thickness revealed, that increases of 20µm in CRT were even observed in control and pegcetacoplan low dose (3.1mg/eye) groups (each 1/group), although the number of affected eyes with increases of 20 to ≤40 µm increased slightly in PEG40 (22.64mg/eye) as well as pegcetacoplan medium (12.4mg/eye) and high dose (24.8mg/eye) groups (2/group, 3/group [+ 1>40µm] and 3/group [+ 1>40µm], respectively). Microscopic changes in the eyes (e.g. fibrosis/pigmented macrophages in the vitreous or the needle track) were similarly seen in control and pegcetacoplan-treated animals and therefore considered related to the injection procedure as well. No serum anti-drug antibodies (ADA) to APL-2 were detected. Systemic exposure to APL-2 (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$)) increased from 3.1 to 24.8 mg/eye/dose less than dose-proportionally and from 12.4 to 24.8 mg/eye/dose dose-proportionally and were lower after the last dose (10^{th}) compared to the 1^{st} dose (accumulation rations from 0.188 to 1.02 across all dose levels). T_{max} was observed 6 days post each injection. $t_{1/2}$ ranged from 205 to 236 hours after the 1^{st} dose and 187 to 194 hours after the 10^{th} dose. Mean sex-combined serum C_{max} and $AUC_{0\text{-}inf}$ values at the highest dose (24.8 mg/eye/dose) were 99.0 µg/mL and 41,400 h × µg/mL, respectively. As for the estimated vitreous concentration reported in this 9-month ocular pivotal study (14CTX-001), maximum dose level tested was 24.8 mg/eye. It would be 1.65-fold the intended clinical dose of 15 mg/eye, which, considering the smaller size of the monkey and vitreous chamber volume (2.0 and 4.0 mL for monkey and human, respectively), would result in a clinical safety margin of 3.3-fold.

2.4.4.3. Genotoxicity

Given that pegcetacoplan is a molecule comprising two peptides, it would not be expected that it can directly interact with DNA or chromosomes. Despite this, the applicant conducted the standard genotoxicity studies battery and submitted seven genotoxicity studies in this dossier, including five Ames tests conducted with five different lots of pegcetatoplan (studies 13BTX-001, 14BTX-001, 19BTX-001, 19BTX-002, 19BTX-003), one *in vitro* micronucleus assay in TK6 cells (study 13BTX-002) and one *in vivo* micronucleus assay in mice [assessing polychromatic erythrocyte (PCE) cells in mouse bone marrow] (study 13BTX-003). Vehicle and positive controls were included in each test system and support the validity of the studies. All *in vitro* assays were conducted in the presence or absence of an *in vitro* metabolic activation system (Aroclor-induced rat-liver S9).

Pegcetatoplan was found to be negative in all strains (Salmonella typhimurium TA1537, TA98, TA100, and TA1535 and E.coli WP2 uvrA) and at all concentrations (up to 5000µg/plate) in the bacterial reverse mutation assays, as well as in the *in vitro* and *in vivo* micronucleus assays, at maximum concentrations/doses of 500 µg/mL and 2000mg/kg/day, respectively. Therefore it can be considered non-mutagenic and non-genotoxic.

2.4.4.4. Carcinogenicity

No carcinogenicity studies were conducted with pegcetacoplan. A short summary of the applicant's literature research regarding the influence of the complement system in cancer development was provided in the toxicology written summary. Genotoxicity and toxicity studies submitted with this MAA did not reveal any potential of pegcetacoplan in cancer development.

2.4.4.5. Reproductive and developmental toxicity

<u>Fertility and early embryonic development</u>

No dedicated fertility and early embryonic development (FEED) studies were conducted with APL-2 in rodents, non-rodents and non-human primates. Assessment of reproductive organs (microscopic examination of testes in males, ovaries and uterus in females) was conducted within the scope of the 9-month toxicity study in cynomolgus monkeys (study 15CATX-004), where it was noted, that most of the animals were too young and consequently sexual immature at the beginning of the study. However, both males and females reached sexual maturity throughout the course of the chronic study. No treatment-related findings on reproductive organs were detected, neither in males, nor in females.

Embryo-foetal development

The applicant submitted three non-GLP pilot embryo-fetal development studies of APL-2, one in rats, one in rabbits and one in cynomolgus monkeys.

In the EFD study 17CATX-001, pregnant cynomolgus monkeys were administered APL-2 (28mg/kg, 5 animals/group) or control article (5% dextrose, 3 animals/group) by subcutaneous (SC) injection once daily during the period of organogenesis through the second trimester of pregnancy [Gestation Day (GD)20 until GD140, 120 doses) to determine the potential maternal toxicity and toxicokinetic profile, the potential effect on pregnancy retention (i.e., abortion) and to evaluate fetuses for teratogenic effects (on GD141 ± 1, including external, visceral, skeletal, brain, and heart examinations).

Mean T_{max}, C_{max} and $AUC_{(0-t)}$ values in pregnant female cynomolgus monkeys following 28mg/kg APL-2 subcutaneous administration sustained and were similar on GD48, GD111 and GD140 (e.g. for GD48: 8hrs, 1940±196µg/mL and 45100±4430hr*µg/mL, respectively). In foetuses, mean APL-2 serum concentrations of 2.50µg/mL were determined, representing 0.15% of the mean APL-2 maternal serum concentrations observed on the C-section day. One female animal and her fetus were screened positive for antidrug antibodies (ADAs) but not considered specific for APL-2, with similar APL-2 serum concentrations compared to ADA negative animals. No treatment-related findings were observed in foetuses (e.g. body weights, morphometric measurements, external and visceral evaluations, gross pathology, heart evaluations, skeletal evaluations including bone count and morphology, placenta evaluations). No treatment related findings in pregnant female monkeys were found in regard to mortality, abortions, clinical signs, injection site reactions, maternal body weight gains, organ weight changes and gross pathology. Microscopic findings were found in the choroid plexus of the brain in APL-2 treated females (mild epithelial vacuolation and minimal to moderate macrophage vacuolation).

In the EFD study 15MTX-001 conducted in pregnant rats, APL-2 was subcutaneously injected as a single daily dose from GD6 to GD17 at 1, 3.5, 7 and 28 mg/kg/day and compared to vehicle (5% Dextrose) and PEG-40 (26.2 mg/kg/day), with each 5 animals/group. Additionally, toxicokinetic analysis was performed with mated females (3 animals/group) treated similarly to the main study animals (dextrose vehicle, PEG -40 control and APL-2) to evaluate systemic exposure.

No PEG-40 or APL-2 treatment-related effects were observed in pregnant rats and their foetuses (maternal survival, clinical findings, gestation body weights, gestation body weight change, food consumption, pregnancy rate, mean corpora lutea and uterine implantation data, macroscopic findings, fetal sex ratios, fetal body weights or fetal external examinations). One fetus in the high dose group showed malformations, but they were considered spontaneous and unrelated to APL-2, as also seen in recent historical control data. Fetal soft tissue and skeletal evaluations, as indicated in ICH S5, were missing. Toxicokinetic analysis revealed no drug accumulation and showed to some extend a kind of dose proportionality (for 1 to 3.5 and 3.5 to 28 mg/kg/day dose levels).

Similar to the EFD study in rats, a prenatal development toxicity study was conducted in New Zealand white rabbits (study 15MTX-002), with 6 mated females/group in the main and 4 animals/group in the toxicokinetic study.

Again, as reported for rats, no PEG-40 or APL-2 treatment-related effects were detected in pregnant rabbits and their foetuses, with one exception observed in adult animals. Soft feces were observed in 1/5 animals (20%) in the PEG-40-treated group on several days and considered a PEG-40 related effect due to its occurrence in several of the APL-2–treated animals [0/5 (0%), 1/5 (20%), 1/5 (20%) and 2/5 (40%) in 1, 3.5, 7 and 28 mg/kg/day dose groups) over a similar period in gestation and its lack in the vehicle control group. Again, fetal soft tissue and skeletal evaluations were missing. Mean serum levels indicated dose proportionality with no drug accumulation observed.

<u>Prenatal and postnatal development</u>

An enhanced pre- and postnatal development toxicity study was conducted with APL-2 in cynomolgus monkeys to assess possible effects on pregnant monkeys and fetal development, postnatal growth and development of infants for 6 months and APL-2 concentrations in mothers' milk while nursing. Therefore, pregnant animals were administered APL-2 (7mg/kg or 28mg/kg, 19 animals/group) or control article (5% dextrose, 20 animals) once daily by subcutaneous (SC) injection from Gestation Day 20-22 (GD20-22) until parturition. Toxicokinetics (TK) and anti-drug antibodies (ADAs) were evaluated for adult females and infants at various time points. Additionally, in infants, developmental immunotoxicology was assessed by T-cell dependent antibody response (TDAR) analysis starting on birthday 140 till approximately birthday 182.

Generally, there were no APL-2-related changes in any of the female cynomolgus monkeys in regard to clinical signs, changes in body weight or body weight gain during the gestation or postpartum periods. No effects were seen on postpartum maternal behaviour and milk availability.

Mortality was observed in two adult females, one of the 7mg/kg/day and one of the 28mg/kg/day group, who had to be euthanised early due to complications of parturition unrelated to APL-2. In both animals, microscopic findings related to APL-2 included vacuolated macrophages (in e.g. adrenal gland, liver sinusoids, mandibular and mesenteric lymph node sinuses, and ovary), histiocytic infiltration (in e.g. subcutaneous tissue of the administration site), or epithelial vacuolation of various tissues. The female of dose group 2 (7mg/kg/day) showed no gross observations in the brain and no microscopic findings in the brain sections related to APL-2 administration, whereas for the other female animal (group 3, 28mg/kg/day) mild to moderate infiltrates of histiocytes (macrophages) with abundant vacuolated cytoplasm (small and large vacuoles) and vacuolation of the epithelial cells in the choroid plexus of the brain were observed.

There were no test-article related effects on gestation length or infant sex. The number of fetal losses in the 28 mg/kg/day group (abortions and stillbirths, 52.6%) was higher compared to the control group (5%) and was outside of the Testing Facility historical range of 6.7% to 38.9% (average 22.1%), and considered related to APL-2 administration. Infant losses (1 of 9, 11.1%) in this group were lower than the control group and were within the Testing Facility historical range (0 to 20.0%). Due to the high fetal losses, the combined fetal/infant loss rate for the 28 mg/kg/day group was 57.9% and higher than in controls and the historical range. Infant losses in the 7 mg/kg/day group (5 of 17, 29.4%) were higher compared to the control group (15.8%) and the Testing Facility historical range (0 to 20.0%). Nevertheless, this finding was supposed to be unlikely related to APL-2 as the incidence was not dose dependent and 3 out of 5 infant losses in this group were related to circumstances as maternal induced trauma or complication of parturition. The combined fetal/infant loss rate (36.8%) in the 7 mg/kg/day group was higher than in the control group (20.0%), but was within the Testing Facility historical range of 20% to 42.9% (average 28.8%) and known published data for NHPs (Jarvis et al., 2010) and therefore not considered APL-2 related. There were no APL-2-related effects on fetal or stillbirth morphometric measurements, external and visceral (including heart), or macroscopic or microscopic changes and fetal heart rates.

In surviving infants, no APL-2-related findings were made in clinical signs, body weight or body weight gain, at physical examinations and during external, visceral and morphometric measurements, gross pathology and histopathology and heart evaluations and there were no effects on neurobehavioral (BD7 and BD14) or neurological (BD91/92 and BD175) evaluations. Skeletal radiograph evaluations revealed similar variations between control and APL-2 animals with the exception of two animals at 28 mg/kg/day, which showed a variation also encountered in control populations of similar studies and was therefore not considered related to APL-2. Furthermore, no test-article-related changes were observed after immunisation of infants with tetanus toxoid (TT) antigen, via detection of primary and secondary anti-TT IgM and IgG centre point titre (CPT) values.

No antidrug-antibodies were confirmed positive, neither in mothers nor in infants.

In maternal serum, the median T_{max} was observed at 8 hours post-dose except at 28 mg/kg/day on GD48 where the median T_{max} was at 24 hours post-dose. On gestation day 48 medium C_{max} and $AUC_{(0-t)}$ values for the 7mg/kg/day and 28mg/kg/day dose groups were 1030± 128µg/mL and 24000±2980hr*µg/mL and 1840±223µg/mL and 42400±5110hr*µg/mL, respectively. Systemic exposure to APL-2 (mean C_{max} and $AUC_{(0-t)}$) increased with increasing dose but was less than dose proportional between 7 and 28 mg/kg/day with dose ratios ranging from 1.78 to 2.16 for C_{max} and from 1.77 to 2.16 for $AUC_{(0-t)}$ for a 4-fold increase in dose. No systemic drug accumulation occurred on GD111 and GD140 when compared to GD48, neither in low nor in high dose groups (e.g. for GD111 accumulation ratios of 0.859 and 1.04 for $AUC_{(0-t)}$ and of 0.871 and 1.04 for C_{max} at 7 and 28 mg/kg/day, respectively). Furthermore, concentrations of APL-2 decreased with time and were only quantifiable until postpartum day (PPD)14 and PPD28 in both APL-2 dose groups. In infant monkeys, APL-2 was not quantifiable in any of the dose levels at any time. Maternal milk concentrations of APL-2 at 7 and 28 mg/kg/day generally decreased or were similar between PPD7 and PPD14 with much higher serum to milk concentrations on PPD14 (624 to 5710 and 192 to 6750 for milk from left or right nipple, respectively).

Juvenile toxicity

No studies in the offspring were conducted by the applicant.

2.4.4.6. Toxicokinetic data

Toxicokinetic analysis were performed within the course of repeat-dose as well as and reproductive and development toxicity studies. Please refer to the applicable studies for review in section 2.4.4.2 and 2.4.4.5 of this report.

2.4.4.7. Tolerance

No dedicated local tolerance studies were conducted by the applicant. Local tolerance was investigated within the course of single- and repeat-dose toxicity studies in rabbits and monkeys. Overall, pegcetacoplan was found to be well tolerated after intravitreal administration. Nevertheless, the applicant was asked for further details in the scope of safety pharmacology. Please refer to the applicable sections of this report (section 2.4.4.1 and 2.4.4.2).

2.4.4.8. Other toxicity studies

No other toxicity studies were conducted by the applicant.

2.4.5. Ecotoxicity/environmental risk assessment

Pegcetacoplan, being a pegylated peptide, would not require the submission ERA studies according to the current EMA "Guideline Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), the applicant followed the recommendations given in the "Draft guideline on the environmental risk assessment of medicinal products for human use- Revision 1" in view of future pegcetacoplan additional applications.

The applicant calculated the predicted environmental concentration in surface water (PEC_{sw}) for both, the registered and the intended new indication, i.e. paroxysmal nocturnal haemoglobinuria (PNH) and GA. The PEC_{sw} values were 0.0031µg/L and 0.0099 µg/L for PHN and GA, respectively, resulting in a combined PEC_{sw} of 0.013 µg/L, which is above the action limit of 0.01 µg/L.

Pegcetacoplan was subjected to OECD Test 301B in order to evaluate its ready biodegradability. Whereas di-NHS-PEG40K, the PEG-moiety, achieved > 60% degradation to CO_2 within 28 days inside a 10-day window, APL-2 did not reach 60% evolution.

Based on the PEC_{sw} of 0.013 µg/ and pegcetacoplan appearing to be not ready biodegradable, a Phase II assessment was triggered.

The fact that pegcetacoplan is not readily biodegradable and the log Koc_{SLUDGE} for pegcetacoplan was determined to be < 4 triggers a risk assessment for groundwater.

PEC_{Gw} was calculated to be 0.0032 µg/L, PEC_{STP} is 0.13 µg/L, PEC_{SED_DW} is 0.12 mg/kg dw.

As a next step, environmental effects analysis including aquatic toxicity, functioning of STP and sediment toxicity was performed.

Consequently, PEC/PNEC ratios were determined and were 0.00001 for aquatic organisms (surface water), 0.000004 aquatic organisms (groundwater), 0.003 for sediment invertebrates and 0.000001 for STP microorganisms. Thus, as all risk quotients were < 1 no environmental risk was identified for pegcetacoplan.

Table 1: Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	< -2	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	< -2	not B
	BCF	-	-
Persistence	ready biodegradability (OECD 301)	Not readily biodegradable, no further information available 9.51 % (28 d), not readily biodegradable	P
Toxicity	NOEC: Invertebrate Reproduction Test (OECD Method 211)	8.8 mg/L	not T
PBT-statement:	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.013	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	sludge: K_{oc} = 3.00 – 4.29 mL/g	3.00 mL/g 4.29 mL/g

		soil: K_{oc} = 23,645 – 89,605 mL/g			23,645 mL/g 26,279 mL/g 89,605 mL/g
Ready Biodegradability Test	OECD 301	9.51 % (28 d), not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Not conducted due to limited sensitivity of analytical method (LLOQ 1 mg/L)			Not performed
Phase iIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ Raphidocelis subcapitata	OECD 201	NOEC	75000	µg/L	Raphidocelis subcapitata
Daphnia sp*.* Reproduction Test	OECD 211	NOEC	8800	µg/L	
Fish, Early Life Stage Toxicity Test/ Pimephales promelas	OECD 210	NOEC	10000	µg/L	Pimephales promelas
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	> 1000.000	µg/L	
Phase iIb Studies					
OECD 218	OECD 218	NOEC	910	mg/kg dw	organic carbon content 2.1%

2.4.6. Discussion on non-clinical aspects

Pharmacology

Importantly, only a single study evaluated PD using the final pegcetacoplan formulation (18mM acetate buffer (pH5.0) and 5.38% (w/v) trehalose). Instead, assays were mainly performed in the presence of 5% dextrose. Given the fact that peptide and protein binding are a complex three-dimensional interactions depending on ion strength and pH values, the in vitro and in vivo experiments should be interpreted with caution. Secondly, IVT application was not investigated in proper animal models. Thus, an intraocular mechanism of action in the proposed indication is not shown for the final pegcetacoplan formulation (18mM acetate buffer (pH5.0) and 5.38% (w/v) trehalose). Further, inhibition of an intraocular inflammatory process by pegcetacoplan is not shown throughout the preclinical assessment. Hence, a functional consequence of intraocular binding of complement factors C3 and C3b is not shown for pegcetacoplan in vivo. Due to these limitations intraocular efficacy in the given indication of geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD) is not shown in the submitted studies.

In studies 19CFPH-001 and 21WPH-001, APL-2 is stated to contain a 13-amino acid peptide while pegcetacoplan is stated to be built up by two 15–amino acid cyclic synthetic peptide conjugated to a linear polyethylene glycol (PEG) chain. This discrepancy represents an error and has been clarified.

In Study 18XTPH-001 APL-9 provided the highest affinity for C3 and C3b proteins, but was not included in further analyses or discussion throughout the application. The applicant explains the structural differences between APL-2 (pegcetacoplan) and APL-9, which results in less favourable pharmacokinetics like shorter half-life of APL-9. Accordingly, APL-9 was not further pursued for testing. Results of study 16CATX-003 show that the alternative pathway is completely inhibited, but not the classical pathway of the complement system (CH50). Thus, it is not clear why a central inhibitor of C3 and C3b components of the complement system shows complete inhibition of the alternative pathway, whereas the classical pathway inhibition does not reach the 40% value. The applicant explained that mechanistically, pegcetacoplan inhibits C3 cleavage directly by binding to C3, which is effective against all three pathways of the complement system (Janssen et al. 2007; Mastellos et al. 2015). Pegcetacoplan also binds to C3b directly and inhibits C3 and C5 convertase activity, when these convertases contain C3b subunits resulting in alternative pathway inhibition (Simon-Tillaux et al. 2019). Further, serum dilution factors impact the apparent inhibition in the CH50 assay more than the AH50 assay. Accordingly, the CH50 assay may significantly underreport the actual level of CP inhibition in a pegcetacoplan patient sample compared to the lower dilution used for the AH50 assay.

Interestingly, pegcetacoplan triggers a rebound phenomenon of enhanced activation of the complement system. These overshoots with increased production of C3 and C3a (3b not shown) and enhanced CH50 and AH50 activity were seen with both galenics. The overall quality of the study is limited by the low sample size (3 animals per group) and lack of statistics. The applicant referred to data from study 22CAPH-001 analysing pegcetacoplan concentrations and C3a levels in aqueous humour after the administration of a single IVT dose of 7.5 mg/eye of pegcetacoplan in five NHPs. Within two weeks relevant pegcetacoplan concentrations were accompanied by a reduction in C3a concentrations by at least 50%. However, beyond day 15 the C3a concentrations started to increase again and exceeded basal levels at day 43 in the virtual absence of pegcetacoplan. This observation may be explained by a rebound phenomenon, which may serve as an indicator that pro-inflammatory side effects accumulating in current clinical phase III studies. This issue is further discussed in the section on clinical safety (3.3.8).

Moreover, the applicant states that target mediated drug disposition (TMDD) predicted from PK modelling may explain decreased clearance rate of C3 bound to pegcetacoplan. The applicant explains that systemic serum pegcetacoplan concentrations at steady state following IVT administration are predicted to be well below any thresholds anticipated to result in meaningful inhibition of systemic C3 at clinically relevant doses in GA patients.

The applicant cited in vivo studies to demonstrate efficacy of a single IVT injection of AL-78898A (APL-1), inhibiting retinal C3a deposition in a monkey model of light-induced damage (Collier et al. 2012). And even more impressive repeated IVT injections of AL-78898A achieved suppression and reversal of drusen depositions in a monkey model of early-onset macular degeneration (Chi et al. 2010). Given these animal models one would like to understand why pegcetacoplan was not extensively investigated in these animal models. The applicant argued that according to the principles of the 3 R’s additional in vivo experiments with pegcetacoplan in the above stated disease models were not carried out. Further, translatability from animal models into efficacy in humans is questioned and thereby used as another argument for not testing the final formulation. In study 22CAPH-001, pegcetacoplan (7.5 mg/eye; IVT) PK was monitored and accompanied by a reduction in C3a concentrations in the aqueous humour. However, beyond day 15 the C3a concentrations started to increase again and exceeded basal levels at day 43 in the virtual absence of pegcetacoplan. As mentioned above this observation may be explained by a rebound phenomenon.

Hence, conclusions on the efficacy of the final formulation of pegcetacoplan in GA disease models are based on analogy and mainly indirect extrapolations of C3 target engagements. In the scope of safety pharmacology assessment, in study 21AWPH-001 an in silico genome wide query running with the 13 amino acid sequence of APL-2 to identify similar sequences was performed. The highest degree of identity to the query sequence were two bacterial proteins, one found in a *Methylobacterium* and the other one in *Morganella morganii*. However, such an approach neglects binding information from the three-dimensional structure. Further, binding or cross-reactivity might be different using the minimal 13 amino acid sequence rather than the complete pegcetacoplan molecule. The applicant stated that the PEG domain represents a not well-ordered molecular moiety with no favoured conformation. Thus, low immunogenicity and reasonable biocompatibility is documented for this polymer. Further, systemic treatment of PNH patients with pegcetacoplan failed to reveal side effects due to off-target binding, in particular plasma protein binding partners.

Cardiovascular and respiratory safety pharmacology were assessed after subcutaneous injection to telemetered cynomolgus monkeys (study 13CATX-005). Control and APL-2 articles (in 5% dextrose) were applied subcutaneously, and this is stated to represent the intended route of administration. The intended route for pegcetacoplan is intravitreal, so that the statement in study 13CATX-005 is due to supporting the systemic pegcetacoplan development programmes of Aspaveli.

Safety pharmacology assays performed with APL-2 raised no safety issues, however, the formulation (5% dextrose) was deviant from the final formulation of pegcetacoplan. In particular, the applicant was asked to comment on the local tolerability of pegcetacoplan in the final formulation on histological level. This issue is considered of relevance since a possible rebound phenomenon may contribute to local inflammatory processes. According to the repeat dose monkey study 17CATX-002 the comparison of 5% dextrose and trehalose/acetate) formulations revealed no differences of ocular microscopic effects between the trehalose-based formulation and the dextrose formulation.

Pharmacokinetics

Overall, validation of the bioanalytical methods (ARAPL2C, ARAPL2D, ARAPL2G) for toxicokinetic evaluation in the scope of GLP-compliant toxicity studies followed the criteria laid down in the EMA "Guideline on bioanalytical method validation"– EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr and were conducted in compliance with GLP principles.

The focus in absorption and distribution sections is on single-dose studies, which is considered not ideal given that the intended treatment duration is chronic and repeat dose toxicity studies have been conducted in non-clinical species.

Study 14CTX-001 is, due to the conduct in non-human primates and the long study-duration (10 intravitreal administrations of 3.1, 12.4, or 24.8 mg/eye/dose), regarded as the most relevant non-clinical study to identify potential safety or PK issues. Serum levels were roughly dose-proportional. Evaluation of the vitreal PEG levels after the first three administrations of the highest dose of 24.5 mg/eye every 4 weeks revealed a very heterogeneous pattern of concentrations. Due to availability of a limited data set only, no conclusions on potential accumulation of PEG in the vitreous humour can be drawn.

Comparative analysis between IVT and suprachoroidal administration of single doses of 12 mg pegcetacoplan/eye revealed relevant exposure to the target tissues RPE and choroid were only achieved by IVT administration.

A literature-based discussion was provided on the unlikeliness of proteolytic degradation of pegcetacoplan in the vitreous. Thus, an inflammatory response caused by degradation product can largely be excluded.

Urine was identified as the major route of elimination.

In the pre- and post-natal toxicity study in cynomolgus monkeys very low levels of pegcetacoplan were detected in the milk, however, no quantifiable levels were detected in the offspring. Placental transfer at very low levels was detected after s.c. administration of pregnant cynomolgus monkeys.

Single-dose toxicity

A number of single-dose toxicity studies have been conducted for specific purposes, such as: testing various batches used in clinical trials in which ocular inflammation occurred in treated batches in the scope of the root cause analysis, tolerability of APL-2 formulated in microparticles, comparative administration of IVT and suprachoroidal administration.

Repeat-dose toxicity

Overall, although not pharmacologically relevant, rabbits, were used as a second species in toxicology studies as they are a sensitive and well-known species to assess local (ocular) tolerability. In the studies 13CATX-001, 13CATX-003, 15CATX-003 and 14CATX-001, pegcetacoplan was administered subcutaneously and in the latter study intravenously as well. Therefore, these studies are not reflecting the supposed way of administration in the clinic, namely the intravitreal injection. Microscopic finding related to PEG40 were observed in several tissues (e.g. femur, bone marrow, choroid plexus of the brain, cervix, ciliary body of the eye, adrenal gland, pituitary gland, salivary gland, kidney, liver sinusoids, mandibular lymph node, ovary, pancreas, skin, stomach, thymus, and uterus) with infiltrates of histiocytes (macrophages) or resident macrophages having abundant vacuolated cytoplasm with occasional flocculent material in the vacuoles, and have been already reported for other PEGylated drug products (EPAR of Aspaveli, SmPC May 2022). At high doses of APL-2 (140mg/kg/day), contribution of the drug substance to this finding cannot be excluded. At high doses of 28 and 140mg/kg/day, APL-2 related changes occurred in haematology parameters (increase in red blood cell counts, haemoglobin, haematocrit and reticulocyte counts and a decrease in platelet counts) and clinical chemistry parameters (decrease in glucose and potassium), which were reversible for reticulocytes, glucose and potassium (high dose recovery group). Again, at a high dose of 140mg/kg/day, organ weight changes (increase in spleen and kidney weights, which were reversible) were observed, as well as minimal tubular degeneration in a small amount of animals. Study 21CATX-002 investigated the intravitreal route of administration in rabbits, with a clinical relevant dose of 15mg/eye. Slight anterior vitreous cells in the eyes, correlating to vitreous infiltrates (vacuolated foamy macrophages) in the vitreous body were noticed in APL-2 treated animals, whereas one eye of one animal developed a moderate inflammation, possibly related to APL-2 as well. As stated by the applicant, ocular macrophage infiltrates in the vitreous have been reported in rabbits following IVT administration with another pegylated ocular product (Macugen EPAR Scientific Discussion 2006) and are therefore considered to be related to the PEG moity.

The applicant submitted nine repeat-dose toxicity studies conducted in the cynomolgus monkey, the species, where pegcetacoplan is supposed to be pharmacology active.

Pegcetacoplan was subcutaneously administered in studies 13CATX-002, 13CATX-004, 14CATX-005, 19CATX-003, 15CATX-004 and 14CATX-002, whereas in the latter, intravenous injection was investigated as well. A comparative assessment of mean systemic exposure to pegcetacoplan at steady state in monkeys following subcutaneous administration (7mg/kg/day) and in humans (estimated, taken from clinical study report APL-EX21-CP-012) following intravitreal administration (15mg/month) revealed a ratio of animal to human exposure for Cmax and AUC0-24 of at least 427 and 533, respectively. Therefore, data obtained from SC studies can be regarded as supportive but provide only limited value for the intended intravitreal clinical route of administration. Overall, APL-2 related changes observed at high doses (28 and 140mg/kg/day) were vacuolation and degeneration of tubules of the kidney and subcutaneous inflammatory cell infiltrates at the injections sites at the highest tested dose (140mg/kg/day). PEG40-associated microscopic findings were similar as reported in rabbit studies with pegcetacoplan, like infiltrates of histiocytes (macrophages) or resident macrophages with vacuolated cytoplasm and occasional flocculent material in the vacuoles in several tissues [e.g. bone marrow (sternum), choroid plexus of the brain, adrenal gland, pituitary gland, liver sinusoids, mandibular and mesenteric lymph node sinuses, ovary, the red pulp of the spleen, stomach, and urinary bladder] and vacuolation of epithelial cells in the choroid plexus of the brain. A dose dependent reduction of CH50 was noticed at 7, 28, and 140 mg/kg/day of APL-2 in study 13CATX-004, but no haemolytic potential of the complement system was observed following lower doses of APL-2 at 0.25, 1 and 3 mg/kg/day in study 14CATX-002, whereas in the latter study inhibition of the complement activity was observed after intravenous injection of 42mg/kg APL-2. In study 15CATX-004, no sign of complement activation was observed at any dose for either sex (no notable changes in CH50 and C3a). At 7mg/kg/day and 28mg/kg/day APL-2, there was a measurable increase in C3 levels between day 1 and 28 but not between pre-dose and 8 hours post-dose, which was supposed to be indicative of a reduction in C3 catabolism and not related to an acute phase response. Minimal to mild changes in haematology (study 19CATX-003 and 15CATX-004) and clinical chemistry parameters were noticed and regarded APL-2 related, e.g. decrease in red blood cell count, haemoglobin concentration, and haematocrit, decrease in cholesterol and minimal decrease in potassium. Despite of study 15CATX004, where ADAs were measured in PEG40 and APL-2 treated animals but considered unreliable due to assay interference (ELISA) at 100-250ng/ml, no anti-drug antibodies were detected.

Intravitreal administration of APL-2 in cynomolgus monkeys was investigated in the 2-month ocular safety studies 14CATX-004 and 17CATX-002, and the 9-month ocular toxicity study 14CTX-001. Administration of APL-2 (IVI) at doses up to 24.8mg/eye/month and till a treatment period of up to 9 month, was well tolerated, with no APL-2 or PEG40 related changes in investigated parameters like clinical signs, body weights, food consumption, ophthalmology (limited to slit-lamp bio-microscopy and indirect ophthalmoscopy, ERG, IOP), clinical pathology (haematology, coagulation, and clinical chemistry), bioanalysis (serum bioanalysis, anti-drug antibody and CH50), organ weights and macro- and microscopic pathology (eyes with optic nerves and a full range of extra-ocular tissues) and intraocular inflammation (modified ophthalmoscopy-based scoring system, Hackett and McDonald 1996). Microscopic changes in the eyes (e.g. fibrosis/pigmented macrophages in the vitreous or the needle track), as well as ocular clinical signs, slit lamp biomicroscopy and tonometry findings [limited to inflammation and associated changes in intraocular pressure (IOP)] were considered procedure-related. In study 14CTX-001, findings based on optical coherence tomography (SD-OCT) were observed in the retina. Central retinal thickness in both eyes of one animal treated with APL-2 12.4 mg/eye were detected at week 13. At week 39 elevated central retinal thickness (between >20 but ≤40 µm or >40 µm) was never seen in group 1 (vehicle, 5% dextrose, no PEG40) or group 3 (3.1mg APL-2/eye/dose). Conversely, central retinal thickness was observed in 2/12 eyes from group 2 (PEG40 control in 5% dextrose), 3/12 eyes from group 4 (12,4mg APL-2/eye/dose) and 4/12 eyes from group 5 (24.8mg APL-2/eye/dose). Accordingly, central retinal thickness was seen in cynomolgus monkeys in groups receiving high levels of PEG40 in 25% of all injected eyes, but was completely absent in groups without or low levels of PEG40 (study 14CTX-001). Hence, the conclusion of the applicant that extent and frequency of these changes were incidental and do not present a pattern to suggest any relationship to the administration of APL-2, could not be followed and the applicant was therefore requested to comment on this incidence. In response to the Day LoQ, the applicant provided a through discussion on this matter. Comparative statistics for groupwise incidences of eyes with increases in central retinal thickness, the range of increase was corrected to be 20 to ≤40 µm instead of >20 to ≤40 µm, revealed, that increases of 20µm in CRT were even observed in control and Pegcetacoplan low dose (3.1mg/eye) groups (each 1/group), although the number of affected eyes with increases of 20 to ≤40 µm increased slightly in PEG40 (22.64mg/eye) as well as pegcetacoplan medium (12.4mg/eye) and high dose (24.8mg/eye) groups (2/group, 3/group [+ 1>40µm] and 3/group [+ 1>40µm], respectively). Changes in CRT from week 39 to pre-dose, presented by groupwise mean and median values, indicated very low increases in CRT in control and pegcetacoplan low dose groups (Mean 6.69µm, SD 8.69 and Mean 4.04µm, SD 10.05, respectively), a slightly higher and similar increase in CRT in PEG40 and pegcetacoplan mid-dose groups (Mean 10.71µm, SD 12.17 and Mean 10.94µm, SD 23.28, respectively) and a further increase in the pegcetacoplan high-dose group (Mean 18.88µm, SD 12.87). To notice, microscopic findings, like occurrence of inflammation, were observed in some eyes with and without increased CRT. However, a high variability in CRT changes from baseline was shown for all measured timepoints of most individual animals in each study group. Therefore, increased CRT levels often decreased and increased again at the various time points. Although observed changes in CRT could not be explained, the applicant pointed out that there were no accompanied adverse findings attributable to pegcetacoplan or PEG40, investigated by a comprehensive ocular safety assessment, that no increases in CRT were seen in IVT pegcetacoplan clinical studies and that the high dose of 24.8mg in this non-clinical study (14CTX-001) represents approximately 3.3 fold the clinical dose of 15mg/eye, which would itself be approximately equivalent to a 7.5mg dose in NHPs (and therefore range between the low dose of 3.1mg/eye and the mid dose of 12.4mg/eye in 14CTX-001). Interestingly, in the clinical studies APL2-304 and APL2-303, an increased incidence of new-onset exudative AMD, with concomitant changes in retinal anatomical parameters, as increases in central retinal thickness (CRT), was observed in pegcetacoplan-treated subjects compared to sham-treated subjects, showing even higher occurrence of exudative AMD with increased administration frequency (once monthly compared to every two month). These changes showed an improvement (e.g. decrease in mean CRT slightly below baseline values) after 24 month following treatment with anti-VEGF therapy. It is acknowledged, that due to the high heterogenicity of data in CRT and the lack of accompanied adverse findings (e.g. eAMD) and clear correlating inflammatory observations in cynomolgus monkeys, the occurrence of slight increases in CRT in PEG40 and pegcetacoplan mid-and high dose groups in study 14CTX-001 does not allow for a distinct interpretation regarding its clinical relevance. The applicant suggests monitoring of patients for signs of neovascular AMD, including CRT changes, after treatment with Syfovre and treatment with anti-VEGF therapy, as applicable.

In the 9-month IVT toxicity study (14CTX-001) in cynomolgus monkeys, AH50 analyses were not performed even though they would have been of interest. The applicant justified this decision by the purpose of the study, which was to assess toxicity and toxicokinetics of APL-2, whereas, in contrast, study 16CATX-003 was focused on the pharmacodynamic response after intravenous administration of APL-2. In study 16CATX-003, a complete inhibition of AH50 assays was shown, while inhibition of the classical pathway of the complement system reached only 35-37% (CH50 assays). Further, a dose-related reduction in CH50 was demonstrated in the 28-day subcutaneous monkey study (13CATX-004), whereas a decrease in CH50 activity was not observed in the 9-month intravitreal study (14CTX-001), which was considered due to the low systemic exposures achieved by the IVT route. However, in the subcutaneous 9-month repeat dose toxicity study in cynomolgus monkeys (Study 15CATX-004), no sign of complement activation was noticed at any dose for any sex (no notable changes in CH50 and C3a) either. In the same 9-month ocular toxicity study, mean sex-combined serum Cmax and AUC0-inf values for APL-2 at 24.8 mg/eye/dose were 99.0 µg/mL and 41,400 h × µg/mL, respectively. A comparative assessment of mean systemic exposure to pegcetacoplan at steady state in monkeys following intravitreal administration of APL-2 at 3.1, 12.4 and 24.8mg/eye and in humans following intravitreal administration of APL-2 at 15mg/month (estimated Cmax and AUCmonthly values in GA patients of 2.1 µg/mL and 47.8 µg.h/mL, respectively, taken from clinical study report APL-EX21-CP-012) revealed a ratio of animal to human exposure for Cmax and AUC(0-t) of 9.71 and 146, 24.9 and 397, and 47.1 and 709, respectively. As for the estimated vitreous concentration reported in this 9-month ocular pivotal study (14CTX-001), maximum dose level tested was 24.8 mg/eye. It would be 1.65-fold the intended clinical dose of 15 mg/eye, which, considering the smaller size of the monkey and vitreous chamber volume (2.0 and 4.0 mL for monkey and human, respectively), would result in a clinical safety margin of 3.3-fold. No ADAs were detected after intravitreal injections in cynomolgus monkeys in neither study.

Genotoxicity

The applicant submitted seven genotoxicity studies in this dossier, including five Ames tests conducted with five different lots of pegcetatoplan (studies 13BTX-001, 14BTX-001, 19BTX-001, 19BTX-002, 19BTX-003), one in vitro micronucleus assay in TK6 cells (study 13BTX-002) and one in vivo micronucleus assay in mice [assessing polychromatic erythrocyte (PCE) cells in mouse bone marrow] (study 13BTX-003). Pegcetatoplan was found to be negative in all strains and at all concentrations in the bacterial reverse mutation assays, as well as in the in vitro and in vivo micronucleus assays and can therefore be considered non-mutagenic and non-genotoxic.

According to the ICH guideline S2(R1), the genotoxicity programme of the investigational compound pegcetacoplan is regarded sufficient to assess its genotoxic profile, with one concern identified.

The bacterial reverse mutation assays 13BTX-001 and 14BTX-001 were performed according to US FDA and OECD GLP regulations, for all other studies, including the in vitro (13BTX-002) and in vivo (13BTX-003) micronucleus assays, only US FDA GLP regulations were applied, for 13BTX-002 and 13BTX-003 it was claimed to be conducted in compliance with the OECD testing guideline 487 (OECD 2010) and the testing guidelines of the ICH (2011) and OECD (1997), respectively and regarded as compatible to non-US regulations as the OECD principles of good laboratory practice (C97)186/Final). Please refer below to the non-clinical concerns on GLP-compliance.

Reproductive and developmental toxicity

No dedicated fertility and early embryonic development studies were conducted. Assessment of reproductive organs was investigated in the 9-month repeat-dose toxicity study, conducted in cynomolgus monkeys, which is accepted. No treatment-related findings on reproductive organs were detected.

The applicant submitted three non-GLP pilot embryo-fetal development studies of APL-2, one in rats (15MTX-001), one in rabbits (15MTX-002) and one in cynomolgus monkeys (17CATX-001). Generally, as in line with the ICH S5 guideline, developmental and reproductive toxicity (DART) studies should be conducted according to good laboratory practice (GLP) regulations and cover all stages of the reproductive cycle as a fertility and early embryonic development (FEED) study, embryo-fetal development (EFD) studies in two species and a pre-and postnatal development (PPND) study. For biopharmaceuticals where non-human primates (NHPs) are the only pharmacology active species, it is considered acceptable to include fertility assessments in repeat-dose toxicity studies and to perform an enhanced pre- and postnatal development (ePPND) study instead of an EFD study. Although pegcetacoplan is a synthetic molecule and its manufacturing process does not involve recombinant DNA technology, fermentation or extraction from biological matrices, but since the NHP is the only pharmacologically relevant species and to allow for 3R's considerations, it is accepted that all three EFD studies conducted in cynomolgus monkeys, rats and rabbits were not compliant to GLP regulations. Therefore, and because no macroscopic findings were observed, the lack of fetal soft tissue and skeletal evaluations in the rat and rabbit EFD studies is considered acceptable as well. Overall, the study design (e.g. minimum number of pregnant females, number of dose groups, administration period, toxicokinetic evaluations, ante- and post-mortem endpoints) in the rodent and rabbit EFD study was appropriate. In cynomolgus monkeys, the design of the EFD study is regarded appropriate as well, even though the number of animals per group was low. Similar findings of vacuolation with PEGylated products, as seen in the choroid plexus of the brain in APL-2 treated monkeys, were reported in literature provided by the applicant and is also documented in the EPAR of Aspaveli (smPC dated 19 May 2022). Due to intravitreal administration in the clinic, the predicted median steady-state serum concentration among GA patients is low (Cmax of 2.20 µg/mL at a dose of 15 mg IVT every month) and the relevance of findings occurring in NHPs at a multiple of the expected systemic exposure in humans is unclear.

An enhanced pre- and postnatal development toxicity study was conducted with APL-2 in cynomolgus monkeys (18CATX-001) to assess possible effects on pregnant monkeys and fetal development, postnatal growth and development of infants for 6 months and APL-2 concentrations in mothers' milk while nursing. In general, the design of this enhanced pre-and post-natal development toxicity study is in line with the current ICH S5 guideline. Because APL-2 is only pharmacology active in non-human primates and humans, the cynomolgus monkey was used for this ePPND study. The study was conducted according to GLP regulations, with some exceptions in regard to bulk test article characterisation (SOP only), stability analysis (SOPs, GMP), dose formulation analysis (GMP), monkey chorionic gonadotropin assessment (test side SOP) and milk sample analysis (qualified rather than validated method). The significant increase in abortions and stillbirth, as well as the occurrence of epithelial vacuolation and infiltrates of vacuolated macrophages in multiple tissues of adult animals after subcutaneous administrations of 28mg/kg pegcetacoplan per day in cynomolgus monkeys was already reported in the EPAR of Aspaveli (SmPC dated 19 May 2022). To note, for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD), pegcetacoplan is supposed to be administered intravitreally. As stated in the clinical overview submitted by the applicant, Median (5^{th}, 95^{th}) steady-state serum Cmax among GA patients is predicted to be 2.20 (1.40, 3.00) µg/mL at a dose of 15 mg IVT every month with an expected 1300-fold higher steady-state exposure in the vitreous. Therefore, having in mind a medium Cmax of 1840±223µg/mL at GD48 for the 28mg/kg/day APL-2 treatment group, the observed increase of abortions and stillbirth in monkeys occurred at a medium maximum systemic exposure (Cmax) being more than 800fold the expected maximum systemic exposure in humans after intravitreal injection. A no-observed-adverse-effect level (NOAEL) for prenatal maternal or developmental effects of APL-2 was determined to be 7 mg/kg/day, corresponding to a maternal GD140 Cmax of 882 µg/mL and an AUC(0-t) of 6890 hr*µg/mL. Comparing the mean systemic exposure to pegcetacoplan at steady state in cynomolgus monkeys following subcutaneous administration at 7mg/kg/day in this ePPN study (mean Cmax: 896µg/ml and AUC0-24: 20500µg*h/mL) with the estimated systemic exposure in humans following intravitreal administration (geometric mean Cmax 2.1µg/mL and average daily AUC exposure at steady state 38.4µg*h/mL, taken from clinical report APL-EX21-CP-012), ratios of animal to human exposures of 427 and 533 for Cmax and AUC0-24, respectively, are obtained. Overall, similar effects have been observed with other PEG-related substances, and effects reported in the ePPND study with pegcetacoplan at a dose level of 28 mg/kg (increase in stillbirth and abortions) are incorporated to the SmPC section 5.3, providing a safety margin calculated, which is acknowledged.

Carcinogenicity

No carcinogenicity studies were conducted with pegcetacoplan. A short summary of the applicant's literature research regarding the influence of the complement system in cancer development was provided in the toxicology written summary. Because genotoxicity and toxicity studies submitted with this MAA do not reveal any potential of pegcetacoplan in cancer development and systemic exposure in humans is expected to be low after intravitreal injections, the lack of carcinogenicity studies is accepted.

Antigenicity

The formation of anti-drug antibodies (ADAs) was investigated in repeat dose toxicity studies in rabbits and monkeys. Based on results of serum ADA assays, pegcetacoplan is weakly to moderately antigenic to rabbits but minimally antigenic to monkeys (the more human-relevant species).

Impurities

In study 19CATX-003, the potential toxicity of heat-degraded pegcetacoplan drug product, containing drug substance impurities considered degradation products formed during drug product storage, was compared to non-degraded pegcetacoplan drug product when given subcutaneously (SC) once daily for 28 days to cynomolgus monkeys. A similar study was conducted in rabbits after intravitreal injections of heat- and non-heat-degraded APL-2 (study 21CATX-002). In both studies, no distressing differences were observed between heat- and non-heat degraded pegcetacoplan. APL-2 related findings (e.g. decrease in haematology and chemical chemistry parameters in monkeys) were observed to be minimally more pronounced in heat-degraded APL-2 treated animals, but not considered noteworthy due to similar, but less pronounced changes in vehicle control groups and the minor magnitude of difference between APL-2 treatment groups. Qualification of impurities and applied specification limits are discussed above under Quality aspects.

Environmental risk assessment

Pegcetacoplan is considered to be P but not B or T. Environmental effects analysis including aquatic toxicity, functioning of STP and sediment toxicity was performed. Risk quotients for aquatic organisms (surface water, groundwater) and for STP organisms were < 1, thus, no environmental risk was identified for pegcetacoplan.

Considering the above data, pegcetacoplan is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

Overall, the applicant submitted a comprehensive non-clinical study programme.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2: Listing of clinical studies

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); dosage; route of administration	Number of subjects	Diagnosis of subjects	Duration of treatment	Study status; type of report
Completed ophthalmology IVT studies									
Safety/PK Phase 1	POT-CP043014	5.3.3.2	To provide initial safety, tolerability, and pharmacokinetics information of IVT administration of APL-2 in order to support further development into larger Phase 2 studies for treatment of patients with AMD.	Open-label, prospective, nonrandomized, single-dose escalation	Cohort 1: single dose of 4 mg pegcetacoplan (100 µL of 40 mg/mL) IVT Cohort 2: single dose of 10 mg pegcetacoplan (100 µL of 100 mg/mL) IVT Cohort 3: single dose of 20 mg pegcetacoplan (100 µL of 200 mg/mL) IVT	13	Subjects with an active choroidal neovascular lesion secondary to AMD receiving treatment with anti-VEGF therapy (Lucentis, Eylea, or Avastin)	Approximately 123 days	Completed Full CSR
Safety Phase 1b	APL2-103	5.3.5.2	To evaluate the safety and tolerability of IVT injected pegcetacoplan in subjects with GA secondary to AMD	Multicenter, open-label study	Cohort 1: pegcetacoplan 15 mg/0.1 mL monthly Cohort 2a: pegcetacoplan 15 mg/0.1 mL monthly Cohort 2b: pegcetacoplan 15 mg/0.1 mL EOM	19 Cohort 1: 16 Cohort 2a: 2 Cohort 2b: 1	Subjects with GA secondary to AMD	Duration of participation: Cohort 1 approximately 61 months Cohort 2 approximately 37 months	Completed Full CSR
Safety Phase 1b/2	APL2-203	5.3.5.2	To establish the safety of IVT injected pegcetacoplan in subjects with neovascular AMD	Open-label, multicenter, nonrandomized	Pegcetacoplan 15 mg/100 µL IVT	17	Subjects with clinical diagnosis of neovascular AMD	Screening: 4 weeks Treatment period: 48 weeks Follow-up period: 24 weeks Duration of participation: approximately 76 weeks	Completed Abbreviated CSR
Safety Phase 2	POT-CP121614	5.3.5.1	To assess the safety, tolerability, and evidence of activity of multiple IVT injections of pegcetacoplan in subjects with GA secondary to AMD	Prospective, multicenter, randomized, single-masked, sham-controlled study	Pegcetacoplan 15 mg/100 µL IVT monthly Pegcetacoplan 15 mg/100 µL IVT EOM Sham injection monthly Sham injection EOM	246	Subjects with GA secondary to AMD	18.5 months	Completed Full CSR
Efficacy/ safety Phase 3	APL2-303	5.3.5.1	To evaluate the efficacy of pegcetacoplan compared to sham injection in subjects with GA secondary to AMD assessed by change in the total area of GA lesions from baseline as measured by FAF	Multicenter, randomized, double-masked, sham-controlled study	Pegcetacoplan 15 mg/0.1 mL IVT monthly Pegcetacoplan 15 mg/0.1 mL IVT EOM Sham IVT monthly Sham IVT EOM	621 assigned to treatment, broken down as follows: PM = 206 PEOM = 208 SM = 102 SEOM = 105	Subjects with GA secondary to AMD	Treatment duration: 24 months Duration of participation: approximately 27 months	Completed Full CSR
Efficacy/ safety Phase 3	APL2-304	5.3.5.1	To evaluate the efficacy of pegcetacoplan compared to sham injection in subjects with GA secondary to AMD assessed by change in the total area of GA lesions from baseline as measured by FAF	Multicenter, randomized, double-masked, sham-controlled study	Pegcetacoplan 15 mg/0.1 mL IVT monthly Pegcetacoplan 15 mg/0.1 mL IVT EOM Sham IVT monthly Sham IVT EOM	637 assigned to treatment, broken down as follows: PM = 213 PEOM = 212 SM = 106 SEOM = 106	Subjects with GA secondary to AMD	Treatment duration: 24 months Duration of participation: approximately 27 months	Completed Full CSR

Ongoing ophthalmology IVT studies									
Safety and efficacy Phase 3	APL2-GA-305	5.3.5.2	To evaluate the long-term safety of IVT injected pegcetacoplan	Open-label, multicenter, long-term extension study	Pegcetacoplan IVT 15 mg/0.1 mL monthly Pegcetacoplan 15 mg/0.1 mL IVT EOM	759	Subjects with GA secondary to AMD who participated in 1 of 3 previous studies (Studies APL2-103, APL2-303, and APL2-304)	Up to 36 months	Ongoing
Population modeling analysis report (population PK)									
Population modeling analysis report (population PK model)	APL-EX21-CP-012	5.3.3.5	To develop a population PK model to characterize the serum concentration-time profile of pegcetacoplan following IVT injection in patients with nAMD or GA, evaluate the effect of pegcetacoplan formulation on the systemic absorption rate of pegcetacoplan following IVT injection, investigate the effects of selected covariates on pegcetacoplan PK parameters to derive a final predictive PK model for IVT administration, and predict vitreous and serum pegcetacoplan concentration-time profiles and derived exposure metrics following IVT injection of pegcetacoplan	This population PK modeling report documents a pooled population PK analysis including data from 4 studies: Study POT-CP043014 (Phase 1), Study APL2-203 (Phase 1b/2), Study POT-CP121614 (Phase 2), and Study APL2-303 (Phase 3). The analysis characterizes the serum concentration-time profile of pegcetacoplan following IVT injection in patients with nAMD or GA.	IVT administration as indicated by study: Study POT-CP043014 = Cohort 1: single dose of 4 mg pegcetacoplan (100 µL of 40 mg/mL) IVT Cohort 2: single dose of 10 mg pegcetacoplan (100 µL of 100 mg/mL) IVT Cohort 3: single dose of 20 mg pegcetacoplan (100 µL of 200 mg/mL) IVT Study APL2-203 = 15 mg/100 µL monthly Study POT-CP121614 = Cohort 1: 15 mg/100 µL monthly; Cohort 2: 15 mg/100 µL EOM Study APL2-303 = Cohort 1: 15 mg/0.1mL monthly; Cohort 2: 15 mg/0.1mL EOM	261	Subjects with nAMD or GA secondary to AMD	Study POT-CP043014 = approximately 123 days Study APL2-203 = approximately 76 weeks Study POT-CP121614 = 18.5 months Study APL2-303 = 24 months	Completed
Exposure-response study									
Population exposure-response model	APL-EX22-CP-014	5.3.5.3	To develop a disease progression model to characterize the progression of GA lesion area in patients receiving sham treatment, including the assessment of disease-specific covariates; develop a population exposure-response model to characterize the impact of pegcetacoplan exposure following IVT administration on GA lesion area progression in patients with GA; and to predict disease progression at landmark timepoints following sham treatment compared to clinically relevant doses of pegcetacoplan via IVT administration	Study design included GA lesion area measurements through 24 months from 3 clinical studies (Studies POT-CP121614, APL2-303, and APL2-304) following sham treatment or IVT administration of pegcetacoplan to patients with GA.	IVT administration as indicated by study: Study POT-CP121614, Study APL2-303, Study APL2-304	Study POT-CP121614: study eye = 245, fellow eye = 201 Study APL2-303: study eye = 620; fellow eye = 486 Study APL2-304: study eye = 636; fellow eye = 524	Subjects with GA secondary to AMD	Study POT-CP121614 = 18.5 months Studies APL2-303 and APL2-304 = 24 months	Completed

Abbreviations: AMD = age-related macular degeneration; CSR = clinical study report; EOM = every other month; FAF = fundus autofluorescence; GA = geographic atrophy; IVT = intravitreal; nAMD = neurovascular age-related macular degeneration; PEOM = pegcetacoplan every other month; PK = pharmacokinetics; PM = pegcetacoplan monthly; SAD = single ascending dose; SEOM = sham every other month; SM = sham monthly; VEGF = vascular endothelial growth factor.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

The PK of pegcetacoplan has been evaluated in subjects with nAMD (Studies POT-CP043014 and APL2-203) and in subjects with GA secondary to AMD (Studies POT-CP121614, APL2-303).

A Population PK model was developed using data from these four studies.

Additionally, a phase 1, double-blind, randomised, placebo-controlled, single ascending dose study of intravenous pegcetacoplan in healthy volunteers (Study APL2-CP-HV-401) has been conducted. As PK after IV administration is not considered relevant for the proposed indication via IVT administration in the current MAA, the latter study is not further discussed.

The analytical method BPAPL2F for the determination of APL-2 in human plasma as well as respective validations (including partial validations) are described adequately; the validations were basically performed according to the requirements of the "ICH Guideline M10 on Bioanalytical Method Validation and Study Sample Analysis" (EMA/CHMP/ICH/172948/2019). Acceptance criteria are in a plausible range and were fulfilled.

The bioanalytical method demonstrates acceptable performance and is suitable for the determination of APL-2 in K2EDTA human plasma over the calibration range.

Absorption

In the following, only the design of the trials of the clinical development phases 1 and 2 will be presented. For the design of the phase 3 trials, please see below.

Study POT-CP043014

This was a phase 1 single-ascending dose study that assessed the safety, tolerability, and PK of IVT pegcetacoplan therapy in subjects with Neovascular Age-Related Macular Degeneration (nAMD) currently receiving anti-vascular endothelial growth factor (VEGF) therapy. Subjects were sequentially enrolled into 3 cohorts (4, 10, and 20 mg of APL-2 in a 100 µL IVT injection). Initially, 3 subjects were enrolled in each cohort. Cohort 3 was expanded to 12 subjects once the initial 3 subjects had reached their Day 7 Visit (only 7 were recruited).

Subjects participated in only 1 cohort. If both eyes were eligible for the study, the participant and Principal Investigator chose the eye that served as the study eye. Subjects were screened and received standard-of-care anti-VEGF therapy within 10 days before receiving APL-2. Standard-of-care anti-VEGF therapy could have been administered on the same day as the Screening Visit after the screening procedures were completed. Subjects who met all entry criteria received IVT APL-2 on Day 1. Subjects returned to the clinical site on Days 3, 8, and 15 during the 14-day acute safety observation period. After the acute safety period, subjects returned to the clinical site for additional follow-up visits on Days 29, 57, 85, and the Termination Visit on Day 113. Safety was assessed throughout the study; blood samples and urine samples were collected for safety laboratory determinations. Blood samples were also collected for the pharmacokinetic assessment of APL-2.

For both Cohorts 1 and 2, at least 3 subjects were required to complete the 14-day acute safety observation period (i.e., dropouts before Day 15 were to be replaced) before enrolment of the next cohort (i.e., next dose level) was initiated. A decision to proceed to the next dose level (i.e., next cohort) was made by the Safety Monitoring Committee following the review of all pertinent safety/tolerability data of the current cohort collected during the 14-day acute safety observation period.

The planned length of participation in the study for each subject was approximately 123 days (from Day -10 through completion of the Day 113 follow-up procedures).

Diagnosis and main criteria for inclusion: Male and female subjects aged ≥50 years with the presence of an active choroidal neovascular lesion secondary had received at least 3 anti-VEGF treatments (Lucentis, Eylea, or Avastin) over the 26-week period prior to screening.

Test product, dose and mode of administration, batch number:

- 4 mg APL-2: administered as a single IVT injection of APL-2 (100 µL of 40 mg/mL; batch number APE40003).

- 10 mg APL-2: administered as a single IVT injection of APL-2 (100 µL of 100 mg/mL; batch number APE40004).
- 20 mg APL-2: administered as a single IVT injection of APL-2 (100 µL of 200 mg/mL; batch number APE40022).

Criteria for evaluation:

Efficacy: Changes in visual acuity (total score, best-corrected visual acuity at 1 meter [$BCVA_1$], and best-corrected visual acuity at 4 meters [$BCVA_4$]) and Spectral Domain Optical Coherence Tomography

(SD-OCT) (including macular cube volume, central retinal lesion thickness, central retinal thickness, central subfield thickness, choroidal neovascularisation [CNV] thickness, sub-retinal fluid thickness, and pigment epithelial defect thickness).

Pharmacokinetic: Pharmacokinetic assessments included exposure after single APL-2 IVT dose (AUC_{0-t}), maximum observed serum concentration (C_{max}), and time to maximum measured concentration (T_{max}).

Safety: Primary safety endpoints included local and systemic adverse events, DLTs (i.e., intraocular inflammation [vitritis or uveitis], endophthalmitis, sustained elevation of intraocular pressure ≥30 mmHg, and/or sustained loss of visual acuity ≥15 letters not attributable to the injection procedure or progression of disease), adverse events of special interest, clinical laboratory evaluations (including urine pregnancy tests for women of childbearing potential), physical examination, and vital signs.

Statistical methods:

The data were summarised by cohort and overall. Where applicable, continuous data were summarised using n, median, minimum, and maximum; categorical data were summarised using counts and percentages. Baseline was taken as the last nonmissing measurement prior to administration of the study treatment.

Efficacy: Total visual acuity, $BCVA_1$, and $BCVA_4$ scores, changes from baseline, and percent changes from baseline (when the baseline score was not equal to zero) were summarised. SD-OCT parameter (macular cube volume, central retinal lesion thickness, central retinal thickness, and central subfield thickness) scores, changes from baseline, and percent changes from baseline were summarised. The presence/absence of SD-OCT morphology (posterior hyaloid, epiretinal membrane, cystoid spaces, and intra-retinal fluid) was summarised categorically by visit.

Pharmacokinetic: To assess the plasma concentration profile of APL-2 after a single dose, concentrations were plotted over time. Linear and log linear individual concentration profile plots against time (with each cohort being identifiable) were displayed.

The following were plotted to visualise the relationship between dose and pharmacokinetic parameters: area under the curve from time 0 to last measurable concentration (AUC_{0-t}) vs. dose; dose-normalised AUC_{0-t} vs. dose; C_{max} vs. dose; and dose-normalised C_{max} vs. dose. Dose normalisation was to a 1-mg dose.

Safety: Adverse events were coded using Medical Dictionary for Regulatory Activities to assign the appropriate System Organ Class and preferred term.

Adverse events were tabulated overall and by cohort. A topline summary of adverse events; adverse events by preferred term in order of total events; adverse events regarded as possibly/probably related to study drug; and adverse events and SAEs by maximum severity and System Organ Class were tabulated. Laboratory values outside the reference range were identified for each subject. Additionally, vital sign data outside of pre-specified ranges were identified for each subject.

Results:

Thirteen subjects (3 subjects in the APL-2 4 mg cohort, 3 subjects in the APL-2 10 mg cohort, and 7 subjects in the APL-2 20 mg cohort) were screened and enrolled into the study. All 13 subjects completed the study.

The following figure displays the profiles of mean serum pegcetacoplan concentrations versus time for the 4, 10, and 20 mg IVT/0.1 mL injection cohorts.

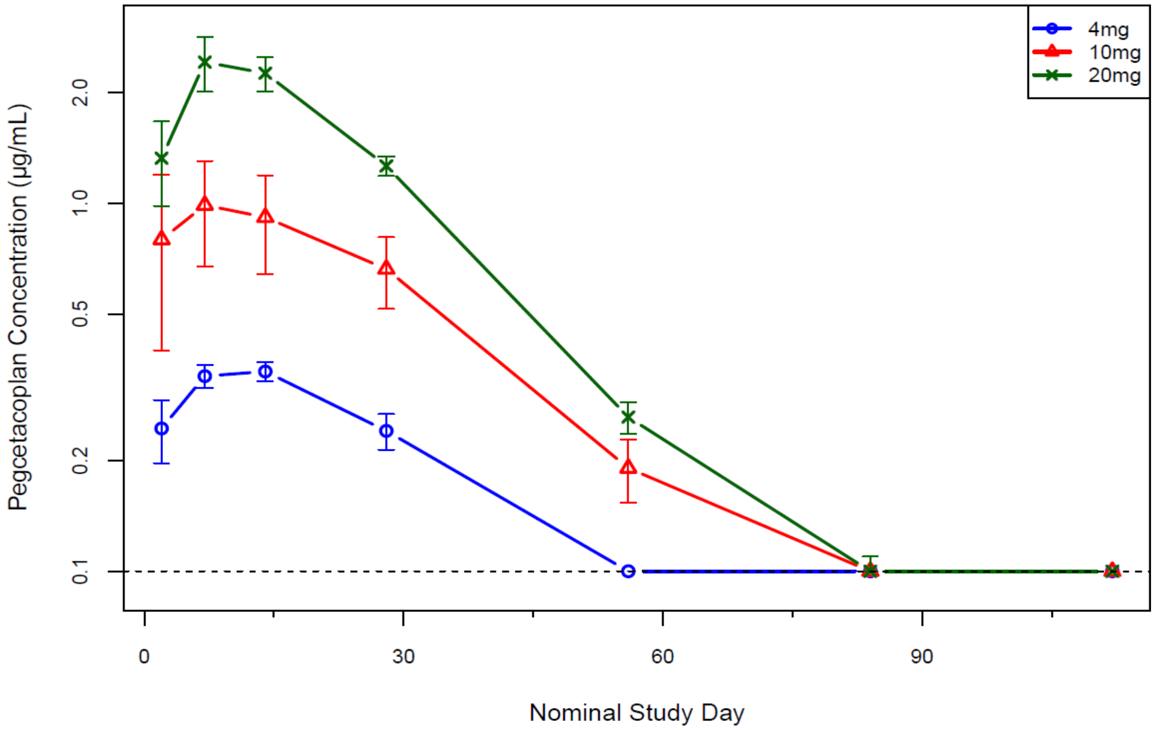


Figure 3: Study POT-CP043014: mean (SE) pegcetacoplan serum concentrations following IVT administration

Abbreviations: BLQ = below the limit of quantification; IVT = intravitreal; LLOQ = lower limit of quantification. Notes: Values that were BLQ were set to the one-half the LLOQ (LLOQ = 0.10 µg/mL, dashed line). Mean (points) and SE (error bars) pegcetacoplan concentrations are presented in semilogarithmic scale with values BLQ censored at the LLOQ in the plot.

Pegcetacoplan was slowly absorbed into the systemic circulation, with tmax values ranging between 7 and 16 days across all subjects. Pegcetacoplan serum concentrations declined in a steady monoexponential manner. There was an apparent dose-related increase in pegcetacoplan serum exposure metrics (C_{max} and AUC_{0-t} [area under the concentration-time curve from zero to the last measurable concentration]) across the doses investigated. Median Cmax and AUC0-t values ranged from 0.383 to 2.14 µg/mL and 11.89 to 69.53 µg·day/mL, respectively.

The following table summarises the pegcetacoplan PK parameters, estimated by noncompartmental analysis, following IVT administration.

Table 3: Study POT-CP043014: summary of pegcetacoplan serum PK parameters

Dose	n	Median (range)				
		t_{max}, day	C_{max}, µg/mL	Dose-normalised C_{max}, µg/mL	AUC_{0-t}, µg·day/mL	Dose-normalised AUC_{0-t}, µg·day/mL
4 mg	3	14.0 (8.9-14.9)	0.383 (0.317-0.387)	0.096 (0.079-0.097)	11.89 (11.49-13.90)	2.97 (2.87-3.47)
10 mg	3	7.9 (7.0-14.9)	0.764 (0.596-1.610)	0.076 (0.060-0.161)	29.95 (24.27-53.59)	3.00 (2.43-5.36)
20 mg	7	15.0 (6.9-16.0)	2.140 (1.440-3.970)	0.107 (0.072-0.199)	69.53 (55.06-86.92)	3.48 (2.75-4.35)

Abbreviations: AUC_{0-t} = area under the curve from time 0 to the last measurable concentration; C_{max} = maximum observed concentration occurring at t_{max}; n = number of evaluable subjects; PK = pharmacokinetic; t_{max} = time of maximum observed concentration sampled during a dosing interval.

In summary, APL-2 was slowly absorbed into the systemic circulation, with T_{max} values between 7 and 16 days across all subjects. APL-2 serum concentrations declined in a steady mono-exponential manner. There was a dose-dependent increase in exposure (C_{max} and AUC_{0-t}), broadly consistent with the APL-2 serum pharmacokinetics being dose-proportional across the doses investigated.

Study APL2-203

This was an 18-month, Phase 1b/2, multicentre, open-label study to assess the safety and tolerability of monthly intravitreal (IVT) injections of pegcetacoplan in subjects with neovascular AMD.

One cohort of 17 subjects with neovascular AMD in the study eye, who were receiving anti-vascular endothelial growth factor (anti-VEGF) IVT injections and who met all selection criteria, were enrolled at 3 sites in the United States. It was planned that subjects, starting at the baseline visit (Day 1; Visit 3), would receive monthly 15 mg pegcetacoplan IVT injections through Visit 15 (Day 360). No subjects completed the treatment phase because of study termination by the sponsor for reasons not related to safety. At the time of study termination, 3 subjects withdrew consent, and 14 subjects completed the early termination visit.

A total of 3 protocol amendments were approved for this study. Study procedures were defined by the original protocol and these amendments.

Screening assessments were performed at Screening Visits 1 and 2 (Days -28 and -14). At Screening Visit 1, it was determined if subjects required an anti-VEGF injection due to the presence of any subretinal, intraretinal, or subretinal pigment epithelium fluid on spectral domain optical coherence tomography (SD-OCT). Those subjects requiring an anti-VEGF injection and who met all other selection criteria received the first mandatory anti-VEGF injection and were asked to return for further evaluation at Screening Visit 2. Subjects that demonstrated a reduction in excess macular fluid or macular thickness (based on SD-OCT comparison from Screening Visits 1 and 2) and who met all other selection criteria at Screening Visit 2 were eligible for the study. At baseline (Day 1), patients received the second mandatory anti-VEGF injection and administration of pegcetacoplan to begin the treatment phase of the study.

During the treatment phase, subjects received monthly pegcetacoplan injections and were assessed by the investigator, at each visit, for the need of an anti-VEGF injection. If required, the anti-VEGF injection was administered ≥30 minutes prior to the pegcetacoplan injection. Ophthalmologic assessments performed during the treatment period included slit-lamp examination, intraocular pressure (IOP), best corrected visual acuity (BCVA), dilated indirect ophthalmoscopy (DIO), fundus fluorescein angiography (FFA), digital colour fundus photography (DCFP), and SD-OCT.

Serial blood and urine samples for assessment of safety were collected at prespecified time points throughout the study. Blood samples were also collected for pharmacokinetic (PK) and immunogenicity assessments.

Number of subjects (planned and analysed):

Number planned: 20 subjects

Number screened: 29 subjects (28 unique subjects; 1 subject rescreened)

Number included in the safety and intent-to-treat (ITT) sets: 17 subjects

Diagnosis and main criteria for inclusion:

Subjects were men or women aged ≥60 years with a clinical diagnosis of neovascular AMD in the study eye. A subject’s study eye had to have a normal luminance BCVA of ≥24 letters using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts (i.e., 20/320 Snellen equivalent). Additionally, the study eye had to have received ≥6 months of IVT anti-VEGF therapy at ≤8-week intervals for the most recent 2 injections and had to be eligible for an anti-VEGF injection with macular fluid present at Screening Visit 1. Following the anti-VEGF injection, the subject’s study eye had to experience, at the investigator’s discretion, a clinically meaningful reduction in excess macular fluid or macular thickness between Screening Day -28 (Visit 1) and Screening Day -14 (Visit 2) as assessed by SD-OCT.

Subjects with a history of intraocular surgery (≤3 months prior to randomisation), vitrectomy, or endophthalmitis in the study eye were excluded from the study. Subjects with ophthalmic conditions, including other causes of choroidal neovascularisation, trabeculectomy, aqueous shunt, aphakia, absence of the posterior capsule, or ocular/periocular infection, were also excluded.

All subjects had to be willing to comply with the study procedures and assessments required by the protocol.

Table 4: Test product; dose, mode, and duration of administration; lot number

Lot number	Expiry date	Dose	Vial	Route of administration
APE15007	10 Jun 2018	15 mg/month	120 mg/vial (150 mg/mL), pegcetacoplan for injection (lyophilized pegcetacoplan to be reconstituted with 5% dextrose)	1 bolus IVT injection (0.1 mL injection volume)
040-001-001	30 Mar 2019	15 mg/month	15 mg/0.1 mL, pegcetacoplan intravitreal injection (solution in 5% dextrose)	1 bolus IVT injection (0.1 mL injection volume)

Lot APE15007 was administered to all 17 subjects and lot 040-001-001 was administered to 4 out of the 17 subjects.

Safety:

Safety was assessed throughout the study by monitoring adverse events, clinical laboratory tests (i.e., haematology, serum chemistry, and urinalysis), vital signs, physical examinations, postinjection assessments, complete ophthalmic examinations, IOP, BCVA, DIO, FFA, DCFP, and SD-OCT (central subfield thickness, cube volume, pigment epithelial detachment thickness, and subretinal thickness).

Other analyses:

Changes from baseline in central macular thickness on SD-OCT were assessed over 12 months.

The frequency of subjects who received an anti-VEGF injection was assessed at all study visits from Visit 4 through the Exit Visit (Visit 17; Day 540).

Immunogenicity:

Blood samples for assessment of antipegcetacoplan antibodies were collected at Visits 4, 9, and 15 (Days 30, 180, and 360).

Pharmacokinetics:

Predose blood samples for PK assessment of pegcetacoplan were collected at Visits 4, 9, and 15.

<u>Statistical methods:</u>

Given the exploratory nature of the study, no formal statistical hypothesis testing was planned or performed. Therefore, the sample size was not based on statistical power.

The screened set included all patients who signed the informed consent form, were screened for participation, and were given initial anti-VEGF therapy in this study. This set was only used for the purpose of describing patient disposition. The Safety and ITT Sets included all subjects who received a dose of pegcetacoplan.

<u>Safety</u>

Adverse events were recorded. Treatment-emergent adverse events (TEAEs) are summarised.

Demographics, medical and surgical histories, prior medications, concomitant medications, and pegcetacoplan exposure are summarised.

Changes of potential clinical significance in vital signs and clinical laboratory values are summarised. Complete ophthalmic examinations, IOPs, BCVAs, DIOs, FFAs, and DCFP are summarised.

Pharmacokinetics

Pharmacokinetic analyses were not performed because the study was terminated, and subjects were not exposed to predetermined number of pegcetacoplan injections necessary for meaningful PK analysis.

Results:

Following IVT administration of a single dosage of 15 mg/0.1 mL pegcetacoplan, mean trough concentration was 0.79 µg/mL at month 1. After multiple monthly doses, pegcetacoplan steady-state mean trough concentration was 0.73 µg/mL at month 6, suggesting that there are no apparent systemic drug accumulations after IVT administration of pegcetacoplan doses of 15 mg/0.1 mL in subjects with nAMD.

Table 5: Study APL2-203: mean pegcetacoplan serum concentration

	Month 1	**Month 6**
15 mg monthly		
n	17	15
Mean (SE), µg/mL	0.792 (0.074)	0.732 (0.109)
SD, µg/mL	0.307	0.420

Abbreviations: BLQ = below the limit of quantification; LLOQ = lower limit of quantification; n = number of evaluable subjects.
Note: Values that were BLQ were set to one-half of the LLOQ (LLOQ = 0.10 µg/mL).

The duration of exposure was shorter than expected since dosing in the study was paused after 4 subjects experienced events of uveitis in the study eye. At the time, events of uveitis were reported in the study eye, dosing with pegcetacoplan was paused, the Safety Monitoring Committee was informed, and a detailed investigation was initiated. The likely root cause of the uveitis events was identified as low-level impurity present in the active pharmaceutical ingredient that was introduced during the scale-up of the manufacturing process. No subject was dosed with pegcetacoplan after the study was paused. The study was subsequently terminated for reasons not due to safety.

Study POT-CP121614

This was a Phase 2, prospective, multicentre, randomised, single-masked, sham-injection controlled study to assess the safety, tolerability, and evidence of activity of multiple IVT injections of pegcetacoplan in subjects with GA secondary to AMD.

Subjects diagnosed with GA secondary to AMD in the study eye who met all other screening criteria were included in the study. The study was designed to randomly assign treatment to approximately 240 subjects across 40 multinational sites to obtain at least 201 evaluable subjects.

Subjects were screened 14 (±5) days before randomisation. Subjects who met all inclusion criteria and no exclusion criteria, and who were confirmed as eligible by the central reading centre, returned to the clinic for the randomisation visit (Day 0; Study Day 1). At this visit, subjects were randomly assigned in a 2:2:1:1 manner to receive treatment with pegcetacoplan monthly (PM), pegcetacoplan every other month (PEOM), sham monthly (SM), or sham every other month (SEOM), respectively. The first IVT administration of investigational product (IP; i.e., pegcetacoplan or sham) occurred on Study Day 1.

All subjects returned to the study site at the Day 7 visit to assess acute safety after the first injection. Thereafter:

- Subjects in the monthly groups (i.e., PM and SM) returned to the study site every month through Month 12 for additional IVT injections of IP and other study procedures.
- Subjects in the every-other-month (EOM) groups (i.e., PEOM and SEOM) returned to the study site every 2 months through Month 12 for additional IVT injections of IP and other study procedures.
- All subjects returned for follow-up visits at Month 15 and Month 18.

Number of Subjects (Planned and Analysed):

Number planned: 240

Number screened: 419

Number included in the intent-to-treat, safety, PK, and PD populations: 246

Number included in the modified intent-to-treat (mITT) population: 242

Number included in the per-protocol population: 210

Diagnosis and Main Criteria for Inclusion:

Subjects were men or women, aged ≥50 years, with BCVA scores in letters read of 24 or better using Early Treatment Diabetic Retinopathy Study charts. Subjects had diagnoses of GA of the macula secondary to AMD confirmed within 14 days prior to randomisation using FAF images. Additionally, the subjects' GA met several other criteria:

- Total GA area must have been ≥2.5 mm^2 and ≤17.5 mm^2 (1 and 7 disk areas, respectively) as determined by FAF images.
- If GA was multifocal, at least 1 focal lesion must have been ≥1.25 mm^2 (0.5 disk areas).
- GA could be completely visualised at the macula centred image.
- GA was photographed in its entirety.
- GA was measured separately from any areas of peripapillary atrophy.
- Presence of any pattern of hyperautofluorescence in the junctional zone of GA.

Subjects with GA due to causes other than AMD, any history or current evidence of exudative AMD in the study eye, retinal disease other than AMD, any ophthalmologic condition that reduced media clarity, any ophthalmic condition that prevented adequate retinal imaging, aphakia or absence of the posterior capsule, or spherical equivalent of the refractive error demonstrating >6 dioptres of myopia or an axial length >26 mm were excluded. History or current evidence of exudative AMD in the contralateral eye was not exclusionary. Furthermore, subjects who had ophthalmic conditions that might have required surgery during the study period, any contraindication to or history of IVT injection, or histories of uveitis or endophthalmitis were ineligible to participate in the study.

Test Product, Dose and Mode of Administration, Batch Number:

Product: Pegcetacoplan

Dosage: 15 mg pegcetacoplan/100 µL administered IVT

Batch number: APE40022

Duration of Treatment:

Subjects in the PM and SM groups received monthly pegcetacoplan injections or sham injections, respectively, for up to 12 months, resulting in a total of 13 IP administrations. Subjects in the PEOM and SEOM groups received EOM pegcetacoplan injections or sham injections, respectively, for up to 12 months, resulting in a total of 7 IP administrations.

Criteria for Evaluation:

Efficacy, PK, and PD:

Efficacy was assessed using FAF images, standard visual acuity assessments, colour photography, spectral domain optical coherence tomography, and other ophthalmic observations.

Genetic marker analysis was performed on blood samples collected at Month 2 for all subjects at selected sites where genetic testing was allowed.

Blood samples were also collected for PK and PD assessments. For PK, samples were drawn before each treatment and at the follow-up and termination visits.

Safety:

Safety was assessed throughout the study, including through the collection and analysis of serial blood and urine samples and the collection. Blood samples were also collected for immunogenicity assessments.

Statistical Methods:

All statistical tests were 2-sided at the 0.1 level of significance. To understand the clinical significance of the estimated treatment effects and to aid interpretation of the formal hypothesis testing, 2-sided 95% CIs were provided. There were no adjustments for multiple comparisons.

For ophthalmic imaging (performed by the reading centre) assessed by 2 independent readers, the mean value was used in the calculation of summary statistics. Where result assessment was available for 3 independent readers, the median value was used.

Continuous variables were summarised using the number of nonmissing observations (n), mean, SD, median, minimum, and maximum. Geometric mean and coefficient of variation were included for PK parameters where appropriate. Categorical variables were summarised using frequencies and percentages.

For all assessments, baseline was the last available nonmissing assessment prior to first study drug administration.

For all summary tables, data were presented by treatment group and by pooled sham and pooled pegcetacoplan.

For analysis of the primary endpoint, CFB in square root area for GA lesion at Month 2, Month 6, and Month 12 was analysed for the mITT population with a linear mixed-effects model for repeated measures (MMRM) approach. If the treatment effect was found to be significant at the 0.1 level, treatment means were compared using the least significant difference method, and the *P* value was presented. The growth rate was also analysed through Month 18.

The robustness of the primary analysis was evaluated by repeating the primary analysis with the per-protocol population.

In addition, sensitivity analyses of the primary endpoint were conducted using the mITT population. The sensitivity analyses were an MMRM analysis that included only data that was within a specific time period of the last injection, last-observation-carried-forward analysis, and completer analysis.

Subgroup analyses of the primary endpoint in the mITT population included country, reticular pseudodrusen at baseline, age group, LL-VA deficit at baseline, fellow eye choroidal neovascularisation (CNV) at baseline, GA presence at baseline, GA lesion size in the study eye, and sex.

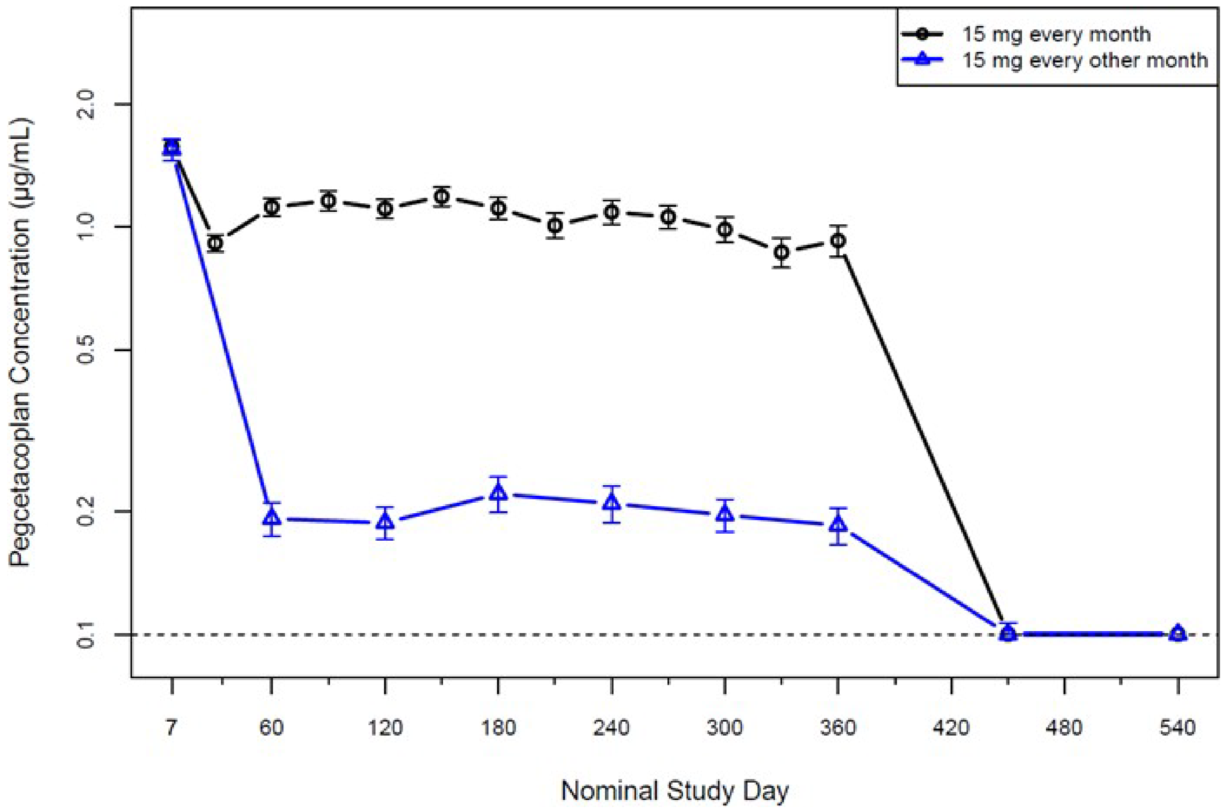
The study was powered for statistical analysis of the primary efficacy endpoint; therefore, statistical values presented for secondary and exploratory efficacy endpoints are descriptive.

No formal statistical analyses of aEs were undertaken. All aEs were tabulated and summarised for descriptive purposes only.

Results:

Serum concentration data from 62 of 86 subjects in the PM group and 60 of 79 subjects in the PEOM group were available for analysis. During the treatment period (until Month 12), the observed median maximum serum concentration of pegcetacoplan was approximately 1.5 µg/mL (at Day 7) for both the PM and PEOM groups. The PM group displayed median trough concentrations ranging from 0.91 to 1.24 µg/mL following multiple dosing during the treatment period, and the PEOM group showed measurable median trough concentrations ranging from 0.14 to 0.17 µg/mL. Median trough pegcetacoplan concentrations observed after the treatment period was completed (i.e., at Month 15 and Month 18) were below the limit of quantification (i.e., <0.10 µg/mL). The results indicate that there are no apparent systemic drug accumulations following IVT administration of 15 mg pegcetacoplan doses in GA patients either monthly or EOM.

The following figure displays the mean pegcetacoplan serum concentrations following IVT administration.



Abbreviations: BLQ = below the limit of quantification; IVT = intravitreal; LLOQ = lower limit of quantification.

Notes: Values that were BLQ were set to the one-half the LLOQ (LLOQ = 0.10 µg/mL). Mean (points) and SE (error bars) pegcetacoplan concentrations are presented in semilogarithmic scale with values BLQ censored at the LLOQ in the plot. The horizontal dashed line indicates the LLOQ of 0.10 µg/mL.

Figure 4: Study POT-CP121614: Mean (SE) pegcetacoplan serum concentrations following IVT administration

Study APL2-303 (Derby)

This was a Phase 3, multicentre, randomised, double-masked, sham-controlled study to compare the efficacy and safety of intravitreal pegcetacoplan therapy with sham injections in subjects with geographic atrophy secondary to age-related macular degeneration.

Subjects were randomly assigned in a 2:2:1:1 manner to receive treatment with PM, PEOM, SM, or SEOM, respectively. Pegcetacoplan was administered as an IVT injection at a dose of 15 mg/0.1 mL in the PM and PEOM groups with a treatment duration of up to 24 months.

Sparse PK and PD samples collected predose and on days 1, 7, 30, 180, 360, and 720 were analysed only in a subset of the enrolled subjects who had at least 1 quantifiable postdose concentration of pegcetacoplan.

101 patients were included in the PK population. All summaries and analyses of the PK data were based on the PK population. Pegcetacoplan concentrations were summarised by pegcetacoplan treatment group (i.e., PM and PEOM) at each scheduled time point using descriptive statistics (including at least mean, SD, CV, median, min, max, geometric mean/%CV). The Cmax values were obtained from serum samples collected at Day 7 following pegcetacoplan treatment. The results were listed and summarised using descriptive statistics.

The following figure displays the mean (SE) serum pegcetacoplan concentrations observed through month 24. The table summarises the mean trough pegcetacoplan concentrations in serum and the number of subjects treated with each dosage.

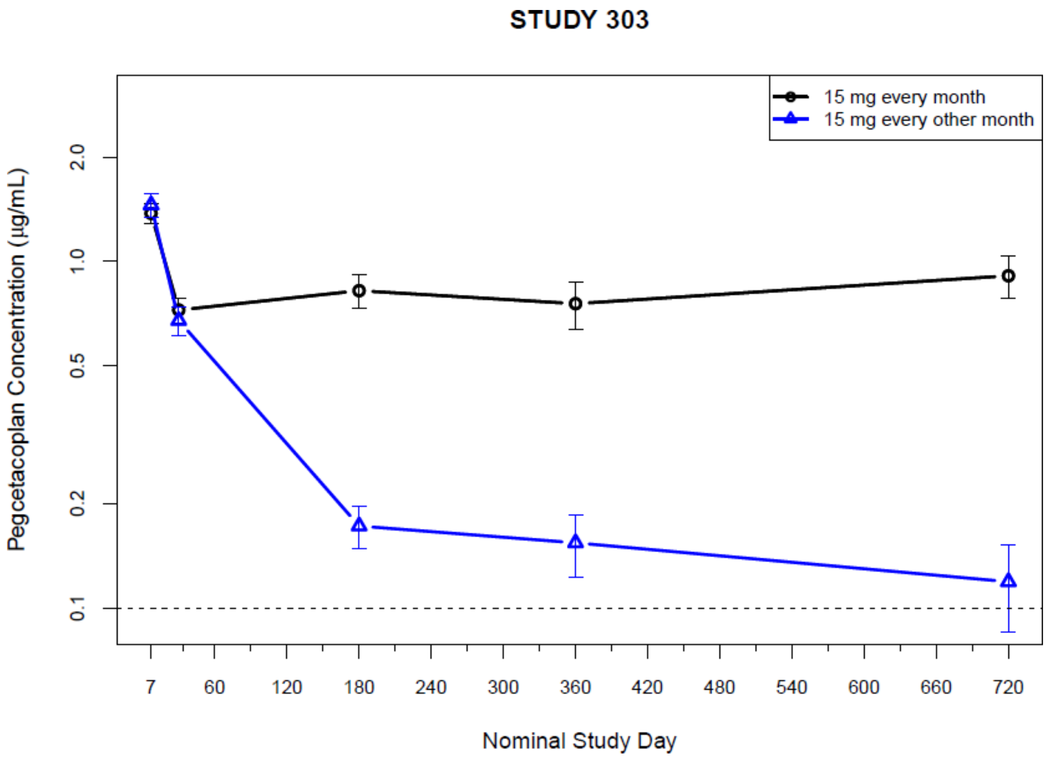


Figure 5: Study APL2-303: Mean (SE) pegcetacoplan serum concentrations following IVT administration

Abbreviations: BLQ = below the limit of quantification; IVT = intravitreal; LLOQ = lower limit of quantification.
Notes: Values that were BLQ were set to the one-half the LLOQ (LLOQ = 0.10 µg/mL). Mean (points) and SE (error bars) pegcetacoplan concentrations are presented in semilogarithmic scale with values BLQ censored at the LLOQ in the plot. The horizontal dashed line indicates the LLOQ of 0.10 µg/mL.

Table 6: Study APL2-303: mean pegcetacoplan serum concentration

	Day 7	Month 1	Month 6	Month 12	Month 24
15 mg monthly (N = 35)					
n	30	25	19	20	17
Mean (SD), µg/mL	1.3747 (0.50487)	0.7220 (0.29895)	0.9621 (0.71331)	0.8324 (0.62643)	0.9061 (0.53777)
CV, %	36.7258	41.4063	74.1404	75.2565	59.3526
15 mg EOM (N = 32)					
n	25	27	15	15	12
Mean (SD), µg/mL	1.4551 (0.59359)	0.6750 (0.34566)	0.1657 (0.10150)	0.1375 (0.13715)	0.0857 (0.13826)
CV, %	40.7933	51.2123	61.2701	99.7689	161.3886

Abbreviations: CV = coefficient of variation; EOM = every other month; N = number of subjects in group; n = number of evaluable subjects.
Source: Study APL2-303 Month 24 Clinical Study Report.

The mean Cmax of pegcetacoplan in this study was 1.37 and 1.46 µg/mL at day 7 for the PM and PEOM groups, respectively. Steady-state mean trough concentrations were observed at the ranges of 0.83 to 0.91 µg/mL and 0.09 to 0.14 µg/mL for the PM and PEOM groups, respectively, following more than 24 months of treatment.

Population PK Analysis

A population PK model (Report APL-EX21-CP-012 Amendment 1) was developed using pegcetacoplan serum concentration-time data from 4 studies following IVT administration.

A total of 261 adult subjects (n = 30 nAMD, n = 231 GA) were included in the population PK analysis. These subjects contributed 2064 PK samples, comprising 1581 (76.6%) quantifiable PK samples and 483 (23.4%) postdose samples below the limit of quantification.

Table 7: Summary of age for subjects included in the population PK analysis population

Covariate	Study POT-CP043014	Study POT-CP121614	Study APL2-203	Study APL2-303	Total[a]
Age category, n (%)					
<65 years	1 (7.7)	3 (1.8)	1 (5.9)	2 (3.0)	7 (2.7)
65-74 years	7 (53.8)	35 (21.3)	7 (41.2)	16 (23.9)	65 (24.9)
75-84 years	4 (30.8)	74 (45.1)	4 (23.5)	26 (38.8)	108 (41.4)
≥85 years	1 (7.7)	52 (31.7)	5 (29.4)	23 (34.3)	81 (31.0)
Total, n (%)	13 (100.0)	164 (100.0)	17 (100.0)	67 (100.0)	261 (100.0)

Abbreviation: PK = pharmacokinetics.
[a] The subject with no quantifiable PK samples (USUBJID POT-CP121614-107-1013) is excluded from this summary.

Summaries of serum and vitreous exposure metrics simulated from the model are provided in the following tables.

Table 8: Simulated first dose and steady-state serum exposure predictions—stratified by dosing regimen

Dosage regimen	Summary statistic	First dose					Steady state					AR
		C_{max}, µg/mL	C_{min}, µg/mL	C_{avg}, µg/mL	$AUC_τ$, µg/mL·day	t_{max}, days	C_{max}, µg/mL	C_{min}, µg/mL	C_{avg}, µg/mL	$AUC_τ$, µg/mL·day	t_{max}, days	
15 mg monthly	Median	1.50	0.200	1.10	34.4	10.0	2.20	1.00	1.70	50.6	8.00	1.40
	5th, 95th percentile	0.800, 2.40	0.100, 0.300	0.500, 1.80	16.4, 53.9	6.00, 14.5	1.10, 3.20	0.300, 1.80	0.800, 2.60	23.3, 78.2	5.50, 10.0	1.10, 2.00
	Geometric mean	1.50	0.200	1.10	32.4	9.80	2.10	0.900	1.60	47.8	7.80	1.50
	Geometric %CV	39.0	35.2	40.3	40.3	29.0	35.1	60.9	41.5	41.5	20.8	18.1
15 mg EOM	Median	1.50	0.100	0.800	47.5	10.5	1.70	0.200	0.900	51.9	10.0	1.10
	5th, 95th percentile	0.800, 2.40	0, 0.200	0.400, 1.20	23.1, 71.4	6.50, 15.0	0.900, 2.50	0, 0.500	0.400, 1.30	25.1, 78.9	6.50, 13.0	1.00, 1.30
	Geometric mean	1.50	0.100	0.700	44.8	10.1	1.60	0.200	0.800	49.0	9.60	1.10
	Geometric %CV	37.4	67.6	39.2	39.2	28.3	34.0	101	39.5	39.5	25.6	7.51

Abbreviations: AR = accumulation ratio; $AUC_τ$ = area under the concentration-time curve for a dosing interval (τ); C_{avg} = average concentration; C_{max} = maximum observed concentration occurring at t_{max}; C_{min} = minimum concentration; CV = coefficient of variation; EOM = every other month; t_{max} = time of maximum observed concentration sampled during a dosing interval.
Source: Report APL-EX21-CP-012 Amendment 1 Table 50.

Table 9: Simulated first dose and steady-state vitreous exposure predictions—stratified by dosing regimen

Dosage regimen	Summary statistic	First dose				Steady state				AR
		C_{max}, µg/mL	C_{min}, µg/mL	C_{avg}, µg/mL	AUC_{τ}, µg/mL·day	C_{max}, µg/mL	C_{min}, µg/mL	C_{avg}, µg/mL	AUC_{τ}, µg/mL·day	
15 mg monthly	Median	4527	797	1920	57594	4730	980	2382	71455	1.20
	5th, 95th percentile	3982, 5254	243, 1527	1296, 2490	38876, 74687	3997, 6261	247, 2511	1348, 4104	40442, 123130	1.00, 1.60
	Geometric mean	4551	725	1877	56322	4845	911	2385	71536	1.30
	Geometric %CV	8.67	64.7	20.7	20.7	14.7	84.5	35.9	35.9	15.0
15 mg EOM	Median	3922	176	1176	70580	3930	180	1217	72987	1.00
	5th, 95th percentile	3769, 4398	19.6, 658	720, 1783	43189, 106971	3769, 4534	18.8, 784	708, 2137	42463, 128197	1.00, 1.20
	Geometric mean	3974	147	1155	69299	4001	152	1215	72902	1.10
	Geometric %CV	4.95	162	28.6	28.6	6.15	178	34.9	34.9	6.48

Abbreviations: AR = accumulation ratio; AUC_{τ} = area under the concentration-time curve for a dosing interval (τ); C_{avg} = average concentration; C_{max} = maximum observed concentration occurring at t_{max}; C_{min} = minimum concentration; CV = coefficient of variation; EOM = every other month.
Source: Report APL-EX21-CP-012 Amendment 1 Table 51.

Pegcetacoplan exhibited the following PK characteristics after IVT administration:

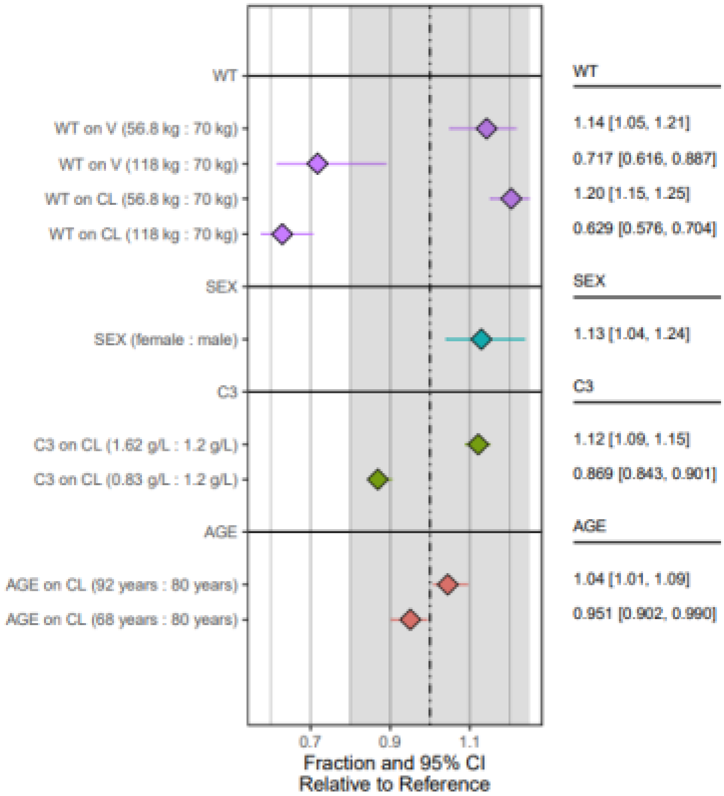
- Pegcetacoplan disposition following IVT administration is absorption limited with median individual predicted absorption and elimination half-lives of 13.1 days (t½,abs) and 4.51 days (t½,elim), respectively.
- Parameters for the typical patient with nAMD or GA (male, aged 80 years, baseline C3 concentration 1.2 g/L) were: CL/F of 0.325 L/day, VC/F of 1.83 L, and KA of 0.0528 day −1).
- Age, sex, and baseline C3 level were identified as covariate on exposure. None of these covariate effects are anticipated to be clinically meaningful given the low absolute maximum serum concentrations achieved across studies.
- Median (^{5t}h, 9^{5t}h) steady-state serum Cmax among GA patients is predicted to be 1.70 (0.70, 2.20) µg/mL and 2.20 (1.40, 3.00) µg/mL at doses of 15 mg IVT EOM and 15 mg IVT every month, respectively.

Steady-state vitreous exposure is predicted to be approximately 1300-fold higher than serum exposure. Comparing IVT dosing frequencies, average steady-state vitreous exposure over the dosing interval is predicted to be approximately 2-fold higher with monthly dosing than with EOM dosing.

Table 10: Summary of individual predicted steady-state serum exposure by formulation

		15 mg IVT every other month			15 mg IVT every month		
		Lyophilized powder (n = 188)	**Phase 1 solution (n = 6)**	**Phase 3 solution (n = 67)**	**Lyophilized powder (n = 188)**	**Phase 1 solution (n = 6)**	**Phase 3 solution (n = 67)**
$Cmax_{\tau,ss}$, μg/mL	Mean (SD)	1.491 (0.4395)	1.305 (0.3653)	1.453 (0.395)	1.967 (0.4506)	1.999 (0.4712)	1.873 (0.4957)
	Geometric mean (CV)	1.418 (34.72%)	1.265 (27.38%)	1.396 (30.26%)	1.908 (26.46%)	1.95 (25.14%)	1.794 (32.88%)
	Median (IQR)	1.505 (1.246, 1.76)	1.238 (1.028, 1.465)	1.412 (1.154, 1.741)	1.997 (1.674, 2.293)	2.089 (1.585, 2.311)	1.935 (1.52, 2.232)
	5th, 95th percentiles	0.7186, 2.167	0.9601, 1.806	0.8374, 2.042	1.206, 2.647	1.44, 2.519	1.147, 2.485
$Cmin_{\tau,ss}$, μg/mL	Mean (SD)	0.143 (0.08226)	0.1501 (0.08651)	0.1696 (0.106)	0.84 (0.3017)	0.9236 (0.4322)	0.7982 (0.3135)
	Geometric mean (CV)	0.114 (94.16%)	0.1288 (70.2%)	0.1348 (86.22%)	0.777 (44.3%)	0.8348 (54.05%)	0.707 (65.22%)
	Median (IQR)	0.1364 (0.08235, 0.1898)	0.1371 (0.09772, 0.1856)	0.1628 (0.08009, 0.2221)	0.8365 (0.6371, 1.031)	0.8681 (0.6071, 1.263)	0.7776 (0.6365, 1.022)
	5th, 95th percentiles	0.02464, 0.2936	0.05809, 0.2687	0.03285, 0.3475	0.317, 1.324	0.4487, 1.448	0.2603, 1.289
$AUC_{\tau,ss}$ μg/mL·d	Mean (SD)	42.55 (11.34)	38.79 (12.62)	43.37 (11.51)	44.31 (10.53)	46.22 (14.43)	42.11 (12.16)
	Geometric mean (CV)	40.5 (36.03%)	37.27 (30.88%)	41.51 (32.84%)	42.78 (29%)	44.23 (34.1%)	39.61 (41.81%)
	Median (IQR)	44.42 (36.48, 51.03)	32.91 (30.19, 45.69)	45.29 (36.73, 53.35)	45.59 (37.4, 52.29)	47.12 (34.23, 58.21)	42.33 (35.91, 52.16)
	5th, 95th percentiles	19.12, 57.42	28.73, 56.82	24.15, 58.71	24.49, 58.29	29.31, 62.07	19.85, 58

Abbreviations: $AUC_{\tau,ss}$ = area under the concentration-time curve over a dosing interval (τ) at steady state; $Cmax_{\tau,ss}$ = maximum concentration over a dosing interval (τ) at steady state; $Cmin_{\tau,ss}$ = minimum concentration over a dosing interval (τ) at steady state; IQR = interquartile range; IVT = intravitreal.



Abbreviations: AUC = area under the concentration-time curve; CL = clearance; V = volume of distribution; WT = body weight.
Source: Technical Summary: Body Weight Imputation and Population Pharmacokinetic Analysis for Pegcetacoplan (APL-2) EMA Information Request, Figure 9.

Figure 6: Influence of covariates on pegcetacoplan AUC

Distribution

PK parameters for distribution and elimination were derived from the popPK analysis and are summarised above.

Elimination

Pegcetacoplan metabolism has not been characterised. The drug substance is composed of 2 identical pentadecapeptides covalently bound to the ends of a linear 40-kDa PEG molecule. As for other PEGylated protein/peptide conjugates, catabolic pathways are expected to be mainly responsible for the metabolism of pegcetacoplan, which is expected to be degraded into smaller peptide-PEG conjugates, peptides, and, eventually, amino acids by endogenous proteases. Peptides are known to be metabolised by proteolytic degradation and eliminated by cellular uptake or renal filtration (Baumann et al. 2014; Carone et al. 1979; Hydery and Coppenrath 2019). PEG molecules >5 kDa typically undergo minimal metabolism and are renally excreted (Ivens et al. 2015; Tibbitts et al. 2016).

Dose proportionality and time dependencies

A dedicated evaluation of dose proportionality has not been presented. The results of the dose escalating study showed increasing exposure with different level of a single pegcetacoplan dose. The following studies all used multiple dosing at a dose level that was not included in the single dose study. Higher steady state levels where observed with monthly dosing frequency as compared to every other month dosing.

No drug accumulation over time was observed.

Special populations

Dedicated studies in special populations have not been conducted.

No data for the paediatric population is available but this population is hardly affected by the disease. Therefore the lack of data it is acceptable.

Based on the target indication, an elderly population has been studied in the clinical development programme. Renal or hepatic impairment were no exclusion factors in the phase 3 studies and thus, such patients were to some extent included in the PK analysis.

Dedicated evaluation of PK in patients with impaired renal or hepatic function is not expected, since the systemic drug exposure is overall low after local IVT injection.

Pharmacokinetic interaction studies

Dedicated PK interaction studies have not been conducted.

According to PK modelling, concomitant intravitreal administration of anti-VEGF medications is not predicted to alter the local disposition of pegcetacoplan. There was a predicted impact on serum disposition, which is, however, considered negligible based on the overall low pegcetacoplan serum levels.

Pharmacokinetics using human biomaterials

In vitro studies have been conducted with pegcetacoplan to investigate its potential to inhibit or induce human CYP enzymes and to evaluate its potential to act as a substrate and/or inhibitor for human drug transporters.

No clinical DDI studies were conducted because the in vitro study results and the evaluations of the absorption, distribution, metabolism, and excretion properties of pegcetacoplan indicate that pegcetacoplan has a low potential for mediating a DDI with coadministered agents via CYP or drug transporter pathways.

In vitro absorption, distribution, metabolism, and excretion studies suggest that:

- Pegcetacoplan (up to 6 mg/mL) does not inhibit any of the cytochrome P450 (CYP) isoforms evaluated (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5) either in a direct or metabolism-dependent manner.
- Pegcetacoplan (up to 6 mg/mL) does not induce the CYP isoforms evaluated (CYP1A2, CYP2B6, or CYP3A4).
- Pegcetacoplan (up to 0.6 mg/mL for uptake transporters and up to 6 mg/mL for efflux transporters) is not a substrate and/or an inhibitor for human drug transporters organic anion transporter (OAT) 1 and OAT3, organic cation transporter (OCT) 2, organic anion-transporting polypeptide (OATP) 1B1, and OATP1B3, P-glycoprotein (P-gp), or breast cancer resistance protein (BCRP).

2.5.2.2. Pharmacodynamics

Mechanism of action

Pegcetacoplan is a pegylated peptide with 2 identical small pharmacologically active pentadecapeptides each bound to one end of a linear polyethylene glycol (PEG) molecule. Pegcetacoplan is a complement inhibitor binding to human C3 and C3b that is being developed for the treatment of adult patients with GA secondary to AMD, applied as a solution for injection for intravitreal (IVT) use.

A major contributing factor to the pathogenesis of GA appears to be overactivation of the complement cascade, resulting in chronic inflammation, cell dysregulation, and retinal cell death (Boyer et al. 2017). Genome-wide association studies have identified 20 chromosomal regions that contain genetic variations associated with AMD, 5 of which are implicated in the complement cascade (Fritsche et al. 2014). In addition, complement factors have been detected within and in proximity to pathologies associated with AMD, including drusen, which are extracellular deposits of cellular debris underneath the RPE (Boyer et al. 2017; Clark et al. 2018). Complement component C3 acts as the central component of the 3 separate complement activation pathways. Therefore, inhibition of C3, with subsequent reduction in inflammation and cell death, is a rational therapeutic strategy for GA (Park et al. 2019; Merle 2015; Katschke et al. 2018).

Primary and Secondary pharmacology

Systemic complement biomarkers were collected in two clinical studies in subjects with GA secondary to AMD: CH50 and C3 were evaluated in studies POT-CP121614 and APL-303; additionally, Study APL-303 also evaluated AH50.

Study POT-CP121614 was a phase 2, multicentre, randomised, single-masked, sham-controlled study of safety, tolerability, and evidence of activity of IVT pegcetacoplan therapy in subjects with GA.

Enrolled subjects were randomly assigned in a 2:2:1:1 manner to receive pegcetacoplan monthly (PM), pegcetacoplan every other month (PEOM), sham monthly (SM), or sham every other month (SEOM). Subjects in the pegcetacoplan arms received 15 mg pegcetacoplan in 0.1 mL formulation by IVT injection for each dose.

Complement biomarkers CH50 and C3 were measured for PD serum samples collected at baseline and at months 2, 6, 12 (during treatment), and 18 (post treatment).

Mean percentage change from baseline CFB in C3 concentration across treatment groups remained within ±4% of the baseline value during the treatment period, indicating that there was no inhibitory effect on systemic C3 activation following monthly or EOM IVT administration of 15 mg pegcetacoplan in subjects with GA.

During the study period, mean percentage CFB in CH50 remained within ±13% of the baseline value for the PM, PEOM, and sham pooled groups, suggesting that there was no apparent impact on systemic CH50 activity following monthly or EOM IVT administration of 15 mg pegcetacoplan in subjects with GA.

Study APL2-303 was a phase 3 multiple-dose study that compared the efficacy and safety of IVT pegcetacoplan treatment with sham injections in subjects with GA secondary to AMD. Subjects were randomly assigned in a 2:2:1:1 manner to receive treatment with PM, PEOM, SM, or SEOM, respectively.

Sparse PK and PD samples collected predose and on days 1, 7, 30, 180, 360, and 720 were analysed only in a subset of the enrolled subjects who had at least 1 quantifiable postdose concentration of pegcetacoplan.

Mean percentage CFBs in C3 concentration for the PM, PEOM, and sham pooled groups were between −10.2% and 13.9% during the 24-month treatment period. These results indicate that there was no inhibitory effect on systemic C3 activation following monthly or EOM IVT administration of 15 mg pegcetacoplan doses in subjects with GA.

Mean percentage CFBs in CH50 for the PM, PEOM, and sham pooled groups were between −13.9% and 12.9% during the 24-month treatment period. These results indicate that there was no apparent impact on systemic CH50 activity following monthly or EOM IVT administration of 15 mg pegcetacoplan doses in subjects with GA.

Mean percentage CFBs in AH50 for the PM, PEOM, and sham pooled groups were between −20.4% and 28.3% during the 24-month treatment period. These results indicate that there was no clinically meaningful impact on systemic AH50 activity following monthly or EOM IVT administration of 15-mg pegcetacoplan doses in subjects with GA.

Additionally, population-based disease progression models (Report APL-EX22-CP-014) were developed to characterise the time course of GA lesion area, including the assessment of disease-specific covariate effects as well as the impact of pegcetacoplan IVT dosage and exposure on the progression of GA lesion area.

No PK electrocardiogram (ECG) analyses or other secondary pharmacology analyses were conducted for IVT pegcetacoplan. A PK ECG analysis (APL-EX20-CP-004) was completed for subcutaneous pegcetacoplan to assess drug effects on QT/corrected QT interval and demonstrated that pegcetacoplan has no clear effect on heart rate, PR and QRS interval duration, cardiac repolarisation (corrected QT interval), or other ECG parameters following subcutaneous administration in PNH subjects and healthy subjects.

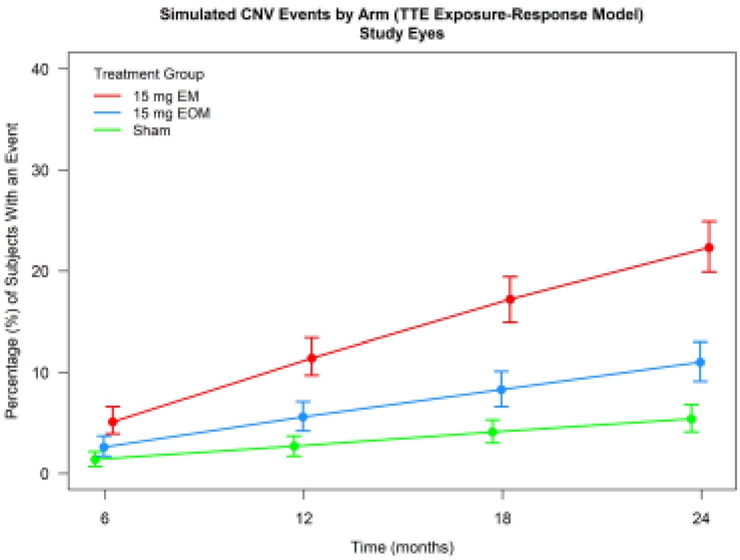
The applicant presented data on the potential pharmacodynamic interaction between pegcetacoplan and anti-VEGF treatment based on populations analysis using the GA lesion area exposure-response model from Study APL-EX22-CP-014. Pharmacodynamic interaction with other medicinal products or substances has not been discussed by the applicant.

Exploratory time-to-event exposure-response safety analysis for new-onset CNV events

Table 11: Response predictions: CNV events

Time point	Frequency (95% CI) of CNV events (percentage)		
	Sham	15 mg IVT EOM	15 mg IVT monthly
6 months	1.40 (0.700, 2.15)	2.6 (1.70, 3.70)	5.10 (3.90, 6.60)
12 months	2.70 (1.70, 3.70)	5.60(4.20, 7.10)	11.4 (9.70, 13.4)
18 months	4.10 (3.00, 5.30)	8.30 (6.60, 10.1)	17.2 (14.9, 19.4)
24 months	5.40 (4.10, 6.80)	11.0 (9.10, 13.0)	22.3 (19.9, 24.9)

Abbreviations: CNV = choroidal neovascularization; EOM = every other month; IVT = intravitreal.
Source: APL-EX22-CP-014, Table 33.



Abbreviations: CNV = choroidal neovascularization; EM = every month; EOM = every other month; TTE = time-to-event; ug/mL = µg/mL.
Note: Points are the frequency of events, and error bars are the 95% CI.
Source: APL-EX22-CP-014, Figure 33.

Figure 7: Simulated CNV events at landmark times—stratified by treatment group

2.5.3. Discussion on clinical pharmacology

The PK of pegcetacoplan has been evaluated in four clinical studies: one phase 1 single-ascending dose study in subjects with nAMD (Studies POT-CP043014), one phase 1b/2 multiple-dose study with monthly treatment and PK evaluation through 6 moths in subjects with nAMD (APL2-203), one phase 2, randomised, sham-controlled study in subjects with GA secondary to AMD receiving monthly or every other month 15 mg pegcetacoplan (Study POT-CP121614) and one phase 3, randomised, sham-controlled study in subjects with GA secondary to AMD receiving monthly or every other month 15 mg pegcetacoplan (APL2-303).

Additionally, a population PK model was developed using data from these four studies.

The analytical method BPAPL2F for the determination of APL-2 in human plasma as well as respective validations are described adequately. The method demonstrates acceptable performance and is suitable for the determination of APL-2 in K2EDTA human plasma over the calibration range.

Three different formulations were used during the clinical development. One lyophilised formulation, one pre-commercial solution and the planned commercial solution. No formal bioavailability or bioequivalence studies were conducted.

Formulation was assessed as a covariate during the development of the Pop PK model. Taken into account that the dataset for the development of the Pop PK model contains only 6 patients using the pre-commercial solution in Study POT-CP043014, this category was grouped with the planned commercial solution for the covariate analysis.

Pegcetacoplan following IVT administration seems to present a “flip-flop” kinetic profile, and therefore, the vitreous to serum absorption constant (ka) is the most influential parameter on pegcetacoplan exposure. The results showed no significant effect of the three formulations on ka. However, the justification that there are no differences in absorption in the absence of statistically significant covariates is not agreed. Precisely, since the PK of the drug depends on its ka (flip-flop kinetics), the covariates identified in CL could also explain differences in the absorption, which would cause differences in the site of action (ocular compartment). Further comments have been included in this sense when clinical relevance is assessed in the population PK model section.

No formal BE study was conducted, but individual subject empirical Bayesian estimates were derived from the Pop PK model and used to predict PK exposure parameters (AUC, C_{max} and C_{min}) at steady state following 15 mg IVT EOM or EM. The results showed comparative predictive exposure for the phase 3 solution and lyophilised powder. Results from the phase 1 solution should be interpreted with caution taking into account that there are only data from 6 patients receiving this dosage form.

Three escalating single doses (4, 10, and 20 mg IVT/0.1 mL injection) were tested in the phase 1 Study POT-CP043014. There was an apparent dose-related increase in pegcetacoplan serum exposure metrics (C_{max} and AUC_{0-t}) across the 3 dose groups. Median C_{max} and AUC_{0-t} values ranged from 0.383 to 2.14 µg/mL and 11.89 to 69.53 µg·day/mL, respectively.

The dose proportionality study has been developed from sparse experimental information (N=3-7) for three dose levels between 4 and 20 mg. Although the evaluated dose range is limited, pegcetacoplan exhibits approximately dose-proportional increases in exposure in plasma in the range of concentrations studied (4 mg to 20 mg doses).

Mean serum C_{trough} values after monthly IVT injections of 15 mg/0.1 mL pegcetacoplan were 0.79 µg/mL and 0.73 µg/mL at month 1 and month 6, respectively, in the phase 1b/2 study APL2-203 in nAMD patients. This shows that the mean pegcetacoplan trough concentration at month 1 after a single dose was similar to steady-state mean trough concentration after multiple monthly doses at month 6.

Also the PK evaluation of the phase 2 study conducted in patients with the target indication displayed stable C_{trough} values over time. Median C_{trough} values ranged from 0.91 to 1.24 µg/mL for monthly dosing, and from 0.14 to 0.17 µg/mL with treatment every other month. The observed median maximum serum concentration of pegcetacoplan was approximately 1.5 µg/mL at Day 7 in that study.

Similarly, the data obtained in the pivotal phase 3 study APL2-303 demonstrate that pegcetacoplan steady state serum concentrations differ between monthly and EOM treatment. Drug accumulation was not observed over 24 months treatment with either dosing regimen. The mean C_{max} of pegcetacoplan in this study was 1.37 and 1.46 µg/mL at Day 7 for the PM and PEOM groups, respectively. Steady-state mean trough concentrations were observed at the ranges of 0.83 to 0.91 µg/mL and 0.09 to 0.14

μg/mL for the PM and PEOM groups, respectively, following more than 24 months of treatment. For monthly treatment with 15 mg, serum trough concentration appears to be stable throughout 24 months. For EOM treatment with the same dose, there appears to be a trend towards decrease in exposure over time. This has not been observed in study POT-CP121614, where serum trough concentration appeared to be stable over time, and might represent a chance finding in study APL2-303. Overall, it is not known if the observed decrease in serum concentration is representative of drug concentration in the vitreous humour.

C_{max} values analysed 7 days after the first dose were comparable between treatments and also comparable to the results of phase 2 study POT-CP121614.

No clinical data have been provided on pegcetacoplan metabolism and degradation of the pegcetacoplan peptide moiety has not been investigated in ocular compartments. However, the applicant has discussed potential catabolism of pegcetacoplan (including dissociation of the active peptides from the PEG moieties) within the eye following IVT administration. Such processes are considered unlikely given the biological stability of the molecule based on considerations of its chemical structure and the intravitreal environment. Further, the applicant presented an estimate of absolute bioavailability following IVT administration using a population approach. The absolute bioavailability estimated for the IVT route of administration was 94.0% (95% CI, 93.3% to 94.6%), which suggests limited ocular degradation of the peptide with near-complete absorption of pegcetacoplan following IVT administration.

Renal impairment

No specific studies in patients with renal impairment were conducted with Syfovre.

eGFR was evaluated as a continuous covariate in the PopPK analysis on CL/F and it was not found as a significant covariate. Of note, most of the patients had normal, mild and moderate renal impairment (19.5%, 42.9% and 31% respectively). Only few patients had severe impairment or End-Stage renal disease (0.8% and 4.2% respectively).

No dose adjustment is necessary.

Impaired hepatic function

No specific studies in patients with hepatic impairment were conducted with Syfovre. Due to the nature of this medicinal product, the lack of dedicated studies in subjects with hepatic impairment is justified.

No dose adjustment is necessary.

Gender

Gender was evaluated as a covariate on CL/F, VC/F and KA parameters in the PopPK analysis. As a result, it was found to be statistically significant only on CL/F. The univariate analysis showed a significant impact on serum exposure with 33%, 26% and 46% higher AUC, C_{max} and C_{min} respectively in women compared to men. However, the effect of female sex appears to be related to the differences in body weight between both sexes as clinical relevance assessment of sex covariate (female vs male) taking into account imputed body weight showed no clinically relevant changes in exposure. AUC in women was estimated to be 1.13 (1.04, 1.24) compared to males. No dose adjustment is necessary based on sex covariate.

Race

Race was not evaluated as a covariate in the Pop PK analysis as 97.3% of the patients in the final dataset were white. Therefore, it seems premature to establish any dose recommendation in non-white patients.

Weight

Weight was initially not evaluated as a covariate in the Pop PK analysis because of the high percentage of missing values (63.2%). Following imputation methods for missing covariates the final Pop PK model was updated including the imputed body weight effects on CL and Vc. The updated model was used to perform the clinical relevance assessment of the final selected covariates. A 30-40% decrease on AUC is expected in patients with high body weight (118 kg) compared to the reference patient (70 kg). However, the applicant justified that differences in exposure due to body weight are influenced by differences in systemic disposition and those differences in body weight will not affect the drug exposure in ocular tissues. The radius of the vitreous globe across species seems to be independent of body weight. In this regard, the systemic pharmacokinetics are not anticipated to affect the exposure at the ocular tissue, since the rate-limiting factor is expected to be related to drug absorption from the ocular tissue to systemic circulation rather than systemic disposition processes.

Elderly

Most subjects included in the population PK analysis were ≥75 years old (72.4%) and only a minority of patients was <65 years old (2.7%).

Children

Pegcetacoplan is not expected to be administered in this population.

Three in vitro studies (Studies 17COTX-001, 17COTX-002, and 17COTX-003) using human biomaterials have been submitted. No effects of pegcetacoplan on inhibition or induction of CYP isoforms or uptake and efflux transporters have been detected.

Additionally, a population PK model was developed using data from these four studies but the majority of subjects and samples were derived from study POT-CP121614 in GA patients: 261 subjects (30 with nAMD and 261 with GA) and a total of 1581 PK serum observations. No samples were obtained from the aqueous humour. PK samples below limit of quantification (BLQ) of total PK observations were high 23.4%.

Pegcetacoplan PK was described using a two-compartment model, one representing the intravitreal space and the second the serum compartment. It has first order absorption following the intravitreal administration into the serum compartment and linear clearance CL/F from the serum compartment. Volume of distribution was estimated to be 1.83 L, a value lower than following systemic administration. The volume of the vitreous compartment was assumed to be 4 mL. Alternative mechanistic descriptions of IVT administration are available in the literature that could represent a more physiological description of the biological system with broader extrapolation capacity. However, additional experimental evidence would have been required in ocular tissues to develop those mechanistic frameworks.

IIV was included in CL/F and KA and it was moderate for both parameters and 24.43% and 33% respectively. Structural model parameters were estimated with relatively good precision (<11%).

The Final Model incorporated 3 significant covariates (Age on CL/F, C3 on CL/F and Female sex on CL/F). Body weight was initially not assessed during the covariate search due to the large number of missing data (>50%). Upon request imputation methods for missing covariates were explored and the final Pop PK model was updated including the imputed body weight effects on CL and Vc. The updated model was used to perform the clinical relevance assessment of the final selected covariates. GOF plots of the final pop PK model including imputed body weight have been presented stratified by sex and a good correlation over the identity line is observed.

A forest plot has been provided to assess the clinical relevance of the significant covariates selected based on the change on the exposure (AUC, C_{max} and C_{min}). Females show clinically relevant exposure increases (33%, 27% and 46% in AUC, C_{max} and C_{min} respectively) compared to men. However, no clinically relevant changes in exposure were identified for sex as covariate when imputed body weight was taken into account. Thus, no dose adjustment is necessary based on sex covariate. Still, it is not agreed that concentrations in the central compartment are not associated to exposure changes in ocular tissue, since flip-flop kinetics are present and, therefore, drug disposition is governed by ka, not CL/V. Therefore, it is very likely that the differences in plasma exposure associated with weight also occur in the ocular tissue (administration site and target site). Furthermore, since the ocular compartment does not represent a physiological unit but rather a kinetic compartment, since a mechanistic approach has not been used, there is no clear evidence of the absence of changes in specific ocular regions as a consequence of the impact of covariates through model predictions.

Based on this model, steady-state vitreous exposure is predicted to be approximately 1300-fold higher than serum exposure. Average steady-state vitreous exposure over the dosing interval is predicted to be approximately 2-fold higher with monthly dosing than with EOM dosing.

In summary, the applicant has characterised pegcetacoplan pharmacokinetics in human serum. As expected following local administration into the eye, serum concentrations were low with C_{max} values around 1.5 µg/mL on Day 7 after a 15 mg IVT dose. Based on the presented data, no systemic drug accumulation is expected after monthly or every other month IVT administration of 15 mg pegcetacoplan.

In terms of PK in vitreous humour, the applicant presented an estimate of absolute bioavailability following IVT administration using a population approach suggesting limited ocular degradation of the peptide with near-complete absorption of pegcetacoplan following IVT administration. This assumption is further supported by non-clinical PK modelling data that is based on actual pegcetacoplan concentration determined in aqueous humour and serum of cynomolgus monkeys. Model parameter estimates were consistent between the model trained on both serum and aqueous humour concentration data and the model trained on serum-only data. The applicant's view that consistency of these parameter estimates supports the approach used to describe the pharmacokinetics of pegcetacoplan in the vitreous humour using serum-only data in clinical studies is endorsed.

During the first assessment round, discussion was requested on the clinical PK of the PEG moiety of pegcetacoplan with regard to a potentially different behaviour compared to the active protein, possible PEG accumulation in the eye and potential consequences regarding safety. Due to the lack of clinical PK data of the PEG40 moiety of pegcetacoplan, the applicant presented popPK predictions of pegcetacoplan PK and it is assumed that PK characteristics of PEG40 would be similar to those of pegcetacoplan based on the similar size/molecular weight. It is further argued that there were no notable adverse findings in a 9-month chronic nonhuman primate toxicity study with doses up to 24.8 mg per eye (Study 14CTX-001). However, this is not in line with non-clinical findings from Study 14CTX-001 where slight increases in central retinal thickness (CRT) were observed upon intravitreal PEG exposure. CRT, in turn, is an important anatomical feature of disease activity in neovascular age-related macular degeneration. A potential relation between PEG and AMD has been discussed in the literature based on a PEG induced mouse model of retinal degeneration (Lyzogubov et al. Exp Eye Res. 2014 Oct;127:143-52; Mitchell et al. Preprints 2023, 2023071318). Thus, it cannot be ruled out that PEG contributes to the development of wet AMD in pegcetacoplan treated patients. As pointed out in the applicant's answers to one of the questions raised during assessment of the list of outstanding issues, the applicant believes that patients potentially receiving Syfovre should be monitored for signs of neovascular AMD (including CRT changes as applicable) and the need for anti-VEGF therapy should be determined.

With regard to pharmacodynamics, the systemic complement biomarkers CH50 and C3 were evaluated in two multiple-dose, sham-controlled studies in subjects with GA secondary to AMD (POT-CP121614 and APL-303); additionally, Study APL-303 also evaluated AH50.

Across the two studies, no relevant effects were observed in mean percentage change from baseline in any of the selected complement biomarkers. Thus, no inhibitory effect of pegcetacoplan on systemic activation of either C3, CH50 or AH50 was demonstrated. This is not unexpected, based on the low systemic exposure of the drug.

However, clinical data supporting the proposed MoA have not been provided. It is acceptable that ocular pharmacology was not evaluated in human clinical studies due to practical limitations. The applicant presented PK/PD modelling data predicting that vitreous humour concentrations corresponding to the estimated aqueous humour IC50 and IC80 values for inhibition of C3a are 130 µg/mL and 520 µg/mL. These levels are exceeded by human predicted vitreous average concentrations for dosing regimens of 15 mg IVT monthly and 15 mg IVT every other month. Thus, according to this model, C3a inhibition can be assumed to be achieved at clinical dosages.

Further pharmacological proof of concept relies on non-clinical data and is discussed in the non-clinical sections of the assessment report. Lack of successful clinical PD data remains an uncertainty in the present MAA submission.

According to the applicant, a PK ECG analysis was conducted for subcutaneous administration of pegcetacoplan as part of a different marketing authorisation application. The applicant was requested to provide an overview of the results of the PK ECG study with subcutaneous administration (APL-EX20-CP-004) and justify the appropriateness of the available data from that study for the present marketing authorisation application. In response to the questions raised during assessment procedure, the applicant has not provided the requested summary of Study APL2-EX20-CP-004 apart from a brief comment on that study. No details on study design, dose, duration or actual results have been provided. Nevertheless, it is acknowledged that ECG data from clinical studies conducted for the marketing authorisation of Aspaveli (INN pegcetacoplan) at dose levels greater than 1000 mg administered subcutaneously justify the claim that QT prolongation with pegcetacoplan is not expected.

Further, the applicant presented data on the potential pharmacodynamic interaction between pegcetacoplan and anti-VEGF treatment based on populations analysis using the GA lesion area exposure-response model from Study APL-EX22-CP-014. No clinically significant impact on pharmacodynamics is expected based on this model.

Potential pharmacodynamic interactions of pegcetacoplan with other medicinal products or substances have not been discussed.

The applicant performed E-R analyses to capture effects on lesion area and developed a disease progression model, a dose response and exposure response model.

The objective of this analysis was to develop a disease progression model to characterise the progression of Geographic atrophy in patients receiving sham treatment and an exposure response model to characterise the impact of pegcetacoplan exposure on GA lesion area progression.

The population PK analysis was based on a pooled dataset from 3 studies, which includes data of pegcetacoplan in patients with GA (Phase II POT-CP121614, Phase III APL2-303 and Phase III APL2-304).

The primary efficacy endpoint was lesion area or change from baseline in lesion area and as exploratory endpoints best-corrected visual acuity (BCVA) and new-onset choroidal neovascularisation (CNV) events. Pegcetacoplan exposure was derived from the population PK model for patients with observed data obtaining their individual predicted concentrations and for patients without PK data using the population predicted concentrations.

The analysis contains measurements of lesion area of study eye (pegcetacoplan or sham) from 1501 subjects and of fellow eye (untreated) from 1246 of these subjects.

Although the disease Progression Model initially was developed using data only from study eyes under sham treatment, subsequently, the model was estimated using both study on sham and fellow eye.

The final model incorporates 5 covariates effects: unilateral GA on study eye initial lesion area and on study eye time slope, No subfoveal involvement on time slope, unifocal GA on time slope and more >20 intermediate/large drusen groups on time slope. Covariate effects were only assessed on parameters describing disease progression in study eyes. The parameters in the final model were estimated with relatively good precision (<40% RSE).

Goodness of fit shows good correlation between observed and predicted geometric mean values.

In addition, the performance was evaluated by visual predictive check (VPC). The observed median 5th and 95th percentiles are within the simulated intervals for the study eye. However, in the case of the fellow eye there is an over-prediction of the 5th and 95th percentile over the first months.

Linear with log concentration model was selected as the final exposure-response model to describe the effect of exposure in the vitreous and serum compartment on disease progression. The parameters were well estimated (25% RSE).

While all VPC plots indicate that the overall trend of the observed data has been adequately captured by the model, several shortcomings of the developed models have been identified.

First of all, all models show a large variability in the observed response, which hampers the interpretability of obtained predictions. Further, given the nature of the to-be-treated disease, the change and size of the respective lesions is highly dependent on the baseline values, which cannot be adequately captured in the presented models.

In addition, the population predictions in all presented models seem to be restricted to a rather narrow range, also questioning the reliability of the respective predictions. In contrast, the individual predictions do not seem to be affected by such restrictions.

In conclusion, while the obtained models capture the general trend of the observed data, the interpretability of the model is severely hampered by several aspects including the variability of the observed response data and the apparently limited range of population prediction. Consequently, no robust conclusions can be drawn based on the presented E-R models.

The impact of potential covariates of disease progression following sham treatment has been studied using the exposure response model. A forest plot has been provided to assess the effect of the covariates selected on change in lesion area at month 24 on sham treatment. The results showed that unilateral GA, unifocal GA and subjects with >20 intermediate/large drusen groups had 0.86, 0.837 and 0.869 fold lower predicted change in lesion area and subjects without subfoveal involvement had 1.12 fold higher predicted change.

The impact of treatments (15 mg IVT every month and 15 mg IVT every other month) was also evaluated using the exposure response model. The change in lesion area at month 24 was slightly lower for the every month treatment, as expected. Ratio of test lesion area change 0.826 and 0.801 for every month and every other month treatment respectively.

Simulations were performed using the final Population PK and Exposure response models at 6 months intervals through 24 months. The results showed that changes in lesion area from baseline at 24 months were lower for both treatments 15 mg every other month (3.38 (3.26 to 3.50) mm^2) and 15 mg every month (3.27 (3.16 to 3.38)) compared to sham treatment (4.08 (3.94 to 4.22) mm^2).

Upon request, the applicant has conducted an exploratory time-to-event exposure-response safety analysis for new-onset of CNV events. The model was used to generate predictions of CNV event rate for GA subjects receiving sham, pegcetacoplan 15 mg IVT monthly, and 15 mg IVT EOM. The frequency of predicted CNV events was higher with the EM scheme than with the EOM scheme at all the different time point studied; 6 months (5.10 vs 2.6), 12 months (11.4 vs 5.6), 18 months (17.2 vs 8.3) and 24 months (19.9 vs 9.10). At the same time, higher pegcetacoplan exposure is associated to a higher incidence of CNV events, which is expected. Based on the current exposure-safety analysis, a superior benefit of 15 mg IVT EOM is observed over 15 mg IVT monthly, although larger differences among both regimens are expected after 12 months of treatment.

2.5.4. Conclusions on clinical pharmacology

Due to the local administration into the eye, systemic exposure to pegcetacoplan is low.

Based on PK modelling, steady-state vitreous exposure is predicted to be approximately 1300-fold higher than serum exposure. Average steady-state vitreous exposure over the dosing interval is predicted to be approximately 2-fold higher with monthly dosing than with EOM dosing.

2.5.5. Clinical efficacy

The efficacy of Syfovre (pegcetacoplan) has been evaluated in subjects with GA secondary to AMD. Results from two Phase III studies APL2-304 and APL2-303 are described as pivotal evidence of the efficacy of IVT pegcetacoplan for GA secondary to AMD, and results from Phase II study POT-CP121614 and Phase Ib study APL2-103 are described as supportive evidence for the efficacy. A long-term extension study (Studies APL2-GA-305) in patients from Studies APL2-103, APL2-303 and APL2-304 is currently ongoing.

2.5.5.1. Dose response study

POT-CP043014 Phase I: Prospective, open-label, uncontrolled, nonrandomised, single-dose escalation study to assess the safety, tolerability, and pharmacokinetics of IVT APL-2 in subjects with exudative AMD currently receiving anti-vascular endothelial growth factor (VEGF) therapy.

Subjects were sequentially enrolled into 3 cohorts (4, 10, and 20 mg of APL-2 in a 100 µL IVT injection). Initially, 3 subjects were enrolled in each cohort. Cohort 3 was expanded to 12 subjects once the initial 3 subjects had reached their Day 7 Visit (only 7 were recruited).

Study objective: The objective of this study was to provide initial safety, tolerability, and pharmacokinetics information of intravitreal (IVT) administration of APL-2 in order to support further development into larger Phase 2 studies for treatment of patients with AMD.

The primary endpoints of the study were the number and severity of TEAEs and PK parameters of APL-2 following a single intravitreal administration.

A dose-related increase in pegcetacoplan serum exposure metrics and area under the curve was observed across the doses investigated, and no dose-limiting toxicity was observed.

Feedback from physicians who injected the 20 mg/0.1 mL IVT pegcetacoplan dose confirmed that 15 mg/0.1 mL is the highest practical concentration that can be routinely administered. This is because the viscosity of pegcetacoplan solution increases exponentially and becomes significant at doses ≥15 mg/0.1 mL. Because no dose-limiting toxicity was observed in the study, the dose for the subsequent Phase II study POT-CP121614 and the Phase III studies APL2-304 and APL2-303 in subjects with GA secondary to AMD was set at 15 mg/0.1 mL.

2.5.5.2. Main studies

Study APL2-303, DERBY: Phase III, multicentre, randomised, double-masked, sham-controlled study to compare the efficacy and safety of intravitreal pegcetacoplan therapy (15 mg/0.1 mL monthly or EOM) with sham injections in subjects with geographic atrophy secondary to age-related macular degeneration.

Study APL2-304, OAKS: A Phase III, multicentre, randomised, double-masked, sham-controlled study to compare the efficacy and safety of intravitreal pegcetacoplan therapy (15 mg/0.1 mL monthly or EOM) with sham injections in subjects with geographic atrophy secondary to age-related macular degeneration.

The two pivotal Phase III studies are of very similar design. Minor design differences refer to the additional secondary functional assessment foreseen in study APL2-304 (i.e. mesopic microperimetry) and the PK- and PD-evaluations, which were only foreseen in study APL2-303

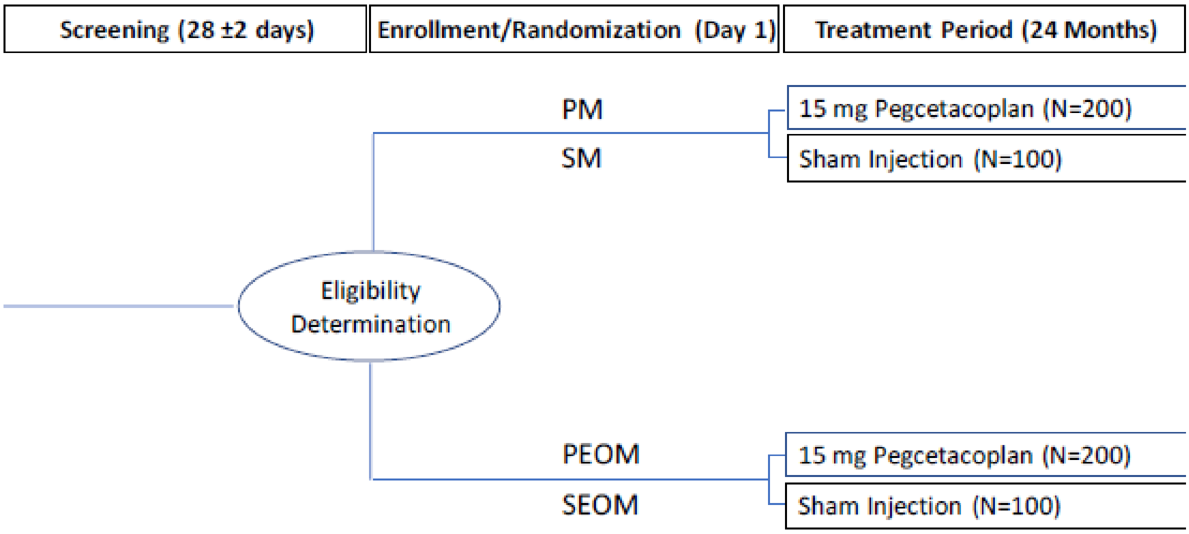
Phase III studies: APL2-304 OAKS and Study APL2-303 DERBY

Methods

The studies were multi-centre, randomised, double-masked, sham-controlled Phase III studies to compare the efficacy and safety of intravitreal pegcetacoplan therapy with sham injections in patients with Geographic Atrophy (GA) secondary to age-related Macular Degeneration (AMD).

In each study, 600 subjects affected by GA secondary to AMD were planned to be assigned on a 2:2:1:1 basis to receive either:

- Group 1: Pegcetacoplan 15 mg/0.1 mL monthly for 24 months (n= approximately 200 subjects; 24 pegcetacoplan injections)
- Group 2: Pegcetacoplan 15 mg/0.1 mL EOM for 24 months (n= approximately 200 subjects; 12 pegcetacoplan injections)
- Group 3: Sham monthly for 24 months (n= approximately 100 subjects; 24 sham injections)
- Group 4: Sham EOM for 24 months (n= approximately 100 subjects; 12 sham injections)



Abbreviations: PM= pegcetacoplan monthly; SM= sham monthly; PEOM= pegcetacoplan every-other-month; SEOM= sham every-other-month.

Figure 8: Study schema

Study Participants

To participate in the study, subjects must have been diagnosed with GA of the macula secondary to AMD in the study eye.

Inclusion criteria

The study eye must have met all inclusion criteria. If both eyes met the inclusion criteria, the eye with the worst normal luminance visual acuity at the screening visit was designated as the study eye. If both eyes had the same visual acuity, the right eye was selected as the study eye.

Ocular-specific inclusion criteria applied to the study eye only, unless otherwise specified.

1. Age ≥60 years.

2. Normal Luminance best corrected visual acuity of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (approximately 20/320 Snellen equivalent).

3. Clinical diagnosis of GA of the macula secondary to AMD as determined by the investigator and confirmed by the reading centre.

4. The GA lesion must meet the following criteria as determined by the central reading centre's assessment of FAF imaging at screening:

   a. Total GA area must be ≥2.5 and ≤17.5 mm2 (1 and 7 disk areas [DA] respectively).

   b. If GA is multifocal, at least 1 focal lesion must be ≥1.25 mm2 (0.5 DA), with the overall aggregate area of GA as specified above in 4a.

   c. The entire GA lesion must be completely visualised on the macula centred image and must be able to be imaged in its entirety and not contiguous with any areas of peripapillary atrophy.

   d. Presence of any pattern of hyperautofluorescence in the junctional zone of GA. Absence of hyperautofluorescence (i.e., pattern = none) is exclusionary.1

5. Adequate clarity of ocular media, adequate pupillary dilation, and fixation to permit the collection of good quality images as determined by the investigator.

6. Meets the following criteria related to microperimetry (*does not apply for study 303*):

   a. Able to detect fixation target.

   b. Total elapsed time to complete the 10-2 68-point exam is ≤30 minutes in duration.

   c. Fixation losses must be ≤20%.

   d. Subject is willing and able to undertake microperimetry assessment in the opinion of the investigator.

7. Female subjects must be:

   a. Women of non–childbearing potential (WONCBP), or

   b. Women of childbearing potential (WOCBP) with a negative serum pregnancy test at screening and must agree to use protocol defined methods of contraception for the duration of the study and refrain from breastfeeding for the duration of the study.

8. Males with female partners of childbearing potential must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study.

9. Willing and able to give informed consent and to comply with the study procedures and assessments.

Exclusion Criteria

Ocular specific exclusion criteria applied to the study eye only, unless otherwise specified.

1. GA secondary to a condition other than AMD such as Stargardt disease, cone rod dystrophy, or toxic maculopathies like plaquenil maculopathy in either eye.

2. Spherical equivalent of the refractive error demonstrating > 6 dioptres of myopia or an axial length >26 mm.

3. Any history or active CNV, associated with AMD or any other cause, including any evidence of retinal pigment epithelium rips or evidence of neovascularisation anywhere based on SD-OCT imaging and/or fluorescein angiography as assessed by the reading centre.

4. Presence of an active ocular disease that in the opinion of the investigator compromises or confounds visual function, including but not limited to, uveitis, other macular diseases (e.g., clinically significant epiretinal membrane [ERM], full thickness macular hole) or uncontrolled glaucoma/ocular hypertension). Benign conditions in the opinion of the investigator such as peripheral retina dystrophy are not exclusionary.

5. Intraocular surgery (including lens replacement surgery) within 3 months prior to randomisation.

6. History of laser therapy in the macular region.

7. Aphakia or absence of the posterior capsule. Note: YAG laser posterior capsulotomy for posterior capsule opacification done at least 60 days prior to screening is not exclusionary.

8. Any ocular condition other than GA secondary to AMD that may require surgery or medical intervention during the study period or, in the opinion of the investigator, could compromise visual function during the study period.

9. Any contraindication to IVT injection including current ocular or periocular infection.

10. History of prior intravitreal injection.

11. Unable to perform microperimetry reliably in the opinion of the investigator (*does not apply for study 303)*

12. Prior participation in another interventional clinical study for intravitreal therapies in either eye (including subjects receiving sham).

13. Prior participation in another interventional clinical study for geographic atrophy in either eye including investigational oral medication and placebo.

14. Participation in any systemic experimental treatment or any other systemic investigational new drug including within 6 weeks or 5 half-lives of the active ingredient (whichever is longer) prior to the start of study treatment. Note: clinical trials solely involving observation, over-the-counter vitamins, supplements, or diets are not exclusionary.

15. Medical or psychiatric conditions that, in the opinion of the investigator, make consistent follow-up over the 24-month treatment period unlikely, or would make the subject an unsafe study candidate.

16. Any screening laboratory value (haematology, serum chemistry or urinalysis) that in the opinion of the investigator is clinically significant and not suitable for study participation.

17. Known hypersensitivity to fluorescein sodium for injection or hypersensitivity to pegcetacoplan or any of the excipients in pegcetacoplan solution.

Concomitant therapies

Metoclopramide or other agents to prevent nausea induced by fluorescein injection were allowed administered at the discretion of the PI.

If the investigator suspected new exudation related to active CNV in the study eye based on fundus examination and/or OCT findings (e.g., subretinal fluid, intraretinal fluid, cystoid macular oedema, serous pigment epithelial detachment), a fluorescein angiography and Optical Coherence Tomography Angiography (OCT-A; select sites only) was to be captured. If evidence of active exudative AMD was present, treatment with anti-VEGF could have been initiated. The determination about initiation of anti-VEGF treatment for the exudation related to active CNV was the sole responsibility of the investigator. If it was determined that the subject required anti-VEGF therapy, ranibizumab or aflibercept should have been selected and administered by the injecting (unmasked) physician. Ranibizumab should have bene given monthly and aflibercept every other month after 3 monthly loading doses. The frequency of aflibercept could have been changed to monthly if deemed necessary by the investigator, however the physician should have refrained from using as-needed treatment (PRN) or treat and extend protocols. If anti-VEGF therapy was administered in the study eye on the same day as a pegcetacoplan (or sham) injection, the anti-VEGF therapy had to be administered first and the pegcetacoplan or sham injection should have occurred at least 30 minutes after the anti-VEGF injection and only if the IOP was ≤21 mm Hg. Anti-glaucomatous medication could have been administered to lower the IOP to the appropriate range to allow for the pegcetacoplan injection. Treatment with anti-VEGF was allowed in the fellow eye.

The decision to treat a participant for endophthalmitis or suspected endophthalmitis was guided by the clinical judgment of the investigator and in accordance with local guidelines (as applicable). A culture sample needed to be performed prior to making a decision on treatment. The treatment method (pars plana vitrectomy vs intravitreal injection of antibiotics) and choice of antimicrobial agents were also at the discretion of the physician and needed to follow current standard practice patterns. The decision to use IVT steroids (e.g., dexamethasone) for the treatment of endophthalmitis was also at the discretion of the physician.

Treatments

Patients were planned to be assigned on a 2:2:1:1 basis to receive either:

- Group 1: Pegcetacoplan 15 mg/0.1 mL monthly for 24 months (n= approximately 200 subjects; 24 pegcetacoplan injections)
- Group 2: Pegcetacoplan 15 mg/0.1 mL EOM for 24 months (n= approximately 200 subjects; 12 pegcetacoplan injections)
- Group 3: Sham monthly for 24 months (n= approximately 100 subjects; 24 sham injections)
- Group 4: Sham EOM for 24 months (n= approximately 100 subjects; 12 sham injections)

After randomisation and during the treatment phase beginning at Day 1, all subjects received a single dose of 15 mg pegcetacoplan/0.1 mL or sham injection intravitreally either monthly or every other month depending on treatment designation, as outlined above.

Only qualified study staff and those delegated the responsibility of study drug administration on the delegation of authority log were allowed to perform this procedure. All staff needed to be appropriately trained on all procedures prior to performing the procedures.

Administration of study treatment (pegcetacoplan or sham) could be done on a separate day from the assessment visit if both days fell within the visit window. If this occurred on the randomisation visit, then the administration of pegcetacoplan or sham should have been done within 3 days of randomisation and after approval from the medical monitor. When study treatment administration was on a day other than a study visit, then the only assessment that must have been done on the day of study treatment administration was the IOP preinjection. If a subject fell outside the visit window for a dosing visit, the dose should have been skipped and the subject should have been scheduled on time for the next dosing visit.

Intravitreal pegcetacoplan administration

Subjects that received active treatment were administered 0.1 mL IVT injection of pegcetacoplan according to their treatment designation using a thin wall needle. Clinic staff involved in the injection tray assembly, anaesthetic preparation, and study drug preparation and administration were following appropriate aseptic techniques to minimise the risk of potential AEs associated with IVT injections. Administration of pegcetacoplan was only allowed if preinjection IOP ≤21 mm Hg. If necessary, antiglaucomatous medication could be given to lower the IOP. To minimise transient IOP elevation after IVT injection of pegcetacoplan, decompression of the eye was performed before all pegcetacoplan injections. This was done by applying moderate pressure to the globe with cotton swabs for 30-60 seconds during anaesthetic preparation.

Sham injection administration

The procedure for sham injection was the same as that used for IVT injection until the actual injection but no actual injection occurred. The injecting physician only touched the study eye with the blunt end of the syringe. No needle or medication was injected inside the eye. Subjects randomised to the monthly or every-other-month sham-injection groups received sham injection monthly or every other month, respectively. The same assessments were performed as for the subjects in the pegcetacoplan groups.

The terms 'sham treatment' and 'sham injection' are used synonymously throughout this report.

Objectives

Primary Objective

The primary objective of this study was to evaluate the efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD assessed by change in the total area of GA lesions from baseline as measured by fundus autofluorescence (FAF).

Key Secondary Objectives

The key secondary objective of this study was to evaluate the efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD with respect to:

- Monocular maximum reading speed (study eye), as assessed by Minnesota Low-Vision Reading Test (MNREAD) or Radner Reading Charts (in select countries)
- Functional Reading Independence (FRI) index score
- Normal luminance best corrected visual acuity score (NL-BCVA) in the study eye

Secondary Objectives

The secondary objective of this study was to evaluate the efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD with respect to:

- Low luminance best corrected visual acuity score (LL-BCVA) in the study eye
- Low luminance deficit (LLD) in the study eye
- Total area of GA lesion(s) in the study eye
- Monocular critical print size (study eye), as assessed by MNREAD or Radner Reading Charts (in select countries)
- National Eye Institute Visual Functioning Questionnaire 25-Item Version (NEI VFQ-25) distance activity subscale score (in select countries)
- Macular functional response as assessed by mesopic microperimetry (*only in study 304*)

To evaluate the PK of pegcetacoplan as assessed by systemic plasma concentration of pegcetacoplan (in selected sites). (*does not apply for study 304*)

Safety Objectives

To evaluate the safety and tolerability of pegcetacoplan compared to sham injection in patients with GA secondary to AMD as indicated by:

- Incidence and severity of ocular and systemic treatment-emergent adverse events
- Incidence of anti-therapeutic antibodies directed against pegcetacoplan
- Incidence of new active CNV in the study eye

Exploratory Objectives

- To evaluate the efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD as indicated by:
  - NEI VFQ-25 composite score
  - NEI VFQ-25 near activity subscale score (in selected countries)

- Comparison between study eye and fellow eye in change in GA lesion size
- To evaluate the binocular maximum reading speed as assessed by MNREAD or Radner Reading Charts (in select countries)
- To evaluate the binocular critical print size as assessed by MNREAD or Radner Reading Charts (in select countries)

- To evaluate the relationship between genetic polymorphisms associated with AMD with GA progression and response to pegcetacoplan
- To evaluate the incidence of new onset of subclinical CNV in the study eye
- To assess sensitivity and specificity of a digital reading speed application to detect disease progression / regression (optional, select sites)
- To assess sensitivity and specificity of a digital visual function application to detect disease progression / regression (optional, select sites)

Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint chosen to assess drug efficacy is the 'change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on fundus autofluorescence (FAF)'.

In more detail, the primary efficacy endpoint is the change from baseline to Month 12 in the total area of GA lesion(s) in eyes injected with pegcetacoplan, either monthly (PM) or every-other month (PEOM), or sham injections. GA lesion area (mm^2) as measured by a quantified central reading centre based on FAF images. The primary analysis is the comparison of pegcetacoplan, either monthly (PM) or every-other month (PEOM) versus the combined 2 sham arms (the 2 sham arms were combined into a single 'control' group).

The following sensitivity and supportive analyses were performed to evaluate the robustness of the results from the primary analysis method:

- Repeated analyses using the mITT and per-protocol sets
- Primary and secondary endpoints were also summarised with no pooling of the 2 sham arms. The comparison for pegcetacoplan and sham injection within each dose regimen (i.e., PM vs SM and PEOM vs SEOM) was conducted
- Multiple imputation (MI) methods and other sensitivity analyses were explored

Fundus Autofluorescence (FAF) images (Heidelberg Spectralis Instrument) were obtained and sent to the reading centre at screening, before initial treatment and every other month up to month 24 for the study eye and for the fellow eye at screening, before initial treatment and at months 6, 12, 18 and 24. A reading centre manual along with training materials were provided to all sites which provided information on standardised procedures for the collection, storage and transmission of all images. Prior to any images being taken at the site, site personnel needed to be properly trained and certified and test images and systems and software must have been certified and validated by the reading centre. Only trained and certified site staff delegated the responsibility of image collection was allowed to perform this task.

Key Secondary Efficacy Endpoints

- Change from baseline in monocular maximum reading speed (study eye), as assessed by MNREAD or Radner Reading Charts at Month 24 (in select countries).

  MNREAD Test or Radner Reading Charts should be administered first monocularly for both eyes and then binocularly. These tests should be administered prior to dilating the eyes.

- Change from baseline in Functional Reading Independence (FRI) index score, at Month 24.

  The FRI is interviewer-administered and is an individualised assessment of functional reading independence. The questionnaire has 7 items with 1 total index score. Higher levels on the scale represent higher functional reading independence. The recall period is 7 days.

- Change from baseline in normal luminance best corrected visual acuity score (NL-BCVA) at Month 24 as assessed by ETDRS chart.

  Best corrected visual acuity was measured by certified study staff. The study staff performing visual acuity should be masked to the treatment assignment. Best corrected visual acuity testing was assessed on ETDRS chart starting at a distance of 4 m, performed by a certified VA examiner, and should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye.

Secondary Efficacy Endpoints

- Change from baseline in low luminance best corrected visual acuity score (LL-BCVA) at Month 12 and Month 24 as assessed by ETDRS chart.

  The LL-BCVA acuity will be measured by placing a neutral density trial lens causing a reduction of 2.0 log units in luminance. The same requirements apply to measurement of low luminance visual acuity as described above for best corrected visual acuity. Low luminance deficit will be auto-calculated.

- Change from baseline in low luminance deficit (LLD) at Month 12 and Month 24.

- Change from baseline at each planned assessment in the total area of GA lesion(s) in the study eye (in mm2) as assessed by FAF.

- Change from baseline in monocular critical print size (study eye), as assessed by MNREAD or Radner Reading Charts, at Month 12 and Month 24 (in select countries).

- Change from baseline in the National Eye Institute Visual Functioning Questionnaire 25-Item Version (NEI VFQ-25) distance activity subscale score at Month 12 and Month 24 (in select sites).

  The NEI-VFQ is an interviewer-administered questionnaire designed to assess patient-reported visual function. The NEI-VFQ is to be administered by the masked staff. It is a 25-item questionnaire with a composite score and covers 12 domains of functional health status and well-being (general health, general vision, ocular pain, near activities (select countries), distance activities (select countries), social functioning, mental health, role difficulties, dependency, driving, colour vision, and peripheral vision). Scoring yields 12 subscales based on the 12 domains covered in the questionnaire. These scales are scored from 0 to 100 with higher scores indicating better visual function.

- Number of scotomatous points assessed by mesopic microperimetry for the evaluation of the macular functional response. (*does not apply for study 303*)

Mesopic Microperimetry was only performed of the study eye (at screening, performed on both eyes). To account for the learning curve of this test, the patient was allowed up to 3 attempts to meet the criteria for this portion. Microperimetry assessments was performed post dilation. Data was forwarded to the reading centre. In the microperimetry test, varying intensities of light are presented directly onto the retina at 68 loci centred around the fovea and threshold sensitivity is measured at each locus. Retinal tracking by microperimetry ensures that the same areas are measured across visits, thereby enabling longitudinal topographic sensitivity information across the lesional and perilesional areas and retinal areas outside of the GA lesion.

- Change in macular sensitivity as assessed by mesopic microperimetry for the evaluation of the macular functional response. (*does not apply for study 303*)
- Systemic plasma concentration of pegcetacoplan over time (in selected sites) (*does not apply for study 304)*

Sample size

A total of approximately 600 subjects was planned be randomised in a 2:2:1:1 ratio to receive treatment with PM, PEOM, SM, or SEOM. The mean annual growth rate in GA lesion area was expected to be 1.47, 1.70 and 2.13 mm2/year for PM, PEOM and Sham-Pooled groups, respectively (as estimated from the results of a Phase 2 trial). The standard deviation of the lesion growth was assumed to be 1.50 mm2 based on the same Phase 2 trial data, or 1.25 mm2 based on natural history data.

The power of the study for the primary endpoint was estimated using PROC POWER ONEWAYANOVA, Statistical Analysis System (SAS) 9.4. Results of these estimations were presented in the corresponding SAPs in tabular form:

Table 12: Power to detect a difference among three groups with an equal size of 200 subjects

Common Standard Deviation (mm^2)	Alpha (two-sided)	Power for a true mean of 1.47, 1.70, and 2.13 mm^2/year for PM, PEOM and Sham, respectively		
		PM vs Sham	PEOM vs Sham	Overall (Among 3 groups)
1.25	0.0495	> 99.9%	92.9%	99.9%
1.25	0.0248	99.9%	88.2%	99.7%
1.40	0.0495	99.7%	86.5%	99.3%
1.40	0.0248	99.3%	79.4%	98.6%
1.50	0.0495	99.2%	81.5%	98.4%
1.50	0.0248	98.4%	73.1%	97.0%

PM = pegcetacoplan Monthly, PEOM = pegcetacoplan Every-Other-Month; Sham = Sham Monthly + Sham Every-Other-Month

Study power was not calculated for key secondary functional endpoints.

Randomisation and blinding (masking)

Randomisation

In the OAKS trial (as in DERBY), each subject was to be assigned a unique screening number after signing the informed consent. Subjects who complete the study screening assessments and met all the eligibility criteria were to be scheduled to enter the study and randomised on Day 1. Subjects were to be randomised 2:2:1:1 to receive treatment with APL-2 Monthly (AM), APL-2 Every-Other-Month (AEOM), Sham injection Monthly (SM) or Sham injection Every-Other-Month (SEOM), respectively.

The randomisation scheme was to be generated and maintained by the Sponsor. Subject randomisation planned to be carried out stratified by GA lesion area at screening (< 7.5 mm2; 2 7.5 mm2) and presence of CNV in the fellow eye (yes; no).

Blinding

This was planned and carried out as double-masked study. Designated masked study site staff (e.g., assistant(s), VA technicians, optical coherence tomography (OCT) technicians, photographers, technicians administering questionnaires, subjects, reading centre personnel, the assigned evaluating physician(s), and the Sponsor) were planned to be masked to treatment assignment. However, the treating physician and any associated support staff involved in performing the intravitreal or sham injections were to remain unmasked to study treatment. These individuals were only responsible for administering the study drug and were not planned to be involved in assessing adverse events. In addition, the unmasked individuals were not allowed to discuss treatment and/or subject outcomes with masked study staff, including the evaluating physician. While the actual study treatment (pegcetacoplan vs. sham) was planned to be masked, the treatment frequency (monthly vs. every other month) for each individual subject was known.

In the event of a medical emergency, an individual Investigator (or designee) was planned to have the ability to unmask the treatment assignment for a specific subject and share that information with the appropriate parties. The Investigator (or designee) must endeavour to notify the Sponsor prior to unmasking a subject. All documentation indicating unmasking were to be retained with the subject's source documentation in a secure manner. A DMC was to be set-up to monitor patient safety and review data. The DMC was planned to be provided unmasked safety data but was planned to masked to efficacy data unless this data was deemed medically necessary.

For regulatory reporting and if required by local regulations, the Sponsor was planned to unmask study treatment for all serious, unexpected adverse reactions that are considered to be related to study drug. Subjects who have had their treatment assignment unmasked secondary to a serious or unexpected adverse event or medical emergency were planned to no longer receive study treatment. However, those patients were supposed to continue to complete as many of the follow-up visits as possible.

The study unmasking for the primary analysis at 12 months was planned to be limited to the analysis team and personnel only on an as-needed basis. All other personnel in the "masked" role was planned to remain masked until the end of study.

Statistical methods

One relevant difference between the trials is one additional secondary functional assessment foreseen in the OAKS trial (i.e. mesopic microperimetry, leading to planned hypothesis testing of 'mean threshold sensitivity of all points'). Another difference between studies pertains to PK- and PD-evaluations, which were only foreseen in DERBY.

Three Statistical Analysis plans (SAPs) are contained in the dossier: one for DERBY, one for OAKS and one for the Integrated Summary of Efficacy (ISE).

Statistical hypothesis testing was based on a strategy mixing type-1-error control in a study-wise and a submission-wise manner:

The null hypotheses (in OAK as ain DERBY) for the primary efficacy endpoint were the following:

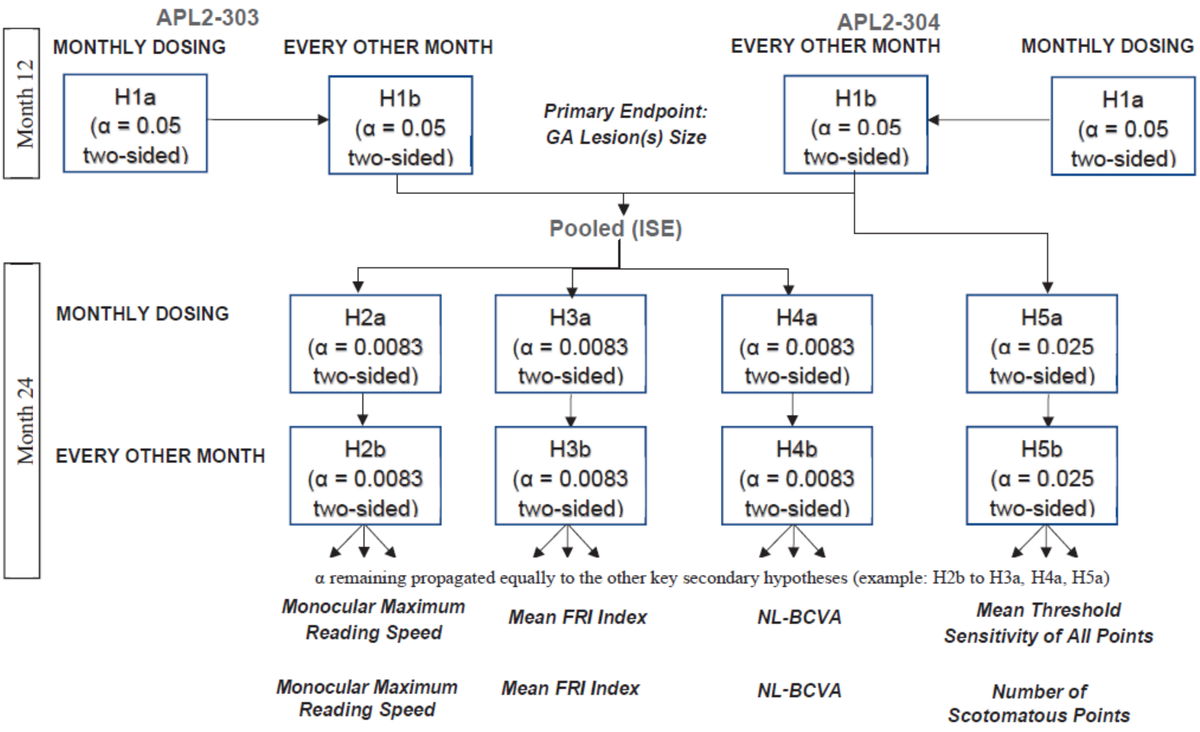
- H_{1a}: There is no difference between PM and Sham in mean change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm2) based on FAF for the mITT set.
- H_{1b}: There is no difference between PEOM and Sham in mean change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm2) based on FAF for the mITT set.

For the analysis using data from DERBY and OAKS it was generally planned to control the type I error rate for the primary endpoint hypotheses testing at the level of the individual studies, and at a level of the submission as a whole for the key secondary endpoints hypotheses testing based on pooling data from DERBY and OAKS. If both hypothesis tests for the primary endpoint in both studies were statistically significant, then hypotheses tests were planned to be performed for the key secondary endpoints within the pooled APL2-303/APL2-304 data for hypotheses H2a – H4b and within OAKS also for H5a and H5b. The key secondary efficacy endpoints hypotheses that were planned to be tested in the pooled APL2-303/APL2-304 studies were:

- H_{2a} : There is no difference between PM and Sham regarding mean change from baseline in monocular maximum reading speed (study eye), as assessed by MNRead or Radner Reading Charts at Month 24.
- H_{2b}: There is no difference between PEOM and Sham regarding mean change from baseline in monocular maximum reading speed (study eye), as assessed by MNRead or Radner Reading Charts at Month 24.
- H_{3a}: There is no difference between PM and Sham regarding mean change from baseline in mean FRI Index score at Month 24.
- H3b: There is no difference between PEOM and Sham regarding mean change from baseline in mean FRI Index score at Month 24.

- H_{4a}: There is no difference between PM and Sham regarding mean change from baseline in NL-BCVA score at Month 24 (study eye) as assessed by ETDRS chart.
- H_{4b}: There is no difference between PEOM and Sham regarding mean change from baseline in NL-BCVA score at Month 24 (study eye) as assessed by ETDRS chart.
- H_{5a}: There is no difference between PM and Sham regarding mean change from baseline in mean threshold sensitivity of all points (study eye) for the evaluation of the macular functional response, as assessed by mesopic microperimetry at Month 24.
- H_{5b}: There is no difference between PEOM and Sham regarding mean change from baseline in mean threshold sensitivity of all points (study eye) for the evaluation of the macular functional response, as assessed by mesopic microperimetry at Month 24.

The figure below presents the chosen overall hypotheses testing strategy involving the two pivotal trials:



Endpoint data are compared to sham injections in hypotheses testing. Hypotheses can only be tested in sequential order as indicated by arrows. Sequential testing will continue as long as all preceding hypotheses can successfully be rejected at the given alpha level. At the study-level, the Type-I error rate (one-sided) is controlled at 0.025 for the primary endpoint hypotheses. In the submission, the Type-I error rate (one-sided) is controlled at 0.000625 (0.025^2) for the primary endpoint hypotheses and at 0.025 for the key secondary endpoints.

Figure 9: APL2-303 and APL2-304 hypothesis testing type I error control

This plan required successful rejection of both primary hypotheses in each of the two trials to enable statistical testing of key-secondary hypotheses. Should at least one of the hypothesis tests for the primary endpoint in one of the two studies have failed to be significant, but both hypothesis tests for the primary endpoint were found significant in the other study, then the preplanned testing strategy foresaw a sub-strategy for hypotheses testing for the key secondary endpoints on the individual study level, following a fixed sequencing approach. The figure below illustrates the plan for the OAKS-trial:

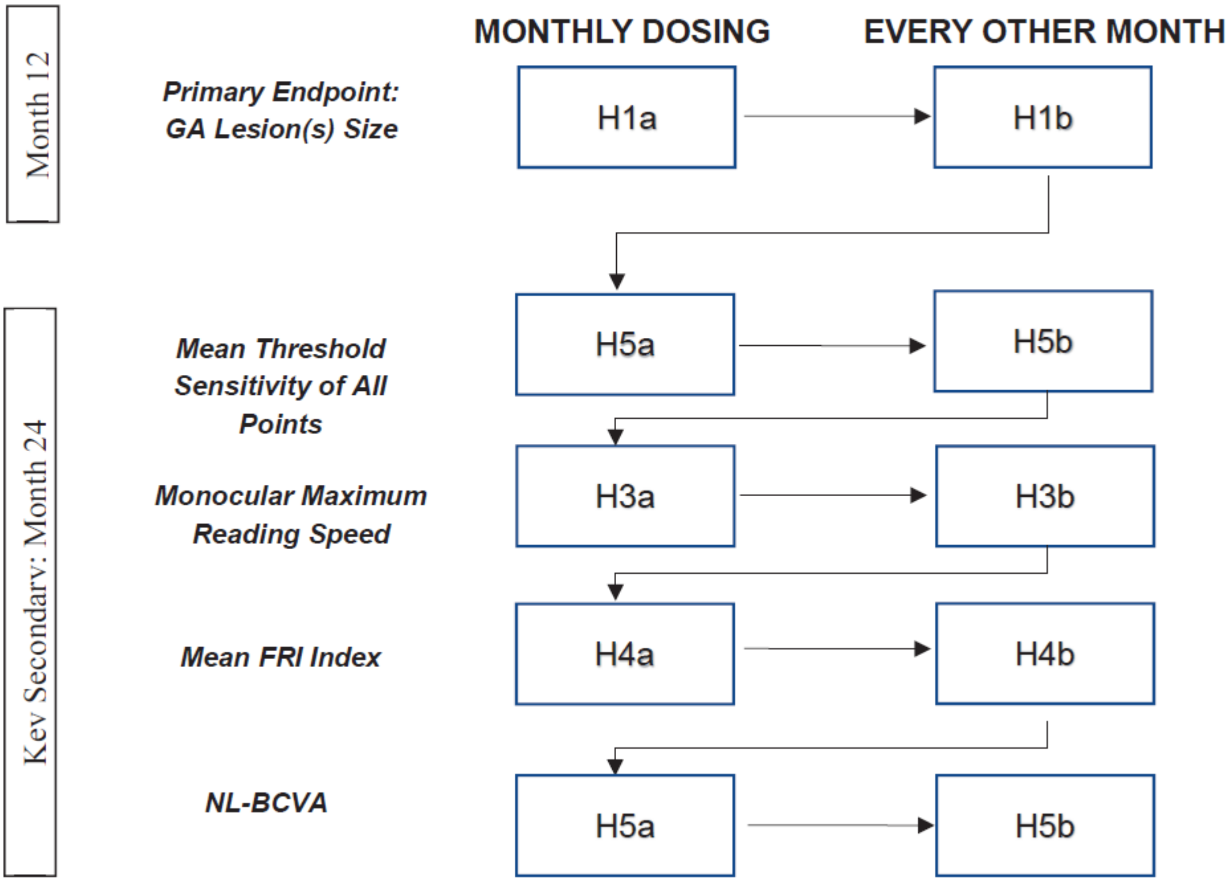


Figure 10: Hypothesis testing plan for the OAKS-trial in case one of the hypothesis tests for the primary endpoint in the other of the two studies have failed to be significant, but both hypothesis tests for the primary endpoint were found significant in the study

An integrated analysis planned via a separate SAP was prepared for analyses conducted at both the Month 12 reporting as well as the Month 24 reporting. No formal hypothesis testing of the primary endpoint was planned at Month 12 in the integrated analysis. In addition, all primary, key secondary, secondary, and exploratory endpoints were planned to be evaluated based on Month 12 pooled dataset in a descriptive manner. Formal hypothesis testing was only foreseen for key secondary functional endpoints at Month 24 reporting. All other endpoints (primary, secondary, and exploratory) were planned to be evaluated based on Month 24 pooled dataset in a descriptive manner.

<u>Estimands and Analysis Sets</u>

The primary scientific research question of this study was to assess the effect of pegcetacoplan compared with that of sham at Month 12 regarding the impact on GA lesion progression. The primary estimand in the study was defined through the following 5 attributes:

Population: GA subjects defined through inclusion and exclusion criteria in the mITT population.

Treatment conditions: The treatment regimens of interest in this study were PM, PEOM and Sham.

Variable (or endpoint): Change in total area of GA lesions in the study eye from baseline measured by FAF to Month 12.

Strategy for addressing intercurrent events: See description of intercurrent events below.

Population-level summary: Difference in mean change of GA lesion from baseline to Month 12 between pegcetacoplan and sham groups according to MMRM analysis.

The intercurrent events that were to be considered are:

- Treatment discontinuation
- Lost to follow up
- Withdrawal from the study

The intercurrent events were to be handled with a "treatment policy"-strategy whereby any measured value was planned be used as is. Missing data resulting from these intercurrent events were planned to be handled implicitly within the MMRM analysis that assumes missing at random.

The key secondary estimands were defined and analysed in the similar fashion as the primary estimand. The primary and key secondary estimands are summarised in Table 13:

Table 13: Estimands of study

Estimand	Definition	Attributes			
		A: Population	B: Variable (or endpoint)	C: Strategy for addressing intercurrent event	D: Population-level summary
		Main Analyses			
Primary	The effect of pegcetacoplan compared to sham at Month 12 in impact on GA progression	mITT	Change in the total area of GA lesions from baseline measured by FAF to Month 12	• Treatment policy strategy for subjects who discontinue treatment, are lost to follow-up, or withdraw from the study	Difference in mean change of GA lesion from baseline at Month 12 between pegcetacoplan and sham groups based on MMRM analysis
Key Secondary #1	The effects of pegcetacoplan compared to sham at Month 24 in impact on macular functional response	mITT	Change in mean threshold sensitivity of all points from baseline to Month 24	• Treatment policy strategy for subjects who discontinue treatment, are lost to follow-up, or withdraw from the study	Difference in mean change in mean threshold sensitivity of all points from baseline at Month 24 between pegcetacoplan and Sham groups based on MMRM analysis
Key Secondary #2	The effects of pegcetacoplan compared to sham at Month 24 in impact on monocular maximum reading speed	mITT	Change in monocular maximum reading speed from baseline to Month 24	• Treatment policy strategy for subjects who discontinue treatment, are lost to follow-up, or withdraw from the study	Difference in mean change in monocular maximum reading speed from baseline at Month 24 between pegcetacoplan and Sham groups based on MMRM analysis
Key Secondary #3	The effects of pegcetacoplan compared to Sham at Month 24 in impact on mean FRI Index score	mITT	Change in mean FRI Index score from baseline to Month 24	• Treatment policy strategy for subjects who discontinue treatment, are lost to follow-up, or withdraw from the study	Difference in mean change in mean FRI Index score, from baseline at Month 24 between pegcetacoplan and sham groups based on MMRM analysis
Key Secondary #4	The effects of pegcetacoplan compared to Sham at Month 24 in impact on NL-BCVA score	mITT	Change in NL-BCVA score from baseline to Month 24	• Treatment policy strategy for subjects who discontinue treatment, are lost to follow-up, or withdraw from the study	Difference in mean change of NL-BCVA score from baseline at Month 24 between pegcetacoplan and sham groups based on MMRM analysis

Supplemental Analyses of the Primary Efficacy Endpoint: COVID-19 Adjusted Estimand

To manage the increase in missed/not received injections due to COVID-19 pandemic (as collected on the eCRF), i.e., undertreatment with an expected relevant impact on efficacy, the "hypothetical strategy" was to be used whereby assessments after the intercurrent event (relevant undertreatment) occurs were to be set to missing/censored in the analysis. The threshold for missed/not received injections due to the COVID-19 pandemic was missing >25% of scheduled injections prior to the analysis timepoint of interest. For the Monthly schedule group, this was missing 4 or more injections and for the EOM schedule group, this was missing 2 or more injections prior to the Month 12 visit attributable due to the COVID-19 pandemic. In terms of the underlying cause of the excessive missing/not received injections and subsequent missing data, it was assumed that the missingness resulting from censoring occurs completely at random because of the ongoing pandemic and not because of the subjects' observed or unobserved outcomes, so missing data resulting from this intercurrent event in the primary analysis model was to be handled implicitly in the MMRM analysis.

The number of subjects with any censoring included in the model, the number of subjects with any censoring not included in the model, and the number of assessments censored by visit was planned to be presented for each treatment group.

All summaries and presentations of the observed values for the total area of GA lesion(s) in the study eye by treatment group and visit described were planned to be repeated for the COVID-19 adjusted estimand.

In addition, a supplemental analysis was to be performed where the threshold for missed/not received injections had been restricted to specific events attributable to COVID-19. These events were defined based on the COVID-19 collection form and include COVID-19 diagnosis, COVID- 19 Suspected, Site Closure, Travel Ban, Shelter in Place, City Lockdown, and Other. Except for the plots, the analyses described above was planned to be repeated for the threshold based only on these external events attributable to COVID-19.

Screened Set

The screened set was planned to consist of all subjects who provided written informed consent and were screened for participation in this study. This population was only planned to be used for the purposes of describing the subject disposition and for listing the data.

Intent-to-Treat Set

The Intent-to-treat (ITT) set was planned to consist of all randomised subjects. Subjects were to be analysed in the treatment arm assigned at randomisation.

Modified Intent-to-Treat Set

The modified ITT (mITT) set was planned to consist of all randomised subjects who received at least one injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye as assessed by FAF. Subjects were to be analysed in the treatment arm assigned at randomisation.

Safety Set

The Safety set was planned to consist of all subjects randomised who received at least one injection of pegcetacoplan or sham. Subjects were to be analysed according to the actual treatment received. This population was to be used for all safety analyses.

Per-Protocol Sets

The Per-Protocol (PP) sets was planned to be identified separately for Month 12 and Month 24 analysis, respectively (i.e., Month 12 PP set and Month 24 PP set). The PP sets were to consist of all mITT subjects who have a valid GA lesion area assessment for either Month 10 or 12 (Month 12 PP set) or a valid GA lesion area assessment for at least one of Month 18, 20, 22, 24 (Month 24 PP set) and who follow the protocol without any major deviation(s) that could affect the primary efficacy data. The SAP contains further details as regards the definition of this set.

Pharmacokinetic Set (DERBY trial only)

The PK set as planned to include all subjects of the safety set who have at least one quantifiable post-dose concentration of pegcetacoplan (even with values below the limit of quantification (BLQ)).

Pharmacodynamic Set (DERBY trial only)

The PD set was planned to include all subjects of the safety set who have at least one quantifiable post-dose PD endpoint (C3, CH50, or AH50) evaluated.

Genotyping Set

The genotyping set was planned to consist of all ITT subjects who have at least one non-missing genotyping result for a single nucleotide polymorphism (SNP) associated with age-related macular degeneration from the genotype sequencing analysis.

General aspects concerning Statistical Analysis methods

Unless otherwise noted, hypothesis testing and estimation of treatment effects were performed with a mixed-effect model for repeated measures (MMRM) that included data from all 3 treatment arms: PM, PEOM, and sham. The sham group represented the pool of the 2 sham treatment groups: SM and SEOM. All hypothesis tests for efficacy endpoints were 2-sided.

Analysis method for primary efficacy endpoint

The observed values for the total area of GA lesion(s) were planned to be summarised by treatment group and visit for both the study and the fellow eye. Summaries would present the descriptive statistics for baseline, absolute values and change from baseline data by visit.

The primary endpoint was planned to be analysed in the mITT population with subjects grouped according to the treatment assigned at randomisation. A MMRM model was to be used to analyse the primary endpoint. The analysis model was to include treatment (PM, PEOM, sham), presence of choroidal neovascularisation in the fellow eye at baseline (Yes, No) and baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) as fixed effects, time (study month, categorical) as a factor, the time × treatment interaction term, and the baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) × time interaction term. The least square [LS] mean change from baseline to Month 12 was to be estimated from the model for each of three arms as well as the comparisons of each of the three arms to each other. For other time points of interest, LS mean change from baseline was to be estimated and compared between treatments. For each estimated LS mean, the corresponding 95% CI was to be presented based on the model. For the comparison of the LSmeans, the corresponding 95% CI and the 2-sided P-value along with the percentage difference (difference in LS means between the arms/the comparison group LS mean) was to be presented. Common unstructured covariance matrix was to be used to model the within-subject errors, the sandwich estimator (Diggle, Liang, and Zeger 1994) to estimate the standard errors of the fixed effects parameters, and the degrees of freedom partitioned into between-subject and within-subject portions. If there are convergence problems with the model, then a heterogeneous autoregressive (1) covariance matrix was pre-specified.

The main analysis described above was planned to be repeated using the Month 12 PP set.

Several sensitivity analyses were planned to be performed to evaluate the robustness of the primary analysis results. For missing data, sensitivity analysis was planned both based on copy-reference multiple imputation and on tipping-point analysis. Another sensitivity analysis without sham-pooling (accounting for separate sham conditions), and one sensitivity analysis excluding GA total area assessments with an indeterminate boundary.

In addition, the mean rate of change in GA area (i.e., slope) was planned to be compared between each pegcetacoplan arm and the pooled sham arm by use of linear mixed effects model assuming time as continuous and linear ("slope model"). The mean rate of change in GA area was also to be compared between each pegcetacoplan arm and the pooled sham arm by use of a piecewise linear mixed effect model assuming time as continuous and piecewise linear ("piecewise slope model"). The analysis to be performed was to be similar to what is described above in the "slope model".

Subgroup analyses were planned to be performed to evaluate the consistency of the primary analysis results across subgroups defined by demographic and baseline characteristics. Thereby the approach described for the main analysis was to be used for each subgroup analysis based on the data subset for the subject subgroup of interest. Baseline covariates included in the main analysis but no longer relevant given the subgroup of interest were be excluded from the model. The estimated treatment effects (PM vs. Sham; PEOM vs. Sham) and corresponding 95% CIs and p-values from the models will be displayed graphically for each pegcetacoplan treatment arm and each level of the subgroups specified (e.g., via forest plots). Analyses were be performed for the primary efficacy endpoint (change from baseline in total area of GA lesion(s) in the study eye at Month 12) for each of the following subgroups:

- Age Group (<75 years, 75 to <85 years, ≥85 years)
- Sex (male, female)
- Race (White, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, multiple, unknown; If most subjects (e.g., >90%) are of a single race, this analysis will not be conducted.
- Geographic Region (United States vs Rest of World)
- Subgroups indicative of disease severity at baseline
  - Study eye baseline GA lesion size (<7.5 mm^2; ≥7.5 mm^2)
  - Study eye baseline GA lesion size categories (approximately tertiles based on APL2-303/304 combined data*)
  - Study eye baseline NL-BCVA categories (≥70, ≥60 - <70, ≥35 - <60, <35 ETDRS letters)
  - Study eye baseline NL-BCVA categories (<60 vs. ≥60 ETDRS letters)
  - Study eye baseline LL-BCVA categories (approximately tertiles based on APL2-303/304 combined data*)
  - Study eye baseline monocular maximum reading speed categories (approximately tertiles based on APL2-303/304 combined data*)
  - Baseline FRI Level (1,2,3,4)
  - Study eye mean threshold sensitivity of all points categories (approximately tertiles)
- Subgroups associated with GA progression
  - Study eye baseline GA focality (multifocal, unifocal)
  - Study eye baseline GA lesion location (subfoveal involvement, without subfoveal involvement)
  - Baseline GA laterality (bilateral GA (with or without CNV in fellow eye) vs. Study eye GA only)

- Baseline CNV in fellow eye (Fellow eye CNV vs. No fellow eye CNV)
- Study eye baseline LLD categories (<20 vs. ≥ 20 ETDRS letters)
- Study eye baseline LLD categories (approximately tertiles based on the APL2- 303/304 combined data*)
- Study eye baseline NL-BCVA (<60 vs. ≥60 ETDRS letters) and LLD (<20 vs. ≥ 20 ETDRS letters) combinations

Analysis method for key secondary efficacy endpoints

Mean threshold sensitivity of all points in the study eye, Monocular maximum reading speed in the study eye, Mean FRI Index score as well as the Mean NL-BCVA score for the study eye were planned to be summarised and analysed in a similar fashion as the primary efficacy endpoint using MMRM.

The missing data analyses based on imputation as described above for primary sensitivity analyses were planned to be repeated for the key secondary efficacy endpoints at the time of the final study analysis for the full 24 months only. The key secondary endpoints were also planned to be analysed without pooling the two sham arms (SM and SEOM) for the full 24 months only.

Analysis methods for other secondary and exploratory efficacy endpoints

Many endpoints of this category were to be summarised and analysed in a similar fashion as the primary efficacy endpoint using MMRM.

Post Hoc Analyses

The CSR of the OAKS-trial describes a number of post hoc analyses carried out after unblinding. Those analyses pertain to the primary endpoint evaluation and involve further adjusting for (imbalanced) baseline characteristics, as well as further previously unplanned comparative analyses making use of data from the fellow eye.

Integrated efficacy data analyses (ISE) based on pooled data from DERBY and OAKS were presented by the applicant but only considered as descriptive supportive information during assessment.

Results

- **Participant flow**

Study APL2-303 DERBY and Study APL2-304 OAKS throughout month 24

Table 14: Subject disposition of the PM, PEOM, and sham pooled groups of the study populations at month 24 for study APL2-304, study APL-303, and pooled data-ITT population

	Study APL2-304			Study APL2-303			Pooled data		
	PM (N = 213)	PEOM (N = 212)	Sham pooled (N = 212)	PM (N = 206)	PEOM (N = 208)	Sham pooled (N = 207)	PM (N =419)	PEOM (N= 420)	Sham pooled (N =419)
Randomized, n	213	212	212	206	208	207	419	420	419
Completed treatment, n (%)	147 (69.0)	167 (78.8)	159 (75.0)	146 (70.9)	163 (78.4)	163 (78.7)	293 (69.9)	330 (78.6)	322 (76.8)
Completed study, n (%)	144 (67.6)	169 (79.7)	158 (74.5)	147 (71.4)	161 (77.4)	161 (77.8)	291 (69.5)	330 (78.6)	319 (76.1)
Withdrawn from treatment, n (%)	65 (30.5)	45 (21.2)	53 (25.0)	60 (29.1)	45 (21.6)	43 (20.8)	125 (29.8)	90 (21.4)	96 (22.9)
Withdrawn from study, n (%)	69 (32.4)	43 (20.3)	54 (25.5)	59 (28.6)	47 (22.6)	46 (22.2)	128 (30.5)	90 (21.4)	100 (23.9)
Primary reason for withdrawal from treatment[a], n (%)									
AE	12 (5.6)	10 (4.7)	7 (3.3)	11 (5.3)	7 (3.4)	8 (3.9)	23 (5.5)	17 (4.0)	15 (3.6)
Lost to follow-up	3 (1.4)	5 (2.4)	5 (2.4)	2 (1.0)	4 (1.9)	3 (1.4)	5 (1.2)	9 (2.1)	8 (1.9)
Physician's decision	0	1 (0.5)	1 (0.5)	2 (1.0)	0	2 (1.0)	2 (0.5)	1 (0.2)	3 (0.7)
Sponsor's decision	NA	NA	NA	NA	NA	NA	NA	NA	NA
Consent withdrawal	24 (11.3)	16 (7.5)	20 (9.4)	34 (16.5)	18 (8.7)	18 (8.7)	58 (13.8)	34 (8.1)	38 (9.1)
Death	17 (8.0)	9 (4.2)	7 (3.3)	7 (3.4)	5 (2.4)	6 (2.9)	24 (5.7)	14 (3.3)	13 (3.1)
Because of COVID impact[b]	9 (4.2)	4 (1.9)	13 (6.1)	4 (1.9)	10 (4.8)	6 (2.9)	13 (3.1)	14 (3.3)	19 (4.5)
Other	0	0	0	0	1 (0.5)	0	0	1 (0.2)	0
Primary reason for withdrawal from study, n (%)									
AE	11 (5.2)	8 (3.8)	6 (2.8)	9 (4.4)	6 (2.9)	8 (3.9)	20 (4.8)	14 (3.3)	14 (3.3)
Lost to follow-up	4 (1.9)	5 (2.4)	5 (2.4)	2 (1.0)	4 (1.9)	4 (1.9)	6 (1.4)	9 (2.1)	9 (2.1)
Consent withdrawal	25 (11.7)	16 (7.5)	21 (9.9)	36 (17.5)	20 (9.6)	19 (9.2)	61 (14.6)	36 (8.6)	40 (9.5)
Physician's decision	0	1 (0.5)	1 (0.5)	1 (0.5)	0	2 (1.0)	1 (0.2)	1 (0.2)	3 (0.7)
Death	20 (9.4)	9 (4.2)	8 (3.8)	7 (3.4)	6 (2.9)	7 (3.4)	27 (6.4)	15 (3.6)	15 (3.6)
Because of COVID impact[b]	9 (4.2)	4 (1.9)	13 (6.1)	4 (1.9)	10 (4.8)	6 (2.9)	13 (3.1)	14 (3.3)	19 (4.5)
Other	0	0	0	0	1 (0.5)	0	0	1 (0.2)	0

Abbreviations: AE = adverse event; CSR = clinical study report; NA = not applicable; ITT = intent-to-treat; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
[a] Includes reasons for patients who discontinued from treatment only and those who discontinued from treatment and study.
[b] Any discontinuation because of COVID impact except for adverse event of COVID. Instances of adverse event of COVID are captured under the adverse event category.

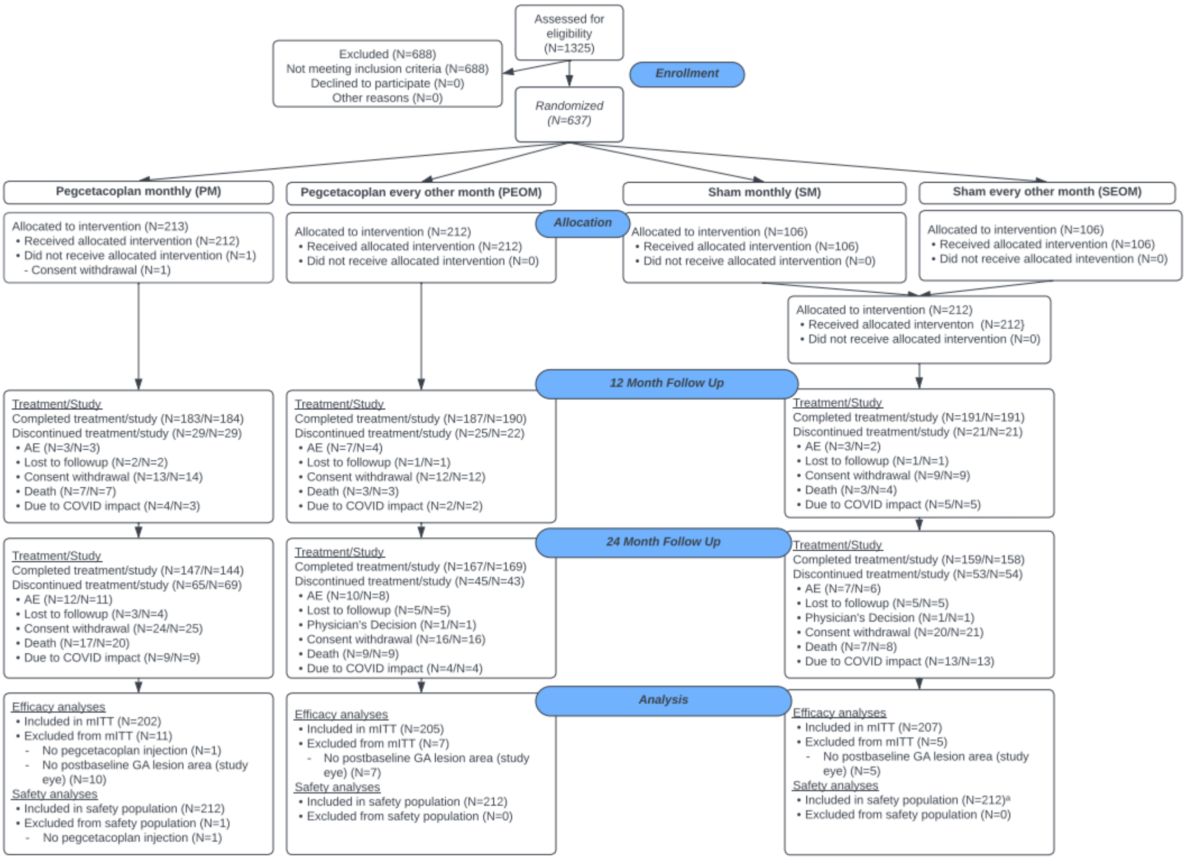


Figure 11: Participant flow diagram study APL2-304

Abbreviations: AE = adverse event; COVID = COVID-19; CSR = clinical study report; mITT = modified intent-to-treat.

[a] One subject, whose planned treatment was SM, received one dose of pegcetacoplan and was presented under PM for all summaries of safety.

Source: Study APL2-304 Month 24 CSR

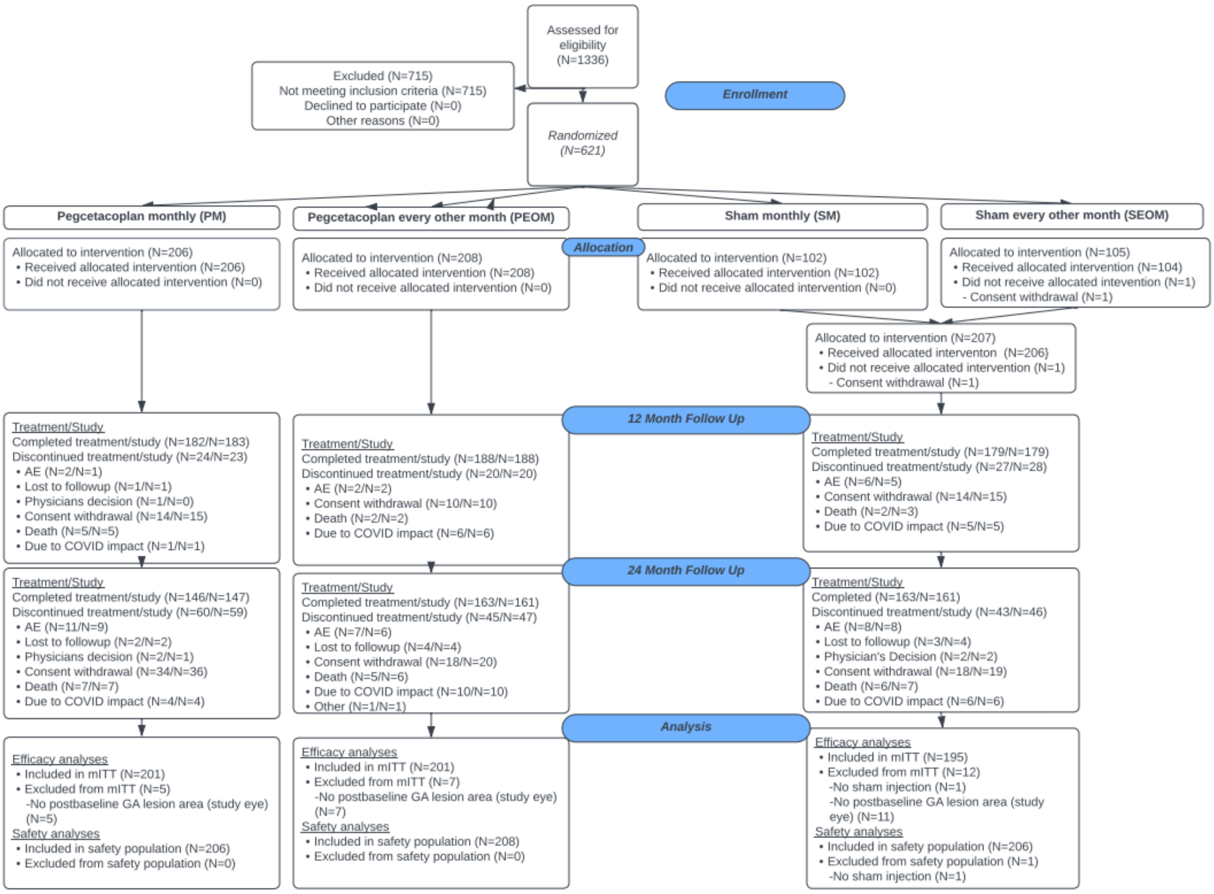


Figure 12: Participant flow diagram study APL2-303

Abbreviations: AE = adverse event; COVID = COVID-19; CSR = clinical study report; mITT = modified intent-to-treat.
Source: Study APL2-303 Month 24 CSR

- **Protocol deviations**

Any deviation from the protocol that potentially affected the scientific soundness of the research plan, rights, safety, or welfare of human subjects were classified as a major deviation. This included any deviation that affects interpretation of the primary safety and tolerability and/or efficacy endpoints, including rendering the subject's data scientifically uninterpretable or unevaluable.

Study APL2-303 DERBY

There were 239 subjects with major protocol deviations noted and (when appropriate) reported to the IEC or IRB in the ITT population. Overall, 75 subjects (36.4%), 81 subjects (38.9%), and 83 subjects (40.1%) in the PM, PEOM, and sham pooled groups, respectively had major protocol deviation(s) as defined by the definition above. The most common study-specific major protocol deviation was no valid GA lesion area assessment for either month 10 or month 12 in 30 subjects (14.6%), 26 subjects (12.5%), and 28 subjects (13.5%) in the PM, PEOM, and sham pooled groups, respectively, followed by missed visit or missed visit window (e.g., visit 10 outside 2-day window) in 21 subjects (10.2%), 18 subjects (8.7%), and 24 subjects (11.6%) in the PM, PEOM, and sham pooled groups, respectively. Unmasking errors for subjects or masked site staff who became unmasked to treatment assignment were low and reported in 4 subjects (1.9%), 5 subjects (2.4%), and 3 subjects (1.4%) in the PM, PEOM, and sham pooled groups, respectively. There were 92 subjects (14.8%) with major protocol deviations in the category of IP (subcategory dispensing/accountability). IP dispensing error was the most common reason for major protocol deviation in this category occurring in 92 subjects (14.8%): 29 subjects (14.1%) in the PM group, 33 subjects (15.9%) in the PEOM group, 14 subjects (13.7%) in the SM group, and 16 subjects (15.2%) in the SEOM group.

Overall, protocol deviations due to COVID-19 occurred in 468 subjects (75.4%). Missed IP dose intake due to COVID-19 occurred in 108 subjects (52.4%) in the PM group, 76 subjects (36.5%) in the PEOM group, 53 subjects (52.0%) in the SM group, and 26 subjects (24.8%) in the SEOM group. Overall, 371 subjects (59.7%) missed a visit or visit window, which included 110 subjects (53.4%) in the PM group, 134 subjects (64.4%) in the PEOM group, and 127 subjects (61.4%) in the sham pooled group.

Study APL2-304 OAKS

There were 225 subjects with major protocol deviations in the ITT population. Subjects with major protocol deviations were similar across PM, PEOM, and the sham pooled groups (39.9%, 30.2%, and 35.8%, respectively). The most frequently seen study-specific major protocol deviation was missed visit or missed visit window (e.g., visit 10 outside 2-day window) in 17 subjects (8.0%), 17 subjects (8.0%), and 18 subjects (8.5%) in the PM, PEOM, and sham pooled groups, respectively.

Unmasking errors for subjects or masked site staff who became unmasked to treatment assignment were low (4 subjects [1.9%] in the PM group; 1 subject [0.5%] in the PEOM group; 6 subjects [2.8%] in the sham pooled group).

There were 82 subjects (12.9%) with major protocol deviations under the IP category (subcategory dispensing/accountability/IP dispensing error) in 31 subjects (14.6%), 26 subjects (12.3%), and 25 subjects (11.8%) in the PM, PEOM, and sham pooled groups, respectively. The majority of these deviations were related to subjects being dosed with IP that had undergone temperature excursions.

Protocol deviations categorised by the site as related to COVID-19 occurred in 450 subjects (70.6%). Missed IP dose intake occurred in 90 subjects (42.3%) in the PM group, 49 subjects (23.1%) in the PEOM group, 51 subjects (48.1%) in the SM group, and 36 subjects (34%) in the SEOM group. Overall, 331 subjects (52.0%) missed a visit or visit window, including 96 subjects (45.1%) in the PM group, 121 subjects (57.1%) in the PEOM group, and 114 subjects (53.8%) in the sham pooled group.

In both studies (APL2-303 and APL2-304), on 08 December 2021, Apellis determined that a potential serious breach of GCP had occurred as a result of subjects being dosed with investigational medicinal product that had experienced unacceptable temperature excursions. According to the Potential Serious Breach Notification, evaluation of subjects dosed with investigational medicinal product temperature excursions showed no impact on subject's safety or the scientific value of the trial. Deficiencies related to insufficient site training, study documentation (e.g., pharmacy manual) and site monitoring processes were addressed through appropriate corrective and preventive actions. The improvements made in site training, the improved pharmacy manual and monitoring processes as well as the process for evaluation of investigational medicinal product stability data, were implemented for the ongoing studies of pegcetacoplan in GA.

- **Recruitment**

Study APL2-303 DERBY

One hundred thirty-five study sites and investigators received IRB or IEC approval to participate in the study; however, subjects were enrolled at only 122 of these study sites (US, Argentina, Australia, Brazil, Canada, Czech Republic, France, Germany, Israel, Italy, New Zealand, Poland, Spain, and UK).

First Patient, First Visit: 31 August 2018

Last Patient, Last Visit: 20 June 2022

Database Lock: 18 July 2022

Study APL2-304 OAKS

One hundred fourteen study sites and investigators received IRB or IEC approval to participate in the study; however, subjects were enrolled at only 110 of these study sites (the US, Australia, Brazil, Czech Republic, France, Germany, Italy, Israel, Netherlands, New Zealand, Poland, Spain, and the UK).

First Patient, First Visit: 31 August 2018

Last Patient, Last Visit: 28 June 2022

Database Lock: 21 July 2022

Both studies (303 and 304) were temporarily paused in September 2018 after 2 subjects had events of intraocular inflammation in the study eye (study 303) and one subject had an SAE of severe acute endophthalmitis in the study eye (study 304). A thorough investigation concluded that these events were caused by an impurity in one starting material that had been introduced during the manufacturing process. The manufacturing process was modified to eliminate the impurity, and additional process controls were implemented to ensure its level remained below the limit of quantitation. Pegcetacoplan was then introduced in a small safety study (Study APL2-103) to evaluate the safety of new lots of drug product in subjects with low vision. Both studies restarted in March 2019.

- **Protocol Amendments**

Study APL2-303 DERBY

The original SAP (version 1.0) was approved on 23 July 2021, and one SAP amendment (version 2.0) was subsequently approved on 10 August 2021. The original protocol (dated 09 December 2017) was amended 5 times: Amendment 1, 31 May 2018; Amendment 2, 08 August 2018; Amendment 3, 14 February 2019; Amendment 4, 27 April 2020; Amendment 5, 12 August 2020. The database was locked for the month 12 analyses on 12 August 2021 and for final analysis (month 24) on 18 July 2022. The final report was released on 19 October 2022.

In addition, a protocol administrative clarification memorandum was sent to all investigators on 20 January 2022.

Study APL2-304 OAKS

The original SAP (version 1.0) was approved on 23 July 2021, and one SAP amendment (version 2.0) was subsequently approved on 10 August 2021.The original protocol (dated 18 April 2018) was amended 5 times: Amendment 1, 31 May 2018; Amendment 2, 08 August 2018; Amendment 3, 14 February 2019; Amendment 4, 27 April 2020; Amendment 5, 12 August 2020. The database was locked for the month 12 analyses on 18 August 2021 and for final analysis (month 24) on 21 July 2022. The final report was released on 24 October 2022. In addition, a protocol administrative clarification memorandum was sent to all investigators on 20 January 2022.

- **Baseline**

Key Demographics and Baseline Characteristics, both studies

Table 15: Key demographics and baseline characteristics of the PM, PEOM, and sham pooled groups of the study populations for study APL2-304, study APL2-303, and pooled data-mITT set

	Study APL2-304			Study APL2-303			Pooled data		
	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 207)**	**PM (N = 201)**	**PEOM (N = 201)**	**Sham Pooled (N = 195)**	**PM (N = 403)**	**PEOM (N = 406)**	**Sham pooled (N = 402)**
Age, years									
n	202	205	207	201	201	195	403	406	402
Mean (SD)	78.8 (7.24)	78.1 (7.74)	78.6 (7.25)	78.7 (6.91)	79.2 (7.08)	78.6 (7.28)	78.7 (7.07)	78.6 (7.43)	78.6 (7.26)
Minimum, maximum	61, 95	60, 100	60, 93	60, 93	61, 93	61, 96	60, 95	60, 100	60, 96
Sex									
Female, n (%)	125 (61.9)	117 (57.1)	133 (64.3)	118 (58.7)	120 (59.7)	123 (63.1)	243 (60.3)	237 (58.4)	256 (63.7)
Male, n (%)	77 (38.1)	88 (42.9)	74 (35.7)	83 (41.3)	81 (40.3)	72 (36.9)	160 (39.7)	169 (41.6)	146 (36.3)
Geographic Region									
US, n (%)	147 (72.8)	142 (69.3)	148 (71.5)	142 (70.6)	122 (60.7)	122 (62.6)	289 (71.7)	264 (65.0)	270 (67.2)
Rest of world, n (%)	55 (27.2)	63 (30.7)	59 (28.5)	59 (29.4)	79 (39.3)	73 (37.4)	114 (28.3)	142 (35.0)	132 (32.8)
Race									
White	185 (91.6)	189 (92.2)	188 (90.8)	187 (93.0)	186 (92.5)	188 (96.4)	372 (92.3)	375 (92.4)	376 (93.5)
Not reported	12 (5.9)	12 (5.9)	14 (6.8)	12 (6.0)	10 (5.0)	6 (3.1)	24 (6.0)	22 (5.4)	20 (5.0)
Asian	3 (1.5)	1 (0.5)	2 (1.0)	0	1 (0.5)	0	3 (0.7)	2 (0.5)	2 (0.5)
Unknown	0	3 (1.5)	3 (1.4)	1 (0.5)	2 (1.0)	1 (0.5)	1 (0.2)	5 (1.2)	4 (1.0)
Black or African American	2 (1.0)	0	0	1 (0.5)	1 (0.5)	0	3 (0.7)	1 (0.2)	0
American Indian or Alaska Native	0	0	0	0	0	0	0	0	0
Multiple	0	0	0	0	1 (0.5)	0	0	1 (0.2)	0
Study eye lesion size, mm^2									
n	202	205	207	201	201	195	403	406	402
Mean (SD)	8.1779 (3.89496)	8.2962 (3.90437)	8.2068 (3.71222)	8.3666 (4.18140)	8.2515 (3.89422)	8.2385 (4.26122)	8.2720 (4.03644)	8.2741 (3.89460)	8.2222 (3.98299)
Minimum, maximum	2.489, 18.111	2.652, 17.706	2.587, 17.771	2.264, 17.832	2.439, 17.151	2.599, 17.490	2.264, (18.111)	2.439, (17.706)	2.587, 17.771
Study eye GA lesion location									
Subfoveal involvement, n (%)	116 (57.4)	131 (63.9)	147 (71.0)	129 (64.2)	120 (59.7)	122 (62.6)	245 (60.8)	251 (61.8)	269 (66.9)
Without subfoveal involvement, n (%)	86 (42.6)	74 (36.1)	60 (29.0)	72 (35.8)	81 (40.3)	73 (37.4)	158 (39.2)	155 (38.2)	133 (33.1)
Study eye GA focality (FAF)									

Unifocal, n (%)	59 (29.2)	62 (30.2)	68 (32.9)	54 (26.9)	53 (26.4)	66 (33.8)	113 (28.0)	115 (28.3)	134 (33.3)
Multifocal, n (%)	143 (70.8)	143 (69.8)	139 (67.1)	147 (73.1)	148 (73.6)	129 (66.2)	290 (72.0)	291 (71.7)	268 (66.7)
Study eye NL-BCVA score, ETDRS letters									
n	202	205	207	201	201	195	403	406	402
Mean (SD)	61.0 (15.30)	58.2 (17.03)	57.6 (16.59)	59.5 (17.40)	58.7 (16.12)	59.0 (16.85)	60.2 (16.37)	58.4 (16.57)	58.3 (16.71)
Minimum, maximum	25, 86	24, 89	24, 87	24, 94	24, 93	23, 89	24, 94	24, 93	23, 89
Study eye LL-BCVA score, ETDRS letters									
n	201	204	207	199	199	192	400	403	399
Mean (SD)	34.2 (17.31)	32.4 (16.45)	32.8 (16.20)	32.2 (17.74)	33.1 (16.05)	33.6 (16.83)	33.2 (17.53)	32.7 (16.24)	33.1 (16.49)
Minimum, maximum	0, 76	0, 72	0, 72	0, 73	0, 78	0, 73	0, 76	0, 78	0, 73
Study eye LLD, ETDRS letters									
n	201	204	207	199	199	192	400	403	399
Mean (SD)	26.7 (16.77)	25.7 (17.58)	24.9 (17.38)	27.3 (17.71)	25.6 (16.41)	25.7 (16.50)	27.0 (17.23)	25.6 (16.99)	25.3 (16.95)
Minimum, maximum	-4, 66	−10, 76	−12, 71	−7, 77	−4, 73	-4, 71	-7, 77	-10, 76	-12, 71
Study eye number of intermediate or large drusen									
0-5	46 (22.8)	43 (21.0)	41 (19.8)	52 (25.9)	60 (29.9)	51 (26.2)	98 (24.3)	103 (25.4)	92 (22.9)
6-10	39 (19.3)	31 (15.1)	34 (16.4)	33 (16.4)	32 (15.9)	21 (10.8)	72 (17.9)	63 (15.5)	55 (13.7)
11-20	23 (11.4)	27 (13.2)	27 (13.0)	38 (18.9)	31 (15.4)	25 (12.8)	61 (15.1)	58 (14.3)	52 (12.9)
>20, n (%)	93 (46.0)	104 (50.7)	104 (50.2)	78 (38.8)	78 (38.8)	98 (50.3)	171 (42.4)	182 (44.8)	202 (50.2)
GA laterality, n (%)									
Bilateral GA[a]	167 (82.7)	174 (84.9)	166 (80.2)	164 (81.6)	161 (80.1)	150 (76.9)	331 (82.1)	335 (82.5)	316 (78.6)
Study eye GA only	35 (17.3)	31 (15.1)	41 (19.8)	37 (18.4)	40 (19.9)	45 (23.1)	72 (17.9)	71 (17.5)	86 (21.4)
Fellow eye lesion size[b], mm^2									
n	167	174	166	164	161	150	331	335	316
Mean (SD)	7.9042 (5.46708)	8.3894 (5.59548)	8.5905 (5.41596)	8.3053 (5.85332)	8.7276 (5.80670)	8.1338 (6.18185)	8.1030 (5.65671)	8.5519 (5.69192)	8.3737 (5.78734)

Minimum, maximum	0.121, 25.227	0.040, 28.057	0.138, 26.026	0.213, 26.416	0.195, 35.857	0.172, 28.487	0.121, 26.416	0.040, 35.857	0.138, 28.487
CNV status in the fellow eye[c]									
Present, n (%)	43 (21.3)	37 (18.0)	43 (21.3)	39 (19.4)	41 (20.4)	36 (18.5)	82 (20.3)	78 (19.2)	80 (19.9)
Absent, n (%)	159 (78.7)	168 (82.0)	163 (78.7)	162 (80.6)	160 (79.6)	159 (81.5)	321 (79.7)	328 (80.8)	322 (80.1)

Abbreviations: AMD = age-related macular degeneration; CNV = choroidal neovascularization; CRF = case report form; CSR = clinical study report; ETDRS = Early Treatment Diabetic Retinopathy Study; FAF = fundus autofluorescence; GA = geographic atrophy; LL-BCVA = low-luminance best-corrected visual acuity; LL-VA = low-luminance visual acuity; LLD = low-luminance deficit; mITT = modified intent-to-treat; NL-BCVA = normal-luminance best-corrected visual acuity; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

[a] For Studies APL2-303 and APL2-304 Fellow eye category percentages are based on the number of subjects with presence of GA lesion in fellow eye at baseline.

[b] For Studies APL2-303 and APL2-304 GA presence in the fellow eye was determined by reading center.

[c] For Studies APL2-303 and APL2-304 CNV presence in the fellow eye was determined by medical history.

Notes: For Studies APL2-303 and APL2-304, age (years) collected on the CRF was used. Because some countries do not allow the collection of race and ethnicity, there is a category of "not reported" to account for this. For Studies APL2-303 and APL2-304 CNV in medical history includes Preferred Term of choroidal neovascularization and neovascular AMD. CNV in medical history includes Preferred Terms of choroidal neovascularization and neovascular AMD.
For Study APL2-304, rest of world included Australia, Brazil, Czech Republic, France, Germany, Israel, Italy, the Netherlands, New Zealand, Poland, Spain, and UK.
For Study APL2-303, rest of world included Argentina, Australia, Brazil, Canada, Czech Republic, France, Germany, Israel, Italy, New Zealand, Poland, Spain, and UK. Fellow Eye category percentages are based on the number of subjects with presence of GA lesion in fellow eye at baseline.

Sources: Study APL2-304 Month 24 CSR, Table 14.1.4.2 and Table 14.1.5.2; Study APL2-303 Month 24 CSR, Table 14.1.4.2 and Table 14.1.5.2; Month 24 Integrated Summary of Efficacy Table 14.1.4.1 and Table 14.1.5.1.

Prior and concomitant ocular medications (study eye)

Study 303

Prior ocular medication

Table 16: Ocular prior medications in study eye reported in ≥2% of subjects by PT in any treatment group-ITT population

	PM (N =206) n (%)	PEOM (N = 208) n (%)	Pegcetacoplan pooled (N = 414) n (%)	SM (N = 102) n (%)	SEOM (N = 105) n (%)	Sham pooled (N = 207) n (%)	Total (N = 621) n (%)
Subjects with any ocular previous medications in study eye	108 (52.4)	110 (52.9)	218 (52.7)	56 (54.9)	56 (53.3)	112 (54.1)	330 (53.1)
ATC Class PT							
Ophthalmologicals	108 (52.4)	110 (52.9)	218 (52.7)	56 (54.9)	56 (53.3)	112 (54.1)	330 (53.1)
Ascorbic acid; betacarotene; cupric oxide; tocopheryl acetate; zinc oxide[a]	24 (11.7)	25 (12.0)	49 (11.8)	17 (16.7)	10 (9.5)	27 (13.0)	76 (12.2)
Ascorbic acid; tocopheryl acetate; xantofyl; zeaxanthin; zinc[a]	20 (9.7)	32 (15.4)	52 (12.6)	8 (7.8)	14 (13.3)	22 (10.6)	74 (11.9)
Ascorbic acid; cupric oxide; DL-α tocopheryl acetate; xantofyl; zeaxanthin; zinc oxide[a]	28 (13.6)	21 (10.1)	49 (11.8)	9 (8.8)	14 (13.3)	23 (11.1)	72 (11.6)
Artificial tears [umbrella term]	9 (4.4)	10 (4.8)	19 (4.6)	8 (7.8)	1 (1.0)	9 (4.3)	28 (4.5)
Macrogol 400; propylene glycol	6 (2.9)	12 (5.8)	18 (4.3)	4 (3.9)	1 (1.0)	5 (2.4)	23 (3.7)
Latanoprost	9 (4.4)	7 (3.4)	16 (3.9)	2 (2.0)	2 (1.9)	4 (1.9)	20 (3.2)
Ciclosporin	3 (1.5)	1 (0.5)	4 (1.0)	5 (4.9)	4 (3.8)	9 (4.3)	13 (2.1)

Abbreviations: ATC = Anatomical Therapeutic Chemical; ITT = intent-to-treat; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; PT = Preferred Term; SEOM = sham every other month; SM = sham monthly; VEGF = vascular endothelial growth factor.

[a] Ocular dietary supplement.

Notes: Prior medications were defined as those medications that started before the date of first study drug administration. Medications started before the date of first study drug administration but continuing after the date of first study drug administration were considered as both prior and concomitant medications. Medications were coded to ATC class (ATC Level 2) and PT using WHODrug-Global-B3 2021-03. Any concomitant medications received within 30 days prior to screening were to be reported. In addition, anti-VEGF treatments given within 5 years prior to screening were to be reported.

Concomitant ocular medication

Table 17: Ocular concomitant medications in study eye reported by ≥2% of subjects by PT in any treatment group-ITT population

	PM (N =206) n (%)	PEOM (N = 208) n (%)	Pegcetacoplan pooled (N = 414) n (%)	SM (N = 102) n (%)	SEOM (N = 105) n (%)	Sham pooled (N = 207) n (%)	Total (N = 621) n (%)
Subjects with any ocular concomitant medications in the study eye	147 (71.4)	140 (67.3)	287 (69.3)	68 (66.7)	73 (69.5)	141 (68.1)	428 (68.9)
ATC class PT							
Ophthalmologicals	146 (70.9)	140 (67.3)	286 (69.1)	68 (66.7)	73 (69.5)	141 (68.1)	427 (68.8)
Ascorbic acid; betacarotene; cupric oxide; tocopheryl acetate; zinc oxide[a]	29 (14.1)	28 (13.5)	57 (13.8)	22 (21.6)	13 (12.4)	35 (16.9)	92 (14.8)
Ascorbic acid; tocopheryl acetate; xantofyl; zeaxanthin; zinc[a]	22 (10.7)	41 (19.7)	63 (15.2)	8 (7.8)	18 (17.1)	26 (12.6)	89 (14.3)
Ascorbic acid; cupric oxide; dl-α tocopheryl acetate; xantofyl; zeaxanthin; zinc oxide[a]	29 (14.1)	24 (11.5)	53 (12.8)	11 (10.8)	14 (13.3)	25 (12.1)	78 (12.6)
Artificial tears [umbrella term]	17 (8.3)	19 (9.1)	36 (8.7)	14 (13.7)	7 (6.7)	21 (10.1)	57 (9.2)
Macrogol 400; propylene glycol	10 (4.9)	17 (8.2)	27 (6.5)	5 (4.9)	3 (2.9)	8 (3.9)	35 (5.6)
Latanoprost	10 (4.9)	15 (7.2)	25 (6.0)	3 (2.9)	2 (1.9)	5 (2.4)	30 (4.8)
Aflibercept	24 (11.7)	9 (4.3)	33 (8.0)	3 (2.9)	3 (2.9)	6 (2.9)	39 (6.3)
Hyaluronate sodium	5 (2.4)	1 (0.5)	6 (1.4)	5 (4.9)	5 (4.8)	10 (4.8)	16 (2.6)
Other ophthalmologicals	3 (1.5)	3 (1.4)	6 (1.4)	2 (2.0)	5 (4.8)	7 (3.4)	13 (2.1)
Xantofyl	6 (2.9)	1 (0.5)	7 (1.7)	2 (2.0)	4 (3.8)	6 (2.9)	13 (2.1)
Carmellose sodium	4 (1.9)	6 (2.9)	10 (2.4)	1 (1.0)	2 (1.9)	3 (1.4)	13 (2.1)
Ciclosporin	3 (1.5)	1 (0.5)	4 (1.0)	4 (3.9)	4 (3.8)	8 (3.9)	12 (1.9)
Zeaxanthin	4 (1.9)	1 (0.5)	5 (1.2)	6 (5.9)	1 (1.0)	7 (3.4)	12 (1.9)
Carmellose	4 (1.9)	1 (0.5)	5 (1.2)	1 (1.0)	2 (1.9)	3 (1.4)	8 (1.3)
Minerals NOS; vitamins NOS	4 (1.9)	1 (0.5)	5 (1.2)	2 (2.0)	1 (1.0)	3 (1.4)	8 (1.3)
Carmellose sodium; glycerol	2 (1.0)	3 (1.4)	5 (1.2)	2 (2.0)	0	2 (1.0)	7 (1.1)
Paraffin; wool fat	5 (2.4)	0	5 (1.2)	0	1 (1.0)	1 (0.5)	6 (1.0)
Tobramycin	2 (1.0)	2 (1.0)	4 (1.0)	2 (2.0)	0	2 (1.0)	6 (1.0)
Boric acid; sodium borate	0	1 (0.5)	1 (0.2)	2 (2.0)	0	2 (1.0)	3 (0.5)
Hyaluronate sodium; trehalose	0	0	0	1 (1.0)	1 (1.0)	2 (1.0)	2 (0.3)
Ascorbic acid; copper citrate; tocopheryl acetate; xantofyl; zeaxanthin; zinc oxide[a]	0	0	0	2 (2.0)	0	2 (1.0)	2 (0.3)

Abbreviations: ATC = Anatomical Therapeutic Chemical; ITT = intent-to-treat; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; PT = Preferred Term; SEOM = sham every other month; SM = sham monthly; VEGF = vascular endothelial growth factor.

[a] Ocular dietary supplement.

Notes: Prior medications were defined as those medications that started before the date of first study drug administration. Medications started before the date of first study drug administration but continuing after the date of first study drug administration were considered as both prior and concomitant medications. Medications were coded to ATC class (ATC Level 2) and PT using WHODrug-Global-B3 2021-03. Any concomitant medications received within 30 days prior to screening were to be reported. In addition, anti-VEGF treatments given within 5 years prior to screening were to be reported.

Study 304

Prior ocular medication

Table 18: Ocular prior medications in the study eye reported by ≥2% of subjects in any treatment group by PT-ITT population

	PM (N = 213) n (%)	**PEOM (N = 212) n (%)**	**Pegcetacoplan pooled (N = 425) n (%)**	**SM (N = 106) n (%)**	**SEOM (N = 106) n (%)**	**Sham pooled (N = 212) n (%)**	**Total (N = 637) n (%)**
Subjects with any ocular prior medications in the study eye	126 (59.2)	118 (55.7)	244 (57.4)	55 (51.9)	45 (42.5)	100 (47.2)	344 (54.0)
ATC class PT							
Ophthalmologicals	126 (59.2)	118 (55.7)	244 (57.4)	55 (51.9)	45 (42.5)	100 (47.2)	344 (54.0)
Ascorbic acid; betacarotene; cupric oxide; tocopheryl acetate; zinc oxide[a]	34 (16.0)	32 (15.1)	66 (15.5)	9 (8.5)	16 (15.1)	25 (11.8)	91 (14.3)
Ascorbic acid; cupric oxide; DL-alpha tocopheryl acetate; xantofyl; zeaxanthin; zinc oxide[a]	33 (15.5)	24 (11.3)	57 (13.4)	10 (9.4)	13 (12.3)	23 (10.8)	80 (12.6)
Ascorbic acid; tocopheryl acetate; xantofyl; zeaxanthin; zinc[a]	14 (6.6)	23 (10.8)	37 (8.7)	11 (10.4)	4 (3.8)	15 (7.1)	52 (8.2)
Other ophthalmologicals	13 (6.1)	9 (4.2)	22 (5.2)	6 (5.7)	7 (6.6)	13 (6.1)	35 (5.5)
Latanoprost	5 (2.3)	7 (3.3)	12 (2.8)	7 (6.6)	1 (0.9)	8 (3.8)	20 (3.1)
Macrogol 400; propylene glycol	5 (2.3)	7 (3.3)	12 (2.8)	3 (2.8)	4 (3.8)	7 (3.3)	19 (3.0)
Tropicamide	7 (3.3)	5 (2.4)	12 (2.8)	1 (0.9)	4 (3.8)	5 (2.4)	17 (2.7)
Artificial tears [umbrella term]	7 (3.3)	4 (1.9)	11 (2.6)	3 (2.8)	3 (2.8)	6 (2.8)	17 (2.7)
Zeaxanthin	6 (2.8)	5 (2.4)	11 (2.6)	1 (0.9)	2 (1.9)	3 (1.4)	14 (2.2)
Phenylephrine	7 (3.3)	4 (1.9)	11 (2.6)	0	2 (1.9)	2 (0.9)	13 (2.0)
Proxymetacaine	6 (2.8)	4 (1.9)	10 (2.4)	0	1 (0.9)	1 (0.5)	11 (1.7)
Carmellose sodium	4 (1.9)	2 (0.9)	6 (1.4)	4 (3.8)	1 (0.9)	5 (2.4)	11 (1.7)
Ciclosporin	5 (2.3)	2 (0.9)	7 (1.6)	1 (0.9)	1 (0.9)	2 (0.9)	9 (1.4)
Xantofyl; zeaxanthin	2 (0.9)	2 (0.9)	4 (0.9)	3 (2.8)	0	3 (1.4)	7 (1.1)
Ascorbic acid; copper gluconate; tocopheryl acid succinate; xantofyl; zeaxanthin; zinc oxide[a]	2 (0.9)	1 (0.5)	3 (0.7)	3 (2.8)	0	3 (1.4)	6 (0.9)
Ascorbic acid; cupric oxide; omega-3 fatty acids; tocopherol; xantofyl; zinc oxide[a]	0	0	0	5 (4.7)	0	5 (2.4)	5 (0.8)

Abbreviations: ATC = Anatomical Therapeutic Chemical; ITT = intent-to-treat; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; PT = Preferred Term; SEOM = sham every other month; SM = sham monthly; VEGF = vascular endothelial growth factor.

[a] Ocular dietary supplement.

Notes: Prior medications were defined as those medications that started before the date of first study drug administration. Medications started before the date of first study drug administration but continuing after the date of first study drug administration were considered as both prior and concomitant medications. Medications were coded to ATC class (ATC Level 2) and PT using WHODrug-Global-B3 2021-03. Any concomitant medications received within 30 days prior to screening were to be reported. In addition, anti-VEGF treatments given within 5 years prior to screening were to be reported.

Concomitant ocular medication

Table 19: Ocular concomitant medications in the study eye reported by≥2% of subjects in any treatment group by PT-ITT population

	PM (N = 213) n (%)	PEOM (N = 212) n (%)	Pegcetacoplan pooled (N = 425) n (%)	SM (N = 106) n (%)	SEOM (N = 106) n (%)	Sham pooled (N = 212) n (%)	Total (N = 637) n (%)
Subjects with any ocular concomitant medications in the study eye	169 (79.3)	159 (75.0)	328 (77.2)	69 (65.1)	68 (64.2)	137 (64.6)	465 (73.0)
ATC class PT							
Ophthalmologicals	169 (79.3)	159 (75.0)	328 (77.2)	69 (65.1)	68 (64.2)	137 (64.6)	465 (73.0)
Ascorbic acid; betacarotene; cupric oxide; tocopheryl acetate; zinc oxide[a]	37 (17.4)	39 (18.4)	76 (17.9)	13 (12.3)	19 (17.9)	32 (15.1)	108 (17.0)
Ascorbic acid; cupric oxide; DL-alpha tocopheryl acetate; xantofyl; zeaxanthin; zinc oxide[a]	38 (17.8)	30 (14.2)	68 (16.0)	11 (10.4)	16 (15.1)	27 (12.7)	95 (14.9)
Ascorbic acid; tocopheryl acetate; xantofyl; zeaxanthin; zinc[a]	16 (7.5)	26 (12.3)	42 (9.9)	12 (11.3)	4 (3.8)	16 (7.5)	58 (9.1)
Other ophthalmologicals	18 (8.5)	14 (6.6)	32 (7.5)	7 (6.6)	10 (9.4)	17 (8.0)	49 (7.7)
Latanoprost	7 (3.3)	12 (5.7)	19 (4.5)	7 (6.6)	5 (4.7)	12 (5.7)	31 (4.9)
Macrogol 400; propylene glycol	13 (6.1)	8 (3.8)	21 (4.9)	4 (3.8)	10 (9.4)	14 (6.6)	35 (5.5)
Artificial tears (umbrella term)	13 (6.1)	13 (6.1)	26 (6.1)	5 (4.7)	4 (3.8)	9 (4.2)	35 (5.5)
Carmellose sodium	9 (4.2)	6 (2.8)	15 (3.5)	6 (5.7)	2 (1.9)	8 (3.8)	23 (3.6)
Tropicamide	7 (3.3)	5 (2.4)	12 (2.8)	1 (0.9)	4 (3.8)	5 (2.4)	17 (2.7)
Aflibercept	18 (8.5)	11 (5.2)	29 (6.8)	1 (0.9)	1 (0.9)	2 (0.9)	31 (4.9)
Phenylephrine	9 (4.2)	5 (2.4)	14 (3.3)	0	2 (1.9)	2 (0.9)	16 (2.5)
Proxymetacaine	7 (3.3)	4 (1.9)	11 (2.6)	0	3 (2.8)	3 (1.4)	14 (2.2)
Zeaxanthin	6 (2.8)	6 (2.8)	12 (2.8)	1 (0.9)	2 (1.9)	3 (1.4)	15 (2.4)
Hyaluronate sodium	8 (3.8)	7 (3.3)	15 (3.5)	2 (1.9)	2 (1.9)	4 (1.9)	19 (3.0)
Levofloxacin	5 (2.3)	7 (3.3)	12 (2.8)	1 (0.9)	1 (0.9)	2 (0.9)	14 (2.2)
Ofloxacin	6 (2.8)	6 (2.8)	12 (2.8)	2 (1.9)	1 (0.9)	3 (1.4)	15 (2.4)
Timolol	7 (3.3)	5 (2.4)	12 (2.8)	4 (3.8)	0	4 (1.9)	16 (2.5)
Povidone-iodine	5 (2.3)	3 (1.4)	8 (1.9)	1 (0.9)	3 (2.8)	4 (1.9)	12 (1.9)
Ranibizumab	9 (4.2)	7 (3.3)	16 (3.8)	1 (0.9)	0	1 (0.5)	17 (2.7)
Ciclosporin	5 (2.3)	2 (0.9)	7 (1.6)	1 (0.9)	1 (0.9)	2 (0.9)	9 (1.4)
Ascorbic acid; copper gluconate; tocopheryl acid succinate; xantofyl; zeaxanthin; zinc oxide[a]	2 (0.9)	1 (0.5)	3 (0.7)	3 (2.8)	1 (0.9)	4 (1.9)	7 (1.1)
Olopatadine hydrochloride	7 (3.3)	0	7 (1.6)	0	0	0	7 (1.1)

Abbreviations: ATC = Anatomical Therapeutic Chemical; ITT = intent-to-treat; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; PT = Preferred Term; SEOM = sham every other month; SM = sham monthly.

[a] Ocular dietary supplement.

Notes: Concomitant medications were defined as those medications taken on or after the date of first study drug administration. Medications started before the date of first study drug administration but continuing after the date of first study drug administration were considered as both prior and concomitant medications. Medications were coded to ATC class (ATC Level 2) and PT using WHODrug-Global-B3 2021-03. Any concomitant medications received within 30 days prior to screening were to be reported. In addition, anti-VEGF treatments given within 5 years prior to screening were to be reported.

- **Treatment compliance**

Table 20: Exposure for the PM, PEOM, and sham pooled groups of the study populations at month 24 for study APL2-304, study APL2-303, and pooled data-mITT population

	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 207)**	**PM (N = 201)**	**PEOM (N = 201)**	**Sham pooled (N = 195)**	**PM (N = 403)**	**PEOM (N = 406)**	**Sham pooled (N = 402)**
Number of injections									
Mean (SD)	18.9 (6.08)	10.2 (2.92)	14.4 (6.50)	18.7 (6.09)	10.0 (2.80)	14.7 (6.46)	18.8 (6.08)	10.1 (2.86)	14.5 (6.47)
Median	21.0	11.0	12.0	22.0	11.0	12.0	22.0	11.0	12.0
Min, max	2, 24	1, 12	0, 24	1, 24	1, 12	1, 24	1, 24	1, 12	0, 24
Duration of treatment (days)									
Mean (SD)	620.6 (185.04)	644.0 (174.78)	634.8 (176.04)	615.9 (183.20)	648.2 (161.42)	649.9 (170.83)	618.2 (183.91)	646.1 (168.10)	642.1 (173.48)
Median	717.0	719.0	717.0	717.0	719.0	719.0	717.0	719.0	719.0
Min, max	91, 735	37, 736	59, 740	31, 735	61, 736	30, 736	31, 735	37, 736	30, 740
Number of subjects with ≥75% of planned injections									
n (%)	153 (75.7)	173 (84.4)	161 (77.8)	142 (70.6)	162 (80.6)	155 (79.5)	295 (73.2)	335 (82.5)	316 (78.6)
Number of subjects with <75% of planned injections									
n (%)	49 (24.3)	32 (15.6)	46 (22.2)	59 (29.4)	39 (19.4)	40 (20.5)	108 (26.8)	71 (17.5)	86 (21.4)

Abbreviations: CSR = clinical study report; mITT = modified intent-to-treat; n = number of evaluable subjects; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Note: Number of injections means number of injections in accordance with the schedule and treatment group allocation.

- **Numbers analysed**

Study APL2-303 DERBY

The analysis populations comprised:

- 1409 subjects for the screened population (this includes 73 subjects who were screened twice)
- 621 subjects for the ITT population
- 597 subjects for the mITT population
- 469 subjects for the month 12 PP population
- 463 subjects for the month 24 PP population
- 620 subjects for the safety population
- 101 subjects for the PK population
- 101 subjects for the PD population
- 303 subjects for the genotyping population

Six hundred twenty-one subjects were assigned to treatment; 206 subjects in the PM group, 208 subjects in the PEOM group, and 207 subjects in the sham pooled group composed the ITT population. Of the subjects in the ITT population, 597 subjects (PM: 201, PEOM: 201, and sham pooled: 195) were included in the mITT population, the analysis population used for the efficacy analyses. Reasons for exclusion of the mITT set were mostly due to 'No post-baseline value of GA lesion area in the study eye' Reasons for exclusion from the 24 per-protocol-set were mostly related to 'Subject had no valid GA lesion area assessment for at least one of Month 18, 20, 22, 24'.

Study APL2-304 OAKS

The analysis populations comprised:

- 1364 subjects for the screened population (this includes 39 subjects who were screened twice)
- 637 subjects (i.e., all subjects assigned to treatment) for the ITT population
- 614 subjects for the mITT population
- 503 subjects for the month 12 PP population
- 482 subjects for the month 24 PP population
- 636 subjects for the safety population
- 344 subjects for the genotyping population

Six hundred thirty-seven subjects were assigned to treatment; 213 subjects in the PM group, 212 subjects in the PEOM group, and 212 subjects in the sham pooled group composed the intent-to-treat (ITT) population. Of the subjects in the ITT population, 614 subjects (PM: 202, PEOM: 205, and sham pooled: 207) were included in the modified intent-to-treat (mITT) population, the population used for the efficacy analyses. Reasons for exclusion of the mITT set were mostly due to 'No post-baseline value of GA lesion area in the study eye'. Reasons for exclusion from the 24 per-protocol-set were mostly related to 'Subject had no valid GA lesion area assessment for at least one of Month 18, 20, 22, 24'.

- **Outcomes and estimation**

Primary efficacy endpoint

Study APL2-303 DERBY and Study APL2-304 OAKS

<u>*Month 12*</u>

Change from baseline in total area of GA lesions (mm^2) at month 12

Table 21: Analysis of CFB in total area of GA lesion(s) (mm²) (FAF) of the study eye with MMRM model at month 12 in study APL2-304, study APL2-303, and pooled data-mITT population

	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 206)**	**PM (N = 201)**	**PEOM (N = 201)**	**Sham pooled (N = 195)**	**PM (N = 403)**	**PEOM (N = 406)**	**Sham pooled (N = 402)**
Number of subjects included in the model	202	204	205	200	199	193	402	403	398
LS mean (SE) CFB of GA lesion area, mm^2	1.5579 (0.08350)	1.6512 (0.08118)	1.9692 (0.08218)	1.7344 (0.07924)	1.7563 (0.07446)	1.9640 (0.09592)	1.6443 (0.05773)	1.7011 (0.05505)	1.9672 (0.06308)
95% CI of LS mean CFB of GA lesion area, mm^2	1.3939-1.7219	1.4918-1.8107	1.8079-2.1306	1.5788-1.8900	1.6101-1.9026	1.7756-2.1524	1.5311-1.7576	1.5931-1.8091	1.8434-2.0909
Difference in LS mean (95% CI) CFB of GA lesion area vs sham pooled group, mm^2	−0.4114 (−0.6397 to −0.1831)	−0.3180 (−0.5423 to −0.0937)	NA	−0.2296 (−0.4703 to 0.0111)	−0.2077 (−0.4444 to 0.0290)	NA	−0.3228 (−0.4887 to −0.1570)	−0.2660 (−0.4286 to −0.1034)	NA
Percentage difference in LS mean CFB of GA lesion area vs sham pooled group	−20.9	−16.1	NA	−11.7	−10.6	NA	−16.4	−13.5	NA
P value vs sham pooled group	.0004	.0055	NA	.0615	.0854	NA	.0001	.0014	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effects model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to the first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. For Studies APL2-304 and APL2-303, the model included treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) × analysis visit. The model for pooled data also included Study as a covariate.

Table 22: Sensitivity analysis: change from baseline in total area of GA lesion(s) (FAF) (mm²) of the study eye without pooling two sham groups at month 12- mITT population

	Study APL2-304				**Study APL2-303**				**Pooled data**			
	PM (N =202)	**PEOM (N =205)**	**SM (N =105)**	**SEOM (N =102)**	**PM (N =201)**	**PEOM (N =201)**	**SM (N =97)**	**SEOM (N =98)**	**PM (N =403)**	**PEOM (N =406)**	**SM (N =202)**	**SEOM (N =200)**
Number of subjects included in the model	202	204	103	102	200	199	97	96	402	403	200	198
LS mean (SE) CFB of GA lesion area, mm^2	1.5578 (0.08350)	1.6514 (0.08115)	1.8528 (0.09550)	2.0810 (0.13069)	1.7350 (0.07925)	1.7570 (0.07445)	1.8547 (0.13398)	2.0632 (0.13583)	1.6443 (0.05774)	1.7011 (0.05504)	1.8540 (0.08113)	2.0729 (0.09444)
95% CI of LS mean CFB of GA lesion area, mm^2	1.3938-1.7218	1.4920-1.8108	1.6652-2.0403	1.8243-2.3376	1.5793-1.8906	1.6108-1.9032	1.5916-2.1178	1.7964-2.3300	1.5310-1.7576	1.5932-1.8091	1.6948-2.0132	1.8876-2.2581
Difference in LS mean (95% CI) CFB of GA lesion area (PM vs SM), mm^2	−0.2950 (−0.5424 to −0.0475)	NA	NA	NA	−0.1197 (−0.4208 to 0.1814)	NA	NA	NA	−0.2097 (−0.4029 to −0.0165)	NA	NA	NA
Percentage difference in LS mean CFB of GA lesion area vs SM	−15.9	NA	NA	NA	−6.5	NA	NA	NA	−11.3	NA	NA	NA
P value vs SM	.0196	NA	NA	NA	.4352	NA	NA	NA	.0334	NA	NA	NA
Difference in LS mean (95% CI) CFB of GA lesion area (PEOM vs SEOM), mm^2	NA	−0.4296 (−0.7289 to −0.1302)	NA	NA	NA	−0.3062 (−0.6105 to −0.0020)	NA	NA	NA	−0.3717 (−0.5851 to −0.1583)	NA	NA
Percentage difference in LS mean CFB of GA lesion area vs SEOM	NA	−20.6	NA	NA	NA	−14.8	NA	NA	NA	−17.9	NA	NA
P value vs SEOM	NA	.0050	NA	NA	NA	.0485	NA	NA	NA	.0007	NA	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; GA = geographic atrophy; LS mean = least-square mean; mITT = modified intent-to-treat; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SEOM = sham every other month; SM = sham monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Percentage difference is derived as the difference in LS means between the groups divided by the comparison group LS means. For Studies APL2-303 and APL2-304, model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion area × analysis visit. The model for pooled data also included study as a covariate

Sources: Study APL2-304 Month 24 CSR, Table 14.2.1.2.3; Study APL2-303 Month 24 CSR, Table 14.2.1.2.3; Month 24 Integrated Summary of Efficacy Table 14.2.1.2.3.

Rate of CFB in Study Eye GA Lesion Area

Two prespecified rate of change analyses using MMRM were performed using the final month 12 data from Studies APL2-304 and APL2-303. These include

- a model assuming a linear trend over time
- a model assuming a piecewise linear trend with a knot at month 6, which allows the slopes over the first 6 months to differ from the slopes over the second 6 months

Table 23: Analysis of CFB in total area of GA lesion(s) (FAF) (mm²) of the study eye with MMRM model at month 12 assuming in linear trend in time in study APL2—304, study APL2-303, and pooled data-mITT population

	Study APL2-304			Study APL2-303			Pooled data		
	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 207)	PM (N = 201)	PEOM (N = 201)	Sham pooled (N = 195)	PM (N = 403)	PEOM (N = 406)	Sham pooled (N = 402)
Number of subjects included in the model	202	205	207	201	201	195	403	406	402
Slope (SE) of GA lesion area growth, mm^2/12 months	1.5610 (0.08028)	1.6561 (0.07609)	1.9673 (0.07975)	1.7633 (0.07632)	1.7523 (0.07369)	1.9590 (0.09051)	1.6666 (0.05620)	1.7108 (0.05317)	1.9620 (0.06064)
95% CI of slope of GA lesion area growth, mm^2/12 months	1.4033-1.7186	1.5067-1.8056	1.8107-2.1240	1.6134-1.9132	1.6075-1.8970	1.7813-2.1368	1.5564-1.7769	1.6064-1.8151	1.8430-2.0809
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm^2/12 months	−0.4063 (−0.6284 to −0.1843)	−0.3112 (−0.5284 to −0.0941)	NA	−0.1957 (−0.4284 to 0.0370)	−0.2068 (−0.4359 to 0.0224)	NA	-0.2953 (−0.4576 to −0.1330)	-0.2512 (−0.4096 to −0.0928)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	−20.7	−15.8	NA	−10.0	−10.6	NA	−15.1	−12.8	NA
P value vs sham pooled group	.0004	.0050	NA	.0991	.0769	NA	.0004	.0019	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; mITT = modified intent-to-treat; MMRM = mixed-effects model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to the first study drug administration. For Studies APL2-303 and APL2-304, the model included treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + time (continuous) + baseline presence of CNV in the fellow eye (yes or no) + time (continuous) × treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) × time (continuous). The model for pooled data also included study as a covariate.

Table 24: Analyses of CFB in total area of GA lesion(s) (FAF) (mm²) of the study eye through month 12 with MMRM model assuming a piecewise linear trend in time with a knot at month 6 in study APL2-304, study APL2-303, and pooled data-mITT population

	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 207)**	**PM (N = 201)**	**PEOM (N = 201)**	**Sham pooled (N = 195)**	**PM (N = 403)**	**PEOM (N = 406)**	**Sham pooled (N = 402)**
Number of subjects included in the model	202	205	207	201	201	195	403	406	402
Estimates for baseline to Month 6									
Slope (SE) of GA lesion area growth, mm^2/6 months	0.7732 (0.04558)	0.8209 (0.04350)	0.9790 (0.04619)	0.8979 (0.04772)	0.8859 (0.04489)	0.9466 (0.04799)	0.8376 (0.03302)	0.8555 (0.03152)	0.9630 (0.03353)
95% CI of slope of GA lesion area growth, mm^2/6 months	0.6837-0.8627	0.7354-0.9063	0.8883-1.0698	0.8042-0.9916	0.7977-0.9741	0.8523-1.0408	0.7728-0.9024	0.7937-0.9174	0.8972-1.0288
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm^2/6 months	−0.2058 (−0.3332 to −0.0785)	−0.1582 (−0.2834 to −0.0329)	NA	−0.0487 (−0.1818 to 0.0845)	−0.0607 (−0.1898 to 0.0685)	NA	−0.1254 (−0.2178 to −0.0330)	−0.1075 (−0.1979 to −0.0170)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	−21.0	−16.2	NA	−5.1	−6.4	NA	−13.0	−11.2	NA
P value vs sham pooled group	0.0016	0.0134	NA	.4732	.3567	NA	0.0079	0.0200	NA
Estimates for Month 6 to Month 12									
Slope (SE) of GA lesion area growth (mm^2/6 months)	0.7925 (0.05686)	0.8392 (0.05403)	0.9910 (0.04909)	0.8561 (0.05141)	0.8626 (0.05041)	1.0286 (0.05966)	0.8258 (0.03903)	0.8550 (0.03685)	1.0090 (0.03885)

95% CI of slope of GA lesion area growth, mm^2/6 months	0.6808-0.9042	0.7331-0.9453	0.8946-1.0874	0.7551-0.9571	0.7636-0.9616	0.9114-1.1457	0.7493-0.9024	0.7827-0.9273	0.9328-1.0852
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm^2/6 months	−0.1985 (−0.3459 to −0.0510)	−0.1517 (−0.2952 to −0.0083)	NA	−0.1724 (−0.3273 to −0.0176)	−0.1660 (−0.3195 to −0.0125)	NA	−0.1832 (−0.2912 to −0.0751)	−0.1540 (−0.2592 to −0.0489)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	−20.0	−15.3	NA	−16.8	−16.1	NA	−18.2	−15.3	NA
P value vs sham pooled group	0.0084	0.0382	NA	.0291	.0341	NA	0.0009	0.0041	NA
Estimates for baseline to Month 12									
Average slope (SE) of GA lesion area growth, mm^2/12 months[a]	1.5657 (0.08236)	1.6601 (0.07785)	1.9700 (0.07965)	1.7540 (0.07620)	1.7485 (0.07414)	1.9751 (0.09258)	1.6635 (0.05704)	1.7105 (0.05383)	1.9720 (0.06147)
95% CI of slope of GA lesion area growth, mm^2/12 months	1.4040-1.7274	1.5072-1.8130	1.8136-2.1264	1.6043-1.9037	1.6029-1.8941	1.7933-2.1569	1.5516-1.7754	1.6049-1.8162	1.8514-2.0926
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm^2/12 months	−0.4043 (−0.6292 to −0.1794)	−0.3099 (−0.5292 to −0.0906)	NA	−0.2211 (−0.4567 to 0.0145)	−0.2266 (−0.4595 to 0.0062)	NA	−0.3086 (−0.4732 to −0.1440)	−0.2615 (−0.4219 to −0.1010)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	−20.5	−15.7	NA	−11.2	−11.5	NA	−15.6	−13.3	NA
P value vs sham pooled group	.0004	.0057	NA	.0658	.0564	NA	.0002	.0014	NA

Abbreviations: CFB = change from baseline; CNV = choroidal vascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; mITT = modified intent-to-treat; MMRM = mixed-effects model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

[a] Slope (SE) for baseline to Month 12 is an average of slope of baseline to Month 6 and Month 6 to Month 12 over the 12 months.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. For Studies APL2-303 and APL2-304, the model included treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + time (continuous) + time spline at month 6 (continuous) + baseline presence of CNV in the fellow eye (yes or no) + time (continuous) × treatment + time spline at month 6 (continuous) × treatment + baseline GA lesion area × time (continuous) + baseline GA lesion area × time spline at month 6 (continuous). The model for pooled data also included study as a covariate.

Prespecified exploratory endpoint comparing GA growth rate between study and fellow eyes in subjects with bilateral GA

Subjects who met the following key study eye criteria in the fellow eye were included:

- presence of GA
- GA lesion size between 2.5 and 17.5 mm2
- absence of CNV in the medical history
- presence of any pattern of hyperautofluorescence in the junctional zone of GA
- GA not confluent with any peripapillary atrophy

Table 25: Analysis of difference in CFB in GA lesion area (mm²) (FAF) for the study eye and fellow eye in subjects with bilateral GA at month 12 in study APL2-304, study APL2-303, and pooled data-mITT population

	Study APL2-304			**Study APL2-303**			**Pooled data**		
Statistic	**PM (N = 167)**	**PEOM (N = 174)**	**Sham pooled (N = 166)**	**PM (N = 164)**	**PEOM (N = 161)**	**Sham pooled (N = 150)**	**PM (N = 331)**	**PEOM (N = 335)**	**Sham pooled (N = 316)**
Number of subjects included in the model	91	106	109	86	105	86	177	211	195
LS mean (SE) CFB in GA lesion area in study eye, mm^2	1.6280 (0.09236)	1.7633 (0.11350)	2.0049 (0.11142)	1.8829 (0.12124)	1.7332 (0.10748)	2.0520 (0.10924)	1.7470 (0.07439)	1.7534 (0.07885)	2.0246 (0.07900)
LS mean (SE) CFB GA lesion area in fellow eye, mm^2	1.9701 (0.09772)	1.8813 (0.09411)	1.8721 (0.10932)	2.1888 (0.13090)	2.0719 (0.10764)	2.0496 (0.12829)	2.0701 (0.08086)	1.9815 (0.07127)	1.9498 (0.08315)
LS mean (SE) difference in CFB in GA lesion area between study eye and fellow eye, mm^2	−0.3421 (0.09964)	−0.1180 (0.09787)	0.1329 (0.08766)	−0.3059 (0.09182)	−0.3386 (0.08931)	0.0024 (0.11101)	−0.3230 (0.06801)	−0.2281 (0.06678)	0.0748 (0.06938)
Percentage difference in CFB in GA lesion area between study eye and fellow eye	−17.4	−6.3	7.1	−14.0	−16.3	0.1	−15.6	−11.5	3.8
P value	.0007	.2295	.1310	.0010	.0002	.9829	<.0001	.0007	.2815
LS mean (SE) CFB in GA lesion area sham-adjusted difference between study eye and fellow eye, mm^2	−0.4750 (0.13269)	-0.2508 (0.13144)	NA	−0.3083 (0.14411)	−0.3410 (0.14235)	NA	−0.3979 (0.09716)	−0.3030 (0.09630)	NA
95% CI of LS mean CFB in GA lesion area sham-adjusted difference between study and fellow eye, mm^2	−0.7365 to −0.2134	−0.5099 to 0.0083	NA	−0.5925 to −0.0241	−0.6217 to −0.0603	NA	−0.5888 to −0.2069	−0.4923 to −0.1137	NA
Sham-adjusted percentage difference in CFB in GA lesion area between study and fellow eye	−24.1	−13.3	NA	−14.1%	−16.5%	NA	−19.2	−15.3	NA
P value	.0004	.0577	NA	.0337	.0175	NA	.0001	.0018	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to the first study drug administration. Percentage difference is derived as the difference in LS means of the CFB in the fellow eye and study eye within a treatment group divided by the CFB in the fellow eye. Sham-adjusted percentage difference was derived as the difference in LS means of the CFB between the study eye and fellow eye within the pegcetacoplan treatment group minus the difference in LS means of the CFB between the study eye and fellow eye within the sham pooled treatment group divided by the CFB in the fellow eye within the pegcetacoplan treatment group. Derived from an MMRM model with the difference in the CFB in the fellow eye and study eye as the outcome that included treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + analysis visit + analysis visit × treatment + baseline GA lesion area × analysis visit + the difference between the study eye and fellow eye lesion areas at baseline + the difference between the study eye + fellow eye lesion areas at baseline × analysis visit + eye + treatment × eye + analysis visit × eye + analysis visit × treatment × eye. The model for pooled data also included study as a covariate. This analysis included subjects with bilateral GA with fellow eyes that satisfied the following characteristics at baseline: absence of CNV in the medical history, baseline GA lesion size between 2.5 mm^2 and 17.5 mm^2, presence of any pattern of hyperautofluorescence in the junctional zone of GA, and GA not confluent with any peripapillary atrophy.

Month 24

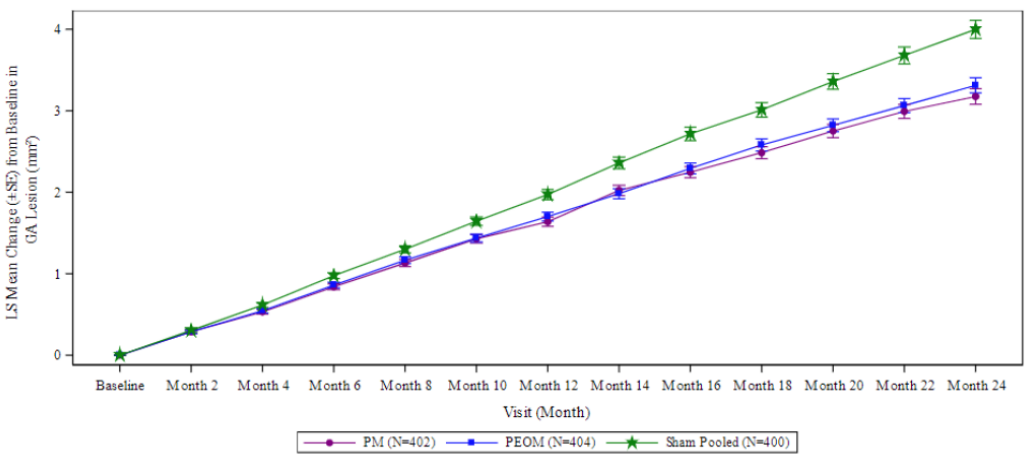
Table 26: Analysis of CFB in total area of GA lesion(s) (mm²) (FAF) of the study eye with MMRM model at month 24 in study APL2-304, study APL2-303, and pooled data-mITT population

	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 207)**	**PM (N = 201)**	**PEOM (N = 201)**	**Sham pooled (N = 195)**	**PM (N = 403)**	**PEOM (N = 406)**	**Sham pooled (N = 402)**
Number of subjects included in the model	202	204	206	200	200	194	402	404	400
LS mean (SE) CFB of GA lesion area, mm^2	3.1237 (0.14327)	3.2826 (0.13238)	4.0252 (0.14642)	3.2275 (0.12457)	3.3395 (0.13034)	3.9726 (0.16820)	3.1750 (0.09534)	3.3118 (0.09294)	3.9986 (0.11118)
95% CI of LS mean CFB of GA lesion area, mm^2	2.8423-3.4051	3.0226-3.5426	3.7376-4.3127	2.9828-3.4721	3.0835-3.5955	3.6422-4.3029	2.9879-3.3621	3.1294-3.4941	3.7805-4.2167
Difference in LS mean (95% CI) CFB of GA lesion area vs sham pooled group, mm^2	−0.9015 (−1.3026 to −0.5004)	−0.7426 (−1.1282 to −0.3570)	NA	−0.7451 (−1.1539 to −0.3362)	−0.6331 (−1.0508 to −0.2153)	NA	−0.8236 (−1.1097 to −0.5375)	−0.6868 (−0.9702 to −0.4035)	NA
Percentage difference in LS mean CFB of GA lesion area vs sham pooled group	−22.4	−18.4	NA	−18.8	−15.9	NA	−20.6	−17.2	NA
P value vs sham pooled group	<.0001	.0002	NA	.0004	.0030	NA	<.0001	<.0001	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effects model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to the first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. For Studies APL2-304 and APL2-303, the model included treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion area × analysis visit. The model for pooled data also included study as a covariate.

LS Mean (± SE) Plot of Change from Baseline in Total Area of GA Lesion(s) (mm²) (FAF) of the Study Eye by Visit and Treatment Group from MMRM Model
mITT Set
Baseline through Month 24



SE = Standard Error.
Note: Baseline is defined as the last available, non-missing observation prior to first study drug administration.
Note: Model includes Study (APL2-303, APL2-304) + Treatment + Baseline GA lesion area (< 7.5 mm^2 or >= 7.5 mm^2) + Analysis Visit + Baseline Presence of CNV in the fellow eye (Yes or No) + Analysis Visit x Treatment + Baseline GA lesion area (< 7.5 mm^2 or >= 7.5 mm^2) x Analysis Visit .

Abbreviations: CNV = choroidal neovascularization; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least square; mITT = modified intent-to-treat; MMRM = mixed-effects model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Source: Month 24 Integrated Summary of Efficacy Figure 14.2.1.1.3.

Figure 13: LS mean (±SE) plot of change from baseline to month 24 in total area of GA lesion(s) (mm²) (FAF) of the study eye by visit and treatment group from MMRM model-mITT population-pooled data

Table 27: Sensitivity analysis: change from baseline in total AREA of GA lesion(s) (FAF) (mm²) of the study eye without pooling sham groups at month 24 in study APL2-304, study APL2-303, and pooled data-mITT population

	Study APL2-304				**Study APL2-303**				**Pooled data**			
	PM (N = 202)	**PEOM (N = 205)**	**SM (N = 105)**	**SEOM (N = 102)**	**PM (N = 201)**	**PEOM (N = 201)**	**SM (N = 97)**	**SEOM (N = 98)**	**PM (N = 403)**	**PEOM (N = 406)**	**SM (N = 202)**	**SEOM (N = 200)**
Number of subjects included in the model	202	204	104	102	200	200	97	97	402	404	201	199
LS mean (SE) CFB of GA lesion area, mm^2	3.1237 (0.14326)	3.2830 (0.13237)	3.8631 (0.17823)	4.1813 (0.22988)	3.2285 (0.12458)	3.3399 (0.13029)	3.6251 (0.22262)	4.3029 (0.24577)	3.1750 (0.09535)	3.3118 (0.09293)	3.7455 (0.14232)	4.2393 (0.16766)
95% CI of LS mean CFB of GA lesion area, mm^2	2.8423-3.4050	3.0230-3.5429	3.5131-4.2132	3.7298-4.6328	2.9838-3.4732	3.0841-3.5958	3.1879-4.0623	3.8202-4.7856	2.9879-3.3620	3.1295-3.4941	3.4662-4.0247	3.9104-4.5682
Difference in LS mean (95% CI) CFB of GA lesion area (PM vs SM), mm^2	−0.7395 (−1.1864 to −0.2925)	NA	NA	NA	−0.3966 (−0.8944 to 0.1013)	NA	NA	NA	−0.5705 (−0.9050 to −0.2360)	NA	NA	NA
Percentage difference in LS mean CFB of GA lesion area vs SM	−19.1	NA	NA	NA	−10.9	NA	NA	NA	−15.2	NA	NA	NA
P value vs SM	.0012	NA	NA	NA	.1182	NA	NA	NA	.0008	NA	NA	NA
Difference in LS mean (95% CI) CFB of GA lesion area (PEOM vs SEOM), mm^2	NA	−0.8983 (−1.4168 to −0.3799)	NA	NA	NA	−0.9630 (−1.5101 to −0.4159)	NA	NA	NA	-0.9275 (−1.3029 to −0.5520)	NA	NA
Percentage difference in LS mean CFB of GA lesion area vs SEOM	NA	−21.5	NA	NA	NA	−22.4	NA	NA	NA	−21.9	NA	NA
P value vs SEOM	NA	.0007	NA	NA	NA	.0006	NA	NA	NA	<.0001	NA	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; GA = geographic atrophy; LS mean = least-square mean; mITT = modified intent-to-treat; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SEOM = sham every other month; SM = sham monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Percentage difference is derived as the difference in LS means between the groups divided by the comparison group LS means. For Studies APL2-304 and APL2-303, model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion area × analysis visit. The model for pooled data also included study as a covariate.

Rate of CFB in Study Eye GA Lesion Area

Two rate of change analyses using MMRM were performed using the month 24 data from Studies APL2-304 and APL2-303. These include

- a prespecified model assuming a linear trend over time
- a post hoc model assuming a piecewise linear trend with a knots at month 6, month

12, and month 18, which allows the slope of lesion growth to differ across the four 6-month intervals

Table 28: Analysis of CFB in total area of GA lesion(s) (FAF) (mm²) of the study eye with MMRM model at month 24 assuming a linear trend in time in study APL2-304, study APL2-303, and pooled data-mITT population

	Study APL2-304			Study APL2-303			Pooled data		
	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 207)	PM (N = 201)	PEOM (N = 201)	Sham pooled (N = 195)	PM (N =403)	PEOM (N =406)	Sham pooled (N = 402)
Number of subjects included in the model	202	205	207	200	200	195	403	406	402
Slope (SE) of GA lesion area growth, mm^2/24 months	3.1038 (0.14518)	3.2830 (0.13594)	3.9669 (0.14354)	3.3637 (0.12547)	3.3588 (0.12839)	3.9923 (0.16868)	3.2002 (0.09268)	3.3166 (0.09171)	3.9987 (0.10875)
95% CI of slope of GA lesion area growth, mm^2/24 months	2.8192-3.3884	3.0165-3.5495	3.6855-4.2483	3.1177-3.6097	3.1071-3.6105	3.6616-4.3229	3.0184-3.3821	3.1366-3.4965	3.7853-4.2120
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm^2/24 months	−0.8630 (−1.2631 to −0.4630)	−0.6839 (−1.0719 to −0.2958)	NA	−0.6285 (−1.0408 to −0.2163)	−0.6335 (−1.0492 to −0.2178)	NA	−0.7984 (−1.0788 to −0.5181)	−0.6821 (−0.9614 to −0.4028)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	−21.8	−17.2	NA	−15.7	−15.9	NA	−20.0	−17.1	NA
P value vs sham pooled group	<.0001	.0006	NA	.0028	.0028	NA	<.0001	<.0001	NA

Abbreviations: CFB = change from baseline; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; mITT = modified intent-to-treat; MMRM = mixed-effects model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to the first study drug administration. Percentage difference is derived as the difference in slopes between the arms divided by the comparison group slopes. For Studies APL2-304 and APL2-303, the model included treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline presence of CNV in the fellow eye (yes or no) + time (continuous) × treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) × time (continuous). The model for pooled data also included study as a covariate.

Table 29: Analysis of CFB in total area of GA lesion(s) (FAF) (mm²) of the study eye through month 24 with MMRM model assuming a piecewise linear trend in time with knots at month 6, month 12, and month 18 in study APL2-304, study APL2-303, and pooled data-mITT population

	Study APL2-304			Study APL2-303			Pooled data		
	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 207)	PM (N = 201)	PEOM (N = 201)	Sham pooled (N = 195)	PM (N = 403)	PEOM (N = 406)	Sham pooled (N = 402)
Number of subjects included in the model	202	205	207	201	201	195	403	406	402
Estimates for baseline to month 6									
Slope (SE) of GA lesion area growth, mm^2/6 months	0.7604 (0.04629)	0.8220 (0.04346)	0.9838 (0.04666)	0.9075 (0.04755)	0.8829 (0.04660)	0.9622 (0.04983)	0.8369 (0.03287)	0.8533 (0.03164)	0.9666 (0.03343)
95% CI of slope of GA lesion area growth, mm^2/6 months	0.6697-0.8512	0.7368-0.9072	0.8923-1.0753	0.8143-1.0007	0.7916-0.9743	0.8645-1.0599	0.7724-0.9014	0.7912-0.9154	0.9011-1.0322
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm^2/6 months	−0.2234 (−0.3522 to −0.0946)	−0.1618 (−0.2874 to −0.0361)	NA	−0.0547 (−0.1899 to 0.0806)	−0.0793 (−0.2131 to 0.0546)	N/A	−0.1298 (−0.2218 to −0.0377)	−0.1133 (−0.2038 to −0.0229)	N/A
Percentage difference in slope of GA lesion area growth vs sham pooled group	−22.7	−16.4	NA	−5.7	−8.2	N/A	−13.4	−11.7	N/A
P value vs sham pooled group	.0007	.0116	NA	.4282	.2457	NA	.0058	.0141	NA
Estimates for month 6 to month 12									
Slope (SE) of GA lesion area growth (mm^2/6 months)	0.7848 (0.05958)	0.8184 (0.05660)	0.9962 (0.03893)	0.8409 (0.05128)	0.8473 (0.05086)	1.0132 (0.05998)	0.8344 (0.03809)	0.8524 (0.03578)	1.0232 (0.03853)
95% CI of slope of GA lesion area growth, mm^2/6 months	0.6680-0.9016	0.7075-0.9294	0.9199-1.0725	0.7404-0.9414	0.7476-0.9470	0.8956-1.1307	0.7597-0.9091	0.7822-0.9226	0.9476-1.0988
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm^2/6 months	−0.1862 (−0.3406 to −0.0318)	−0.1526 (−0.3030 to −0.0023)	NA	−0.1722 (-0.3270 to −0.0174)	−0.1659 (−0.3202 to −0.0115)	N/A	−0.1888 (−0.2951 to −0.0825)	−0.1708 (−0.2741 to −0.0676)	N/A
Percentage difference in slope of GA lesion area growth vs sham pooled group	−19.2	−15.7	NA	−17.0	−16.4	N/A	−18.5	−16.7	N/A

P value vs sham pooled group	.0181	.0467	NA	.0292	.0352	N/A	.0005	.0012	N/A
Estimates for month 12 to month 18									
Slope (SE) of GA lesion area growth, mm^2/6 months	0.8004 (0.05034)	0.8682 (0.04959)	1.0269 (0.05288)	0.9033 (0.04917)	0.8803 (0.05105)	1.0483 (0.05574)	0.8323 (0.03354)	0.8687 (0.03277)	1.0473 (0.03714)
95% CI of slope of GA lesion area growth, mm^2/6 months	0.7017-0.8991	0.7710-0.9654	0.9232-1.1305	0.8069-0.9997	0.7803-0.9804	0.9391-1.1576	0.7664-0.8981	0.8044-0.9330	0.9708-1.1166
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm^2/6 months	−0.2265 (−0.3696 to −0.0834	−0.1586 (−0.3009 to −0.0164)	NA	−0.1450 (−0.2909 to 0.0009)	-0.1680 (−0.3164 to −0.0196)	NA	−0.2114 (−0.3097 to −0.01132)	−0.1750 (−0.2723 to −0.0777)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	−22.1	−15.4	NA	−13.8	−16.0	NA	−20.3	−16.8	NA
P value vs sham pooled group	.0019	.0288	NA	.0514	.0265	NA	<.0001	.0004	NA
Estimates for month 18 to month 24									
Slope (SE) of GA lesion area growth, mm^2/6 months	0.7617 (0.06650)	0.7499 (0.04372)	0.9958 (0.05824)	0.6262 (0.06809)	0.6946 (0.05256)	0.9794 (0.05469)	0.6794 (0.04446)	0.7336 (0.03367)	0.9671 (0.03759)
95% CI of slope of GA lesion area growth, mm^2/6 months	0.6313-0.8921	0.6642-0.8356	0.8816-1.1100	0.4927-0.7597	0.5915-0.7976	0.8722-1.0866	0.5922-0.7667	0.6676-0.7997	0.8933-1.0408
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm^2/6 months	−0.2341 (−0.4071 to −0.0611)	−0.2459 (−0.3886 to −0.1031)	NA	-0.3532 (−0.5245 to −0.1819)	-0.2848 (−0.4336 to −0.1361	NA	-0.2876 (−0.4018 to −0.1734)	-0.2334 (−0.3324 to −0.1344	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	−23.5	−24.7	NA	−36.1	−29.1	NA	−29.7	−24.1	NA
P value vs sham pooled group	.0080	.0007	NA	<.0001	.0002	NA	<.0001	<.0001	NA
Estimates for baseline to month 24									
Average slope (SE) of GA lesion area growth, mm^2/24 months[a]	3.1073 (0.14841)	3.2586 (0.13420)	3.9775 (0.14310)	3.2780 (0.12525)	3.3051 (0.12871)	4.0031 (0.16880)	3.1830 (0.09426)	3.3080 (0.09172)	4.0006 (0.10935)
95% CI of slope of GA lesion area growth, mm^2/24 months	2.8164-3.3982	2.9955-3.5217	3.6970-4.2580	3.0324-3.5235	3.0528-3.5574	3.6722-4.3340	2.9980-3.3679	3.1281-3.4880	3.7861-4.2151
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm^2/24 months	−0.8702 (−1.2740 to −0.4664)	−0.7189 (−1.1039 to −0.3339)	NA	−0.7251 (−1.1373 to −0.3129)	−0.6980 (−1.1142 to −0.2817)	NA	−0.8176 (−1.1009 to −0.5344)	−0.6926 (−0.9728 to −0.4124)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	−21.9	−18.1	NA	−18.1	−17.4	NA	−20.4	−17.3	NA
P value vs sham pooled group	<.0001	.0003	NA	.0006	.0010	NA	<.0001	<.0001	NA

Abbreviations: CFB = change from baseline; CNV = choroidal vascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; mITT = modified intent-to-treat; MMRM = mixed-effects model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

[a] Slope (SE) for baseline to month 24 is an average of slope of baseline to month 6, month 6 to month 12, month 12 to month 18, and month 18 to month 24.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Percentage difference is derived as the difference in slopes between the arms divided by the comparison group slopes. For Studies APL2-304 and APL2-303, model included treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + time (continuous) + time spline at month 6 (continuous) + time spline at month 12 (continuous) + time spline at month 18 (continuous) + baseline presence of CNV in the fellow eye (yes or no) + time (continuous) × treatment + time spline at month 6 (continuous) × treatment + time spline at month 12 (continuous) × treatment + time spline at month 18 (continuous) × treatment + baseline GA lesion area × time (continuous) + baseline GA lesion area × time spline at month 6 (continuous) + baseline GA lesion area × time spline at month 12 (continuous) + baseline GA lesion area × time spline at month 18 (continuous). The model for pooled data also included study as a covariate.

Prespecified exploratory endpoint comparing GA growth rate between study and fellow eyes in subjects with bilateral GA

Table 30: Analysis of difference in CFB in GA lesion area (mm²) (FAF) for the study eye and fellow eye in subjects with bilateral GA at month 24 in study APL2-304, study APL2-303, and pooled data-mitt population

Statistic	Study APL2-304			Study APL2-303			Pooled data		
	PM (N = 167)	PEOM (N = 174)	Sham pooled (N = 165)	PM (N = 164)	PEOM (N = 161)	Sham pooled (N = 150)	PM (N =331)	PEOM (N =335)	Sham pooled (N =316)
Number of subjects included in the model	93	107	109	88	105	87	181	212	196
LS mean (SE) CFB in GA lesion area in study eye, mm^2	3.1904 (0.17157)	3.3555 (0.18153)	4.1764 (0.20945)	3.5649 (0.17905)	3.2863 (0.17274)	4.0551 (0.19007)	3.3694 (0.12468)	3.3301 (0.12626)	4.1173 (0.14300)
LS mean (SE) CFB GA lesion area in fellow eye, mm^2	3.9576 (0.18124)	3.7452 (0.17429)	4.0164 (0.21384)	4.2265 (0.23167)	3.9786 (0.19136)	4.1058 (0.21702)	4.0816 (0.14671)	3.8682 (0.12915)	4.0515 (0.15237)
LS mean (SE) difference in CFB in GA lesion area between study eye and fellow eye, mm^2	−0.7673 (0.15728)	−0.3897 (0.15804)	0.1600 (0.15709)	−0.6616 (0.16445)	−0.6923 (0.13747)	−0.0507 (0.15964)	−0.7122 (0.11430)	−0.5380 (0.10567)	0.0658 (0.11212)
Percentage difference in CFB in GA lesion area between study eye and fellow eye	−19.4	−10.4	4.0	−15.7	−17.4	−1.2	−17.4	−13.9	1.6
P value	<.0001	.0139	.3089	.0001	<.0001	.7509	<.0001	<.0001	.5573
LS mean (SE) CFB in GA lesion area sham-adjusted difference between study eye and fellow eye, mm^2	−0.9272 (0.22241)	−0.5497 (0.22279)	NA	−0.6108 (0.22935)	−0.6416 (0.21065)	NA	−0.7780 (0.16020)	−0.6039 (0.15407)	NA
95% CI of LS mean CFB in GA lesion area sham-adjusted difference between study and fellow eye, mm^2	−1.3639 to −0.4905	−0.9872 to −0.1122	NA	−1.0612 to −0.1605	−1.0553 to −0.2279	NA	−1.0923 to −0.4637	−0.9061 to −0.3016	NA
Sham-adjusted percentage difference in CFB in GA lesion area between study and fellow eye	−23.4	−14.7	NA	−14.5	−16.1	NA	−19.1	−15.6	NA
P value	<.0001	.0139	NA	.0079	.0024	NA	<.0001	.0001	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to the first study drug administration. Table is presented for subjects with bilateral GA with fellow eyes that satisfied the following characteristics at baseline: absence of CNV in the medical history, baseline GA lesion size between 2.5 and 17.5 mm^2, presence of any pattern of hyperautofluorescence in the junctional zone of GA, and GA not confluent with any peripapillary atrophy. Percentage difference is derived as the difference in LS means of the CFB between the study eye and fellow eye within a treatment group divided by the CFB in the fellow eye. Sham adjusted percentage difference is derived as the difference in LS means of the CFB between the study eye and fellow eye within the pegcetacoplan treatment group minus the difference in LS means of the CFB between the study eye and fellow eye within the sham pooled treatment group and finally divided by the CFB in the fellow eye within the pegcetacoplan treatment group. Derived from an MMRM model with the difference in the CFB in the fellow eye and study eye as the outcome and includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + analysis visit + analysis visit × treatment + baseline GA lesion area × analysis visit + the difference between the study eye and fellow eye lesion areas at baseline + the difference between the study eye + fellow eye lesion areas at baseline × analysis visit + eye + treatment × eye + analysis visit × eye + analysis visit × treatment × eye. The model for pooled data also included study as a covariate.

Key secondary endpoints

Key secondary endpoints, all of which are measures of visual function or vision-related patient-reported outcomes, were prespecified to be assessed at month 24 because changes in visual function in GA were hypothesised to be more detectable using the selected measures of visual function with longer follow-up. Key secondary endpoints other than microperimetry were prespecified to be evaluated in the combined Study APL2-304 and Study APL2-303 data where possible. Microperimetry measures were not performed in study APL2-303.

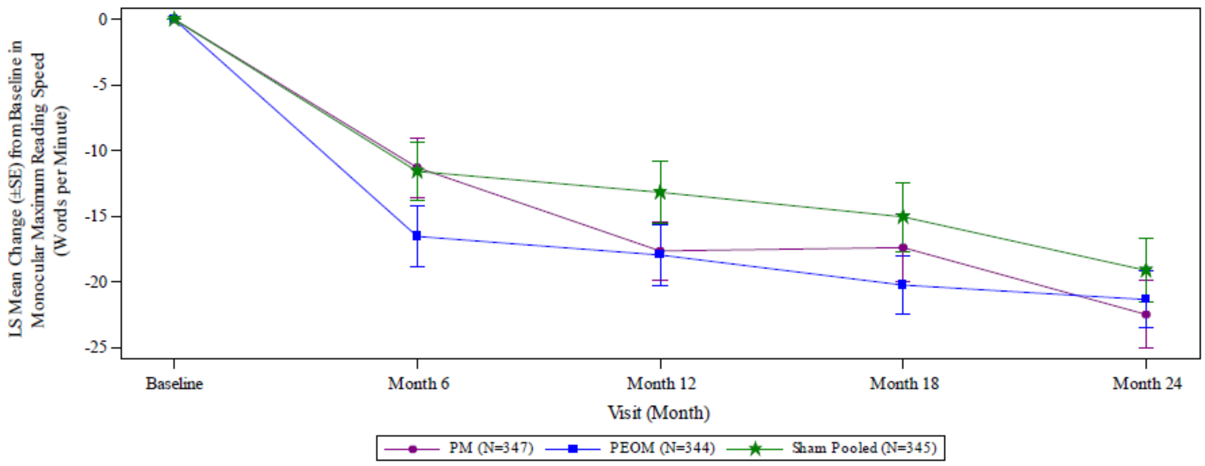
Monocular Maximum Reading Speed

Table 31: Analysis of CFB at month 24 in monocular maximum reading speed (wpm) of the study eye with MMRM model in study APL2-304, study APL2-303, and pooled data-mITT population

	Study APL2-304			Study APL2-303			Pooled data		
	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 207)**	**PM (N = 201)**	**PEOM (N = 201)**	**Sham pooled (N = 195)**	**PM (N = 403)**	**PEOM (N = 406)**	**Sham pooled (N = 402)**
Baseline, n Mean (SD)	185 73.4 (50.5)	192 67.2 (51.85)	192 72.0 (51.40)	194 76.1 (54.62)	182 70.6 (49.39)	181 73.8 (52.21)	379 74.8 (52.39)	374 68.9 (50.63)	373 72.9 (51.73)
Number of subjects included in the model	168	181	181	179	163	164	347	344	345
LS mean (SE) CFB in maximum reading speed, wpm	−22.446 (3.0329)	−17.533 (3.2886)	−16.211 (3.8129)	−22.897 (4.1171)	−25.532 (2.7676)	−22.355 (2.9341)	−22.490 (2.5657)	−21.354 (2.1580)	−19.129 (2.4001)
95% CI of LS mean CFB in maximum reading speed, wpm	−28.404 to −16.488	−23.993 to −11.072	−23.701 to −8.721	−30.986 to −14.808	−30.970 to −20.094	−28.120 to −16.590	−27.525 to −17.456	−25.589 to −17.120	−23.838 to −14.419
Difference (95% CI) in LS mean CFB in maximum reading speed (vs sham pooled), wpm	−6.235 (−15.182 to 2.712)	−1.322 (−10.562 to 7.918)	NA	−0.542 (−19.922 to 8.838)	−3.177 (−10.619 to 4.265)	NA	−3.362 (−9.890 to 3.167)	−2.225 (−8.201 to 3.750)	NA
P value (vs sham pooled)	.1716	.7788	NA	.9096	.4020	NA	.3125	.4651	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; MNREAD = Minnesota Low-Vision Reaching Chart; NA = not applicable; PEOM = pegcetacoplan evei other month; PM = pegcetacoplan monthly; wpm = words per minute.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Pooled data from 2 charts: MNREAD and Radner. Maximum reading speed was calculated as the mean of the 3 highest nonzero reading speeds (or 2 or 1 value, as available), except when all words per minute were calculated as 0 then th maximum reading speed was calculated as 0. Maximum reading speed was calculated without an adjustment for reading inaccuracy. For Studies APL2-304 and APL2–303, the model included treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline monocular maximum reading speed + chart types + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline monocular maximum reading speed × analysis visit. The model for pooled data also included study as a covariate.



SE = Standard Error.
Note: Pooled data from two charts: MNRead and Radner.
Note: Baseline is defined as the last available, non-missing observation prior to first study drug administration.
Note: Maximum reading speed will be calculated as the mean of the three highest nonzero reading speeds (or two, or one value, as available), except when all words per minute are calculated as 0: then the maximum reading speed will be calculated as 0.
Note: Maximum reading speed will be calculated without an adjustment for reading inaccuracy.
Note: Model includes Study (APL2-303, APL2-304) + Treatment + Baseline Presence of CNV in the fellow eye (Yes or No) + Baseline GA lesion area (< 7.5 mm^2 or >= 7.5 mm^2) + Baseline Monocular Maximum Reading Speed + Chart Types + Analysis Visit + Treatment x Analysis Visit + Baseline Monocular Maximum Reading Speed x Analysis Visit.

Figure 14: LS mean (±) plot of change from baseline in monocular maximum reading speed (words per minute) of the study eye by visit and treatment group from MMRM model mITT set baseline through month 24

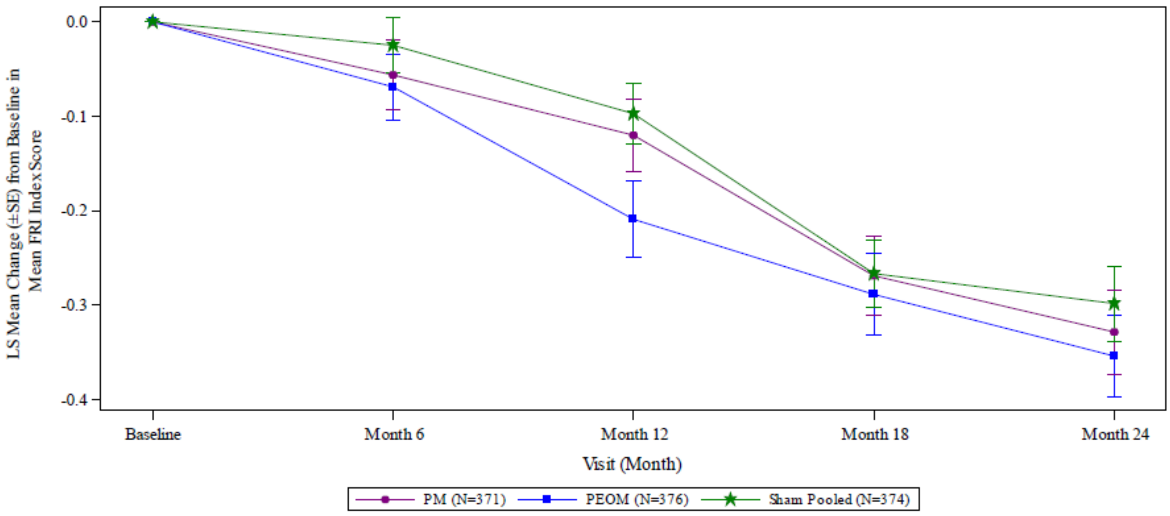
__Mean FRI Index Score__

Table 32: Analysis of CFB in mean FRI index score with MMRM model at month 24 in study APL2-304, study APL2-303, and pooled data-mITT population

	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 207)**	**PM (N = 201)**	**PEOM (N = 201)**	**Sham pooled (N = 195)**	**PM (N = 403)**	**PEOM (N = 406)**	**Sham pooled (N = 402)**
Baseline, n Mean (SD)	201 2.74 (0.825)	205 2.71 (0.785)	207 2.73 (0.809)	198 2.73 (0.816)	197 2.68 (0.821)	190 2.70 (0.860)	399 2.73 (0.819)	402 2.69 (0.802)	397 2.72 (0.833)
Number of subjects included in the model	185	193	196	186	183	178	371	376	373
LS mean (SE) CFB in mean FRI Index score	−0.287 (0.0563)	−0.379 (0.0536)	−0.273 (0.0554)	−0.408 (0.0570)	−0.371 (0.0562)	−0.360 (0.0601)	−0.346 (0.0403)	−0.372 (0.0387)	−0.316 (0.0409)
95% CI of LS mean CFB in mean FRI Index score	−0.398 to −0.177	−0.484 to −0.274	−0.382 to −0.164	−0.520 to −0.296	−0.481 to −0.260	−0.478 to −0.242	−0.425 to −0.267	−0.448 to −0.296	−0.396 to −0.236
Difference (95% CI) in LS mean CFB in mean FRI Index score (vs sham pooled)	−0.015 (−0.162 to 0.133)	−0.106 (−0.252 to 0.039)	NA	−0.048 (−0.204 to 0.108)	−0.011 (−0.163 to 0.142)	NA	−0.030 (−0.138 to 0.077)	−0.056 (−0.161 to 0.049)	NA
P value (vs sham pooled)	.8450	.1508	NA	.5483	.8921	NA	.5799	.2979	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; GA = geographic atrophy; FRI = Functional Reading Independence; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. For Studies APL2-304 and APL2-303, the model includ treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline mean FRI Index score + baseline study eye status (better-seeing eye or worse-seeing eye) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline mean FRI Index score × analysis visit. The mode for pooled data also included study as a covariate.



SE = Standard Error.
Note: Baseline is defined as the last available, non-missing observation prior to first study drug administration.
Note: Model includes Study (APL2-303, APL2-304) + Treatment + Baseline GA Lesion Area (< 7.5 mm^2 or >= 7.5 mm^2) + Baseline Mean FRI Index Score + Baseline Study Eye Status (Better-seeing Eye or Worse-seeing Eye) + Analysis Visit + Baseline Presence of CNV in the fellow eye (Yes or No) + Analysis Visit x Treatment + Baseline Mean FRI Index Score x Analysis Visit

Figure 15: LS Mean (± SE) plot of change from baseline in mean FRI index score by visit and treatment group from MMRM model mITT set baseline through month 24

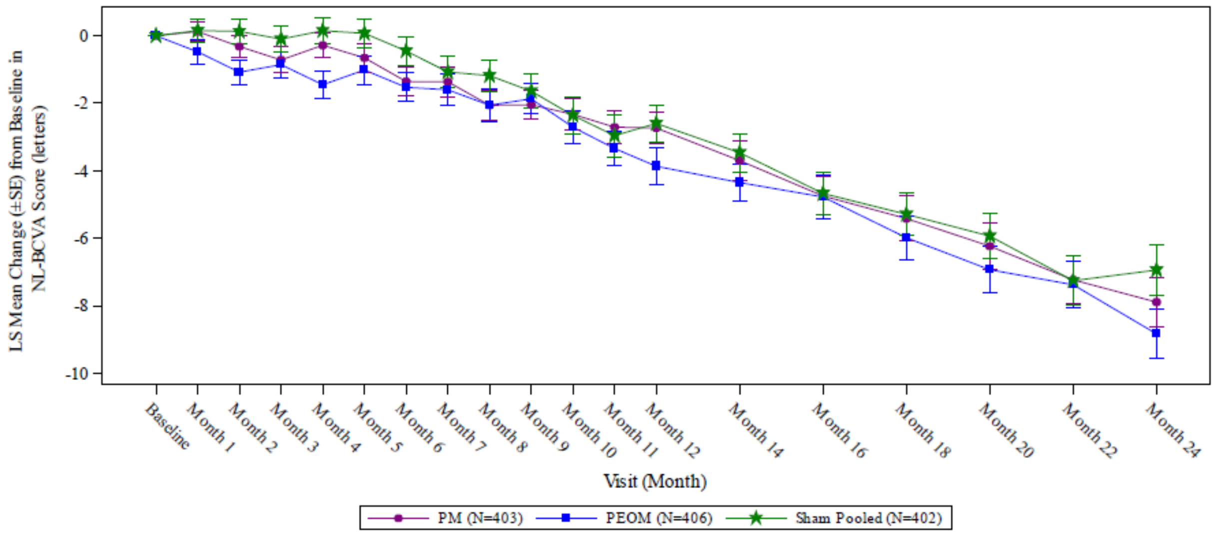
NL-BCVA

Table 33: Analyses of CFB at month 24 in NL-BCVA score (ETDRS letters) of the study eye with MMRM model in study APL2-304, study APL2-303, and pooled data-mITT population

	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 207)**	**PM (N = 201)**	**PEOM (N = 201)**	**Sham pooled (N = 195)**	**PM (N = 403)**	**PEOM (N = 406)**	**Sham pooled (N = 402)**
Baseline, n Mean (SD)	202 61.0 (15.30)	205 58.2 (17.03)	207 57.6 (16.59)	201 59.5 (17.40)	201 58.7 (16.12)	195 59.0 (16.85)	403 60.2 (16.37)	406 58.4 (16.57)	402 58.3 (16.71)
Number of subjects included in the model	202	205	207	201	201	195	403	406	402
LS mean (SE) CFB in NL-BCVA score, ETDRS letters	−7.477 (1.0512)	−8.526 (1.0525)	−7.660 (1.0734)	−8.126 (1.0182)	−8.947 (1.0322)	−6.217 (1.0167)	−7.889 (0.7355)	−8.830 (0.7365)	−6.940 (0.7373)
95% CI of LS mean CFB in NL-BCVA score, ETDRS letters	−9.541 to −5.412	−10.593 to −6.459	−9.768 to −5.552	−10.126 to −6.126	−10.975 to −6.920	−8.214 to −4.220	−9.332 to −6.446	−10.275 to −7.385	−8.386 to −5.493
Difference (95% CI) in LS mean CFB in NL-BCVA score vs sham pooled group, ETDRS letters	0.183 (−2.724 to 3.090)	−0.866 (−3.793 to 2.062)	NA	−1.909 (−4.701 to 0.833)	−2.730 (−5.565 to 0.105)	NA	−0.949 (−2.966, 1.067)	−1.890 (−3.927, 0.147)	NA
P value (vs sham pooled)	.9015	.5615	NA	.1799	.0590	NA	.3558	.0690	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; ETDRS = Early Treatment Diabetic Retinopathy Study; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; NL-BCVA = normal-luminance best-corrected visual acuity; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. For Studies APL2-304 and APL2-303, the model included treatment + baseline GA lesion area (<7.5 mm^2 or ≥ 7.5mm^2) + baseline NL-BCVA score + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline NL-BCVA score × analysis visit. The model for pooled data also included study as a covariate.



SE = Standard Error; NL-BCVA = Normal Luminance Best Corrected Visual Acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.
Note: Baseline is defined as the last available, non-missing observation prior to first study drug administration.
Note: Model includes Study (APL2-303, APL2-304) + Treatment + Baseline GA Lesion Area (< 7.5 mm^2 or >= 7.5 mm^2) + Baseline NL-BCVA Score + Analysis Visit + Baseline Presence of CNV in the fellow eye (Yes or No) + Analysis Visit x Treatment + Baseline NL-BCVA Score x Analysis Visit.

Figure 16: LS mean (± SE) plot of change from baseline in NL-BCVA score (EDTRS letters) of the study eye by visit and treatment group from MMRM model mitt set baseline through month 24

Mean Threshold Sensitivity Based on Microperimetry (study APL2-304 only)

Table 34: Study APL2-304: analysis of CFB at month 24 in mean threshold sensitivity (Db) of all points of the study eye with MMRM model-mITT population

	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 207)**
Baseline, n Mean (SD)	199 11.519 (5.1920)	203 11.449 (5.6279)	203 11.008 (5.4941)
Number of subjects included in the model	179	187	186
LS mean (SE) CFB in mean threshold sensitivity, dB	−3.319 (0.2969)	−3.064 (0.2331)	−2.954 (0.2156)
95% CI of LS mean CFB in mean threshold sensitivity, dB	−3.903 to −2.736	−3.522 to −2.606	−3.377 to −2.530
Difference (95% CI) in LS mean CFB in mean threshold sensitivity vs sham pooled group, dB	−0.365 (−1.057 to 0.326)	−0.110 (−0.693 to 0.473)	NA
P value vs sham pooled group	.2998	.7106	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥ 7.5 mm^2) + baseline mean threshold of all points + analysi visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline mean threshold sensitivity of all points × analysis visit.

- **Ancillary analyses**

Primary Efficacy Endpoint

Baseline adjustment for major imbalances in ocular characteristics (Post hoc Analyses)

To account for any major imbalances observed across the treatment groups within each study and to understand the impact of these imbalances on the estimated treatment effect across studies, a systematic post hoc covariate-adjusted analysis was conducted. The scope of these analyses is based on the individual study results for Study APL2-304, Study APL2-303 and Study POT-CP121614. Four variables were identified as imbalanced via a systematic approach:

- lesion location (Study APL2-304)
- focality (Study APL2-303)
- intermediate/large drusen (Studies APL2-303 and POT-CP121614)
- LLD (Study POT-CP121614)

Month 12

Table 35: Post hoc analysis of CFB in total area of GA lesion(s) (FAF) (mm2) of the study eye with MMRM model at Month 12 – adjusted for baseline characteristics with major imbalances: study APL2-204, study APL2-303, and pooled data – mITT population

	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 202)	**PEOM** (N = 205)	**Sham pooled** (N = 207)	**PM** (N = 201)	**PEOM** (N = 200)	**Sham pooled** (N = 195)	**PM** (N = 403)	**PEOM** (N = 406)	**Sham pooled** (N = 402)
Number of subjects included in the model	202	204	205	200	199	193	402	403	398
LS mean (SE) CFB of GA lesion area, mm^2	1.5098 (0.07927)	1.6656 (0.07488)	2.0082 (0.07770)	1.7056 (0.07424)	1.7271 (0.07097)	2.0171 (0.08967)	1.6069 (0.05436)	1.6923 (0.05102)	2.0141 (0.05926)
95% CI of LS Mean CFB of GA lesion area, mm^2	1.3541-1.6655	1.5185-1.8126	1.8556-2.1608	1.5598-1.8514	1.5877-1.8665	1.8410 to −2.1932	1.5002-1.7135	1.5922-1.7924	1.8978-2.1303
Difference in LS mean (95% CI) vs sham pooled group, mm^2	−0.4984 (−0.7179 to −0.2788)	−0.3426 (−0.5506 to −0.1346)	NA	−0.3115 (−0.5362 to −0.0868)	−0.2900 (−0.5147 to −0.0654)	NA	−0.4072 (−0.5640 to −0.2504)	−0.3217 (−0.4736 to −0.1698)	NA
Percentage difference in LS mean CFB of GA lesion area vs sham pooled group	−24.8	−17.1	NA	−15.4	−14.4	NA	−20.2	−16.0	NA
P value vs sham pooled group	<.0001	0.0013	NA	.0067	.0115	NA	<0.0001	<0.0001	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effects model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to the first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. For Studies APL2-304 and APL2-303, the model included treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion size × analysis visit + study eye focality (unifocal/multifocal) + study eye focality (unifocal/multifocal) × analysis visit + study eye intermediate/large drusen (>20 vs ≤ 20) + study eye intermediate/large drusen (>20 vs ≤ 20) × analysis visit + study eye lesion location (subfoveal vs without subfoveal) + study eye lesion location (subfoveal vs without subfoveal) × analysis visit + study eye low-luminance deficit (continuous) + study eye low-luminance deficit (continuous) × analysis visit. The model for pooled data also included Study as a covariate. Covariates added to the model beyond the primary analysis are entered as continuous so LS means are generated on the basis of the overall population level distribution of the covariate. Nine subjects missing low-luminance deficit had missing data imputed with the median low-luminance deficit, 24. Two subjects missing intermediate/large drusen had missing data imputed with the mode number of intermediate/large drusen, ≤20.

Sources: Study APL2-304 Month 24 CSR, Post-Hoc Table 14.5.6.1; Study APL2-303 Month 24 CSR, Post-Hoc Table 14.5.6.1.1; Month 24 Integrated Summary of Efficacy Post-Hoc Table 14.5.4.2.2.1.

Table 36: Post hoc analysis of CFB in total area of GA lesion(s) (mm2) (FAF) of the study eye without pooling sham groups at month 12 – adjusted for baseline characteristics with major imbalances – mITT population

	Study APL2-304				**Study APL2-303**				**Pooled data**			
	PM (N =201)	**PEOM** (N =201)	**SM** (N =97)	**SEOM** (N =98)	**PM** (N =201)	**PEOM** (N =201)	**SM** (N =97)	**SEOM** (N =98)	**PM**	**PEOM**	**SM**	**SEOM**
Number of subjects included in the model	202	204	103	102	200	199	97	96	402	403	200	198
LS mean (SE) CFB of GA lesion area, mm^2	1.5100 (0.07925)	1.6654 (0.07490)	1.9448 (0.09183)	2.0669 (0.12176)	1.7053 (0.07427)	1.7275 (0.07092)	1.8849 (0.12099)	2.1388 (0.12775)	1.6069 (0.05435)	1.6923 (0.05101)	1.9192 (0.07479)	2.1013 (0.08873)
95% CI of LS mean CFB of GA lesion area, mm^2	1.3543-1.6656	1.5184-1.8125	1.7644-2.1251	1.8278-2.3060	1.5595-1.8512	1.5882-1.8668	1.6473-2.1225	1.8879-2.3897	1.5002-1.7135	1.5922-1.7924	1.7725-2.0660	1.9272-2.2754
Difference in LS mean (95% CI) CFB of GA lesion area (PM vs SM), mm^2	−0.4348 (−0.6720 to −0.1976)	NA	NA	NA	−0.1796 (−0.4558 to 0.0967)	NA	NA	NA	−0.3124 (−0.4921 to −0.1326)	NA	NA	NA
Percentage difference in LS mean CFB of GA lesion area vs SM	−22.4	NA	NA	NA	−9.5	NA	NA	NA	−16.3	NA	NA	NA
P value vs SM	.0003	NA	NA	NA	.2022	NA	NA	NA	.0007	NA	NA	NA
Difference in LS mean (95% CI) CFB of GA lesion area (PEOM vs SEOM), mm^2	NA	−0.4014 (−0.6805 to −0.1224)	NA	NA	NA	−0.4114 (−0.6982 to −0.1245	NA	NA	NA	−0.4090 (−0.6090 to −0.2090)	NA	NA
Percentage difference in LS mean CFB of GA lesion area vs SEOM	NA	−19.4	NA	NA	NA	−19.2	NA	NA	NA	−19.5	NA	NA
P value vs SEOM	NA	.0049	NA	NA	NA	.0050	NA	NA	NA	<.0001	NA	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SEOM = sham every other month; SM = sham monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Percentage difference is derived as the difference in LS means between the groups divided by the comparison group LS means. For Studies APL2-304 and APL2-303, model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥ 7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion size × analysis visit + study eye focality (unifocal/multifocal) + study eye focality (unifocal/multifocal) × analysis visit + study eye intermediate/large drusen (>20 vs ≤ 20) + study eye intermediate/large drusen (>20 vs ≤ 20) × analysis visit + study eye lesion location (subfoveal vs without subfoveal) + study eye lesion location (subfoveal vs without subfoveal) × analysis visit + study eye low-luminance deficit (continuous) + study eye low-luminance deficit (continuous) × analysis visit. The model for pooled data also included study as a covariate. Covariates added to the model beyond the primary analysis are entered as continuous so LS means are generated on the basis of the overall population level distribution of the covariate. Two subjects missing intermediate/large drusen had missing data imputed with the mode number of intermediate/large drusen, ≤20. Nine subjects missing low-luminance deficit had missing data imputed with the median low-luminance deficit, 24.

Sources: Study APL2-304 Month 24 CSR, Post-Hoc Table 14.5.10.1; Study APL2-303, Post-Hoc Table 14.5.10.1; Month 24 Integrated Summary of Efficacy Post-Hoc Table 14.5.4.2.9.1.

Month 24

Table 37: Post hoc analysis of CFB in total area of GA lesion(s) (mm2) (FAF) of the study eye with MMRM model at Month 24 – adjusted for baseline characteristics with major imbalances in study APL2-304, study APL2-303, and pooled data - mITT population

	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 207)**	**PM (N = 201)**	**PEOM (N = 201)**	**Sham pooled (N = 195)**	**PM (N =403)**	**PEOM (N =406)**	**Sham pooled (N =402)**
Number of subjects included in the model	202	204	206	200	200	194	402	404	400
LS mean (SE) CFB of GA lesion area, mm^2	3.0101 (0.13350)	3.2981 (0.11714)	4.0906 (0.13604)	3.1820 (0.12143)	3.2660 (0.12247)	4.0428 (0.15571)	3.0954 (0.09028)	3.2767 (0.08429)	4.0728 (0.10336)
95% CI of LS Mean CFB of GA lesion area, mm^2	2.7479-3.2723	3.0681-3.5282	3.8234-4.3577	2.9435-3.4205	3.0255-3.5066	3.7370-4.3486	2.9183-3.2726	3.1113-3.4421	3.8700-4.2756
Difference in LS mean (95% CI) vs sham pooled group, mm^2	−1.0805 (−1.4573 to −0.7036)	−0.7924 (−1.1410 to −0.4439)	NA	−0.8608 (−1.2454 to −0.4762)	−0.7768 (−1.1674 to −0.3862)	NA	−0.9773 (−1.2462 to −0.7084)	−0.7961 (−1.0567 to −0.5355)	NA
Percentage difference in LS mean CFB of GA lesion area vs sham pooled group	−26.4	−19.4	NA	−21.3	−19.2	NA	−24.0	−19.5	NA
P value vs sham pooled group	<.0001	<.0001	NA	<.0001	.0001	NA	<.0001	<.0001	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effects model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to the first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. For Studies APL2-304 and APL2-303, the model included treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion size × analysis visit + study eye focality (unifocal/multifocal) + study eye focality (unifocal/multifocal) × analysis visit + study eye intermediate/large drusen (>20 vs ≤ 20) + study eye intermediate/large drusen (>20 vs ≤ 20) × analysis visit + study eye lesion location (subfoveal vs without subfoveal) + study eye lesion location (subfoveal vs without subfoveal) × analysis visit + study eye low-luminance deficit (continuous) + study eye low-luminance deficit (continuous) × analysis visit. The model for pooled data also included study as a covariate. 2 subjects missing the number of intermediate/large drusen had missing data imputed with the mode number of intermediate/large drusen, ≤20. 9 subjects missing low-luminance deficit had missing data imputed with the median low-luminance deficit, 24.

Table 38: Post hoc analysis of CFB in total area of GA lesion(s) (mm2) (FAF) of the study eye without pooling sham groups at month 24 – adjusted for baseline characteristics with major imbalances – in study APL2-304, study APL2-303, and pooled data - mITT population

	Study APL2-304				Study APL2-303				Pooled data			
	PM (N = 202)	PEOM (N = 205)	SM (N = 105)	SEOM (N = 102)	PM (N = 201)	PEOM (N = 200)	SM (N = 97)	SEOM (N = 97)	PM (N=403)	PEOM (N=406)	SM (N=202)	SEOM (N=200)
Number of subjects included in the model	202	204	104	102	200	200	97	97	402	404	201	199
LS mean (SE) CFB of GA lesion area, mm^2	3.0104 (0.13346)	3.2984 (0.11717)	4.0344 (0.16828)	4.1429 (0.21103)	3.1808 (0.12156)	3.2660 (0.12232)	3.6663 (0.20247)	4.4057 (0.22754)	3.0954 (0.09026)	3.2768 (0.08429)	3.8561 (0.13111)	4.2772 (0.15558)
95% CI of LS mean CFB of GA lesion area, mm^2	2.7483-3.2725	3.0682-3.5285	3.7040-4.3649	3.7284-4.5573	2.9421-3.4195	3.0258-3.5063	3.2687-4.0640	3.9588-4.8526	2.9183-3.2725	3.1114-3.4422	3.5989-4.1134	3.9720-4.5825
Difference in LS mean (95% CI) CFB of GA lesion area (PM vs SM), mm^2	−1.0241 (−1.4420 to −0.6061)	NA	NA	NA	−0.4855 (−0.9481 to −0.0230)	NA	NA	NA	−0.7607 (−1.0716 to −0.4499)	NA	NA	NA
Percentage difference in LS mean CFB of GA lesion area vs SM	−25.4%	NA	NA	NA	−13.2%	NA	NA	NA	−19.7	NA	NA	NA
P value vs SM	<.0001	NA	NA	NA	.0397	NA	NA	NA	<.0001	NA	NA	NA
Difference in LS mean (95% CI) CFB of GA lesion area (PEOM vs SEOM), mm^2	NA	−0.8445 (−1.3177 to −0.3713)	NA	NA	NA	−1.1397 (−1.6453 to −0.6340)	NA	NA	NA	−1.0004 (−1.3472 to −0.6537)	NA	NA
Percentage difference in LS mean CFB of GA lesion area vs SEOM	NA	−20.4	NA	NA	NA	−25.9	NA	NA	NA	−23.4	NA	NA
P value vs SEOM	NA	.0005	NA	NA	NA	<.0001	NA	NA	NA	<.0001	NA	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SEOM = sham every other month; SM = sham monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Percentage difference is derived as the difference in LS means between the groups divided by the comparison group LS means. For Studies APL2-304 and APL2-303, model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion size × analysis visit + study eye focality (unifocal/multifocal) + study eye focality (unifocal/multifocal) × analysis visit + study eye intermediate/large drusen (>20 vs ≤20) + study eye intermediate/large drusen (>20 vs ≤20) × analysis visit + study eye lesion location (subfoveal vs without subfoveal) + study eye lesion location (subfoveal vs without subfoveal) × analysis visit + study eye low-luminance deficit (continuous) + study eye low-luminance deficit (continuous) × analysis visit. The model for pooled data also included study as a covariate. Covariates added to the model beyond the primary analysis are entered as continuous so LS means are generated on the basis of the overall population level distribution of the covariate. Two subjects missing intermediate/large drusen had missing data imputed with the mode number of intermediate/large drusen, ≤20. Nine subjects missing low-luminance deficit had missing data imputed with the median low-luminance deficit, 24.

The rate of change analyses assuming a linear trend and assuming a piecewise linear trend (with a knot at month 6 for 12 months data, and a knot at month 6, 12, and 18 for 24 months data) were also repeated adjusting for the same baseline characteristics with major imbalance as the covariate-adjusted analyses (results tables not shown in this report).

Key Subgroup analyses

Subgroup analyses were performed for age, sex, and geographic region. Additional subgroup analyses were performed for baseline GA lesion size and baseline ocular characteristics associated with GA progression that had major imbalances because of chance in any of the 3 efficacy studies in the clinical development programme (i.e., GA lesion location, GA lesion focality, the number of intermediate/large drusen category (>20/≤20), and LLD).

Age: The results of the analyses by age showed a consistent treatment effect across age groups in both the PM and PEOM groups.

Sex: The subgroup analyses by sex showed a consistent treatment effect across sex in both the PM and PEOM groups.

Race: No subgroup analyses were conducted by race in all 3 studies because of the uniform racial distribution of the study population: over 90% of subjects were White.

Geographic Region: Study eye CFB in total area of GA lesions was assessed by geographic region, that is, study subjects from the geographic regions of US and ROW in Study APL2-304, Study APL2-303, and pooled data. The majority of subjects enrolled were from the US. A consistent treatment effect between the US and the ROW for the PM and PEOM groups was observed in both studies and for pooled data.

Study Eye Baseline GA Lesion Size

Table 39: Analyses of CFB in total area of GA lesion(s) (mm²) (FAF) in the study eye at month 24 with MMRM model in study APL2-304, study APL2-303, and pooled data by study eye GA lesion area at baseline-mITT population

GA lesion area at baseline: <7.5 mm²									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 101)	**PEOM (N = 98)**	**Sham pooled (N = 104)**	**PM (N = 99)**	**PEOM (N = 98)**	**Sham pooled (N = 95)**	**PM (N = 200)**	**PEOM (N = 196)**	**Sham pooled (N = 199)**
Number of subjects included in the model	101	98	103	98	98	95	199	196	198
LS mean (SE) CFB in GA lesion area, mm²	2.6317 (0.15577)	2.9972 (0.19426)	3.1992 (0.18486)	2.8656 (0.16909)	3.0935 (0.19671)	3.4107 (0.22987)	2.6624 (0.12129)	2.9739 (013672)	3.2292 (0.14679)
95% CI of LS mean CFB in GA lesion area, mm²	2.3251-2.9382	2.6149-3.3795	2.8354-3.5630	2.5341-3.1972	2.7077-3.4792	2.9599-3.8615	2.4246-2.9002	2.7058-3.2419	2.9414-3.5169
Difference (95% CI) in LS mean CFB in GA lesion area vs sham pooled group, mm²	−0.5675 (−1.0445 to −0.0906)	−0.2020 (−0.7295 to 0.3255)	NA	−0.5450 (−1.1011 to 0.0110)	−0.3172 (−0.9072 to 0.2728)	NA	−0.5668 (−0.9414 to −0.1922)	−0.2553 (−0.6539 to −0.1433)	NA
Percentage difference in LS mean CFB in GA lesion area vs sham pooled group	−17.7	−6.3	NA	−16.0	−9.3	NA	−17.6	−7.9	NA
P value vs sham pooled group	.0199	.4517	NA	.0547	.2918	NA	.0030	.2093	NA
GA lesion area at baseline: ≥7.5 mm²									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 101)	**PEOM (N = 107)**	**Sham pooled (N = 102)**	**PM (N = 102)**	**PEOM (N = 102)**	**Sham Pooled (N = 100)**	**PM (N = 203)**	**PEOM (N = 210)**	**Sham Pooled (N = 203)**
Number of subjects included in the model	101	106	103	102	102	99	203	208	202
LS mean (SE) CFB in GA lesion area, mm²	3.6105 (0.24141)	3.5980 (0.17817)	4.8505 (0.22210)	3.6314 (0.19188)	3.5117 (0.17406)	4.5703 (0.25903)	3.5650 (0.15835)	3.4801 (0.13422)	4.6164 (0.17043)
95% CI of LS mean CFB in GA lesion area, mm²	3.1355-4.0855	3.2474-3.9486	4.4135-5.2875	3.2552-4.0077	3.1704-3.8531	4.0623-5.0782	3.2546-3.8755	3.2170-3.7432	4.2823-4.9505
Difference (95% CI) in LS mean CFB in GA lesion area vs sham pooled group, mm²	−1.2400 (−1.8830 to −0.5970)	−1.2525 (−1.8059 to −0.6991)	NA	−0.9388 (−1.5654 to −0.3123)	−1.0585 (−1.6692 to −0.4478)	NA	−1.0514 (−1.5039 to −0.5989)	−1.1363 (−1.5488 to −0.7239)	NA
Percentage difference in LS mean CFB in GA lesion area vs sham pooled group	−25.6	−25.8	NA	−20.5	−23.2	NA	−22.8	−24.6	NA
P value vs sham pooled group	.0002	<.0001	NA	.0033	.0007	NA	<.0001	<.0001	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. For Studies APL2-303 and APL2-304, model includes treatment + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment. The model for pooled data also included study as a covariate.

Table 40: Analyses of CFB in total area of GA lesion(s) (mm²) (FAF) of the study eye at month 24 with MMRM model by Tertile of GA lesion area of the study eye at baseline in study eye baseline APL2-304, study APL2-303, and pooled data-mITT population

GA lesion area at baseline: <5.695 mm²									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 66)	**PEOM (N = 64)**	**Sham pooled (N = 61)**	**PM (N = 75)**	**PEOM (N = 61)**	**Sham pooled (N = 77)**	**PM (N = 141)**	**PEOM (N = 125)**	**Sham pooled (N = 137)**
Number of subjects included in the model	66	64	60	74	61	77	140	125	137
LS mean (SE) CFB in lesion area, mm^2	2.4290 (0.21392)	2.9601 (0.26091)	2.7739 (0.23927)	2.5768 (0.16743)	2.7042 (0.23345)	3.1094 (0.23739)	2.4427 (0.13435)	2.7993 (0.17603)	2.9103 (0.16962)
95% CI of LS mean CFB in lesion area, mm^2	2.0093-2.8486	2.4483-3.4719	2.3046-3.2432	2.2484-2.9051	2.2463-3.1621	2.6438-3.5750	2.1793-2.7061	2.4532-3.1445	2.5777-3.2429
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm^2	−0.3449 (−0.9750 to 0.2851)	0.1862 (−0.5080 to 0.8804)	NA	−0.5326 (−1.0996 to 0.0343)	−0.4052 (−1.0576 to 0.2473)	NA	−0.4676 (−0.8970 to −0.0382)	−0.1110 (−0.5961 to 0.3741)	NA
Percentage difference in LS mean CFB in lesion area vs sham pooled group	−12.4	6.7	NA	−17.1	−13.0	NA	−16.1	−3.8	NA
P value vs sham pooled group	0.2830	0.5989	NA	.0655	.2234	NA	.0328	.6538	NA

GA lesion area at baseline: ≥5.695 and <9.655 mm²									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 72)	**PEOM (N = 71)**	**Sham pooled (N = 77)**	**PM (N = 52)**	**PEOM (N = 74)**	**Sham Pooled (N = 53)**	**PM (N = 124)**	**PEOM (N = 145)**	**Sham Pooled (N = 131)**
Number of subjects included in the model	72	71	78	52	74	53	124	144	131
LS mean (SE) CFB in lesion area, mm²	3.4917 (0.29287)	3.2211 (0.19448)	4.0418 (0.20968)	3.5021 (0.26332)	3.4167 (0.20392)	4.3252 (0.29824)	3.4026 (0.20509)	3.1747 (0.14089)	4.0575 (0.17512)
95% CI of LS mean CFB in lesion area, mm²	2.9173-4.0661	2.8397-3.6025	3.6305-4.4530	2.9855-4.0186	3.0167-3.8168	3.7401-4.9102	3.0005-3.8048	2.8985-3.4510	3.7141-4.4008
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm²	−0.5501 (−1.2504 to 0.1502)	−0.8207 (−1.3716 to −0.2698)	NA	−0.8231 (−1.5947 to −0.0514)	−0.9084 (−1.6104 to −0.2065)	NA	−0.6548 (−1.1807 to −0.1290)	−0.8827 (−1.3165 to −0.4490)	NA
Percentage difference in LS mean CFB in lesion area vs sham pooled group	−13.6	−20.3	NA	−19.0	−21.0	NA	−16.1	−21.8	NA
P value vs sham pooled group	0.1236	0.0035	NA	.0366	.0112	NA	.0147	<.0001	NA
GA lesion area at baseline: ≥9.655 mm²									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 64)	**PEOM (N = 70)**	**Sham pooled (N = 68)**	**PM (N = 74)**	**PEOM (N = 65)**	**Sham Pooled (N = 65)**	**PM (N = 138)**	**PEOM (N = 136)**	**Sham Pooled (N = 133)**
Number of subjects included in the model	64	69	68	74	66	64	138	135	132
LS mean (SE) CFB in lesion area, mm²	3.3240 (0.25768)	3.6793 (0.24707)	4.9454 (0.28462)	3.7994 (0.23219)	3.7734 (0.23060)	4.8534 (0.35391)	3.5347 (0.17346)	3.6863 (0.17500)	4.8571 (0.22636)
95% CI of LS mean CFB in lesion area, mm²	2.8186-3.8294	3.1947-4.1639	4.3871-5.5036	3.3440-4.2549	3.3211-4.2257	4.1592-5.5475	3.1946-3.8748	3.3432-4.0294	4.133-5.3009
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm²	−1.6214 (−2.3690 to −0.8737)	−1.2661 (−1.9913 to −0.5409)	NA	−1.0539 (−1.8775 to −0.2304)	−1.0799 (−1.9084 to −0.2515)	NA	−1.3225 (−1.8767 to −0.7682)	−1.1708 (−1.7211 to −0.6206)	NA
Percentage difference in LS mean CFB in lesion area vs sham pooled group	−32.8	−25.6	NA	−21.7	−22.3	NA	−27.2	−24.1	NA
P value vs sham pooled group	<.0001	.0006	NA	.0122	.0106	NA	<.0001	<.0001	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. For Studies APL2-303 and APL2-304, model includes treatment + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment. The model for pooled data also included study as a covariate.

GA Focality of the Study Eye at Baseline (unifocal, multifocal)

Table 41: Analyses of CFB in total area of GA lesion(s) (mm²) (FAF) of the study eye at month 24 with MMRM model by GA focality of the study eye at baseline in study APL2-304, study APL2-303, and pooled data-mITT population

GA focality at baseline: unifocal									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 59)	**PEOM (N = 62)**	**Sham pooled (N = 68)**	**PM (N = 54)**	**PEOM (N = 53)**	**Sham pooled (N = 66)**	**PM (N = 112)**	**PEOM (N = 115)**	**Sham pooled (N = 134)**
Number of subjects included in the model	59	61	68	53	53	65	112	114	133
LS mean (SE) CFB in lesion area, mm^2	2.2651 (0.20947)	2.7751 (0.19566)	3.3819 (0.23591)	2.8287 (0.22117)	2.6165 (0.19515)	3.5156 (0.23739)	2.5447 (0.14858)	2.7184 (0.13868)	3.4473 (0.16457)
95% CI of LS mean CFB in lesion area, mm^2	1.8542-2.6760	2.3913-3.1589	2.9192-3.8447	2.3948-3.2625	2.2336-2.9993	3.0499-3.9813	2.2524-2.8369	2.4456-2.9911	3.1236-3.7709
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm^2	−1.1169 (−1.7390 to −0.4947)	−0.6069 (−1.1994 to −0.0143)	NA	−0.6869 (−1.3223 to −0.0515)	−0.8991 (−1.5015 to -0.2968)	NA	−0.9026 (−1.3384 to −0.4668)	−0.7289 (−1.1494 to −0.3084)	NA
Percentage difference in LS mean CFB in lesion area vs sham pooled group	−33.0	−17.9	NA	−19.5	−25.6	NA	−26.2	−21.1	NA
P value vs sham pooled group	.0004	.0447	NA	.0341	.0035	NA	<.001	.0007	NA
GA focality at baseline: multifocal									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 143)	**PEOM (N = 143)**	**Sham pooled (N = 138)**	**PM (N = 147)**	**PEOM (N = 147)**	**Sham Pooled (N = 128)**	**PM (N = 290)**	**PEOM (N = 291)**	**Sham Pooled (N = 268)**
Number of subjects included in the model	143	143	138	147	147	129	290	290	267
LS mean (SE) CFB in lesion area, mm^2	3.4078 (0.18318)	3.5061 (0.17423)	4.2647 (0.17648)	3.3950 (0.15546)	3.5543 (0.15968)	4.2393 (0.22895)	3.4049 (0.11507)	3.5494 (0.11517)	4.2691 (0.14132)
95% CI of LS mean CFB in lesion area, mm^2	3.0487-3.7670	3.1645-3.8477	3.9187-4.6107	3.0902-3.6998	3.2413-3.8674	3.7904-4.6882	3.1791-3.6308	3.3233-3.7755	3.9917-4.5464
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm^2	−0.8569 (−1.3534 to −0.3604)	−0.7586 (−1.2406 to −0.2766)	NA	−0.8443 (−1.3823 to −0.3063)	−0.6850 (−1.2296 to −0.1403)	NA	−0.8642 (−1.2208 to −0.5075)	−0.7197 (−1.0761 to −0.3633)	NA
Percentage difference in LS mean CFB in lesion area vs sham pooled group, mm^2	−20.1	−17.8	NA	−19.9	−16.2	NA	−20.2	−16.9	NA
P value vs sham pooled group	.0007	.0020	NA	.0021	.0137	NA	<.0001	<.0001	NA

Abbreviations CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. For Studies APL2-303 and APL2-304, model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥ 7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion area × analysis visit. The model for pooled data also included study as a covariate.

GA Lesion Location of the Study Eye at Baseline (with subfoveal involvement or without subfoveal involvement)

Table 42: Analyses of CFB in total area of GA lesion(s) (mm²) (FAF) in the study eye at month 24 with MMRM model in study APL2-304, study APL2-303, and pooled data by study eye GA lesion location at baseline-mITT population

GA lesion location at baseline: without subfoveal involvement									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 86)	**PEOM (N = 74)**	**Sham pooled (N = 60)**	**PM (N = 72)**	**PEOM (N = 81)**	**Sham pooled (N = 73)**	**PM (N = 158)**	**PEOM (N = 155)**	**Sham pooled (N = 133)**
Number of subjects included in the model	86	73	59	72	81	72	158	154	131
LS mean (SE) CFB in lesion area, mm^2	3.5877 (0.24229)	4.2865 (0.25753)	5.1814 (0.28037)	3.8576 (0.22522)	3.6599 (0.18531)	4.9448 (0.33349)	3.7308 (0.17865)	3.9200 (0.16135)	5.0326 (0.22932)
95% CI of LS mean CFB in lesion area, mm^2	3.1101-4.0653	3.7789-4.7942	4.6288-5.7341	3.4137-4.3014	3.2947-4.0251	4.2876-5.6021	3.3805-4.0810	3.6037-4.2364	4.5830-5.4822
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm^2	−1.5938 (−2.3266 to −0.8610)	−0.8949 (−1.6437 to −0.1461)	NA	−1.0872 (−1.8805 to −0.2940)	−1.2849 (−2.0351 to −0.5347)	NA	−1.3018 (−1.8706 to −0.7331)	−1.1125 (−1.6582 to −0.5669)	NA
Percentage difference in LS mean CFB in lesion area vs sham pooled group	−30.8	−17.3	NA	−22.0	−26.0	NA	−25.9	−22.1	NA
P value vs sham pooled group	<.0001	.0194	NA	.0074	.0009	NA	<.0001	<.0011	NA

GA lesion location at baseline: with subfoveal involvement									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 116)	**PEOM (N = 131)**	**Sham pooled (N = 146)**	**PM (N = 129)**	**PEOM (N = 119)**	**Sham pooled (N = 121)**	**PM (N = 245)**	**PEOM (N = 251)**	**Sham pooled (N = 269)**
Number of subjects included in the model	116	131	147	128	119	122	244	250	269
LS mean (SE) CFB in lesion area, mm^2	2.7787 (0.16414)	2.7554 (0.12758)	3.5423 (0.15464)	2.8641 (0.13797)	3.1252 (0.17747)	3.3914 (0.15566)	2.8077 (0.10889)	2.8954 (0.10879)	3.4596 (0.11202)
95% CI of LS mean CFB in lesion area, mm^2	(2.4560-3.1014)	2.5046-3.0062	3.2382-3.8463	2.5928-3.1354	2.7762-3.4742	3.0853-3.6975	2.5942-3.0211	2.6822-3.1087	3.2400-3.6792
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm^2	−0.7636 (−1.2062 to −0.3210)	−0.7869 (−1.1793 to −0.3944)	NA	−0.5273 (−0.9329 to −0.1218)	-0.2662 (−0.7319 to 0.1995)	NA	−0.6520 (−0.9559 to −0.3480)	-0.5642 (−0.8689 to −0.2594)	NA
Percentage difference in LS mean CFB in lesion area vs sham pooled group	−21.6	−22.2	NA	−15.5	−7.8	NA	−18.8	−16.3	NA
P value vs sham pooled group	.0008	<.0001	NA	.0110	.2617	NA	<.0001	.0003	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. For Studies APL2-303 and APL2-304, model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion area × analysis visit. The model for pooled data also included study as a covariate.

LLD Categories of the Study Eye at Baseline (Approximate Tertiles)

Table 43: Analyses of CFB in total area of GA lesion(s) (mm²) (FAF) of the study eye at month 24 with MMRM model by tertile of LLD of the study eye at baseline in study APL2-304, study APL2-303 and pooled data-mITT population

Tertile of LLD of the study eye: <16 ETDRS letters									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 57)	**PEOM (N = 66)**	**Sham pooled (N = 74)**	**PM (N = 63)**	**PEOM (N = 63)**	**Sham pooled (N = 57)**	**PM (N = 120)**	**PEOM (N = 129)**	**Sham pooled (N = 129)**
Number of subjects included in the model	57	66	73	62	63	56	119	129	129
LS mean (SE) CFB in lesion area, mm^2	2.5841 (0.24881)	2.5649 (0.16079)	3.4512 (0.22920)	2.8644 (0.20279)	2.5607 (0.17787)	3.0607 (0.23913)	2.7241 (0.15953)	2.5683 (0.11984)	3.2766 (0.16649)
95% CI of LS mean CFB in lesion area, mm^2	2.0961-3.0722	2.2495-2.8803	3.0016-3.9008	2.4666-3.2623	2.2118-2.9096	2.5916-3.5298	2.4113-3.0369	2.3333-2.8033	2.9501-3.6030
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm^2	−0.8670 (−1.5226 to −0.2115)	−0.8863 (−1.4252 to −0.3474)	NA	−0.1962 (−0.8091 to 0.4166)	−0.5000 (−1.0826 to 0.0827)	NA	−0.5524 (−1.0026 to −0.1023)	−0.7083 (−1.1075 to −0.3090)	NA
Percentage difference in LS mean CFB in lesion area vs sham pooled group	−25.1	−25.7	NA	−6.4	−16.3	NA	−16.9	−21.6	NA
P value vs sham pooled group	.0096	.0013	NA	.5301	.0925	NA	.0162	.0005	NA

Tertile of LLD of the study eye: ≥16 to <32 ETDRS letters									
	Study APL2-304			Study APL2-303			Pooled data		
	PM (N = 69)	PEOM (N = 68)	Sham pooled (N = 70)	PM (N = 62)	PEOM (N = 73)	Sham Pooled (N = 72)	PM (N = 131)	PEOM (N = 140)	Sham Pooled (N = 142)
Number of subjects included in the model	69	68	70	62	72	72	131	140	142
LS mean (SE) CFB in lesion area, mm^2	2.8713 (0.17007)	3.3049 (0.25135)	4.0475 (0.26857)	3.3548 (0.23614)	3.4850 (0.22155)	4.1263 (0.25919)	3.0995 (0.14428)	3.4051 (0.16767)	4.0809 (0.18566)
95% CI of LS mean CFB in lesion area, mm^2	2.5377-3.2049	2.8120-3.7979	3.5207-4.5743	2.8916-3.8179	3.0505-3.9196	3.6180-4.6347	2.8166-3.3823	3.0764-3.7339	3.7159-4.4449
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm^2	−1.1762 (−1.8055 to −0.5468)	−0.7426 (−1.4650 to −0.0201)	NA	−0.7716 (−1.4516 to −0.0915)	−0.6413 (−1.3108 to 0.0282)	NA	−0.9814 (−1.4420 to −0.5209)	−0.6758 (−1.1665 to −0.1851)	NA
Percentage difference in LS mean CFB in lesion area vs sham pooled group, mm^2	−29.1	−18.3	NA	−18.7	−15.5	NA	−24.0	−16.6	NA
P value vs sham pooled group	.0003	.0440	NA	.0262	.0605	NA	<.0001	.0070	NA

Tertile of LLD of the study eye: ≥32 ETDRS letters									
	Study APL2-304			Study APL2-303			Pooled data		
	PM (N = 75)	PEOM (N = 70)	Sham pooled (N = 63)	PM (N = 74)	PEOM (N = 63)	Sham Pooled (N = 63)	PM (N = 149)	PEOM (N = 133)	Sham Pooled (N = 126)
Number of subjects included in the model	75	69	63	74	63	63	149	132	126
LS mean (SE) CFB in lesion area, mm^2	3.7205 (0.32631)	3.9522 (0.24759)	4.4792 (0.23618)	3.5580 (0.22295)	3.8074 (0.24103)	4.7265 (0.36623)	3.6353 (0.19505)	3.8877 (0.17469)	4.5944 (0.21926)
95% CI of LS mean CFB in lesion area, mm^2	3.0804-4.3605	3.4666-4.4379	4.0159-4.9425	3.1207-3.9953	3.3346-4.2802	4.0081-5.4449	3.2529-4.0177	3.5452-4.2302	4.1645-5.0243
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm^2	−0.7587 (−1.5502 to 0.0327)	−0.5270 (−1.1877 to 0.1338)	NA	−1.1685 (−2.0046 to −0.3323)	−0.9190 (−1.7726 to −0.0655)	NA	−0.9591 (−1.5341 to −0.3841)	−0.7067 (−1.2510 to −0.1624)	NA
Percentage difference in LS mean CFB in lesion area vs sham pooled group	−16.9	−11.8	NA	−24.7	−19.4	NA	−20.9	−15.4	NA
P value vs sham pooled group	.0602	.1179	NA	.0062	.0348	NA	.0011	.0109	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; ETDRS = Early Treatment Diabetic Retinopathy Study; FAF = fundus autofluorescence; GA = geographic atrophy; LLD = low-luminance deficit; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. For Studies APL2-303 and APL2-304, model includes treatment + baseline GA lesion area (7.5 mm^2 or ≥7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion area × analysis visit. The model for pooled data also included study as a covariate.

Number of Intermediate/Large Drusen at Baseline (number of intermediate/large drusen >20 or ≤20)

Table 44: Analyses of CFB in total area of GA lesion(s) (mm²) (FAF) of the study eye at month 24 with MMRM model by number of intermediate/large drusen (>20 vs ≤20) of the study eye at baseline in study APL2-304, study APL2-303, and pooled data-mITT population

Number of intermediate/large drusen >20									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 93)	**PEOM (N = 104)**	**Sham pooled (N = 103)**	**PM (N =78)**	**PEOM (N = 78)**	**Sham pooled (N = 98)**	**PM (N =171)**	**PEOM (N = 182)**	**Sham pooled (N = 202)**
Number of subjects included in the model	93	103	104	78	77	98	171	180	202
LS mean (SE) CFB in lesion area, mm^2	2.6584 (0.16364)	2.7583 (0.13748)	3.5246 (0.18005)	3.1880 (0.18733)	2.8539 (0.18143)	3.4185 (0.23831)	2.9275 (0.12411)	2.8096 (0.10827)	3.4934 (0.14521)
95% CI of LS mean CFB in lesion area, mm^2	2.3375-2.9793	2.4887-3.0279	3.1715-3.8776	2.8207-3.5554	2.4981-3.2097	2.9512-3.8858	2.6838-3.1713	2.5970-3.0223	3.2082-3.7787
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm^2	−0.8662 (−1.3380 to −0.3944)	−0.7663 (−1.2068 to −0.3258)	NA	−0.2305 (−0.8179 to 0.3569)	−0.5646 (−1.1496 to 0.0204)	NA	−0.5659 (−0.9358 to −0.1960)	−0.6838 (−1.0395 to −0.3281	NA
Percentage difference in LS mean CFB in lesion area vs sham pooled group	−24.6	−21.7	NA	−6.7	−16.5	NA	−16.2	−19.6	NA
P value vs sham pooled group	.0003	.0007	NA	.4417	.0585	NA	.0028	.0002	NA

Number of intermediate/large drusen: ≤20									
	Study APL2-304			**Study APL2-303**			**Pooled data**		
	PM (N = 108)	**PEOM (N = 101)**	**Sham pooled (N = 102)**	**PM (N = 123)**	**PEOM (N = 123)**	**Sham pooled (N = 97)**	**PM (N = 231)**	**PEOM (N = 224)**	**Sham pooled (N = 199)**
Number of subjects included in the model	108	101	101	122	123	96	230	224	197
LS mean (SE) CFB in lesion area, mm^2	3.5727 (0.24109)	3.7984 (0.22441)	4.4785 (0.21852)	3.2775 (0.17198)	3.6086 (0.17745)	4.6878 (0.23530)	3.3942 (0.13845)	3.7250 (0.13766)	4.5856 (0.15955)
95% CI of LS mean CFB in lesion area, mm^2	3.1000-4.0455	3.3583-4.2384	4.0500-4.9070	2.9403-3.6147	3.2606-3.9565	4.2265-5.1492	3.1224-3.6661	−0.8607 (−1.2701 to −0.4512	4.2723-4.8989
Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm^2	−0.9058 (−1.5426 to −0.2690)	−0.6801 (−1.2860 to −0.0743)	NA	−1.4103 (−1.9766 to −0.8440)	−1.0792 (−1.6511 to −0.5073)	NA	−1.1914 (−1.6047 to −0.7781)	−0.8607 (−1.2701 to −0.4512	NA
Percentage difference CFB in lesion area vs sham pooled group	−20.2	−15.2	NA	−30.1	−23.0	NA	−26.0	−18.8	NA
P value vs sham pooled group	.0053	.0278	NA	<.0001	.0002	NA	<.0001	<.0001	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. For Studies APL2-303 and APL2-304, model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion area × analysis visit. The model for pooled data also included study as a covariate.

Secondary Endpoints

Correlation Analyses (Post hoc)

Spearman partial correlation coefficients for the CFB in GA lesion size and CFB of visual function measures were calculated at month 24 for Study APL2-304, Study APL2-303, and pooled data adjusting for treatment groups.

Table 45: Post hoc correlation between GA lesion growth and visual function endpoints – baseline to month 24 – study APL2-304, study APL2-303, and pooled data

Functional endpoint	APL2-304 correlation coefficient with lesion growth (*P* value)	APL2-303 correlation coefficient with lesion growth (*P* value)	Pooled data correlation coefficient with lesion growth (*P* value)
CFB in monocular maximum reading speed, words per minute	−0.1468 (*P* = .0057)	−0.1586 (*P* = .0018)	−0.163 (*P* < .0001)
CFB in mean FRI Index score	−0.1224 (*P* = .0214)	−0.0519 (*P* = .3082)	−0.0976 (*P* = .0058)
CFB in NL-BCVA score	−0.1189 (*P* = .0255)	−0.1934 (*P* < .0001)	−0.1494 (*P* < .0001)
CFB in mean threshold sensitivity, dB—Study APL2-304 only	−0.2370 (*P* < .0001)	NA	N/A
CFB in number of scotomatous points—Study APL2-304 only	0.5116 (*P* < .0001)	NA	N/A

Abbreviations: CFB = change from baseline; ETDRS = Early Treatment Diabetic Retinopathy Study; FRI = Functional Reading Independence; GA = geographic atrophy; NA = not applicable; NL-BCVA = normal-luminance best-corrected visual acuity.

Note: The Spearman partial correlation, adjusted for treatment group, is presented.

Change in lesion growth from baseline to month 24 was categorised into quartiles to investigate whether the magnitude of lesion growth correlates to the magnitude of visual function changes in the pooled data combining all treatment arms from Study APL2-303 and Study APL2-304 (quartiles: 1.3509 mm^2, 2.5653 mm^2, 3.7859 mm^2, and 6.1672 mm^2).

Table 46: Post hoc analysis of change from baseline for each visual function endpoint based on GA lesion growth quartiles – baseline to month 24 – pooled studies APL2-304 and APL2-303

Quartile group	Mean GA lesion growth, mm^2	Maximum reading speed, words per minute	FRI Index score	NL-BCVA score (EDTRS letters)	Mean threshold sensitivity, dB[a]	Number of scotomatous points[a]
Quartile 1 (≤2.076 mm^2)						
n	225	199	219	224	99	99
Mean (SD)	1.3509	−11.6 (35.93)	−0.19 (0.683)	−4.2 (13.48)	−2.52 (2.9163)	6.51 (6.9830)
Quartile 2 (>2.076 to ≤3.133 mm^2)						
n	225	206	222	224	104	104
Mean (SD)	2.5653	−12.3 (50.96)	−0.30 (0.726)	−6.5 (13.04)	−2.85 (2.8744)	9.23 (9.2066)
Quartile 3 (>3.133 to ≤4.534 mm^2)						
n	225	207	220	225	100	100
Mean (SD)	3.7859	−17.5 (43.16)	−0.44 (0.753)	−8.2 (14.60)	−3.02 (2.6860)	10.43 (8.4042)
Quartile 4 (>4.534 mm^2)						
n	225	206	217	224	85	85
Mean (SD)	6.1672	−26.0 (51.73)	−0.36 (0.741)	−8.5 (13.86)	−3.67 (3.2410)	14.88 (8.5278)

Abbreviations: FRI = Functional Reading Independence; GA = geographic atrophy; NL-BCVA = normal-luminance best-corrected visual acuity.

[a] Mean threshold sensitivity and number of scotomatous points are from Study APL2-304 only.

Sources: Month 24 Integrated Summary of Efficacy Table 14.5.4.2.14, Table 14.5.4.2.15, Table 14.5.4.2.16, Table 14.5.4.2.17, Table 14.5.3.2.4, Table 14.5.3.2.5, and Post-Hoc Table 14.5.4.2.18.

Further exploration of refined analyses of scotomatous points to better understand underlying lesion growth -visual function correlation was performed.

Overall Number of Scotomatous Points (prespecified)

Table 47: Analysis of change baseline in number of scotomatous points of the study eye with MMRM model at month 24-mITT population

	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 207)**
Baseline, n Mean (SD)	199 14.9 (10.76)	203 16.3 (13.12)	203 16.3 (13.76)
Estimates/comparisons at month 24			
Number of subjects included in the model	179	187	186
LS mean (SE) CFB in number of scotomatous points	10.400 (0.9096)	9.569 (0.6777)	10.372 (0.6867)
95% CI of LS mean CFB in number of scotomatous points	8.613-12.186	8.238-10.900	9.023-11.721
Difference (95% CI) in LS mean CFB in number of scotomatous points (vs sham pooled)	0.027 (−2.137 to 2.192)	−0.803 (−2.623 to 1.017)	NA
P value (vs sham pooled)	.9803	.3863	NA

Abbreviations: CNV = choroidal neovascularization; CSR = clinical study report; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measure; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline number of scotomatous points + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline number of scotomatous points × analysis visit.
Sources: Study APL2-304 Month 24 CSR, Table 14.2.5.5.1 and Table 14.2.5.5.3.

Number of Scotomatous Points in the Junctional Zone (spanning ±250 µm on either side of the lesion border) (post hoc)

Table 48: Post hoc analysis of change from baseline in number of scotomatous points of the study eye with MMRM model junctional zone -250 to 250 µm of baseline atrophy border – mITT population, baseline through month 24

	PM **N=202**	**PEOM** **N=205**	**Sham pooled** **N=207**
Baseline, n Mean (SD)	197 6.4 (5.95)	200 6.0 (6.37)	199 6.3 (6.26)
Number of subjects included in the model	178	184	182
LS mean (SE)	6.487 (0.3424)	6.029 (0.3309)	7.167 (0.3391)
95% CI of LS mean	5.814-7.159	5.379-6.678	6.501-7.833
Difference (95% CI) in LS mean vs sham pooled	−0.680 (−1.595 to 0.234)	−1.138 (−2.045 to −0.231)	NA
Percentage difference vs sham pooled	−9.5	−15.9	NA
P value vs sham pooled	.1444	.0140	NA

Abbreviations: CNV = choroidal neovascularization; GA = geographic atrophy; LS = least-square; NA = not applicable; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measure; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: Model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + the total number of points between −250 µm and 250 µm + the baseline number of scotomatous points between −250 µm and 250 µm + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + the baseline number of scotomatous points between −250 µm and 250 µm × analysis visit + the total number of points between −250 µm and 250 µm × analysis visit.
Sources: Microperimetry Statistical Report APL2-304-EFF02, Table 4 (Table 14.5.2.3.1) and Post-Hoc Table 14.5.2.3.

Microperimetry Functional Assessment in the Area of High Risk of Central Vision Loss (Central 4 stimuli in the microperimetry grid) (post hoc)

Analyses were performed in the subgroup of subjects in whom not all the 4 central stimulus loci were scotomatous at baseline, (i.e., the at-risk population). An event of conversion of all 4 central points in the study eye to scotoma was defined as a subject having scotomatous points for all central 4 points of the study eye. Time to conversion of all 4 central points is defined as time from date of first dose of investigational product to the first time when conversion occurred.

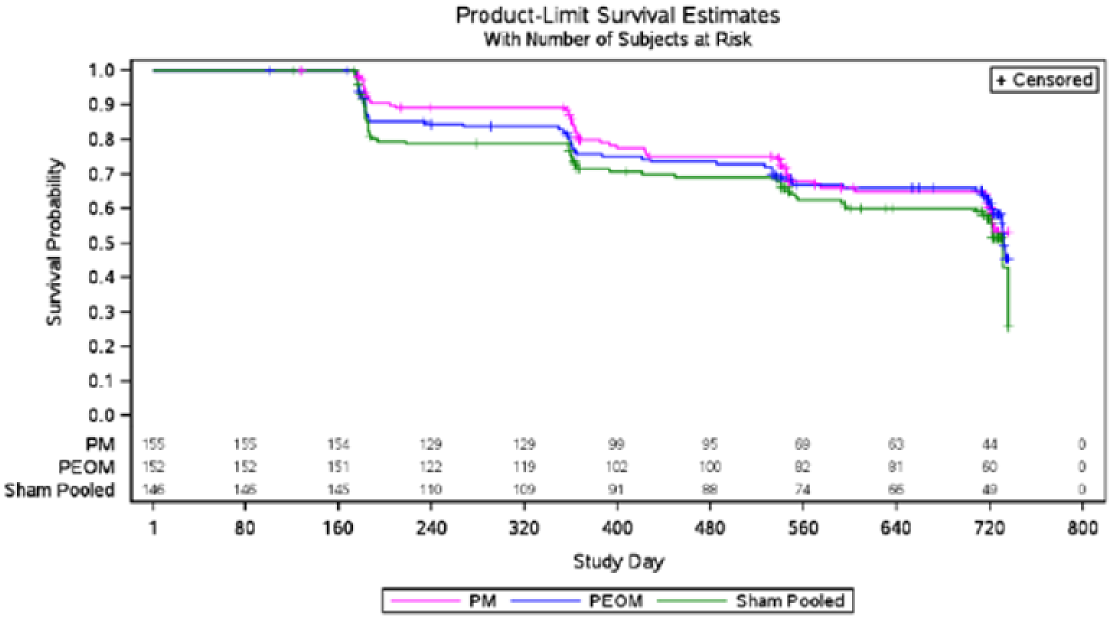
A Cox proportional hazards model with covariates for treatment, stratification factors (baseline GA lesion area [<7.5mm2, ≥7.5mm2], baseline presence of CNV in the fellow eye [Yes, No]), and the baseline number of central 4 scotomatous points) was used to estimate hazard ratios, 95% CIs, and P-values for comparing the time to conversion of all central 4 points in the study eye to scotoma between treatment groups.

Table 49: Post hoc analysis of conversion of all 4 central points to scotoma in the study eye with Cox Proportional Hazards model – mITT set – baseline through month 24 – study APL2-304

Overall	**PM** **N = 202**	**PEOM** **N = 202**	**Sham pooled** **N = 207**
Number of subjects included in the model	155	152	146
Total number (%) of events	54 (34.8)	59 (38.8)	64 (43.8)
Total number (%) of censored	101 (65.2)	93 (61.2)	82 (56.2)
Hazard ratio (95% CI) (vs sham pooled)	0.66 (0.46-0.96)	0.64 (0.44-0.92)	
P value (vs sham pooled)	.0282	.0164	

Abbreviations: mITT = modified intent-to-treat; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

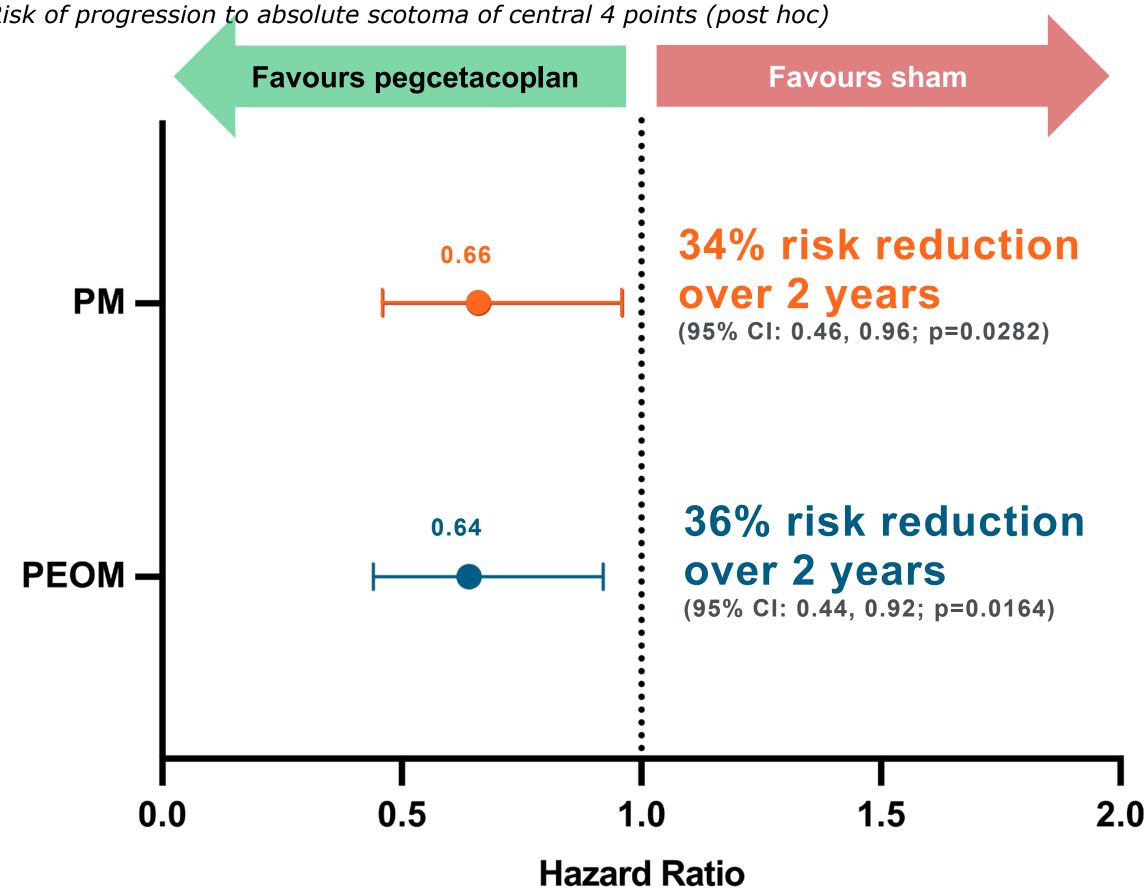
Note: Subjects censored on day 1 due to no postbaseline assessment or not at risk for the event are excluded from analysis. The first observed postbaseline assessment with 4 central scotomatous points is counted as the event. Model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline presence of CNV in the fellow eye (yes or no) + baseline number of central 4 scotomatous points (categorical).



Note: Subjects censored on day 1 due to no postbaseline assessment or not at risk for the event are excluded from analysis. The first observed postbaseline assessment with 4 central scotomatous points is counted as the event.

Figure 17: Kaplan Meier Plot for conversion of all 4 central points to scotoma in the study eye – mITT set – baseline to month 24 – study APL2-304 (post hoc)

Risk of progression to absolute scotoma of central 4 points (post hoc)



Notes: Post hoc analysis, p-values are nominal. Hazard ratio estimated from Cox proportional hazards model, including patients in the modified intent-to-treat population at-risk for the event with at least one post-baseline assessment. The first observed post-baseline assessment with 4 central scotomatous points is counted as the event. Microperimetry performed only in OAKS. CI, confidence interval; PEOM, pegcetacoplan every other month; PM, pegcetacoplan monthly.

Figure 18: Risk of progression to absolute scotoma of central 4 points (post hoc)

Relationship between mean (SE) NL-BCVA and number of scotomatous points (central 4 stimuli in the microperimetry grid) (post hoc)

The relationship between mean (SE) NL-BCVA and number of scotomatous points among the central 4 stimuli at baseline for all treatment groups combined was investigated.

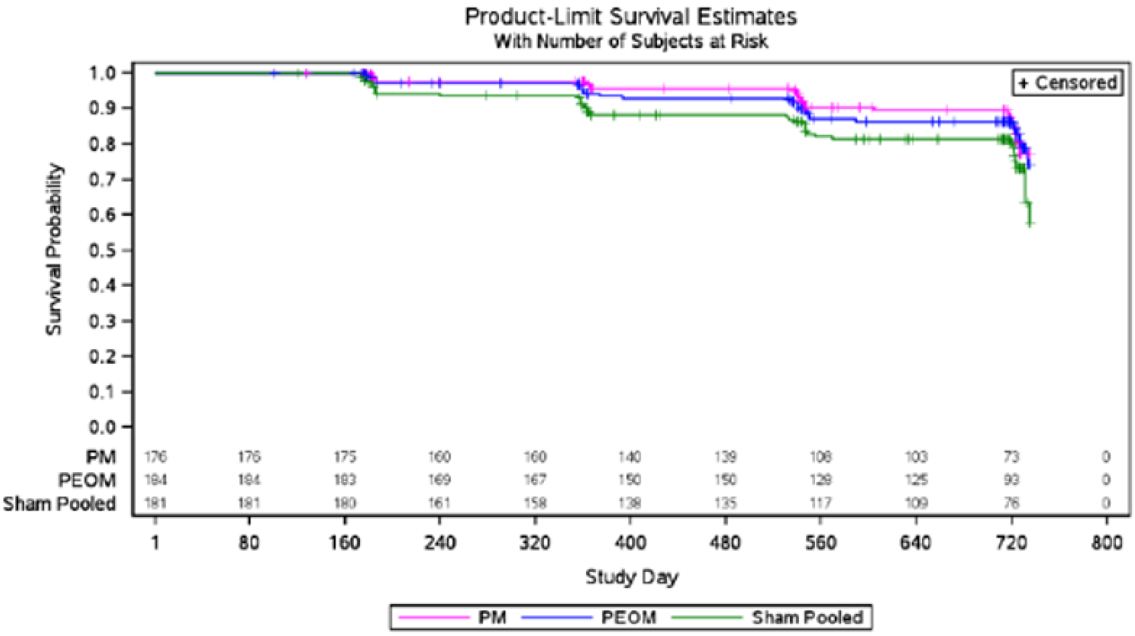
Table 50: Summary of NL-BCVA score (ETDRS letters) in the study eye at baseline by number of scotomatous points in the central 4 points at baseline in the study eye – mITT population (post hoc)

Number of scotomatous points	n (%)	Mean	Standard error of mean
0	147 (23.9)	68.5	1.09
1	136 (22.1)	61.8	1.30
2	121 (19.7)	58.4	1.41
3	90 (14.7)	54.7	1.67
4	111 (18.1)	47.1	1.38
Missing	9 (1.5)	53.7	3.87

Source: Study APL2-304 Table 14.6.2.19.1.

Microperimetry Functional Assessment in the Area of High Risk of Central Vision Loss (Central 16 stimuli in the microperimetry grid) (post hoc)

The Figure below presents the Kaplan Meier plot for time to conversion of all 16 central points in the study eye to scotoma across the 3 treatment groups. The Table below shows the results of the Cox proportional hazards regression model.



Note: Subjects censored on day 1 due to no post-baseline assessment or not at risk for the event are excluded from analysis. The first observed post-baseline assessment with 4 central scotomatous points is counted as the event.
Source: Study APL2-304 Month 24, Figure 14.3.1.14.

Figure 19: Kaplan Meier Plot for conversion of all 16 central points to scotoma in the study eye – mITT population – baseline to month 24 (post hoc)

Table 51: Post hoc analysis of conversion of all 16 central points to scotoma in the study eye with Cox Proportional Hazards model – mITT population – baseline through Month 24

Overall	**PM** **N=202**	**PEOM** **N=205**	**Sham pooled** **N=207**
Number of subjects included in the model	176	184	181
Total number (%) of events	22 (12.5)	28 (15.2)	39 (21.5)
Total number (%) of censored	154 (87.5)	156 (84.8)	142 (78.5)
Hazard ratio (95% CI) (vs sham pooled)	0.57 (0.33 to 0.96)	0.52 (0.32 to 0.85)	NA
P value (vs sham pooled)	0.0361	0.0084	NA

Abbreviations: CI = confidence interval; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Note: Subjects censored on day 1 due to no post-baseline assessment or not at risk for the event are excluded from analysis. The first observed post-baseline assessment with 16 central scotomatous points is counted as the event. Model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline presence of CNV in the fellow eye (yes or no) + baseline number of central 16 scotomatous points.
Source: Study APL2-304 Table 14.6.2.19.5.

Relationship between mean (SE) NL-BCVA and number of scotomatous points (central 16 stimuli in the microperimetry grid) (post hoc)

The relationship between mean (SE) NL-BCVA and number of scotomatous points among the central 16 stimuli at baseline for all treatment groups combined was investigated.

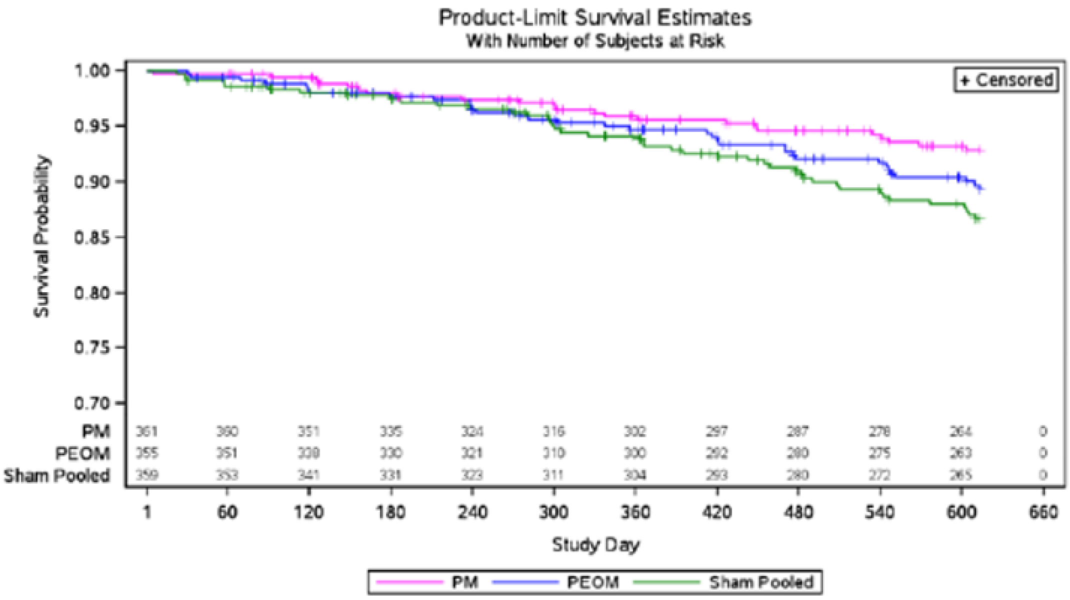
Table 52: Summary of NL-BCVA score (ETDRS letters) in the study eye at baseline by number of scotomatous points in the central 16 points at baseline in the study eye – mITT population (post hoc)

Number of scotomatous points	n (%)	Mean	Standard error of mean
0	14 (2.3)	65.4	4.16
1	19 (3.1)	65.9	3.55
2	48 (7.8)	62.0	2.13
3	61 (9.9)	62.5	2.09
4	54 (8.8)	59.4	2.17
5	56 (9.1)	60.7	2.09
6	45 (7.3)	65.0	2.19
7	33 (5.4)	62.8	2.77
8	44 (7.2)	53.7	2.52
9	34 (5.5)	58.5	2.75
10	30 (4.9)	56.9	3.28
11	35 (5.7)	60.5	2.49
12	30 (4.9)	56.6	3.09
13	34 (5.5)	57.5	2.51
14	28 (4.6)	54.4	2.56
15	25 (4.1)	47.6	3.52
16	15 (2.4)	38.5	3.65
Missing	9 (1.5)	53.7	3.87

Source: Study APL2-304 Table 14.6.2.19.3.

<u>Reduction in Progression to Severe Visual Impairment (NL-BCVA < 35 ETDRS Letters) (post hoc)</u>

Analyses were performed in the subgroup of subjects in the pooled APL2-304 and APL2-303 studies without severe visual impairment at baseline. An event of severe visual impairment was defined as the first time a subject experienced a sustained reduction below 35 ETDRS letters for at least 4 months post-baseline without later recovery to above ≥40 letters at a subsequent assessment. Subjects without an event are censored at their last post-baseline BCVA assessment. Subjects with an event or censored were summarised and described with the Kaplan Meier method. A Cox proportional hazards model with covariates for treatment, stratification factors (baseline GA lesion area [<7.5mm2, ≥7.5mm2], baseline presence of CNV in the fellow eye [Yes, No]), baseline BCVA, and study (for pooled data) was used to estimate hazard ratios, 95% confidence intervals and P values for comparing the time to severe visual impairment between treatment groups.



Abbreviations: ETDRS = Early Treatment Diabetic Retinopathy Study; mITT = modified intent-to-treat; NL-BCVA = no luminance best-corrected visual acuity; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Note: An event was defined as the first time a subject experienced a sustained reduction below 35 ETDRS letters for at least 4 months post-baseline (including both scheduled and unscheduled visits) and without a later recovery to ≥40 at a subsequent assessment.
Source: Pooled APL2-304 and APL2-303 Figure 14.6.2.19.1.

Figure 20: Kaplan Meier Plot for sustained reduction in NL-BCVA to < 35 ETDRS letters in the study eye in subjects with ≥ 35 ETDRS letters in the study eye at baseline – mITT population – baseline to month 24 (post hoc)

Table 53: Post hoc analysis of sustained reduction in NL-BCVA to < 35 ETDRS letters in the study eye in subjects with ⩾ 35 ETDRS letters in the study eye at baseline with Cox Proportional Hazards model – mITT population – baseline through month 24

	PM **N=403**	**PEOM** **N=406**	**Sham pooled** **N=402**
Number of subjects included in the model	361	355	359
Total number (%) of events	23 (6.4)	34 (9.6)	43 (12.0)
Total number (%) of censored	338 (93.6)	321 (90.4)	316 (88.0)
Hazard ratio (95% CI) (vs sham pooled)	0.62 (0.37 to 1.04)	0.88 (0.56 to 1.39)	N/A
P value (vs sham pooled)	.0684	.5910	N/A

Abbreviations: CI = confidence interval; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; mITT = modified intent-to-treat; NL-BCVA = no luminance best-corrected visual acuity; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Note: An event was defined as the first time a subject experienced a sustained reduction below 35 ETDRS letters for at least 4 months post-baseline (including both scheduled and unscheduled visits) and without a later recovery to ≥40 at a subsequent assessment. Model includes study + treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline presence of CNV in the fellow eye (Yes or No) + baseline BCVA.

Source: Pooled APL2-304 and APL2-303 Table 14.6.2.19.1.

Prediction of Treatment Effect Beyond 24 Months (post hoc)

Time Gained with Preserved Vision

Table 54: Estimated months gained with treatment to reach lesion growth levels without treatment over time in Studies APL2-304, APL2-303, and APL2-GA-305 – pooled APL2-303 and APL2-304 mITT population (post hoc)

Time point for lesion growth without treatment	Untreated lesion growth, mm^2	Months gained with treatment	
		PM	PEOM
3 years (month 36)	6.00	13.5	11.2
3.5 years (month 42)	7.00	16.5	13.7
4 years (month 48)	8.00	19.5	16.2
4.5 years (month 54)	9.00	22.6	18.7
5 years (month 60)	10.01	25.6	21.2

Abbreviations: CNV = choroidal neovascularization; GA = geographic atrophy; LS = least square; mITT = modified intent-to-treat; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: The mean rate of change of sham after integrated month 24 is estimated by calculating the average of the mean rate of change of each 6-month periods (from antecedent study baseline to integrated month 6, from integrated month 6 to integrated month 12, from integrated month 12 to integrated month 18, from integrated month 18 to integrated month 24) of sham group. Time to reach sham LS mean is defined as the time at which each treatment arm (PM/PEOM) reaches the estimated sham LS mean at a reference time point based on the estimated month 18 to month 30 slope in each treatment arm extrapolated forward from month 30. Months growth delayed vs sham is defined as the difference between the time to reach sham LS mean and the reference time point (months 36, 42, 48, 54, and 60). A heterogeneous autoregressive (1) covariance matrix is used to model the within-subject errors. The model included treatment + baseline GA lesion area (<7.5 mm2 or ≥7.5 mm2) + baseline presence of CNV in the fellow eye (Yes or No) + time + time spline at month 6 + time spline at month 12 + time spline at month 18 + time spline at month 24 + time × treatment + time spline at month 6 × treatment + time spline at month 12 × treatment + time spline at month 18 × treatment + time spline at month 24 × treatment + baseline GA lesion area × time + baseline GA lesion area × time spline at month 6 + baseline GA lesion area × time spline at month 12 + baseline GA lesion area × time spline at month 18 + baseline GA lesion area × time spline at month 24.

Sources: APL2-305 Month 6 Interim Analysis Table 14.6.2.19.1.

Area of Preserved Retinal Tissue

Table 55: Post hoc analysis of estimated growth of GA lesion(s) at clinically relevant timepoints in studies APL2-304, APL2-303, and APL2-GA-305 – pooled APL2-303 and APL2-304 mITT population

	PM N=406	PEOM N=406	Sham pooled N=402
Estimates/comparisons at month 30			
LS mean (SE)	3.84 (0.123)	3.98 (0.120)	5.00 (0.139)
Difference (95% CI) in LS mean (vs sham pooled)	−1.16 (−1.53 to −0.80)	−1.02 (−1.38 to −0.66)	N/A
Estimates/comparisons at month 36			
LS mean (SE)	4.51 (0.156)	4.69 (0.151)	6.00 (0.166)
Difference (95% CI) in LS mean (vs sham pooled)	−1.50 (−1.94 to −1.05)	−1.32 (−1.76 to −0.88)	N/A
Estimates/comparisons at month 42			
LS mean (SE)	5.17 (0.191)	5.39 (0.182)	7.00 (0.194)
Difference (95% CI) in LS mean (vs sham pooled)	−1.83 (−2.37 to −1.30)	−1.61 (−2.13 to −1.09)	N/A
Estimates/comparisons at month 48			
LS mean (SE)	5.84 (0.226)	6.10 (0.215)	8.00 (0.222)
Difference (95% CI) in LS mean (vs sham pooled)	−2.17 (−2.79 to −1.55)	−1.90 (−2.51 to −1.30)	N/A
Estimates/comparisons at month 54			
LS mean (SE)	6.50(0.263)	6.81 (0.249)	9.00 (0.249)
Difference (95% CI) in LS mean (vs sham pooled)	−2.50 (−3.21 to −1.79)	−2.20 (−2.89 to −1.51)	N/A
Estimates/comparisons at month 60			
LS mean (SE)	7.17 (0.300)	7.51 (0.283)	10.01 (0.277)
Difference (95% CI) in LS mean (vs sham pooled)	−2.84 (−3.64 to −2.04)	−2.49 (−3.27 to −1.72)	N/A

Abbreviations: GA = geographic atrophy; LS = least squares; mITT = modified intent-to-treat; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: The same extrapolation model as was used for Table 14 above, was used to derive the GA growth differences at the clinically relevant timepoints.
Sources: APL2-305 Month 6 Interim Analysis Table 14.6.2.19.2.

Time with Preserved Sensitivity in the Central Foveal Area

Table 56: Predicted percentages of subjects without conversion of central 4 and central 16 points to scotomatous over time – APL2-304 mITT population (post hoc)

Time point	Central 4			Central 16		
	PM	PEOM	Sham Pooled	PM	PEOM	Sham Pooled
3 years (month 36)	36.5%	37.6%	21.3%	77.4%	77.5%	60.5%
3.5 years (month 42)	25.9%	26.9%	12.6%	69.3%	69.5%	48.8%
4 years (month 48)	17.5%	18.4%	6.9%	60.7%	60.9%	37.6%
4.5 years (month 54)	11.3%	12.0%	3.5%	51.9%	52.1%	27.7%
5 years (month 60)	7.0%	7.5%	1.7%	43.3%	43.5%	19.4%

Abbreviations: CNV = choroidal neovascularization; GA = geographic atrophy; mITT = modified intent-to-treat; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Notes: Predictions obtained from a parametric survival model with a Weibull distribution. For Central 4, the model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline presence of CNV in the fellow eye (Yes or No) + baseline number of central 4 scotomatous points (categorical). For central 16, the model includes treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline presence of CNV in the fellow eye (Yes or No) + baseline number of central 16 scotomatous points.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 57: Summary of efficacy for trial APL2-304

Title: A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, SHAM-CONTROLLED STUDY TO COMPARE THE EFFICACY AND SAFETY OF INTRAVITREAL PEGCETACOPLAN THERAPY WITH SHAM INJECTIONS IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION (OAKS)	
Study identifier	APL2-304 OAKS EudraCT No.: 2018-001436-22
Design	Study APL2304 was a phase 3, multicentre, randomised, double-masked, sham injection-controlled study to assess the efficacy and safety of multiple intravitreal (IVT) injections of pegcetacoplan (also known as APL2) in subjects with GA secondary to AMD. The study assigned 637 subjects across 110 multinational sites to randomly selected treatment. Subjects were screened within 28 days before receiving pegcetacoplan or sham injection. Upon entry into the study, subjects were assigned a screening number. Subjects who met all inclusion and none of the exclusion criteria returned to the clinic for randomisation and treatment on visit 2 (day 1). At this visit, subjects were assigned in a 2:2:1:1 manner to receive pegcetacoplan monthly (PM), pegcetacoplan every other month (PEOM), sham injection monthly (SM), or sham injection every other month (SEOM), respectively. Randomisation was stratified according to GA lesion area at screening (<7.5 mm^2; ≥7.5 mm^2) and presence of CNV in the fellow eye.

	Duration of main phase: Duration of run-in phase: Duration of extension phase:		24 months Not applicable For extension, patients enrolled in a separate study.
Hypothesis	Superiority: The null hypotheses for the primary endpoint were as follows: H_{1a}: There is no difference between PM and sham in mean change from baseline to month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF for the mITT set. H_{1b}: There is no difference between PEOM and sham in mean change from baseline to month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF for the mITT set.		
Treatment groups	PM		Pegcetacoplan monthly, 24 months, 213
	PEOM		Pegcetacoplan every other month, 24 months, 212
	SM		Sham injection monthly, 24 months, 106
	SEOM		Sham injection every other month, 24 months, 106
Endpoints and definitions	Primary endpoint	Change from baseline in total area of GA lesion at Month 12 in the study eye	The primary endpoint is the change from baseline to month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF.
	Primary endpoint at M24	Change from baseline in total area of GA lesion at month 24 in the study eye	The primary endpoint at month 24 is the change from baseline to month 24 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF.
	Key secondary endpoint 1	Change from baseline in mean threshold sensitivity of all points of the study eye at month 24	Change from baseline in the mean threshold sensitivity of all points (study eye) assessed by mesopic microperimetry at month 24
	Key secondary endpoint 2	Change from baseline in monocular maximum reading speed of the study eye at month 24	Change from baseline in monocular maximum reading speed (study eye) at month 24 as assessed by MNREAD or Radner Reading Charts (in select countries)
	Key secondary endpoint 3	Change from baseline in mean Functional Reading Independence Index score at month 24	Change from baseline in mean FRI Index score (subject-level assessment) at month 24

	Key secondary endpoint 4	Change from baseline in normal-luminance best corrected visual acuity of the study eye at month 24	Change from baseline in NL-BCVA score (study eye) at month 24 as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) chart
Database lock	12M: 18 August 2021 24M (final): 21 July 2022		

Results and Analysis				
Analysis description	**Prespecified Primary Analysis**			
Analysis population and time point description	mITT Population The mITT population consists of all subjects who received at least one injection of pegcetacoplan or sham and had baseline and at least one postbaseline value of GA lesion area in the study eye as assessed by FAF. Month 12			
Descriptive statistics and estimate variability	Treatment group	PM	PEOM	Sham pooled
	Number of subjects	202	204	205
	Change from baseline in total area of GA lesion at month 12 in the study eye, least-square mean, mm^2	1.5579	1.6512	1.9692
	Standard error, mm^2	0.08350	0.08118	0.08218

Effect estimate per comparison	Primary endpoint	Comparison groups	PM compared to sham pooled
		Difference in least-square means, mm^2	−0.4114
		Percentage difference in least-square means	−20.9%
		95% confidence interval for difference in least-square means, mm^2	−0.6397 to −0.1831
		P value from MMRM for difference in least-square means	.0004
	Primary endpoint	Comparison groups	PEOM compared to sham pooled
		Difference in least-square means, mm^2	−0.3180
		Percentage difference in least-square means	−16.1%
		95% confidence interval for difference in least-square means, mm^2	−0.5423 to −0.0937

		P value from MMRM for difference in least-square means	.0055	
Notes	At month 12, the study met its primary endpoint by confirming a positive effect in reduction of GA progression in the PM and PEOM groups in comparison with the sham pooled group; these differences were statistically significant for both pegcetacoplan treatment groups at the prespecified α level (0.0496).			
Analysis description	**Prespecified Analysis of Change From Baseline in GA Lesion Size in the Study Eye at Month 24 (Primary Endpoint at Month 24)**			
	mITT Population The mITT population consists of all subjects who received at least one injection of pegcetacoplan or sham and had baseline and at least one postbaseline value of GA lesion area in the study eye as assessed by FAF. Month 24			
Descriptive statistics and estimate variability	Treatment group	PM	PEOM	Sham pooled
	Number of subjects	202	204	206
	Change from baseline in total area of GA lesion in the study eye at month 24, least-square mean, mm^2	3.1237	3.2826	4.0252
	Standard error, mm^2	0.14327	0.13238	0.14642
Effect estimate per comparison	Primary endpoint at month 24	Comparison groups	PM compared to sham pooled	
		Difference in least-square means, mm^2	–0.9015	
		Percentage difference in least-square means	–22.4%	
		95% confidence interval for difference in least-square means, mm^2	−1.3026 to −0.5004	
		P value from MMRM for difference in least-square means	<.0001	
	Primary endpoint at month 24	Comparison groups	PEOM compared to sham pooled	
		Difference in least-square means, mm^2	–0.7426	
		Percentage difference in least-square means	–18.4%	
		95% confidence interval for difference in least-square means, mm^2	−1.1282 to −0.3570	
		P value from MMRM for difference in least-square means	.0002	

Notes	At month 24, in the PM and PEOM groups, GA lesion growth was reduced compared with the sham pooled group. This endpoint was not within the type I error control algorithm for hypothesis testing to be able to declare statistical significance.			
Analysis description	**Prespecified Key Secondary Endpoint Analysis of Mean Threshold Sensitivity of All Points of the Study Eye**			
	mITT Population The mITT population consists of all subjects who received at least one injection of pegcetacoplan or sham and had baseline and at least one postbaseline value of GA lesion area in the study eye as assessed by FAF. Month 24			
Descriptive statistics and estimate variability	Treatment group	PM	PEOM	Sham pooled
	Number of subjects	179	187	186
	Change from baseline in mean threshold sensitivity of all points of the study eye at month 24, least-square mean, dB	−3.319	−3.064	−2.954
	Standard error, dB	0.2969	0.2331	0.2156
Effect estimate per comparison	Key secondary endpoint 1	Comparison groups	PM compared to sham pooled	
		Difference in least-square means, words per minute	−0.365	
		95% confidence interval for difference in least-square means, words per minute	−1.057 to 0.326	
		P value from MMRM for difference in least-square means	.2998	
	Key secondary endpoint 1	Comparison groups	PEOM compared to sham pooled	
		Difference in least-square means, words per minute	−0.110	
		95% confidence interval for difference in least-square means, words per minute	−0.693 to 0.473	
		P value from MMRM for difference in least-square means	.7106	
Notes	No meaningful differences were observed through month 24 for the 3 treatment groups.			
Analysis description	**Prespecified Key Secondary Endpoint Analysis of Monocular Maximum Reading Speed of the Study Eye**			
	mITT Population			

<table>
<tr><td></td><td colspan="4">The mITT population consists of all subjects who received at least one injection of pegcetacoplan or sham and had baseline and at least one postbaseline value of GA lesion area in the study eye as assessed by FAF.
Month 24</td></tr>
<tr><td rowspan="4">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>PM</td><td>PEOM</td><td>Sham pooled</td></tr>
<tr><td>Number of subjects</td><td>168</td><td>181</td><td>181</td></tr>
<tr><td>Change from baseline in monocular maximum reading speed of the study eye at month 24, least-square mean, words per minute</td><td>−22.446</td><td>−17.533</td><td>−16.211</td></tr>
<tr><td>Standard error, words per minute</td><td>3.0329</td><td>3.2886</td><td>3.8129</td></tr>
<tr><td rowspan="8">Effect estimate per comparison</td><td rowspan="4">Key secondary endpoint 2</td><td colspan="2">Comparison groups</td><td>PM compared to sham pooled</td></tr>
<tr><td colspan="2">Difference in least-square means, words per minute</td><td>−6.235</td></tr>
<tr><td colspan="2">95% confidence interval for difference in least-square means, words per minute</td><td>−15.182 to 2.712</td></tr>
<tr><td colspan="2">P value from MMRM for difference in least-square means</td><td>.1716</td></tr>
<tr><td rowspan="4">Key secondary endpoint 2</td><td colspan="2">Comparison groups</td><td>PEOM compared to sham pooled</td></tr>
<tr><td colspan="2">Difference in least-square means, words per minute</td><td>−1.322</td></tr>
<tr><td colspan="2">95% confidence interval for difference in least-square means, words per minute</td><td>−10.562 to 7.918</td></tr>
<tr><td colspan="2">P value from MMRM for difference in least-square means</td><td>.7788</td></tr>
<tr><td>Notes</td><td colspan="4">No meaningful differences were observed through month 24 for the 3 treatment groups.</td></tr>
<tr><td>Analysis description</td><td colspan="4">Prespecified Key Secondary Endpoint Analysis of Functional Reading Independence Index Score</td></tr>
<tr><td></td><td colspan="4">mITT Population
The mITT population consists of all subjects who received at least one injection of pegcetacoplan or sham and had baseline and at least one postbaseline value of GA lesion area in the study eye as assessed by FAF.
Month 24</td></tr>
<tr><td></td><td>Treatment group</td><td>PM</td><td>PEOM</td><td>Sham pooled</td></tr>
</table>

Descriptive statistics and estimate variability	Number of subjects	185	193	195
	Change from baseline in mean Functional Reading Independence Index score at month 24, least-square mean	−0.287	−0.379	−0.273
	Standard error	0.0563	0.0536	0.0554
Effect estimate per comparison	Key secondary endpoint 3	Comparison groups	PM compared to sham pooled	
		Difference in least-square means	−0.015	
		95% confidence interval for difference in least-square means	−0.162 to 0.133	
		P value from MMRM for difference in least-square means	.8450	
	Key secondary endpoint 3	Comparison groups	PEOM compared to sham pooled	
		Difference in least-square means	−0.106	
		95% confidence interval for difference in least-square means	−0.252 to 0.039	
		P value from MMRM for difference in least-square means	.1508	
Notes	No meaningful differences were observed through month 24 for the 3 treatment groups.			
Analysis description	**Prespecified Key Secondary Endpoint Analysis of Normal-Luminance Best Corrected Visual Acuity of the Study Eye**			
	mITT Population The mITT population consists of all subjects who received at least one injection of pegcetacoplan or sham and had baseline and at least one postbaseline value of GA lesion area in the study eye as assessed by FAF. Month 24			
Descriptive statistics and estimate variability	Treatment group	PM	PEOM	Sham pooled
	Number of subjects	202	205	207
	Change from baseline in normal luminance best corrected visual acuity of the study eye at month 24, least-square mean, ETDRS letters	−7.477	−8.526	−7.660

	Standard error, ETDRS letters	1.0512	1.0525	1.0734
Effect estimate per comparison	Key secondary endpoint 4	Comparison groups	PM compared to sham pooled	
		Difference in least-square means, ETDRS letters	0.183	
		95% confidence interval for difference in least-square means, ETDRS letters	–2.724 to 3.090	
		P value from MMRM for difference in least-square means	.9015	
	Key secondary endpoint 4	Comparison groups	PEOM compared to sham pooled	
		Difference in least-square means	–0.866	
		95% confidence interval for difference in least-square means	–3.793 to 2.062	
		P value from MMRM for difference in least-square means	.5615	
Notes	No meaningful differences were observed through month 24 for the 3 treatment groups.			

Table 58: Summary of efficacy for trial APL2-303

<table>
<tr><td colspan="4"><u>Title</u>: A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, SHAM-CONTROLLED STUDY TO COMPARE THE EFFICACY AND SAFETY OF INTRAVITREAL PEGCETACOPLAN THERAPY WITH SHAM INJECTIONS IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION (DERBY)</td></tr>
<tr><td>Study identifier</td><td colspan="3">APL2-303
DERBY
EudraCT No.: 2018-001436-22</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">Study APL2-303 was a phase 3, multicentre, randomised, double-masked, sham injection-controlled study to assess the efficacy and safety of multiple intravitreal (IVT) injections of pegcetacoplan (also known as APL-2) in subjects with GA secondary to AMD.

The study assigned 621 subjects across 122 multinational sites to randomly selected treatment. Subjects were screened within 28 days before receiving pegcetacoplan or sham injection. Upon entry into the study, subjects were assigned a screening number. Subjects who met all inclusion and none of the exclusion criteria returned to the clinic for randomisation and treatment on visit 2 (day 1). At this visit, subjects were assigned in a 2:2:1:1 manner to receive pegcetacoplan monthly (PM), pegcetacoplan every other month (PEOM), sham injection monthly (SM), or sham injection every other month (SEOM), respectively. Randomisation was stratified according to GA lesion area at screening (<7.5 mm^2; ≥7.5 mm^2) and presence of CNV in the fellow eye.</td></tr>
<tr><td colspan="2">Duration of main phase:
Duration of run-in phase:
Duration of extension phase:</td><td>24 months
Not applicable
For extension, patients enrolled in a separate study.</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority: The null hypotheses for the primary endpoint are as follows:
H_{1a}: There is no difference between PM and sham in mean change from baseline to month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF for the mITT set.
H_{1a}: There is no difference between PEOM and sham in mean change from baseline to month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF for the mITT set.</td></tr>
<tr><td rowspan="4">Treatment groups</td><td colspan="2">PM</td><td>Pegcetacoplan monthly, 24 months, 206</td></tr>
<tr><td colspan="2">PEOM</td><td>Pegcetacoplan every other month, 24 months, 208</td></tr>
<tr><td colspan="2">SM</td><td>Sham injection monthly, 24 months, 102</td></tr>
<tr><td colspan="2">SEOM</td><td>Sham injection every other month, 24 months, 105</td></tr>
<tr><td rowspan="2">Endpoints and definitions</td><td>Primary endpoint</td><td>Change from baseline in total area of GA lesion at month 12 in the study eye</td><td>The primary endpoint is the change from baseline to month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF.</td></tr>
<tr><td>Primary endpoint at M24</td><td><u>Change from baseline in total area of</u></td><td>Prespecified analysis of change from baseline in GA lesion size in the study eye at month 24</td></tr>
</table>

		GA lesion at month 24 in the study eye	
	Key secondary endpoint 1	Change from baseline in monocular maximum reading speed of the study eye at month 24	Change from baseline in monocular maximum reading speed (study eye), at month 24 as assessed by MNREAD or Radner Reading Charts (in select countries)
	Key secondary endpoint 2	Change from baseline in mean Functional Reading Independence Index score at month 24	Change from baseline in mean FRI Index score (subject-level assessment) at month 24
	Key secondary endpoint 3	Change from baseline in normal-luminance best corrected visual acuity of the study eye at month 24	Change from baseline in NL-BCVA score (study eye) at month 24 as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) chart
Database lock	12M: 12 August 2021 24M (final): 18 July 2022		

Results and Analysis				
Analysis description	**Prespecified Primary Analysis**			
Analysis population and time point description	mITT Population The mITT population consists of all subjects who received at least one injection of pegcetacoplan or sham and had baseline and at least one postbaseline value of GA lesion area in the study eye as assessed by FAF. Month 12			
Descriptive statistics and estimate variability	Treatment group	PM	PEOM	Sham pooled
	Number of subjects	200	199	193
	Change from baseline in total area of GA lesion at month 12 in the study eye, least-square mean, mm^2	1.7344	1.7563	1.9640
	Standard error, mm^2	0.07924	0.07446	0.09592

Effect estimate per comparison	Primary endpoint	Comparison groups	PM compared to sham pooled
		Difference in least-square means, mm^2	–0.2296

		Percentage difference in least-square means	−11.7%
		95% confidence interval for difference in least-square means, mm^2	−0.4703 to 0.0111
		P value from MMRM for difference in least-square means	.0615
	Primary endpoint	Comparison groups	PEOM compared to sham pooled
		Difference in least-square means, mm^2	−0.2077
		Percentage difference in least-square means	−10.6%
		95% confidence interval for difference in least-square means, mm^2	−0.4444 to 0.0290
		P value from MMRM for difference in least-square means	.0854
Notes	At month 12, GA lesion growth was reduced from baseline in the PM and PEOM groups compared with the sham pooled group; however, the confirmatory hypothesis testing narrowly missed meeting statistical significance at the prespecified α level (0.0496).		
Analysis description	**Prespecified Analysis of Change From Baseline in GA Lesion Size in the Study Eye at Month 24 (Primary Endpoint at Month 24)**		
	mITT Population The mITT population consists of all subjects who received at least one injection of pegcetacoplan or sham and had baseline and at least one postbaseline value of GA lesion area in the study eye as assessed by FAF. Month 24		

Descriptive statistics and estimate variability	Treatment group	PM	PEOM	Sham pooled
	Number of subjects	200	200	194
	Change from baseline in total area of GA lesion in the study eye at month 24, least-square mean, mm^2	3.2275	3.3395	3.9726
	Standard error, mm^2	0.12457	0.13034	0.16820

Effect estimate per comparison	Primary endpoint at month 24	Comparison groups	PM compared to sham pooled
		Difference in least-square means, mm^2	−0.7451
		Percentage difference in least-square means	18.8%
		95% confidence interval for difference in least-square means, mm^2	−1.1539 to −0.3362

		P value from MMRM for difference in least-square means	.0004
	Primary endpoint at month 24	Comparison groups	PEOM compared to sham pooled
		Difference in least-square means, mm^2	−0.6331
		Percentage difference in least-square means	−15.9%
		95% confidence interval for difference in least-square means, mm^2	−1.0508 to −0.2153
		P value from MMRM for difference in least-square means	.0030
Notes	At month 24, in the PM and PEOM groups, GA lesion growth was reduced compared with the sham pooled group. This endpoint was not within the type I error control algorithm for hypothesis testing to be able to declare statistical significance.		
Analysis description	**Prespecified Key Secondary Endpoint Analysis of Monocular Maximum Reading Speed of the Study Eye**		
	mITT Population The mITT population consists of all subjects who received at least one injection of pegcetacoplan or sham and had baseline and at least one postbaseline value of GA lesion area in the study eye as assessed by FAF. Month 24		

Descriptive statistics and estimate variability	Treatment group	PM	PEOM	Sham pooled
	Number of subjects	179	163	164
	Change from baseline in monocular maximum reading speed of the study eye at month 24, least-square mean, words per minute	−22.897	−25.532	−22.355
	Standard error, words per minute	4.1171	2.7676	2.9341

Effect estimate per comparison	Key secondary endpoint 1	Comparison groups	PM compared to sham pooled
		Difference in least-square means, words per minute	−0.542
		95% confidence interval for difference in least-square means, words per minute	−9.922 to 8.838

		P value from MMRM for difference in least-square means	.9096
	Key secondary endpoint 1	Comparison groups	PEOM compared to sham pooled
		Difference in least-square means, words per minute	−3.177
		95% confidence interval for difference in least-square means, words per minute	−10.619 to 4.265
		P value from MMRM for difference in least-square means	.4020
Notes	No meaningful differences were observed through month 24 for the 3 treatment groups.		
Analysis description	**Prespecified Key Secondary Endpoint Analysis of Functional Reading Independence Index Score**		
	mITT Population The mITT population consists of all subjects who received at least one injection of pegcetacoplan or sham and had baseline and at least one postbaseline value of GA lesion area in the study eye as assessed by FAF. Month 24		

Descriptive statistics and estimate variability	Treatment group	PM	PEOM	Sham pooled
	Number of subjects	186	183	178
	Change from baseline in mean Functional Reading Independence Index score at month 24, least-square mean	−0.408	−0.371	−0.360
	Standard error	0.0570	0.0562	0.0601

Effect estimate per comparison	Key secondary endpoint 2	Comparison groups	PM compared to sham pooled
		Difference in least-square means	0.048
		95% confidence interval for difference in least-square means	−0.204 to 0.108
		P value from MMRM for difference in least-square means	.5483
	Key secondary endpoint 2	Comparison groups	PEOM compared to sham pooled
		Difference in least-square means	−0.011

		95% confidence interval for difference in least-square means		−0.163 to 0.142	
		P value from MMRM for difference in least-square means		.8921	
Notes	No meaningful differences were observed through month 24 for the 3 treatment groups.				
Analysis description	**Prespecified Key Secondary Endpoint Analysis of Normal-Luminance Best Corrected Visual Acuity of the Study Eye**				
	mITT Population The mITT population consists of all subjects who received at least one injection of pegcetacoplan or sham and had baseline and at least one postbaseline value of GA lesion area in the study eye as assessed by FAF. Month 24				
Descriptive statistics and estimate variability	Treatment group	PM		PEOM	Sham pooled
	Number of subjects	201		201	195
	Change from baseline in normal luminance best corrected visual acuity of the study eye at month 24, least-square mean, ETDRS letters	−8.126		−8.947	−6.217
	Standard error, ETDRS letters	1.0182		1.0322	1.0167
Effect estimate per comparison	Key secondary endpoint 3	Comparison groups		PM compared to sham pooled	
		Difference in least-square means, ETDRS letters		−1.909	
		95% confidence interval for difference in least-square means, ETDRS letters		−4.701 to 0.833	
		P value from MMRM for difference in least-square means		.1799	
	Key secondary endpoint 3	Comparison groups		PEOM compared to sham pooled	
		Difference in least-square means		−2.730	
		95% confidence interval for difference in least-square means		−5.565 to 0.105	
		P value from MMRM for difference in least-square means		.0590	

Notes	No meaningful differences were observed through month 24 for the 3 treatment groups.

2.5.5.3. Analysis performed across trials (pooled analyses and meta-analysis)

An integrated efficacy analysis (ISE) was carried out according to a separate SAP, mentioned earlier in this report. Due to the fact that:

(a) all but the key secondary endpoints were analysed in a descriptive manner in this ISE, and

(b) key secondary endpoints could not be statistically tested in the pooled setting as the DERBY trial failed to show statistical significance in the primary endpoint evaluation,

the presentation of methodological details concerning the ISE analyses are not further outlined in this report. Most relevant outcome of the ISE is presented in tabular form above.

2.5.5.4. Supportive study(ies)

Results from Phase II study POT-CP121614 and Phase Ib study APL2-103 are described as supportive evidence of the effectiveness.

Study POT-CP121614: A Phase 2, multicentre, randomised, single-masked, sham-controlled study of safety, tolerability and evidence of activity of intravitreal pegcetacoplan therapy in patients with geographic atrophy.

Study APL2-103: A Phase Ib, multicentre, open-label study to evaluate the safety of intravitreal pegcetacoplan therapy in patients diagnosed with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

The table below summarises the study design of study POT-CP121614 and study APL2-103.

Table 59: Study design summary for study POT-CP121614 and study APL2-103

	Study POT-CP121614	**Study APL2-103**
Study title	A Phase 2, Multicenter, Randomized, Single-Masked, Sham-Controlled Study of Safety, Tolerability and Evidence of Activity of Intravitreal Pegcetacoplan Therapy in Patients With Geographic Atrophy	A Multicenter, Open-Label Study to Evaluate the Safety of Intravitreal Pegcetacoplan Therapy in patients Diagnosed With Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)
Study phase	Phase 2	Phase 1b
Study type	Prospective, multicenter, randomized, masked, sham-controlled study	Prospective, multicenter, nonrandomized, open-label, uncontrolled study
Study population	Patients with GA secondary to AMD	Patients with GA secondary to AMD
Primary objective	To assess the safety, tolerability, and evidence of activity of multiple IVT injections of pegcetacoplan in subjects with GA secondary to AMD	To evaluate the safety and tolerability of IVT injected pegcetacoplan in subjects with GA secondary to AMD
Primary endpoint	CFB in square root area of GA lesion(s) in the study eye at month 12 based on FAF Primary endpoint collection: Masked, independent review of FAF images by the reading center	The incidence and severity of ocular and systemic AEs
Secondary and exploratory endpoint(s)	Untransformed mean CFB in area of GA lesion at month 12 based on FAF Change in area of GA lesion from • Month 6 to Month 12 • Month 6 to Month 18 • Month 12 to Month 18 CFB in NL-BCVA score Incidence of MNV in the study eye CFB in LL-VA deficit CFB in LL-BCVA score CFB in square root area of GA lesion in the study eye as measured by SD-OCT Genetic marker analysis at month 2 of SNPs highly associated with AMD Drusen size in the study eye	CFB in clinical ocular examination at various time points CFB in GA lesion size between the study eye and fellow eye for subjects with bilateral GA
	No. of intermediate or large drusen in the study eye CFB in distance of GA lesion from fovea in the study eye as measured by FAF	

	Study POT-CP121614	Study APL2-103
Safety endpoints	Number and severity of AEs CFB in antigenicity data Anterior segment examination in the study and fellow eyes LOCS III endpoints for abnormal lens findings Posterior segment examination in the study and fellow eyes CFB in laboratory safety data CFB in vital signs CFB in IOP in the study eye Acute change in IOP after each injection	The incidence and severity of ocular and systemic AEs
Number of subjects	246	19
Number of sites	52	5
Country	US, Australia, New Zealand	US
Key inclusion criteria	Subjects aged ≥50 years[a] NL-BCVA ≥24 letters using ETDRS charts in the study eye Diagnosis of GA of the macula secondary to AMD in the study eye confirmed by the reading center via FAF with the following criteria: • total GA area ≥2.5 mm^2 and ≤17.5 mm2 via FAF • if GA was multifocal, ≥1 focal lesion ≥1.25 mm2 • entire GA lesion was completely visualized on the macula-centered image • GA lesion was imaged in its entirety • GA lesion was not contiguous with any areas of peripapillary atrophy • presence of any pattern of	Cohort 1 Subjects aged ≥60 years NL-BCVA between 35 and 5 letters using ETDRS charts in the study eye Diagnosis of GA of the macula secondary to AMD in the study eye confirmed by the reading center via FAF with the following criteria: • total GA area ≥2.5 mm^2 via FAF • if GA was multifocal, ≥1 focal lesion ≥1.25 mm^2 Cohort 2 Participated in Study APL2-303 or APL2-304 and completed the month 24 visit
	hyperautofluorescence in the junctional zone of GA in the study eye	

	Study POT-CP121614	Study APL2-103
Key exclusion criteria	GA secondary to a condition other than AMD in the study eye Spherical equivalent of refractive error in the study eye demonstrating • >6 diopters of myopia or • an axial length >26 mm History of or active CNV in the study eye associated with AMD or any other cause including any evidence of • retinal pigment epithelium rips or • evidence of neovascularization anywhere in the retina based on FA Any contraindication to IVT injection in the study eye History of IVT injection in the study eye Retinal disease other than AMD in the study eye Any ophthalmic condition in the study eye that • reduced clarity of the media • prevented adequate retinal imaging • may have required surgery during the study period	Cohort 1 GA secondary to a condition other than AMD in the study eye Spherical equivalent of refractive error in the study eye demonstrating • >6 diopters of myopia or • an axial length >26 mm History of or active CNV in the study eye associated with AMD or any other cause including any evidence of • retinal pigment epithelium rips or • evidence of neovascularization anywhere in the retina based on FA and/or SD-OCT Any contraindication to IVT injection in the study eye History of IVT injection in the study eye Presence of an active ocular disease in the study eye that confounds visual function (eg, uveitis) Any ocular condition other than GA secondary to AMD in the study eye that could require surgery or medical intervention or that could compromise visual function Cohort 2 Subjects who discontinued the study drug prior to month 24 and remained in Study APL2-303 or APL2-304
Test product, dose, and mode of administration	Pegcetacoplan 15 mg/0.1 mL administered IVT	Pegcetacoplan 15 mg/0.1 mL, in acetate-buffered, 6.2% trehalose solution for injection, administered IVT
Screening and initial treatment	Subjects were screened 14 (±5) days before randomization. Subjects who met all inclusion criteria and no exclusion criteria, and who were confirmed as eligible by the reading center, returned to the clinic for the randomization visit on day 1. At this visit, subjects were randomly assigned in a 2:2:1:1 manner to receive treatment with PM, PEOM, SM, or SEOM, respectively. No stratification was used.	Subjects were screened within 28 days prior to treatment. Subjects who met all inclusion criteria and no exclusion criteria returned to the clinic for treatment at visit 2 (day 0).

	Study POT-CP121614	Study APL2-103
Study assessments and treatment regimen	All subjects returned to the study site at the day 7 visit to assess acute safety after the first injection. Thereafter: • Subjects in the PM and SM groups returned to the study site every month through Month 12 for additional IVT injections of IP and other study procedures. • Subjects in the PEOM and SEOM groups returned to the study site every 2 months through Month 12 for additional IVT injections of IP and other study procedures. • All subjects returned for follow-up visits at month 15 and month 18.	All subjects returned to the clinical site on days 1, 2, and 7 for assessments. Subsequently, subjects returned to the clinical site at month 1 and monthly thereafter for assessments and additional pegcetacoplan injections for up to 30 months. Prior to study termination, subjects rolled over into the long-term extension study, Study APL2-GA-305, after the month 24 visit.
Efficacy assessments	Efficacy assessments included ocular imaging (fundus autofluorescence) and best-corrected visual acuity.	Exploratory efficacy assessment included ocular imaging (fundus autofluorescence).
Safety assessments	Safety was assessed throughout the study, including through the collection and analysis of serial blood and urine samples and the collection of ocular observations. Immunogenicity/PK: Blood samples were collected for immunogenicity and PK assessments.	Safety was assessed throughout the study, including through the collection and analysis of serial blood and urine samples and the collection of ophthalmic observations.
Treatment duration	12 months	Up to 30 months

	Study POT-CP121614	Study APL2-103
Statistical analysis of the primary endpoint	MMRM analysis of the mITT set including Fixed effects • treatment (PM, PEOM, sham pooled) • baseline square root of GA lesion area • visit (categorical) Interaction terms • treatment × visit • visit × baseline square root of GA lesion area Within-subject error was modeled using an unstructured covariance structure. Denominator degrees of freedom were estimated using the Kenward-Roger approximation. The analysis model table was presented. The treatment comparisons (PM vs sham pooled, PEOM vs sham pooled, and PM vs PEOM) at months 2, 6, and 12 were also presented with the estimate, SE, and 95% CI. Robustness of the primary analysis was investigated through multiple sensitivity, supplementary, and subgroup analyses. Type I error control and multiplicity adjustment for the primary endpoint: All statistical tests were 2-sided at the 0.1 level of significance. There were no adjustments for multiple comparisons in the analysis.	The safety analysis was performed using the safety set. Safety variables included AEs, clinical laboratory variables, vital signs, ocular assessments (eg, IOP and ophthalmic examinations). For each safety variable, the last value collected before the first dose of IP was used as baseline for all summaries of that safety variable. The last observed value was defined as the last valid assessment obtained after baseline. AEs were coded using MedDRA version 23.1 and summarized separately for those that occurred in the study eye, the fellow eye, and those that were nonocular. The number of subjects reporting each AE was tabulated for all AEs and separately for those considered as possibly related to study treatment by the investigator. Descriptive statistics for clinical laboratory values and vital signs, and CFB at each assessment time point, were presented by cohort and overall. Descriptive summaries of the NL-BCVA letter score and their changes from baseline at each postbaseline visit were presented by cohort, visit, and eye (study vs fellow).

	Study POT-CP121614	Study APL2-103
Statistical analysis of the secondary and exploratory endpoints	Where appropriate, secondary endpoints were summarized and analyzed in a similar fashion as the primary efficacy endpoint using MMRM. Descriptive statistics were presented in the by-treatment comparisons of endpoints where MMRM analyses were not conducted.	Results of the following ocular assessments were summarized by cohort, visit, and eye (study vs fellow) using descriptive summaries: NL-BCVA score, preinjection IOP, slitlamp examination, and dilated indirect ophthalmoscopy. Ocular imaging data collected was summarized descriptively by cohort, visit, and eye (study vs fellow). CFB to various time points in the total area of GA lesions in eyes injected with pegcetacoplan was summarized. Descriptive statistics were presented for the observed GA lesion sizes and the changes from baseline at each postbaseline visit. Summaries were presented using both the actual lesion size measured in mm^2 and the square-root transformation of the lesion size measured in mm. No data were imputed for missing values. For the changes from baseline between the study eye and fellow eye for subjects with bilateral GA, the mean difference between eyes was tested at each visit using a paired t test. Figures of the mean changes were also presented.
Statistical analysis of the safety endpoints	AEs were coded using MedDRA version 20 and summarized separately for those occurring in the study eye, those in the fellow eye, and the nonocular events. Results from laboratory assessments, vital sign assessments, ocular assessments, IOP assessments, ophthalmology imaging assessments, and immunogenicity assessments were analyzed with descriptive statistics by treatment group and eye, where appropriate.	Safety was the primary and secondary endpoint and is described above in the corresponding rows.
Masking	Masked study design in which the following study personnel were masked: • subjects • site assessors (eg, photographers, visual acuity technicians) • reading center personnel	Not applicable because this study was not masked

	Study POT-CP121614	Study APL2-103
Handing of exudative AMD events	Subjects who had exudative AMD were discontinued from IP administration and encouraged to stay in the study for safety follow-up assessment. Treatment for exudative AMD was done following the site's standard of care.	Subjects who developed exudative AMD were kept on study and continued to receive pegcetacoplan administration per protocol. The determination about initiation of anti-VEGF treatment for exudation related to active CNV was the responsibility of the investigator.
Study drug formulation	Lyophilized drug substance (with no excipients) reconstituted prior to IVT injection with 5% w/v dextrose	Solution for IVT injection with drug product in 18 mM acetate buffer, pH 5.0, containing 6.2% trehalose

Abbreviations: ADA = antidrug antibody; AE = adverse event; CFB = change from baseline; CNV = choroidal neovascularization; DMC = data monitoring committee; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; FAF = fundus autofluorescence; GA = geographic atrophy; IOP = intraocular pressure; IP = investigational product; IVT = intravitreal; MedDRA = Medical Dictionary for Regulatory Activities; mITT = modified intent-to-treat; MMRM = mixed-effects model for repeated measures; MNREAD = Minnesota Low-Vision Reaching Chart; MNV = macular neovascularization; NA = not applicable; NL-BCVA = normal-luminance best-corrected visual acuity; OCT-A = optical coherence tomography angiography; PEOM = pegcetacoplan every other month; PK = pharmacokinetics; PM = pegcetacoplan monthly; PRN = as-needed treatment; SD-OCT = spectral domain optical coherence tomography; SEOM = sham every other month; SM = sham monthly; SNP = single nucleotide polymorphism; VEGF = vascular endothelial growth factor; w/v = weight per volume.

[a] All subjects enrolled in Study POT-CP121614 were aged ≥60 years.

Study POT-CP121614:

Demographics

Table 60: Demographic characteristics modified intent to treat population

Demographic Characteristics
Modified Intent to Treat Population

		APL-2 Monthly (N=84)	APL-2 EOM (N=78)	APL-2 Pooled (N=162)	Sham Monthly (N=41)	Sham EOM (N=39)	Sham Pooled (N=80)	Total (N=242)
Age (years)	n	84	78	162	41	39	80	242
	Mean	79.5	80.9	80.2	78.5	78.5	78.5	79.6
	SD	7.50	7.55	7.53	6.28	8.62	7.46	7.54
	Median	81.0	81.0	81.0	78.0	78.0	78.0	80.0
	Min	63	60	60	61	60	60	60
	Max	95	97	97	90	96	96	97
	<65 years	2 (2.4%)	1 (1.3%)	3 (1.9%)	1 (2.4%)	2 (5.1%)	3 (3.8%)	6 (2.5%)
	=65 - <75 years	21 (25.0%)	14 (17.9%)	35 (21.6%)	10 (24.4%)	10 (25.6%)	20 (25.0%)	55 (22.7%)
	=75 - <85 years	37 (44.0%)	37 (47.4%)	74 (45.7%)	23 (56.1%)	17 (43.6%)	40 (50.0%)	114 (47.1%)
	=85 years	24 (28.6%)	26 (33.3%)	50 (30.9%)	7 (17.1%)	10 (25.6%)	17 (21.3%)	67 (27.7%)
Sex	Female	55 (65.5%)	49 (62.8%)	104 (64.2%)	23 (56.1%)	25 (64.1%)	48 (60.0%)	152 (62.8%)
	Male	29 (34.5%)	29 (37.2%)	58 (35.8%)	18 (43.9%)	14 (35.9%)	32 (40.0%)	90 (37.2%)
Country	Australia	12 (14.3%)	11 (14.1%)	23 (14.2%)	5 (12.2%)	7 (17.9%)	12 (15.0%)	35 (14.5%)
	New Zealand	3 (3.6%)	3 (3.8%)	6 (3.7%)	1 (2.4%)	3 (7.7%)	4 (5.0%)	10 (4.1%)
	United States	69 (82.1%)	64 (82.1%)	133 (82.1%)	35 (85.4%)	29 (74.4%)	64 (80.0%)	197 (81.4%)
Race	American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	1 (1.2%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	Black or African American	1 (1.2%)	1 (1.3%)	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	White	82 (97.6%)	75 (96.2%)	157 (96.9%)	41 (100.0%)	39 (100.0%)	80 (100.0%)	237 (97.9%)
	Other	0 (0.0%)	2 (2.6%)	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)
Ethnicity	Hispanic or Latino	2 (2.4%)	1 (1.3%)	3 (1.9%)	2 (4.9%)	0 (0.0%)	2 (2.5%)	5 (2.1%)
	Not Hispanic or Latino	79 (94.0%)	75 (96.2%)	154 (95.1%)	38 (92.7%)	38 (97.4%)	76 (95.0%)	230 (95.0%)
	Not Reported	2 (2.4%)	0 (0.0%)	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)
	Unknown	1 (1.2%)	2 (2.6%)	3 (1.9%)	1 (2.4%)	1 (2.6%)	2 (2.5%)	5 (2.1%)

Changes in GA Lesion Area From Baseline to Month 12

Table 61: Primary endpoint: square root GA lesion size measured by FAF in the study eye at month 12 – mITT population

Statistic	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
n included in the model	84	78	80
LS mean (SE), mm	0.25 (0.025)	0.28 (0.026)	0.35 (0.025)
95% CI of LS mean	0.20 to 0.30	0.23 to 0.33	0.30 to 0.40
Difference in LS mean (95% CI) versus sham pooled group, mm	−0.10 (−0.16 to −0.03)	−0.07 (−0.14 to 0)	NA
Percentage difference in LS mean from sham pooled group	−29%	−20%	NA
P value versus sham pooled group	.008	.063	NA
Difference in LS mean (95% CI) versus PEOM group	−0.03 (−0.10 to 0.04)	NA	NA
P value versus PEOM group	.444	NA	NA

Abbreviations: FAF = fundus autofluorescence photographs; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: Baseline was defined as the last available nonmissing observation prior to first study drug administration. The model included treatment + baseline value + visit + treatment × visit + visit × baseline.

In subjects with bilateral GA regardless of whether fellow eyes met key study eye inclusion criteria, there was slower GA lesion growth in the study eye than in the untreated fellow eye. At month 12, the percentage difference in CFB in GA lesion growth between study and fellow eyes was −18.0% in the PM group, −12.2% in the PEOM group, and 3.5% in the sham pooled group. The sham-adjusted difference in CFB in GA lesion growth between the study eye and fellow eye were −21.8% in the PM group and −16.1% in the PEOM group.

Study APL2-103:

Efficacy endpoints in this study were exploratory.

Growth of GA lesions following pegcetacoplan treatment was explored in subjects from Cohort 1, all of whom had bilateral GA. These subjects exhibited relatively reduced growth of GA lesions in the study eye compared with the fellow eye, particularly at Months 18 and 24 (n=7, P=.0111 and n=8, P=.0245, respectively) indicating slower progression of GA with monthly intravitreal pegcetacoplan treatment. Lesion size of the study eye compared with the fellow eye was reduced by 31% at Month 12, 52% at Month 18, and 46% at Month 24. The square-root data of GA lesion size also showed similar results at Months 18 and 24 (n=7, P=.0107 and n=8, P=.0073, respectively).

Study APL2-305:

Study APL2-305 is a 36-month, open-label, ongoing extension study for subjects who completed treatment in studies APL2-304 and APL2-303 or rolled over from study APL2-103.

An interim analysis was performed through the month 6 visit (month 30 in total) with a data cut off on 01 February 2023, when almost all subjects (783/790, 99.1%) had completed the month 6 visit. Another interim data snapshot through the month 12 visit (integrated month 36 from the baseline of

APL2-304 and APL2-303) as of 29 September 2023, when all subjects had completed the month 12 visit was performed, focusing on microperimetry data.

GA lesion size - Integrated month 30 data

Primary Endpoint Data

Analysis Methods

Analyses for the antecedent study baseline to integrated month 30 were performed on the APL2GA-305 modified full analysis set, which consists of all enrolled subjects who receive at least 1 injection of pegcetacoplan- in Study APL2-GA-305. In this extension study the GA lesion size endpoint was investigated via the following analyses: <Source: APL2-GA-305 Interim SAP>

- change from antecedent study baseline to integrated month 30 in the total area of GA lesion size (mm^2) in the study eye
- rate of change from antecedent study baseline to integrated month 30 in total area of GA lesion size (mm^2) in the study eye

Subjects were analysed by their combined Studies APL2-304, APL2-303, and APL-GA-305 treatment groups: PM to PM (subjects received pegcetacoplan monthly in all studies), PEOM to PEOM (subjects received pegcetacoplan every other month in all studies), and sham pooled to pegcetacoplan (subjects received sham monthly or every other month in Studies APL2-304 and APL2-303 and pegcetacoplan monthly or EOM in Study APL2-GA-305).

The change from antecedent study baseline to integrated month 30 in the total area of GA lesion size (mm^2) in the study eye was summarized and assessed with a MMRM approach in the modified full analysis set. The analysis model included change from antecedent study baseline to integrated month 30 in the total area of GA lesion size (mm^2) in the study eye as the dependent variable, treatment group (PM to PM, PEOM to PEOM, and sham pooled to pegcetacoplan), presence of choroidal neovascularisation in the fellow eye at antecedent study baseline (Yes, No), and antecedent study baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) as fixed effect, time (study month, categorical) as a factor, the time × antecedent study baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2), and time × treatment as interaction terms.

The mean rate of change in GA area (i.e., slope) was analysed by use of a piecewise linear mixed-effect model assuming time as continuous and piecewise linear ("piecewise slope model") in modified full analysis set. A knot at the integrated month 6, integrated month 12, integrated month 18, and integrated month 24 visit was added which allows for the slope of lesion growth to differ between each 6-month periods for each of the treatment groups.

The analysis model included treatment group (PM to PM, PEOM to PEOM, and sham pooled to pegcetacoplan), presence of choroidal neovascularisation in the fellow eye at antecedent study baseline (Yes, No), antecedent study baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) as fixed effect, time (study month, continuous assuming linearity), knot at integrated month 6, knot at integrated month 12, knot at integrated month 18, knot at integrated month 24, interaction between time and antecedent study baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2), interaction between each knot and antecedent study baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2), interaction between treatment and time, and interaction between treatment and each knot.

Results

Main MMRM Analysis—Observed Data

Table 62: Analysis of change from antecedent study baseline in total area of GA lesion(s) (mm²) (FAF) of the study eye with MMRM model at integrated month 30-APL2-GA-305 modified full analysis set

	PM to PM **N = 241**	**PEOM to PEOM** **N = 267**	**Sham pooled to pegcetacoplan** **N = 272**
Number of subjects included in the model	241	266	272
Estimates/comparisons at integrated month 30			
LS mean (SE) CFB of GA lesion area, mm²	3.79 (0.137)	3.92 (0.135)	4.82 (0.163)
95% CI of LS mean	3.52-4.06	3.66-4.19	4.50-5.14
Difference (95% CI) in LS mean (vs sham pooled to pegcetacoplan), mm²	−1.03 (−1.45 to −0.61)	−0.90 (−1.31 to −0.49)	
Percentage difference (versus sham pooled to pegcetacoplan)	−21.3	−18.7	
P value (vs sham pooled to pegcetacoplan)	<.0001	<.0001	

Abbreviations: AMD = age-related macular degeneration; CFB = change from baseline; GA = geographic atrophy; LS = least-square; MMRM = mixed-effect model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Note: Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + analysis visit + antecedent study baseline presence of exudative AMD in the fellow eye (yes or no) + analysis visit × treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) × analysis visit.
Source: APL2-GA-305 Month 6 Interim Analysis Table 14.2.1.2.1.3.

Rate of Change Analysis—Observed Data

Table 63: Analysis of change from antecedent study baseline in total area of GA lesions(s) (mm²)(FAF) of the study eye with MMRM model assuming a piecewise linear trend in time with a knot at integrated month 6, integrated month 12, integrated month 18, and integrated month 6, integrated month 12, integrated month 18, and integrated month 24-study APL2-GA-305 modified full analysis set, antecedent study baseline through integrated month 30

	PM to PM **N = 241**	**PEOM to PEOM** **N = 267**	**Sham pooled to pegcetacoplan** **N = 272**
Number of subjects included in the model	241	267	272
Estimates for antecedent study baseline to integrated month 6			
Slope (SE) of GA lesion area growth, mm^2/6 months	0.84 (0.047)	0.83 (0.040)	0.96 (0.041)
95% CI of slope of GA lesion area growth, mm^2/6 months	(0.75-0.93)	(0.75-0.91)	(0.88-1.04)
Difference (95% CI) in slope (vs sham pooled to pegcetacoplan), mm^2/6 months	−0.12 (−0.24 to 0.00)	−0.13 (−0.25 to −0.02)	
Percentage difference (vs sham pooled to pegcetacoplan)	−12.6	−13.8	

P value (vs sham pooled to pegcetacoplan)	.0527	.0206	
Estimates for integrated month 6 to integrated month 12			
Slope (SE) of GA lesion area growth, mm^2/6 months	0.81 (0.042)	0.84 (0.042)	1.01 (0.043)
95% CI of slope of GA lesion area growth, mm^2/6 months	(0.73-0.90)	(0.76-0.93)	(0.93-1.10)
Difference (95% CI) in slope (vs sham pooled to pegcetacoplan), mm^2/6 months	−0.20 (−0.31 to −0.08)	−0.17 (−0.29 to −0.05)	
Percentage difference (vs sham pooled to pegcetacoplan)	−19.4	−16.5	
P value (vs sham pooled to pegcetacoplan)	.0011	.0055	
Estimates for integrated month 12 to integrated month 18			
Slope (SE) of GA lesion area growth, mm^2/6 months	0.86 (0.040)	0.85 (0.036)	1.04 (0.042)
95% CI of slope of GA lesion area growth, mm^2/6 months	(0.78-0.94)	(0.78-0.93)	(0.96-1.12)
Difference (95% CI) in slope (vs sham pooled to pegcetacoplan), mm^2/6 months	−0.18 (−0.29 to −0.06)	−0.18 (−0.29 to −0.07)	

Percentage difference (vs sham pooled to pegcetacoplan)	−16.9	−17.6	
P value (vs sham pooled to pegcetacoplan)	.0027	.0010	
Estimates for integrated month 18 to integrated month 24			
Slope (SE) of GA lesion area growth, mm^2/6 months	0.65 (0.049)	0.70 (0.036)	0.95 (0.041)
95% CI of slope of GA lesion area growth, mm^2/6 months	(0.56-0.75)	(0.63-0.77)	(0.87-1.03)
Difference (95% CI) in slope (vs sham pooled to pegcetacoplan), mm^2/6 months	−0.30 (−0.42 to −0.17)	−0.25 (−0.36 to −0.14)	
Percentage difference (vs sham pooled to pegcetacoplan)	−31.3	−26.4	
P value (vs sham pooled to pegcetacoplan)	<.0001	<.0001	
Estimates for integrated month 24 to integrated month 30			
Slope (SE) of GA lesion area growth, mm^2/6 months	0.61 (0.052)	0.67 (0.051)	0.86 (0.051)
95% CI of slope of GA lesion area growth, mm^2/6 months	(0.50-0.71)	(0.57-0.77)	(0.75-0.96)
Difference (95% CI) in slope (vs sham pooled to	−0.25 (−0.40 to −0.10)	−0.18 (−0.33 to −0.03)	

pegcetacoplan), mm^2/6 months			
Percentage difference (vs sham pooled to pegcetacoplan)	−29.0	−21.2	
P value (vs sham pooled to pegcetacoplan)	.0011	.0166	
Estimates for antecedent study baseline to integrated month 30			
Average slope (SE) of GA lesion area growth, mm^2/30 months	3.78 (0.137)	3.90 (0.135)	4.82 (0.163)
95% CI of average slope of GA lesion area growth, mm^2/30 months	(3.51-4.05)	(3.64-4.17)	(4.50-5.14)
Difference (95% CI) in average slope (vs sham pooled to pegcetacoplan), mm^2/30 months	−1.04 (−1.46 to −0.62)	−0.92 (−1.33 to −0.50)	
Percentage difference (vs sham pooled to pegcetacoplan)	−21.6	−19.0	
P value (vs sham pooled to pegcetacoplan)	<.0001	<.0001	

Abbreviations: AMD = age-related macular degeneration; GA = geographic atrophy; MMRM = mixed-effect model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan.

Note: Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + time (continuous) + time spline at integrated month 6 (continuous) + time spline at integrated month 12 (continuous) + time spline at integrated month 18 (continuous) + time spline at integrated month 24 (continuous) + presence of exudative AMD in the fellow eye (yes or no) + time (continuous) × treatment + time spline at integrated month 6 (continuous) x treatment + time spline at integrated month 12 (continuous) × treatment + time spline at integrated month 18 (continuous) × treatment + time spline at integrated month 18 (continuous) × treatment + antecedent study baseline GA lesion area × time (continuous) + antecedent study baseline GA lesion area x time spline at integrated month 6 (continuous) + antecedent study baseline GA lesion area × time spline at integrated month 12 (continuous) + antecedent study baseline GA lesion area × time spline at integrated month 18 (continuous) + antecedent study baseline GA lesion area × time spline at integrated month 24 (continuous).

Source: Study APL2-GA-305 Month 6 Interim Analysis Table 14.2.1.2.1.6.

Secondary/Functional Endpoint Data

Analysis Methods

Comparator

Analyses of functional endpoints are conducted compared to the data observed in the sham pooled to pegcetacoplan group from month 24 to month 30 after subjects initiated pegcetacoplan. Differences between PM to PM and PEOM to PEOM compared to sham pooled to pegcetacoplan when using the observed data from month 24 to month 30 are estimates of early vs late initiation of pegcetacoplan rather than estimates of a treatment effect versus sham. In addition, the functional data from integrated month 24 to integrated month 30 for all subjects is collected under open-label conditions making estimates at integrated month 30 potentially susceptible to confounding.

NL-BCVA

Descriptive Analyses

The observed values for NL-BCVA in the study eye and change from antecedent study baseline were summarised by treatment group and visits.

Main MMRM Analysis

The change from antecedent study baseline to integrated month 30 in NL-BCVA score in the study eye was summarised and assessed with a MMRM approach in the modified full analysis set. The analysis model included change from antecedent study baseline to integrated month 30 in the NL-BCVA score (ETDRS letters) in the study eye as the dependent variable, treatment group (PM to PM, PEOM to PEOM, and sham pooled to pegcetacoplan), presence of choroidal neovascularisation in the fellow eye at antecedent study baseline (yes, no), and antecedent study baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) as fixed effect, antecedent study baseline NL-BCVA score as a covariate, time (study month, categorical) as a factor, the time × antecedent study baseline NL-BCVA score and time × treatment as interaction terms. The LS mean change from antecedent study baseline in NL-BCVA score in the study eye was plotted over time by treatment group.

This analysis approach is the same approach as what was used to analyse the key secondary endpoint at month 24.

Main MMRM Analysis – Sensitivity Analysis Based on Studies APL2-303 and APL2-304 mITT Population

The same analysis as described above was repeated based on the pooled Studies APL2-304 and APL2-303 mITT population to access robustness of the findings from the analyses based on subjects who enrolled in Study APL2-GA-305 (Study APL2-GA-305 modified full analysis set).

LL-BCVA

Descriptive Analyses

The observed values for LL-BCVA in the study eye and change from antecedent study baseline were summarised by treatment group and visits.

Main MMRM Analysis

The change from antecedent study baseline to integrated month 30 in LL-BCVA score in the study eye was summarised and assessed with a MMRM approach in the modified full analysis set. The analysis model included change from antecedent study baseline to integrated month 30 in the LL-BCVA score (ETDRS letters) in the study eye as the dependent variable, treatment group (PM to PM, PEOM to PEOM, and sham pooled to pegcetacoplan), presence of exudative AMD in the fellow eye at antecedent study baseline (yes, no), and antecedent study baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) as fixed effect, antecedent study baseline LL-BCVA score as a covariate, time (study month, categorical) as a factor, the time × antecedent study baseline LL-BCVA score and time × treatment as interaction terms. The LS mean change from antecedent study baseline in LL-BCVA score in the study eye was plotted over time by treatment group.

This analysis approach is the same approach as what was used to analyse the secondary endpoint at month 24.

Main MMRM Analysis – Sensitivity Analysis Based on Studies APL2-303 and APL2-304 mITT Population

The same analysis as described above was repeated based on the pooled Studies APL2-304 and APL2-303 mITT population to access robustness of the findings from the analyses based on subjects who enrolled in Study APL2-GA-305 (Study APL2-GA-305 modified full analysis set).

Monocular Maximum Corrected Reading Speed

Descriptive Analyses

The observed values for the monocular maximum corrected reading speed in the study eye and change from antecedent study baseline were summarised by treatment group and visits.

Main MMRM Analysis

The change from antecedent study baseline to integrated month 30 in monocular maximum corrected reading speed in the study eye was summarised and assessed with a MMRM approach in the modified full analysis set. The analysis model included change from antecedent study baseline to integrated month 30 in monocular maximum corrected reading speed (words per minute) in the study eye as the dependent variable, treatment group (PM to PM, PEOM to PEOM, and sham pooled to pegcetacoplan), presence of exudative AMD in the fellow eye at antecedent study baseline (yes, no), and antecedent study baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) as fixed effect, antecedent study baseline monocular maximum corrected reading speed as a covariate, time (study month, categorical) as a factor, the time × antecedent study baseline monocular maximum corrected reading speed and time × treatment as interaction terms. The LS mean change from antecedent study baseline in monocular maximum corrected maximum reading speed in the study eye was plotted over time by treatment group.

This analysis approach is the same approach as what was used to analyse the key secondary endpoint at month 24. However, the endpoint has been changed from the monocular maximum reading speed (calculated without adjustment for reading inaccuracy) to the monocular maximum corrected reading speed (calculated with an adjustment for reading inaccuracy). The analyses of the monocular maximum corrected reading speed through month 24 are presented in the MAA for pooled Studies APL2-304 and APL2-303 and Month 24 CSR for the individual studies.

Main MMRM Analysis – Sensitivity Analysis Based on Studies APL2-303 and APL2-304 mITT Population

The same analysis as described above was repeated based on the pooled Studies APL2-304 and APL2-303 mITT population to access robustness of the findings from the analyses based on subjects who enrolled in Study APL2-GA-305 (Study APL2-GA-305 modified full analysis set).

Mean Threshold Sensitivity of All Points Based on Microperimetry

Descriptive Analyses

The observed values for mean threshold sensitivity of all points in the study eye and change from antecedent study baseline were summarised by treatment group and visits.

Main MMRM Analysis

The change from antecedent study baseline to integrated month 30 in mean threshold sensitivity of all points in the study eye was summarised and assessed with a MMRM approach in the modified full analysis set for antecedent Study APL2-304 subjects. The analysis model included change from antecedent study baseline to integrated month 30 in the mean threshold sensitivity of all points (decibels) in the study eye as the dependent variable, treatment group (PM to PM, PEOM to PEOM, and sham pooled to pegcetacoplan), presence of choroidal neovascularisation in the fellow eye at antecedent study baseline (yes, no), and antecedent study baseline GA lesion area (<7.5 mm^2 or ≥ 7.5 mm^2) as fixed effect, antecedent study baseline mean threshold sensitivity of all points as a covariate, time (study month, categorical) as a factor, the time × antecedent study baseline mean threshold sensitivity of all points and time × treatment as interaction terms. The LS mean change from antecedent study baseline in mean threshold sensitivity of all points in the study eye was plotted over time by treatment group.

This analysis approach is the same approach as what was used to analyse the key secondary endpoint at month 24.

Main MMRM Analysis – Sensitivity Analysis Based on Study APL2-304 mITT Population

The same analysis as described above was repeated based on the Study APL2-304 mITT population to access robustness of the findings from the analyses based on subjects who enrolled in Study APL2-GA-305 (Study APL2-GA-305 modified full analysis set for antecedent Study APL2-304 subjects).

<u>Number of Scotomatous Points Based on Microperimetry</u>

Descriptive Analyses

The observed values for the number of scotomatous points in the study eye and change from antecedent study baseline were summarised by treatment group and visits.

Main MMRM Analysis

The change from antecedent study baseline to integrated month 30 in the number of scotomatous points in the study eye was summarised and assessed with a MMRM approach in the modified full analysis set for antecedent Study APL2-304 subjects. The analysis model included change from antecedent study baseline to integrated month 30 in the number of scotomatous points in the study eye as the dependent variable, treatment group (PM to PM, PEOM to PEOM, and sham pooled to pegcetacoplan), presence of choroidal neovascularisation in the fellow eye at antecedent study baseline (yes, no), and antecedent study baseline GA lesion area (<7.5 mm^2 or ≥ 7.5 mm^2) as fixed effect, antecedent study baseline number of scotomatous points as a covariate, time (study month, categorical) as a factor, the time × antecedent study baseline number of scotomatous points and time × treatment as interaction terms. The LS mean change from antecedent study baseline in the number of scotomatous points in the study eye was plotted over time by treatment group.

This analysis approach is the same approach as what was used to analyse the secondary endpoint at month 24.

Main MMRM Analysis – Sensitivity Analysis Based on Study APL2-304 mITT Population

The same analysis as described above was repeated based on the Study APL2-304 mITT population to access robustness of the findings from the analyses based on subjects who enrolled in Study APL2-GA-305 (Study APL2-GA-305 modified full analysis set for antecedent Study APL2-304 subjects).

<u>Mean Threshold Sensitivity of Junctional Zone Points Based on Microperimetry</u>

Descriptive Analyses

The observed values for mean threshold sensitivity of junctional zone (-250 μm to 250 μm) points in the study eye and change from antecedent study baseline were summarised by treatment group and visits.

Main MMRM Analysis

The change from antecedent study baseline to integrated month 30 in mean threshold sensitivity of junctional zone points in the study eye was summarised and assessed with a MMRM approach in the modified full analysis set for antecedent Study APL2-304 subjects. The analysis model included change from antecedent study baseline to integrated month 30 in the mean threshold sensitivity of junctional zone points (decibels) in the study eye as the dependent variable, treatment group (PM to PM, PEOM to PEOM, and sham pooled to pegcetacoplan), presence of choroidal neovascularisation in the fellow eye at antecedent study baseline (yes, no), and antecedent study baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) as fixed effect, antecedent study baseline mean threshold sensitivity of junctional zone points as a covariate, time (study month, categorical) as a factor, the time × antecedent study baseline mean threshold sensitivity of junctional zone points and time × treatment as interaction terms. The LS mean change from antecedent study baseline in mean threshold sensitivity of junctional zone points in the study eye was plotted over time by treatment group.

This analysis approach is the same approach as what was used as the same analysis performed at month 24.

Main MMRM Analysis – Sensitivity Analysis Based on Study APL2-304 mITT Population

The same analysis as described above was repeated based on the Study APL2-304 mITT population to access robustness of the findings from the analyses based on subjects who enrolled in Study APL2-GA-305 (Study APL2-GA-305 modified full analysis set for antecedent Study APL2-304 subjects).

<u>Number of Scotomatous Points in the Junctional Zone Based on Microperimetry</u>

Descriptive Analyses

The observed values for the number of scotomatous points in the junctional zone (-250 μm to 250 μm) in the study eye and change from antecedent study baseline were summarized by treatment group and visits.

Main MMRM Analysis

The change from antecedent study baseline to integrated month 30 in the number of scotomatous points in the junctional zone in the study eye was summarised and assessed with a MMRM approach in the modified full analysis set for antecedent Study APL2-304 subjects. The analysis model included change from antecedent study baseline to integrated month 30 in the number of scotomatous points in the junctional zone in the study eye as the dependent variable, treatment group (PM to PM, PEOM to PEOM, and sham pooled to pegcetacoplan), presence of choroidal neovascularisation in the fellow eye at antecedent study baseline (yes, no), and antecedent study baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) as fixed effect, antecedent study baseline number of scotomatous points in the junctional zone and total number of points in the junctional zone as covariates, time (study month, categorical) as a factor, the time × antecedent study baseline number of scotomatous points in the junctional zone, time × antecedent study baseline total number of points in the junctional zone and time × treatment as interaction terms. The LS mean change from antecedent study baseline in the number of scotomatous points in the junctional zone in the study eye was plotted over time by treatment group.

This analysis approach is the same approach as what was used as the same analysis performed at month 24.

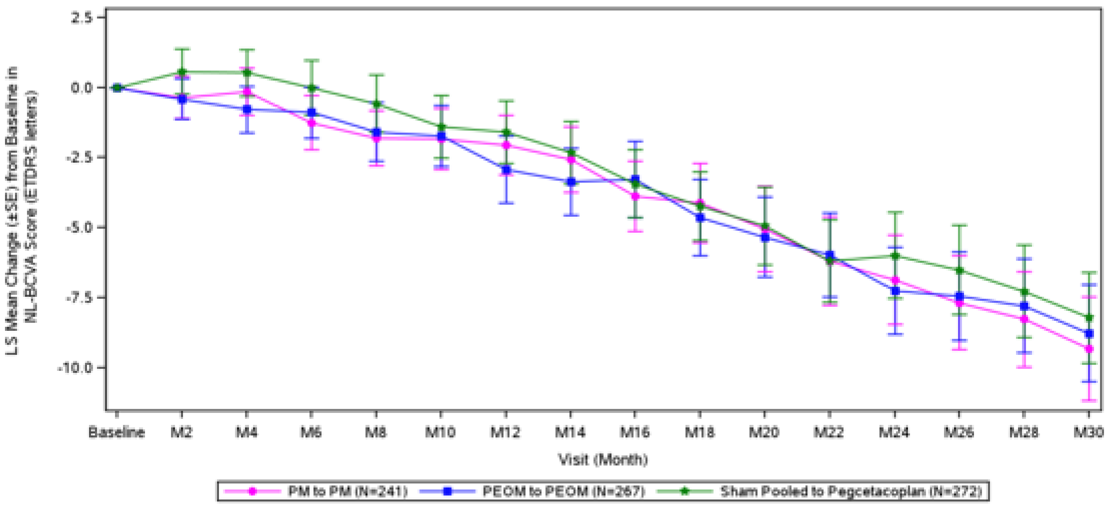
Main MMRM Analysis – Sensitivity Analysis Based on Study APL2-304 mITT Population

The same analysis as described above was repeated based on the Study APL2-304 mITT population to access robustness of the findings from the analyses based on subjects who enrolled in Study APL2-GA-305 (Study APL2-GA-305 modified full analysis set for antecedent Study APL2-304 subjects).

Results

Normal-Luminance Best-Corrected Visual Acuity Score

The Figure below presents the analysis of the change from antecedent study baseline to integrated month 30 in normal-luminance best-corrected visual acuity (NL BCVA) score (Early Treatment Diabetic Retinopathy Study [ETDRS] letters) of the study eye with the mixed-effects model for repeated measures (MMRM) model for the modified full analysis set (mFAS).



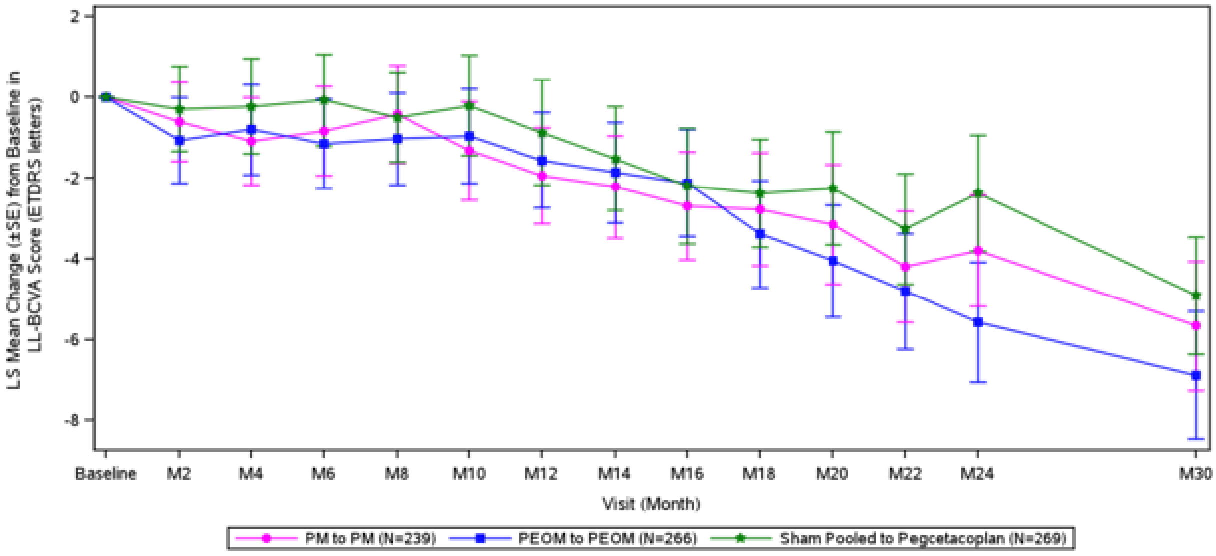
Abbreviations: ETDRS = Early Treatment Diabetic Retinopathy Study; LS = least-square; mFAS = modified full analysis set; MMRM = mixed-effects model for repeated measures; NL-BCVA = normal-luminance best-corrected visual acuity; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly, SE = standard error.

Notes: Antecedent study baseline is defined as the baseline value used in the antecedent study the subject has enrolled in. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥ 7.5 mm²) + antecedent study baseline NL-BCVA score + analysis visit + antecedent study baseline presence of exudative AMD in the fellow eye (yes or no) + analysis visit × treatment + antecedent study baseline NL-BCVA score × analysis visit.

Figure 21: LS mean (± SE) plot of change from antecedent study baseline in NL-BCVA score (ETDRS Letters) of the study eye by visit and treatment group from MMRM model (mFAS) – antecedent study baseline through integrated month 30

Low-Luminance Best-Corrected Visual Acuity Score

The Figure below presents the analysis of the change from antecedent study baseline to integrated month 30 in low-luminance best-corrected visual acuity score (LL BCVA) score (ETDRS letters) of the study eye with the MMRM model for the mFAS.



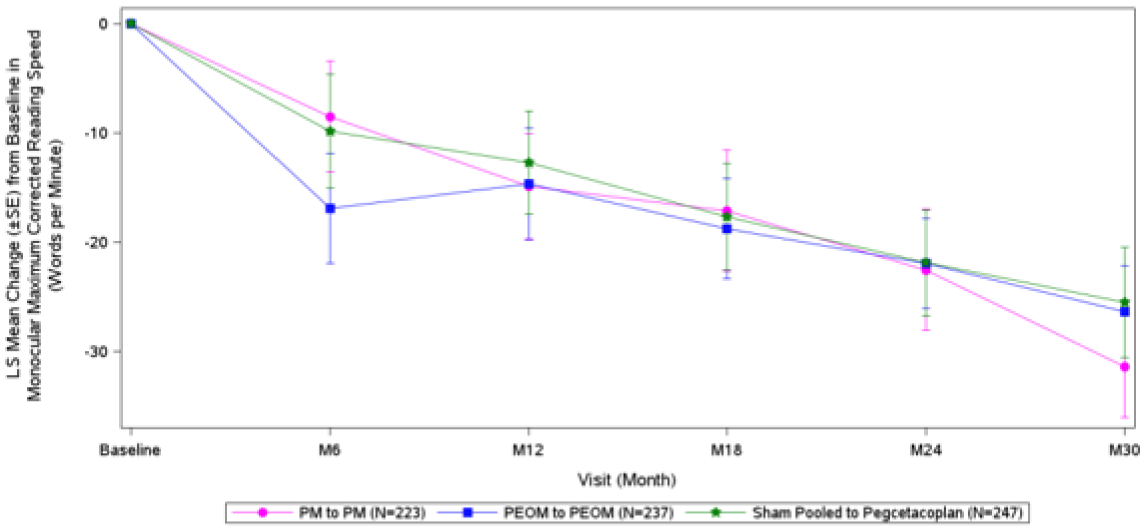
Abbreviations: ETDRS = Early Treatment Diabetic Retinopathy Study; LL-BCVA = low-luminance best-corrected visual acuity; LS = least-square; mFAS = modified full analysis set; MMRM = mixed-effects model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly, SE = standard error.

Notes: Antecedent study baseline is defined as the baseline value used in the antecedent study the subject has enrolled in. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥ 7.5 mm²) + antecedent study baseline LL-BCVA score + analysis visit + antecedent study baseline presence of exudative AMD in the fellow eye (yes or no) + analysis visit × treatment + antecedent study baseline LL-BCVA score × analysis visit.

Figure 22: LS mean (± SE) plot of change from antecedent study baseline in LL-BCVA score (ETDRS letters) of the study eye by visit and treatment group from MMRM model (mFAS) – antecedent study baseline through integrated month 30

Monocular Maximum Corrected Reading Speed

The Figure below presents the analysis of the change from antecedent study baseline to integrated month 30 in monocular maximum corrected reading speed of the study eye with the MMRM model for the mFAS.



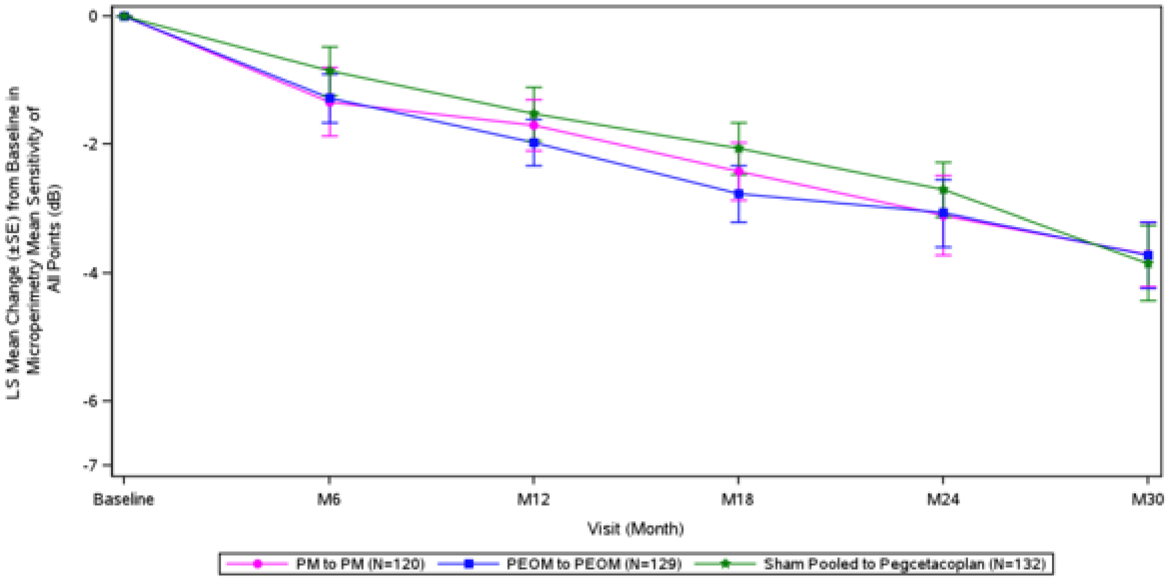
Abbreviations: LS = least-square; mFAS = modified full analysis set; MMRM = mixed-effects model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly, SE = standard error.

Notes: Pooled data from 2 charts: MNRead and Radner. Antecedent study baseline is defined as the baseline value used in the antecedent study subject had enrolled in. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + antecedent study baseline monocular maximum corrected reading speed + chart types + analysis visit + antecedent study baseline presence of exudative AMD in the fellow eye (yes or no) + analysis visit × treatment + antecedent study baseline monocular maximum corrected reading speed × analysis visit. Maximum reading speed will be calculated as the mean of the 3 highest nonzero reading speeds (or 2, or one value, as available), except when all words per minute are calculated as 0: then the maximum reading speed will be calculated as 0. Maximum reading speed will be calculated with an adjustment for reading inaccuracy.

Figure 23: LS mean (± SE) plot of change from antecedent study baseline in monocular maximum corrected reading speed (words per minute) of the study eye by visit and treatment group from MMRM model (mFAS) – antecedent study baseline through integrated month 30

Mean Threshold Sensitivity of All Points Based on Microperimetry

The Figure below presents the analysis of the change from antecedent study baseline to integrated month 30 in microperimetry mean sensitivity of all points (dB) of the study eye with the MMRM model for the mFAS.



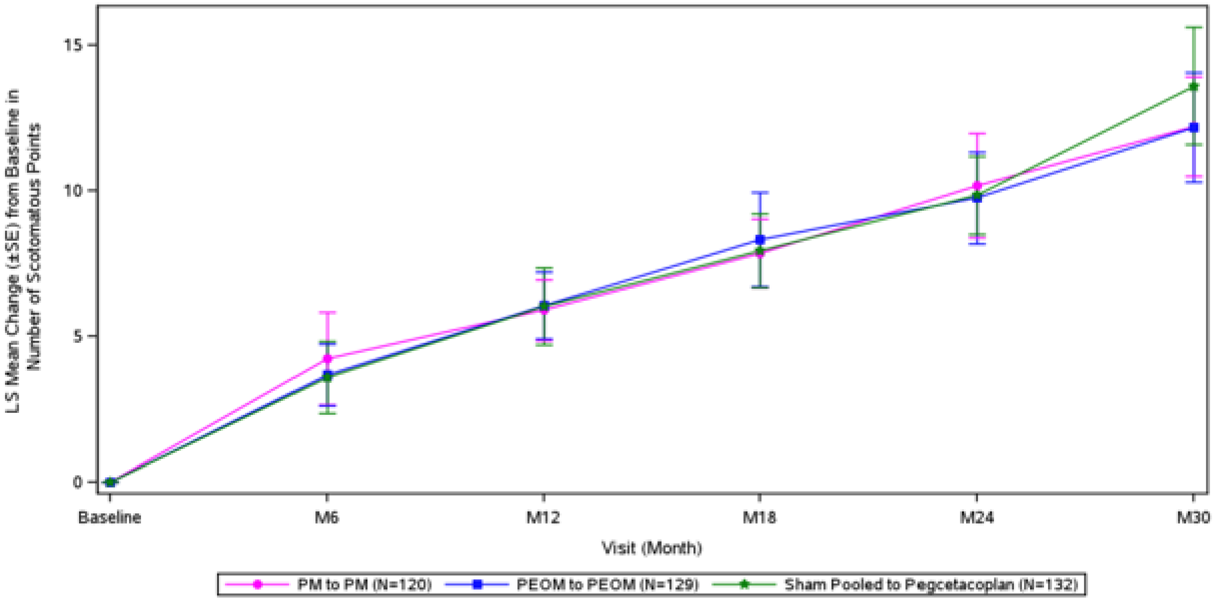
Abbreviations: LS = least-square; mFAS = modified full analysis set; MMRM = mixed-effects model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly, SE = standard error.

Notes: Antecedent study baseline is defined as the baseline value used in the antecedent study subject had enrolled in. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + antecedent study baseline mean threshold sensitivity of all points + analysis visit + antecedent study baseline presence of exudative AMD in the fellow eye (yes or no) + analysis visit × treatment + antecedent study baseline mean threshold sensitivity of all points × analysis visit.

Figure 24: LS Mean (± SE) plot of change from antecedent study baseline in microperimetry mean sensitivity of all points (dB) of the study eye by visit and treatment group from MMRM model (mFAS, antecedent study APL2-304 subjects only) – antecedent study baseline through integrated month 30

Number of Scotomatous Points Based on Microperimetry

The Figure below presents the analysis of the change from antecedent study baseline to integrated month 30 in number of scotomatous points of the study eye with the MMRM model for the mFAS.



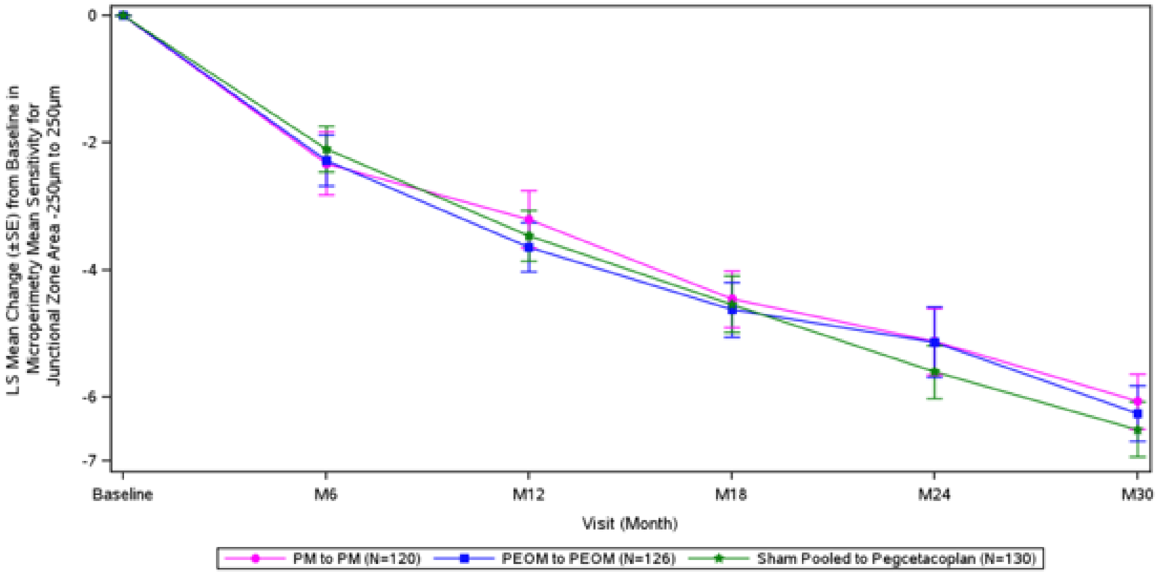
Abbreviations: LS = least-square; mFAS = modified full analysis set; MMRM = mixed-effects model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly, SE = standard error.

Notes: Antecedent study baseline is defined as the baseline value used in the antecedent study subject had enrolled in. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + antecedent study baseline number of scotomatous points + analysis visit + antecedent study baseline presence of exudative AMD in the fellow eye (yes or no) + analysis visit × treatment + antecedent study baseline number of scotomatous points × analysis visit.

Figure 25: LS mean (± SE) plot of change from antecedent study baseline in number of scotomatous points of the study eye by visit and treatment group from MMRM model (mFAS, antecedent study APL2-304 subjects only) – antecedent study baseline through integrated month 30

Mean Threshold Sensitivity of Junctional Zone Points Based on Microperimetry

The Figure below presents the analysis of the change from antecedent study baseline to integrated month 30 in microperimetry mean sensitivity (dB) of the study eye junctional zone area −250 μm to 250 μm of antecedent study baseline atrophy border with the MMRM model for the mFAS.



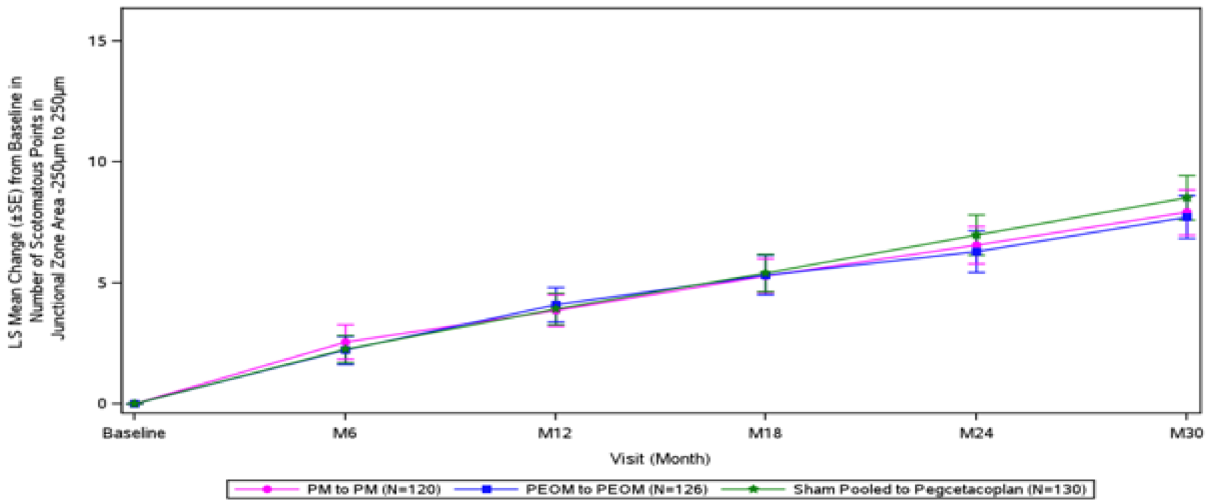
Abbreviations: LS = least-square; mFAS = modified full analysis set; MMRM = mixed-effects model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly, SE = standard error.

Notes: Antecedent study baseline is defined as the baseline value used in the antecedent study subject had enrolled in. The measured distances to the atrophy border used to classify each retinal region are based on antecedent study baseline. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + mean sensitivity of points between −250 μm and 250 μm at antecedent study baseline + analysis visit + presence of exudative AMD in the fellow eye (yes or no) + analysis visit × treatment + mean sensitivity of points between −250 μm and 250 μm at antecedent study baseline × analysis visit.

Figure 26: LS mean (± SE) plot of change from antecedent study baseline in microperimetry mean sensitivity (dB) of the study eye by visit and treatment group from MMRM model in junctional zone area - 250µm to 250 µm of antecedent study baseline atrophy border (mFAS, antecedent study APL2-304 subjects only) – antecedent study baseline through integrated month 30

Number of Scotomatous Points in the Junctional Zone Based on Microperimetry

The Figure below presents then analysis of the change from antecedent study baseline to integrated month 30 in number of scotomatous points of the study eye junctional zone area −250 µm to 250 µm of antecedent study baseline atrophy border with the MMRM model for the mFAS.



Abbreviations: LS = least-square; mFAS = modified full analysis set; MMRM = mixed-effects model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly, SE = standard error.
Notes: Antecedent study baseline is defined as the baseline value used in the antecedent study subject had enrolled in. The measured distances to the atrophy border used to classify each retinal region are based on antecedent study baseline. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + total number of points between −250 µm and 250 µm + antecedent study baseline number of scotomatous points between −250 µm and 250 µm + analysis visit + presence of exudative AMD in the fellow eye (yes or no) + analysis visit × treatment + antecedent study baseline number of scotomatous points between −250 µm and 250 µm × analysis visit + total number of points between −250 µm and 250 µm × analysis visit.

Figure 27: LS mean (± SE) plot of change from antecedent study baseline in number of scotomatous points of the study eye by visit and treatment group from MMRM model in junctional zone area -250µm to µm of antecedent study baseline atrophy border (mFAS, antecedent study APL2-304 subjects only) – antecedent study baseline through integrated month 30

Integrated month 36 data

Secondary Endpoint Data (Microperimetry)

Analysis Methods

Analyses of change from baseline endpoints were performed on two populations, the APL2-304 modified intent-to-treat population and the APL2-GA-305 modified full analysis population. Time to event analyses were performed on the APL2-304 modified intent-to-treat population. Analyses for the antecedent study baseline to integrated month 36 were performed on the Study APL2-304 mITT population, which consists of all randomised subjects who received at least one injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye as assessed by FAF in Study APL2-304.

Subjects were analysed by their combined Studies APL2-304 and APL2-GA-305 treatment groups: PM to PM (subjects were assigned to have received pegcetacoplan monthly in both studies), PEOM to PEOM (subjects were assigned to have received pegcetacoplan every other month both studies), and sham pooled to pegcetacoplan (subjects were assigned to have received sham monthly or every other month in Studies APL2-304 and pegcetacoplan monthly or EOM in Study APL2-GA-305).

Subjects were not required to participate in Study APL2-GA-305 to be in this population. Analyses for the antecedent study baseline to integrated month 36 were also performed on the Study APL2-GA-305 modified full analysis set(mFAS) population, which consists of all subjects who are in APL2-304 study's ITT set, have not been enrolled in APL2-103, and receive at least one injection of pegcetacoplan in APL2-GA-305. Subjects were analysed by their combined Studies APL2-304 and APL2-GA-305 treatment groups: PM to PM (subjects were assigned to have received pegcetacoplan monthly in both studies), PEOM to PEOM (subjects were assigned to have received pegcetacoplan every other month both studies), and sham pooled to pegcetacoplan (subjects were assigned to have received sham monthly or every other month in Studies APL2-304 and pegcetacoplan monthly or EOM in Study APL2-GA-305). Subjects were required to participate in Study APL2-GA-305 to be in this population.

Results

Mean Threshold Sensitivity of All Points Based on Microperimetry

The table below presents the analysis of the change from antecedent study baseline to integrated month 36 in microperimetry mean sensitivity of all points (dB) of the study eye with the MMRM model in the Study APL2-304 mITT population.

Table 64: Analysis of change from antecedent study baseline to integrated month 36 in microperimetry mean sensitivity of all points (dB) of the study eye with MMRM model-mITT set antecedent study APL2-304 subjects only

	PM to PM N = 202	**PEOM to PEOM** N = 205	**Sham pooled to pegcetacoplan** N = 207
Number of subjects included in the model	179	190	187
Estimates/comparisons at integrated month 36			
LS mean (SE)	−4.09 (0.245)	−4.26 (0.226)	−4.71 (0.242)
95% CI of LS mean	(−4.57, −3.61)	(−4.71, −3.82)	(−5.19, −4.24)
Difference (95% CI) in LS mean (vs sham pooled to pegcetacoplan)	0.62 (−0.06, 1.30)	0.45 (−0.20, 1.09)	NA
Percentage difference (vs sham pooled to pegcetacoplan)	−13.2	−9.5	NA
P value (vs sham pooled to pegcetacoplan)	.0729	.1745	NA

Abbreviations: CI = confidence interval; MMRM = mixed model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SE = standard error.

Notes: Antecedent study baseline is defined as the baseline value used in the antecedent study subject had enrolled in. Percentage Difference is derived as the difference in LS means between the arms divided by the comparison group LS means. Model includes Treatment + Antecedent Study Baseline GA lesion area (< 7.5 mm² or ≥ 7.5 mm²) + Antecedent Study Baseline mean sensitivity of all points + Analysis Visit + Antecedent Study Baseline presence of exudative AMD in the fellow eye (Yes or No) + Analysis Visit x Treatment + Antecedent Study Baseline mean sensitivity of all points x Analysis Visit. Data after Integrated Month 24 for subjects who initially enrolled in APL2-304 and later enrolled in APL2-103 are excluded from this analysis. Data through Integrated Month 36 consist of all data collected through the analysis visit windowed Integrated Month 36 visit based on antecedent study baseline in the Integrated 36 dataset.

Source: Integrated APL2-303, APL2-304, and APL2-GA-305 Month 36 Report Table 14.2.2.2.1.3.

Number of Scotomatous Points Based on Microperimetry

The table below presents the analysis of the change from antecedent study baseline through integrated month 36 in number of scotomatous points of the study eye with the MMRM model in the Study APL2-304 mITT population.

Table 65: Analysis of change from antecedent study baseline to integrated month 36 in number of scotomatous points of the study eye with MMRM model-mITT set antecedent APL2-304 subjects only

	PM to PM **N = 202**	**PEOM to PEOM** **N = 205**	**Sham pooled to pegcetacoplan** **N = 207**
Number of subjects included in the model	179	190	187
Estimates/comparisons at integrated month 36			
LS mean (SE)	13.2 (0.77)	14.1 (0.88)	16.1 (0.92)
95% CI of LS mean	(11.6, 14.7)	(12.4, 15.8)	(14.3, 17.9)
Difference (95% CI) in LS mean (vs sham pooled to pegcetacoplan)	−2.9 (−5.3, −0.6)	−2.0 (−4.5, 0.5)	NA
Percentage difference (vs sham pooled to pegcetacoplan)	−18.1	−12.2	NA
P value (vs sham pooled to pegcetacoplan)	.0156	.1233	NA

Abbreviations: CI = confidence interval; mITT = modified intent to treat; MMRM = mixed model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SE = standard error.

Notes: Antecedent study baseline is defined as the baseline value used in the antecedent study subject had enrolled in. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + antecedent study baseline scotomatous points + analysis visit + antecedent study baseline presence of exudative AMD in the fellow eye (yes or no) + analysis visit x treatment + antecedent study baseline scotomatous points x analysis visit. Data after Integrated Month 24 for subjects who initially enrolled in APL2-304 and later enrolled in APL2-103 are excluded from this analysis. Data through Integrated Month 36 consist of all data collected through the analysis visit windowed Integrated Month 36 visit based on antecedent study baseline in the Integrated 36 dataset.

Source: Integrated APL2-303, APL2-304 and APL2-GA-305 Month 36 Report Table 14.2.2.3.1.3.

Mean Threshold Sensitivity of Junctional Zone Points Based on Microperimetry

The table below presents the analysis of the change from antecedent study baseline through integrated month 36 in microperimetry mean sensitivity (dB) of the study eye junctional zone area -250 µm to 250 µm of baseline atrophy border with the MMRM model in the Study APL2-304 mITT population.

Table 66: Analysis of change from antecedent study baseline to integrated month 36 in microperimetry mean sensitivity (dB) of the study eye with MMRM model junctional zone area – 250 µm of baseline atrophy border-mITT Set antecedent study APL2-304 subjects only

	PM to PM **N = 202**	**PEOM to PEOM** **N = 205**	**Sham pooled to pegcetacoplan** **N = 207**
Number of subjects included in the model	178	187	183
Estimates/comparisons at integrated month 36			
LS mean (SE)	−6.34 (0.203)	−6.83 (0.184)	−7.12 (0.164)
95% CI of LS mean	(−6.74, −5.94)	(−7.19, −6.47)	(−7.45, −6.80)
Difference (95% CI) in LS mean (vs sham pooled to pegcetacoplan)	0.78 (0.26, 1.30)	0.30 (−0.19, 0.78)	NA
Percentage difference (vs sham pooled to pegcetacoplan)	−11.0	−4.2	NA
P value (vs sham pooled to pegcetacoplan)	.0032	.2329	NA

Abbreviations: CI = confidence interval; mITT = modified intent to treat; MMRM = mixed model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SE = standard error.

Notes: Antecedent study baseline is defined as the baseline value used in the antecedent study subjec had enrolled in. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + antecedent study baseline mean sensitivity points in junctional zone between −250 µm and 250 µm + analysis visit + antecedent study baseline presenc of exudative AMD in the fellow eye (yes or no) + analysis visit x treatment + antecedent study baseline mean sensitivity points in junctional zone between −250 µm and 250 µm x analysis visit. The measured distances to the atrophy border used to classify each anatomical region are based on antecedent study baseline. Data after Integrated Month 24 for subjects who initially enrolled APL2-304 and later enrolled in APL2-103 are excluded from this analysis. Data through Integrated Month 36 consist of all data collected through the analysis visit windowed integrated month 36 visit based on antecedent study baseline in the integrated 36 dataset.

Source: Integrated APL2-303, APL2-304 and APL2-GA-305 Month 36 Report Table 14.2.2.2.2.2.

Number of Scotomatous Points in Junctional Zone Based on Microperimetry

The table below presents the analysis of change from antecedent study baseline to integrated month 36 in number of scotomatous points of the study eye with MMRM model junctional zone area -250 µm to 250 µm of baseline atrophy border with the MMRM model in the Study APL2-304 mITT population.

Table 67: Analysis of change from antecedent study baseline to integrated month 36 in number of scotomatous points of the study eye with MMRM model junctional zone area – 250 µm to 250 µm of baseline atrophy border-mITT set antecedent study APL2-304 subjects only

	PM to PM **N = 202**	**PEOM to PEOM** **N = 205**	**Sham pooled to pegcetacoplan** **N = 207**
Number of subjects included in the model	178	187	183
Estimates/comparisons at integrated month 36			
LS mean (SE)	8.8 (0.47)	8.8 (0.43)	9.7 (0.42)
95% CI of LS mean	(7.9, 9.8)	(7.9, 9.6)	(8.9, 10.6)
Difference (95% CI) in LS mean (vs sham pooled to pegcetacoplan)	−0.9 (−2.1, 1.3)	−1.0 (−2.1, 0.2)	NA
Percentage difference (vs sham pooled to pegcetacoplan)	−9.3	−10.0	NA
P value (vs sham pooled to pegcetacoplan)	.9110	.1038	NA

Abbreviations: CI = confidence interval; GA = geographic atrophy; MMRM = mixed model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SEOM = sham every other month; SM = sham monthly.

Notes: Antecedent study baseline is defined as the baseline value used in the antecedent study subject had enrolled in. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + antecedent study baseline total number of points between -250 µm and 250 µm + antecedent study baseline number of scotomatous points between -250 µm and 250 µm + analysis visit + presence of exudative AMD in the fellow eye (yes or no) + analysis visit x treatment + antecedent study baseline number of scotomatous points between -250 µm and 250 µm x analysis visit + antecedent study baseline total number of points between -250 µm and 250 µm x analysis visit. The measured distances to the atrophy border used to classify each anatomical region are based on antecedent study baseline. Data after integrated month 24 for subjects who initially enrolled in APL2-304 and later enrolled in APL2-103 are excluded from this analysis. Data through integrated month 36 consist of all data collected through the analysis visit windowed integrated month 36 visit based on antecedent study baseline in the integrated 36 dataset.

Source: Integrated APL2-303, APL2-304, and APL2-GA-305 Month 36 Report Table 14.2.2.3.2.2.

Results of Microperimetry Functional Assessment in Central 2 Degrees (Central 4 Points)

The table below presents the analysis of conversion of all 4 central points to scotoma in the study eye with cox proportional hazards model in the Study APL2-304 mITT population from antecedent study baseline through integrated month 36.

Table 68: Analysis of conversion of all 4 central points to scotoma in the study eye with Cox Proportional Hazards model, mITT set – antecedent study APL2-304 subjects only, antecedent study baseline through integrated month 36

	PM to PM N = 202	**PEOM to PEOM N = 205**	**Sham pooled to pegcetacoplan N = 207**
Number of subjects included in the model	155	155	146
Total number (%) of subjects with an event	68 (43.9)	75 (48.4)	82 (56.2)
Total number (%) of subjects censored	87 (56.1)	80 (5.16)	64 (43.8)
Cox proportional hazards model results			
Hazard ratio (95% CI) (vs sham pooled to pegcetacoplan	0.66 (0.47, 0.91)	0.60 (0.43, 0.84)	
P-value (vs sham pooled to pegcetacoplan)	.0118	.0025	

Abbreviations: CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly

Notes: Subjects censored on Day 1 due to no post-baseline assessment or not at risk for the event are excluded from analysis. An event of conversion of all 4 central points in the study eye to scotoma is defined as a subject having scotomatous points for all central 4 points of the study eye. Time to conversion of all 4 central points is defined as time from first dose date of study drug in antecedent study to the first time when conversion occurred. Subjects without an event are censored at their last post-baseline visit. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + antecedent study baseline presence of CNV in the fellow eye (yes or no) + antecedent study baseline number of central 4 scotomatous points (categorical). Data after integrated month 24 for subjects who initially enrolled in APL2-304, and later enrolled in APL2-103 are excluded from this analysis. Data through integrated month 36 consist of all data collected through the analysis visit windowed integrated month 36 visit based on antecedent study baseline in the integrated 36 dataset.

Source: Integrated APL2-303, APL2-304, and APL2-GA-305 Month 36 Report Table 14.6.4.1.6.

Results of Microperimetry Functional Assessment in Central 6 Degrees (Central 16 Points)

The table below presents the analysis of conversion of all 16 central points to scotoma in the study eye with cox proportional hazards model in the Study APL2-304 mITT population from antecedent study baseline through integrated month 36.

Table 69: Analysis of conversion of all 16 central points to scotoma in the study eye with Cox Proportional Hazards model, mITT set – antecedent study APL2-304 subjects only, antecedent study baseline through integrated month 36

	PM to PM N = 202	**PEOM to PEOM N = 205**	**Sham pooled to pegcetacoplan N = 207**
Number of subjects included in the model	176	187	181
Total number (%) of subjects with an event	35 (19.9)	44 (23.5)	51 (28.2)
Total number (%) of subjects censored	141 (80.1)	143 (76.5)	130 (71.8)
Cox proportional hazards model results			
Hazard ratio (95% CI) (vs sham pooled to pegcetacoplan	0.59 (0.38, 0.92)	0.55 (0.36, 0.83)	
P-value (vs sham pooled to pegcetacoplan)	.0192	.0044	

Abbreviations: CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly

Notes: Subjects censored on Day 1 due to no post-baseline assessment or not at risk for the event are excluded from analysis. An event of conversion of all 16 central points in the study eye to scotoma is defined as a subject having scotomatous points for all central 16 points of the study eye. Time to conversion of all 16 central points is defined as time from first dose date of study drug in antecedent study to the first time when conversion occurred. Subjects without an event are censored at their last post-baseline visit. Model includes treatment + antecedent study baseline GA lesion area (<7.5 mm² or ≥7.5 mm²) + antecedent study baseline presence of CNV in the fellow eye (yes or no) + antecedent study baseline number of central 16 scotomatous points. Data after integrated month 24 for subjects who initially enrolled in APL2-304, and later enrolled in APL2-103 are excluded from this analysis. Data through integrated month 36 consist of all data collected through the analysis visit windowed integrated month 36 visit based on antecedent study baseline in the integrated 36 dataset.

Source: Integrated APL2-303, APL2-304, and APL2-GA-305 Month 36 Report Table 14.6.4.1.5.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical evidence submitted is primarily based on two pivotal Phase III studies of very similar design: APL2-303 (DERBY) and APL2-304 (OAKS). Both pivotal trials were randomised, double-masked and sham-controlled studies and investigated the efficacy and safety of intravitreal pegcetacoplan therapy administered monthly (M) or every other month (EOM) compared to sham injections also administered EM or EOM in subjects with GA secondary to AMD. The study design is adequate for the outlined efficacy evaluations up to 24 months and the presence of two pivotal trials similarly designed and conducted also allows replication of the results. When the design of the studies was discussed in the context of Scientific Advice, the CHMP – anticipating a possible need for longer-term data to confirm that an anatomical effect translates into patient benefit – recommended in its advice in 2018 to extend the double-blind phase of the studies beyond 24 months, the applicant preferred to only roll-over patients to an ongoing open-label study, APL2-305.

The included patient population as defined by inclusion and exclusion criteria reflects the target population and appears adequate. However, the study population was enriched for fast-progressing subjects based on inclusion criteria regarding the GA lesion (lesion size and presence of hyperautofluorescence in the junctional zone). Since GA lesions grow slowly, the inclusion of patients at risk of faster progression is considered acceptable in order to detect an effect in the planned period of treatment. Moreover, in the 2018 advice it was noted that Sunness et al. (Retina, 2007) reported that visual acuity declined most rapidly in eyes with baseline BCVA in the range of 20/25 to 20/50 where a 3 line VA loss was experienced in 41% of patients over 2 years; whereas 29% patients with initial visual acuity of 20/50 to 20/100 experienced equivalent losses over the same period. The applicant was encouraged to plan for subgroup analyses also in this regard as such analyses could provide the “clinical anchors” to support the relevance of an effect on the lesion.

Selection of dose and dosing schedule for the pivotal Phase III trials was discussed during Scientific Advice procedures (2018: EMEA/H/SA/3633/2/2018/SME/II; 2020: EMA/SA/0000050229). Based on data from pre-clinical studies and dose-escalation Phase I study CP043014, the applicant decided to apply 15 mg IVT pegcetacoplan (in 100 µl) monthly or every other month in both pivotal Phase III studies for 24 months, resulting in 12 or 24 treatment/sham injections. The selection of the 15 mg dose and the dosing schedules for Phase III is considered acceptable.

IVT injection of pegcetacoplan was performed using a thin wall needle following aseptic techniques to minimise the risk of potential AEs associated with IVT injections. Administration of pegcetacoplan was only allowed if preinjection IOP was ≤21 mm Hg. If necessary, antiglaucomatous medication could be given to lower the IOP. Sham injections following the exact schedule as for active treatment (monthly or EOM) were chosen as control. Since no approved therapy or standard of care treatment for dry AMD (GA) exists in Europe to date, the sham treatment is endorsed. The sham injection procedure was the same as for pegcetacoplan, but no actual injection occurred. No needle or medication was injected inside the eye. In principle, the sham injection procedure is acceptable due to the inherent risks associated with the intravitreal injections, however, less injection specific AEs are expected to occur in the sham groups (please refer to safety section). For subjects with bilateral GA, exploratory analyses were also performed between the study eye and fellow eye, which has the potential to serve as intra-patient control. This is acknowledged. Ocular medication such as IOP lowering medicinal products, anti-VEGF therapy (ranibizumab or aflibercept) in case of active wet AMD and IVT antibiotics or steroids for treatment of endophthalmitis were allowed per protocol.

Only one eye was treated, which appears acceptable from practical reasons, but which does increase uncertainty in terms of safety of bilateral administration. The condition is usually bilateral and the need of treating both eyes will occur in clinical practice. According to the applicant, currently ongoing Study APL2-305 is including patients on bilateral treatment. The results are planned to be submitted in 2026.

Primary and secondary efficacy endpoint selection was thoroughly discussed during Scientific Advice procedures and pre-submission interactions. The use of GA area (as measured with FAF) as a primary efficacy variable was agreed during Scientific Advice procedure, but it was repeatedly stressed that the applicant needs to justify that this represents a valid surrogate measure for visual function or AMD progression. It was outlined that this justification could be based partly on literature demonstrating the prognostic value of GA area on visual function. In addition, to support the prognostic value and relevance of the change of the lesion, evidence from the pivotal studies showing at least a positive trend of treatment on visual function parameters was considered imperative. The use of NL-BCVA and LL-BCVA scores, reading speed, central visual field sensitivity via microperimetry, vision-related function (i.e., quality of life) and FRI Index score were supported as relevant functional outcomes.

Moreover, the applicant was recommended to include microperimetry in both studies and was also requested to justify why mesopic microperimetry was used over scotopic microperimetry. There are, for example, reports suggesting rod function being more severely affected than cone function in areas with reticular drusen. The applicant's argumentation on the use of mesopic microperimetry was largely followed, still it is questioned if scotopic microperimetry measurements would have provided more robust results, considering rod and cone activity. Due to logistical challenges, microperimetry measures were only performed in study APL2-304. This however in addition to their secondary nature poses additional uncertainty as the respective results thereby lack replication.

The change in total GA lesion area over time (e.g., millimetres squared per year) is frequently used as primary endpoint for assessing GA progression and efficacy of therapeutic interventions in several clinical developments currently ongoing in the field. However, the impact of the treatment on visual function represents a more meaningful outcome for patients and physicians. In this regard the selected secondary endpoints are considered adequate to demonstrate the relevance of the observed differences.

Overall, primary and secondary efficacy endpoint selection appears very challenging and critical for the proposed indication. GA lesion growth could only be accepted as PEP, provided its surrogacy value for clinical benefit was established. The necessary information on surrogacy would also inform on the magnitude of GA-growth slowing effect needed, such that a minimal clinically relevant effect on functional outcome (e.g. in FRI or reading speed) could be expected. However, such information is not available at the current stage. Regarding timing, primary evaluation not earlier than month 24 was strongly suggested by CHMP during Scientific Advice procedures. The applicant performed primary study evaluations at month 12 for all studies contributing efficacy and safety data, but the MAA submission also contains final, 24-month primary endpoint evaluation data from both pivotal Phase III studies. These 24-months data analyses followed the same statistical analysis approach as the 12-months analyses. Given pre-specification of adequate statistical analysis methods, all secondary efficacy endpoint evaluations at month 24 can be considered to provide reliable estimates.

Planning assumptions for power/sample size calculations for the pivotal trials were based on Phase II outcome data for the primary endpoint. At the planning stage no attempt was made to account for key secondary (functional) efficacy endpoints. In consequence, there was also no thorough methodological exploration of the question what could be gained in terms of power for key secondary endpoints when pooling outcome data from DERBY and OAKS.

In calculating the sample size, the applicant has used target treatment differences between the active and sham treatment in reduction of lesion growth at M12 based on the results of Phase II study (Study POT-CP121614). However, there is no sufficient basis to consider it as a (minimal) clinically relevant difference.

Descriptions of plan and conduct of the randomisation procedure foreseen in DERBY and OAKS are high level only. In order to exclude any noteworthy bias potentially introduced by erroneous treatment allocation the applicant was asked to provide a more detailed description of the randomisation process. In relation to that request the applicant added further details for the description of the randomisation process. Overall, provided information suffices to conclude that the potential for bias caused by non-optimal treatment allocation is acceptably low.

In the assessment of the estimand framework defined, the applicant refers to a "treatment policy" strategy in relation to the MMRM analysis of the primary endpoint (MAR assumption for missing values). This cannot be entirely followed, as the chosen estimator would have been more aligned to a hypothetical strategy, which is not acceptable. The analyses currently reported as sensitivity analysis might be an estimator better aligned with the targeted primary Estimand. However, as descriptions in the dossier were not sufficiently detailed, the applicant was invited to clarify several aspects in relation to imputation methods and models which were used in these sensitivity analyses. In this regard, the applicant provided further information concerning estimand and handling of intercurrent events. A sufficiently detailed differentiation was presented as regards the handling strategies applied. These clarifications pertain to the primary and the sensitivity analyses. Those discussed methodological issues also apply to analyses carried out in study APL2-305. However, regardless of a discussion on model-choice preferences in general, the range of analyses eventually carried out is considered sufficiently wide to conclude on robustness of the observed treatment (slowing) effect on GA-lesion growth over the treatment period investigated.

Study protocol, SAP and CSR show discrepancies as regards the order of key secondary endpoints to be tested. However, in light of the fact that all statistical tests for key secondary endpoints revealed non-significant results, this issue was not pursued further.

Concerning control group conditions, all primary results were planned to be shown in comparison to pooled sham groups. SM (sham monthly) and SEOM (sham every other month) groups were pooled for the analysis and compared to PM (pegcetacoplan monthly) and PEOM (pegcetacoplan every other month) groups in both studies. The applicants rationale behind pooling sham groups into a single large group of untreated subjects was that it better represents the heterogenous subject population and thus the sham pooled group provides a valid control to assess the treatment effect of the PM and PEOM groups. This argument is not accepted, as this heterogeneity then only applies for the control group, but not the test treatment. In addition, a different number of sham injections is then applied in the two treatment arms. In principle, pooling the sham groups is therefore not the preferred approach, since it cannot be seen free from risks potentially introducing bias/difficulties for outcome interpretation. However, for sensitivity purposes the applicant also presented results from data comparisons to the separate (treatment-frequency corresponding) sham-groups, which reveal that these results are largely in line with the pooled data. Therefore, this is considered sufficient in this context, and in the following, though not the preferred approach, the pooled data as presented by the applicant are described in the assessment.

The additional ’slope-model’- and ‘piecewise linear slope model’- analyses do not deliver extra/ independent evidence for clinical efficacy, due to strong dependence to the actual primary analysis.

The overall strategy implemented for type-1-error control is not endorsed. A strategy combining study-wise and submission-wise error control is seen problematic and meaningless. Whilst the general idea to make use of pooled data analysis to solve a problem of two separate underpowered trials for some relevant (key secondary functional) endpoints could be supported, the approach chosen is not seen to have a sound interpretation in line with common standards of type-1-error protection in pivotal/ confirmatory Phase III trial-setting. The key point of criticism is not the fact that DERBY could not fully replicate the OAKS outcome, it is rather the methodological issue related to alpha propagation to key-secondary hypothesis tests. Nevertheless, it is noted that alpha was split between the key secondary endpoints, and that microperimetry (that was only investigated in one-study) was assigned an alpha of 0.025 (two-sided). In the end, this methodological aspect does not require further elaboration, as all of the statistical analyses carried out for the key secondary functional endpoints reveal nominal p-values substantially larger than 5%, making any discussion of the potential of false positive conclusions of efficacy in key secondary endpoints superfluous.

The methodological approach chosen by the applicant to do post hoc adjustments accounting for any major imbalances observed across the treatment groups within the two pivotal trials and in the pooled analyses is not considered adequate, as the identification of unbalanced variables is methodologically flawed, and interpretation of post hoc analyses generally difficult. It is hence emphasised that the benefit/risk assessment on effect sizes is based on the original plans as pre-specified in the SAPs.

Efficacy data and additional analyses

In study APL2-303, 622 subjects were assigned to treatment; 206 subjects in the PM group, 208 subjects in the PEOM group, and 207 subjects in the sham pooled group composed the ITT population. Of the subjects in the ITT population, 597 subjects (PM: 201, PEOM: 201 and sham pooled: 195) were included in the mITT population, the analysis population used for the efficacy analyses. In study APL2-304, 637 subjects were assigned to treatment; 213 subjects in the PM group, 212 subjects in the PEOM group, and 212 subjects in the sham pooled group composed the intent-to-treat (ITT) population. Of the subjects in the ITT population, 614 subjects (PM: 202, PEOM: 205 and sham pooled: 207) were included in the modified intent-to-treat (mITT) population.

The most common reasons for study/treatment discontinuation prior to month 24 were consent withdrawal, AEs, death and COVID-19 impact in both studies. It needs to be noted that in both studies throughout month 24, subjects in the monthly arms had higher study discontinuation rates, more missing visits and more missing GA data. The applicant’s explanation that differences observed between monthly and EOM arms were probably driven by subjects’ knowledge of the injection procedure schedule, as well as the minimised assessment schedules implemented in the first 12 months for the EOM arms during the COVID-19 pandemic and greater treatment burden in the monthly arms is considered conclusive. No major imbalances were identified when comparing treatment with sham within the monthly and EOM groups. The applicant was asked to provide a summary describing the numbers of patients discontinuing treatment that were related to GA progression or lack of treatment effect. Potential imbalances would require further elaboration concerning treatment effect estimation. The information provided on that matter revealed that all 10 patients from both trials who stated withdrawal reasons related to (lack of) treatment effect are either PM or PEOM. None of the sham treated patients withdrew for that reason. This constitutes a noteworthy imbalance, which needs to be understood as a signal against perceived efficacy of treatment with pegcetacoplan.

It is noted that withdrawals of consent generally appear high and were slightly higher in the PM groups than in the PEOM and sham pooled groups in both studies, this is considered in the B/R assessment. Withdrawals of consent were mainly driven by reasons such as subjects’ poor general health, study burden, concerns about treatment effectiveness and personal reasons not related to study procedures.

Percentages of subjects that experienced a major protocol deviation is considered generally high, but were evenly distributed between PM, PEOM and sham pooled groups throughout month 24. The most common study-specific major protocol deviations were related to no valid GA lesion area assessment and missed visits or missed visit window.

Unmasking errors for subjects or masked site staff who became unmasked to treatment assignment were generally low. Following the descriptions provided with the dossier, it can be assumed that analysis at month 12 did not jeopardise blinding and trial integrity in any relevant manner in the trial phase thereafter.

Subjects in the PM and SM groups were scheduled to have received 24 pegcetacoplan or sham injections; subjects in the PEOM and SEOM groups were scheduled to have received 12 pegcetacoplan or sham injections over 24 months. The number of subjects with ≥75% of planned injections was slightly lower for the PM groups than for the PEOM and sham pooled groups. It needs to be noted that the overall treatment compliance is considered rather low. Clarification and further discussion were requested. After review of additionally submitted data on that matter, it is agreed with the applicant that the overall compliance within the Phase III trials allows reasonable interpretation of study outcomes. Further, no relevant imbalances persist within posology between sham-treated and pegcetacoplan-treated subjects. However, compliance within a clinical trial is not necessarily the same as in clinical practice and the potential for low compliance in this geriatric population and implications thereof are considered in the B/R. Information regarding treatment compliance from the US market was requested, however, there is no reliable data available yet, due to the limited time the drug has been available in the US.

A potential serious breach of GCP occurred in both studies as a result of subjects being dosed with investigational medicinal product that had experienced unacceptable temperature excursions. Nevertheless, in the end this did not impact subject's safety or the scientific value of the trial. No concerns arise from IP dispensing errors.

Considering the recruitment period, both studies were temporarily paused from September 2018 to March 2019 due to an intraocular inflammation event (study 303) and two severe acute endophthalmitis events (study 304). Events were caused by an impurity in one starting material, which was removed during the study hold and the manufacturing process was modified. A concern was raised regarding numbers of affected patients. The applicant submitted additional information showing that only a small proportion of subjects were affected by the study pause in each study. Hence, a bias in the efficacy and safety analysis and interpretation of the study results is considered highly unlikely. Moreover, during the COVID-19 pandemic, many patients experienced treatment interruptions, missing single or consecutive administrations due to lockdowns, etc. Therefore, a separate COVID-19 estimand was defined and supplemental analyses performed. A question was raised regarding the attribution of missed doses to the pandemic (i.e. was it attributed to the pandemic only when centres were closed or whenever doses were missed during acute phases of the pandemic?). This concern was resolved, as the approach taken to categorise outcome data for the impact evaluation of missed doses via the COVID-19-adjusted sensitivity analyses has been sufficiently clarified.

Both protocols were amended five times. Amendment 1 and 2 were finalised before enrolment of the first patient in both studies. The changes applied in the amendment can be followed and appear principally acceptable. No concern arises regarding the study conduct.

The study population is considered to reflect the population for the intended indication. Baseline demographics appear balanced across treatment groups in both studies and do not give rise to concern. Baseline ocular characteristics in the study eye associated with risk for faster GA progression were generally balanced across treatment groups. However lesion location (study 304: pegcetacoplan groups had lower percentage of patients with lesions without subfoveal involvement than sham), focality (study 303: pegcetacoplan groups presented higher percentage of multifocal lesions than sham groups), number of intermediate/large drusen (>20 to ≤20; study 303: higher percentage of patients in pegcetacoplan with ≤20 intermediate/large drusen than sham patients and study POT-CP121614) and LLD (study POT-CP121614) were identified as characteristics with major imbalances at baseline via a rough systematic approach. Baseline GA lesion size is consistently associated with progression. For example, in the observational study by Sunness et al, lesions measuring <1.3 mm^2, 1.3 to 8.3 mm^2, and ≥8.3 mm^2 had progression rates of 0.8 mm^2/year, 2.1 mm^2/year, and 3.0 mm^2/year, respectively. A meta-analysis conducted by Wang and Ying[2] reported also larger mean growth rate in patients with larger mean baseline GA area. For every mm^2 increase in mean baseline GA area, the mean GA growth rate increased by 0.14 mm^2/year (95% CI: 0.08–0.21 mm^2/year).

Primary endpoint data were adjusted for the four imbalanced variables in both Phase III studies via post-hoc analyses (results are discussed below). Moreover, imbalances were noticed regarding concomitant ocular medications, especially concerning the use of Aflibercept. This concern is discussed in the safety section.

The presence of any pattern of hyperautofluorescence (except for "absence") was one of the inclusion criteria. This is accepted because specific FAF patterns in the junctional zone have been correlated with

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varying risk of GA progression[3,4]. The FAM study[5] reported that the GA progression rate was associated with FAF patterns, with the lowest observed in eyes with no or focal patterns and the highest with banded or diffuse patterns (median, 0.38, 0.81, 1.81, 1.77 mm^2/year, respectively; none+focal vs. banded + diffuse, P <0.0001). According to the additionally provided information, autofluorescence patterns were evenly distributed among the different treatment groups.

Regarding the primary outcome, it should be noted that similar populations were included in both studies, and the conduct of the studies and the methods for evaluating the effect were identically performed. Results are shown in comparison to pooled sham groups (SM+SEOM), which is not the preferred approach, however, no concerns arise in that regard since data are also available for comparisons vs separate sham groups (SM, SEOM) and are presented as sensitivity analyses for month 12 and month 24 for both studies. Primary endpoint analysis was pre-specified for month 12 but is also presented for month 24. At month 12, there was a reduction of GA lesion growth compared to sham consistently observed in both studies. Study APL2-304 met the primary endpoint and demonstrated a statistically significant difference in CFB through month 12 in total area of GA lesions in the PM group of −0.4114 mm2 with 95% CI (−0.6397 mm2 to −0.1831 mm2; p=0.0004) and in the PEOM group of −0.3180 mm2 with 95% CI (−0.5423 mm2 to −0.0937 mm2; p=0.0055) vs the sham pooled group. Study APL2-303 showed a reduction in GA lesion growth for the PM group of −0.2296 mm2 with 95% CI (−0.4703 mm2 to 0.0111 mm2; p=0.0615) and in the PEOM group of −0.2077 mm2 with 95% CI (−0.4444 mm2 to 0.0290 mm2; p=0.0854); however, the confirmatory hypothesis testing narrowly missed meeting statistical significance at the pre-specified α level. This poses an uncertainty and is considered in the B/R assessment. More pronounced effects were observed at month 24. Study APL2-304 showed a reduction in GA lesion growth of −0.9015 mm2 with 95% CI (−1.3026 mm2 to −0.5004 mm2; p=<.0001) in the PM group and −0.7426 mm2 with 95% CI (−1.1282 mm2 to −0.3570 mm2; p=0.0002) in the PEOM group compared to sham. Study APL2-303 showed a reduction in GA lesion growth of −0.7451 mm2 with 95% CI (−1.1539 mm2 to −0.3362 mm2; p=0.0004) in the PM group and −0.6331 mm2 with 95% CI (−1.0508 mm2 to −0.2153 mm2; p=0.0030) in the PEOM group compared to sham. Looking at the effect sizes observed, the growth of GA lesions treated with pegcetacoplan for 1 year, were found below the effect sizes seen in Phase II study (Study POT-CP121614).

In a late stage during the assessment procedure, the applicant provided results of the spectral-domain optical coherence tomography (SD-OCT) imaging. Retinal pigment epithelium (RPE) and photoreceptor (PR) loss were estimated based on a certified artificial intelligence (AI) solution that quantified the extent of atrophy and degeneration. Corresponding analyses indicate that treatment with pegcetacoplan reduced the growth of RPE loss measured by SD-OCT versus sham at 24 months, consistent with what was observed with FAF imaging. In addition, treatment with pegcetacoplan also reduced the growth of PR loss measured by SD-OCT versus sham at 24 months, with more pronounced differences between pegcetacoplan groups and the sham group than what was observed in RPE loss or FAF imaging. These results are acknowledged, and a dose dependent effect was obtained with SD-OCT, showing preservation of PR and confirming anatomical results observed with FAF in preserving RPE cells. It should be noted, however, that this represents yet another post-hoc analysis and again relates to specific aspects of lesion growth and are as such per se a correlate measure of the primary analyses. Consequently, the strong correlation with results on the primary lesion growth endpoint are not surprising and can therefore provide only limited additional evidence of efficacy. Most importantly,

[3] Bui, P.T.A., Reiter, G.S., Fabianska, M. et al. Fundus autofluorescence and optical coherence tomography biomarkers associated with the progression of geographic atrophy secondary to age-related macular degeneration. Eye 36, 2013–2019 (2022).
4 Sahinoglu-Keskek N, Sermet F. Impact of ocular and systemic risk factors on progression of geographic atrophy in age-related macular degeneration. Photodiagnosis and Photodynamic Therapy 33, 102171 (2021).
5 Holz FG, Bindewald-Wittich A, Fleckenstein M, et al. Am J Ophthalmol. 2007;143:463-472.

the observed reduction of the GA lesion growth rate (regardless of the specific measurement) remains an anatomical endpoint that can in itself not demonstrate clinically relevant patient benefit.

To substantiate the clinical relevance of the GA lesion growth endpoint, the applicant compares the magnitude of the observed effects with known anatomical features of the retina. The magnitude of PR and RPE preservation determined by FAF and SD-OCT after two years of treatment is in the range of up to $2mm^2$ (FAF *RPE*: 0.82 mm^2 PM and 0.69 mm^2 PEOM at M24; SD-OCT *RPE*: 0.92 mm^2 PM, 0.73 mm^2 PEOM at M24; SD-OCT *PR*: 2.24 mm^2 PM, 2.08 mm^2 PEOM at M24), which the applicant compares with the size of the blind spot (optic disc, around 2 mm^2). The applicants argumentation is that the optic disc can be regarded as the largest area without light perception that can be compensated by the fellow eye/brain. However, this argumentation is not followed. This observation does not allow for a conclusion that theoretically a compensation for other spots on different regions of the retina cannot be achieved for the same or larger spots in other areas. Anyway, the comparison to the size of the blind spot is considered less relevant.

Overall, primary outcome data demonstrate that IVT pegcetacoplan administered monthly or EOM provides a reduction in GA lesion growth through month 24 compared to sham. This effect is overall supported by sensitivity analyses (comparison to separate sham groups), rate of change in GA lesion area analyses, COVID-19 adjusted analyses and comparisons to the fellow eye in bilateral GA subjects. However, some inconsistencies were identified. The effect appears to be consistently higher in the PM groups vs. the PEOM groups when comparing to sham pooled, however, this changes in some analyses when comparing to the corresponding individual sham control (higher treatment effects in PEOM compared to PM). There were also inconsistencies in the treatment effect reported when assuming a piecewise linear trend in time with a knot at month 6, month 12, and month 18 in both studies, where for some intervals the treatment effect was higher for the PEOM than for the PM group. These data would result in additional uncertainty concerning optimal dosing schedules. In a late stage of the procedure, the applicant decided to exclude the initially proposed monthly dosing regimen and focus only on the 15 mg pegcetacoplan every other month regimen in order to address concerns from the CHMP on the higher rate of AEs (e.g., exudative AMD) with the monthly use of pegcetacoplan (please refer to Safety section).

In response to a major objection raised during assessment, the applicant performed an interim analysis through the month 6 visit (month 30 in total) in APL2-GA-305 study with a data cut off on 01 February 2023, when almost all subjects (783/790, 99.1%) had completed the month 6 visit. The analysis on the GA lesion area endpoint in this interim analysis were expressed by 1) *change from antecedent study baseline to integrated month 30 in the total area of GA lesion size (mm2) in the study eye* and 2) *rate of change from antecedent study baseline to integrated month 30 in total area of GA lesion size (mm2) in the study eye.* The main MMRM analyses of the CFB in GA lesion area as well as the rate of change analyses continue to demonstrate a sustained treatment effect of pegcetacoplan in reduction of GA lesion growth.

As described in literature, atrophic areas typically initially appear in the extrafoveal region and progress into the fovea only late in the course of the disease, the loss of these cells starting typically from the parafoveal region and progressing towards the centre of the fovea has no immediate effect on central vision. Severe vision loss occurs when the areas of atrophy enlarge and expand into the centre of the fovea. Against this background it is an obvious challenge for the assessment of benefit/risk to estimate the potential functional patient benefit which may be caused by slowing anatomic progression, as long as any treatment effect primarily manifests in extrafoveal regions. Within the two pivotal trials conducted, such estimation of potential benefit seems to depend on the specific FAF imaging setup chosen. This would include information concerning the imaging area of the retina in order to get a better understanding regarding the locations of lesions recorded, relative to the fovea. For the interpretation of the magnitude of the treatment effect (i.e. up to 1 mm^2 after 24 months of treatment in the monthly dosing regimen) context is required in terms of total area of the retina investigated, eventually corresponding to maximum lesion size possible at a hypothetical “terminal” stage or worst long-term outcome. Further discussion and information were requested in that regard during the assessment. In their response the applicant further clarified that the retinal area captured by FAF imaging was ~60 mm2, including the macula (a circular region in the retina that is approximately 5.5 mm in diameter with the foveal pit as the centre). The average size of the central fovea is 1.75 mm^2 (1.5 mm diameter). All subjects in studies APL2-304 and APL2-303 were recruited with lesion sizes between 2.5 mm^2 and 17.5mm^2 with a requirement that the entire lesion area is captured within the field of view of the FAF image. The baseline average GA lesion size in the pooled data (across all treatment groups) was 8.2562 mm^2 (inter quartile range, 4.8595 mm^2 to 11.0330 mm^2).

In addition, the applicant performed Exposure-Response analyses (based on studies POT-CP121614, APL2-303, APL2-304) to capture effects on lesion area. While the obtained models capture the general trend of the observed data, the interpretability of the model is severely hampered e.g. by the variability of the observed response data and the apparently rather limited prediction range. Consequently, no robust conclusions can be drawn based on the E-R model.

As mentioned above and in the Scientific Advice, secondary outcomes were to be key to adjudicate clinical meaningfulness of the efficacy profile of Syfovre in context of the benefit risk assessment. Neither meaningful differences nor positive trends in key secondary endpoints (reading speed, FRI index score, NL-BCVA, threshold sensitivity measured by microperimetry) were observed for visual function changes or quality of life over 24 months across the 3 treatment groups in studies APL2-304 and APL2-303. This is considered a major deficiency of the dossier. Since the primary endpoint is an anatomical marker, it needs to be ensured that the primary EP represents a valid surrogate measure for visual function or AMD progression. However, having in parallel also the clinical functional endpoint data available, this is neither demonstrated nor supported by study data. It is not clear to what extent and when this profile could translate into a clinically meaningful benefit to the patient. In the 2-year randomised controlled duration of the study this has not led to any signal of clinical patient benefit, and it cannot be concluded which treatment period will be required to indeed result in a treatment effect that would be of benefit to the patient and of sufficient magnitude.

In its argumentation of a relevant functional benefit, the applicant focusses on the secondary microperimetry endpoint “number of scotomatous points”. At month 24, the difference in least-square (LS) mean (95% CI) CFB between PM and sham pooled groups was 0.027 points (−2.137 to 2.192 points) and the difference between PEOM and sham pooled groups was −0.803 points (−2.623 to 1.017 points). While the PM group performed numerically worse – though with a difference close to zero - than the sham pooled group, according to the applicant, a signal is observed with the PEOM group. The same analysis of the CFB in the total number of scotomatous points among the 68 points of the grid was performed at integrated month 30 and integrated month 36, after subjects on the sham received 6 and 12 months of pegcetacoplan (long-term open-label study APL2-305). Results at integrated M30 and M36 point in the same direction as results observed at M18 and M24 (PEOM group only).

To understand the result that the PM regimen performed worse than the sham group at M24, the applicant conducted an investigation to identify outlier datapoints across all treatment groups and assess these as unexpected/unreliable outcomes, in response to the list of outstanding issues Major Objection. Outliers were identified in 4 PM subjects and 3 PEOM subjects, no outlier was identified in the sham group. Subsequently a clinical review in these, identified two samples (corresponding to two different subjects) in the PM group to be clinically spurious. A sensitivity analysis excluding these 2 samples at month 24 yields a point estimate similar to that observed in the PEOM group. No information was provided regarding the remaining outliers identified on the basis of large residuals or whether further outliers may be present in results from other study visits. According to the applicant, the most likely explanation for the unexpected finding in number of scotomatous points in the PM arm at month 24 is a technical error (e.g., a faulty clicker). While apparently plausible, it would however be unclear to what extent such technical malfunction may have also affected other measurements and importantly such would indicate issues with the reliability of the microperimetry measurements or associated procedures itself. Therefore, such argumentation undermines the credibility of the whole measurement/endpoint itself. Moreover and in general, post-hoc removal of suspected outliers on the basis of inconsistent results is not appropriate and corresponding results need to be interpreted with caution and are not convincing.

The applicant – upon request- presented data from the APL2-305 long term extension study with the list of outstanding issues responses. No significant or meaningful differences between early vs. late initiation of pegcetacoplan from month 24 to integrated month 30 have been observed. After the responses, the applicant has performed another interim data snapshot through the month 12 visit (integrated month 36 from the baseline of APL2-304 and APL2-303) in study APL2-GA-305 as of 29 September 2023, when all subjects had completed the month 12 visit. The data update focussed on microperimetry results (mean threshold sensitivity overall/junctional zone, number of scotomatous points overall/junctional zone, number of scotomatous points in central 2/6 degrees). While in some of the analyses results compared to M24 are similar or numerically larger at integrated M36, others show numerically smaller effects. Despite the comparison to the sham-to-pegcetacoplan group, additional treatment with pegcetacoplan up to M36 seems not to convey additional effects.

A reliable estimate of which magnitude of an effect on GA growth rate to observe a clinically relevant effect on preserved visual function is necessary to outweigh the risks (see safety section below). It is stressed that extrapolation to a predicted effect in future is both not demonstrated in ideal condition and of questionable value in practical terms. In light of the dry AMD patient population, a population with comorbidities and no effect on visual function after two years is seen in the clinical trial, a clinical benefit is not only questioned from a translational/efficacy side, but also questioned regarding further compliance. Although agreed with the applicant that with increasing GA lesion size, a decrease in visual function parameters is expected, further evidence would be needed to substantiate that this association predicts a clinically relevant treatment effect/change in visual function in presence of treatment with Syfovre. Correlation between anatomical and functional endpoints is per se not a sufficient argument in favour of a treatment effect. In addition, no meaningful differences were observed between the 3 treatment groups in the pre-specified secondary QoL endpoint NEI-VFQ-25 distance activity subscale score.

The applicants argumentation that demonstrating a meaningful difference between treatment groups within the context of a clinical trial may not be feasible with the applied functional assessments (which are the best available options), due to heterogenous patient population, high variability, possible confounding by learning effects and patient effort and the fact that the sham pooled group only lost 6.94 BCVA letters after 24 months is not supported. In fact, the consistent argumentation for downweighing initially predefined key secondary endpoints when knowing their results is not convincing and questions credibility of the argumentation and study. Even if correct, this argument would not constitute a demonstration of efficacy. This is while it is agreed and was previously acknowledged by CHMP in its 2018 advice, that BCVA may not be the most suitable measure, since it may not capture the full extent of visual function loss or its progression in GA, due to the phenomenon of foveal sparing, However, an overall clinical effect to the patient is considered key. The BCVA endpoint was indeed sensitive enough to detect a change in this endpoint over time in all groups. The applicant claims based on a weak correlation between GA lesion growth and the change in BCVA after 24 months that only 2 of the 7 letters lost in the sham group can be explained by GA lesion size (while the cause for the decline of the remaining 5 letters is unknown). This reasoning is not followed, a weak correlation may just describe the problem, and besides this factually no treatment effect or trends at all between the groups were observed after 24 months (not even the 2 BCVA letters as described above). Given the capability of this endpoint to observe continuous changes compared to baseline with little fluctuation over time, CHMP is still of the opinion that a truly existing treatment effect of reasonable size would have been expected to be demonstrated with statistical significance in these sufficiently sized trials, and smaller but non-zero treatment effects should have at least resulted in trends for a treatment effect in this endpoint. Instead, in none of the two replicated trial such was observed. Other endpoints such as reading speed or FRI were considered more adequate. Reading speed tests may provide a more direct, objective measure of a patient's ability to read continuous text, measured monocularly or binocularly, determining average maximum reading speed, critical print size and reading acuity. It is also acknowledged that reading speed is a measure subject to variability and influenced by other factors, including cognitive performance. However, this effect is less pronounced when considering within-patient changes as is the case here and is not expected to be unbalanced between randomised groups. This phenomenon only adds variability, but still leads to interpretable results in large enough groups (as it is the case here) and in case a treatment effect truly existed. Instead, any trend of such is lacking in the data presented by the applicant. Additional evidence of validity for the MNREAD test, used binocularly, is available from a Phase Ib/II clinical trial of lampalizumab in GA, still acknowledging issues such as the impact of variability, lesion location, confounding factors, potential learning effects, adequacy of standardisation and comparability of the different charts. The functional reading independence index (FRI index) is a patient-reported outcome measure developed specifically for use in GA patients. The FRI index has explored evidence of content validity based on qualitative research with GA patients and provided evidence of quantitative validity and reliability based on data from a Phase Ib/II study of lampalizumab in GA (EMA/727910/2016; Letter of support for reading speed and functional reading independence FRI index in geographic atrophy). Challenges such as sensitivity to change, precision, and impact of the better seeing eye are acknowledged. Regarding threshold sensitivity measured by microperimetry, it is reiterated that no difference between groups was observed in mean threshold sensitivity after 24 months in Study APL2-304. While acknowledging the applicant's argument that inclusion of stimulus points further away from the border of the lesion are unlikely to be affected by the disease and may dilute the results, it is known that in GA, photoreceptors throughout the retina (also further away from the lesion border) are losing sensitivity. This should have been detected after 2 years treatment.

Taking into account that no differences or even a trend was observed at Month 24, the observed changes in GA lesion size could also be compatible with a negligible/no effect and question the benefit-risk relationship of a (bi)monthly intravitreal treatment.

In the post-hoc covariate adjusted analyses, estimated treatment effects were generally slightly higher after baseline adjustment for major imbalances in ocular characteristics. This would impose, that even a greater effect in lesion growth deceleration did not translate into a functional vision benefit. Results of these covariate-adjusted analyses can only be considered supportive due to their post hoc nature and further methodological deficiencies identified. The B/R assessment is therefore mainly based on data of pre-specified analyses.

Subgroup analyses were performed for age, sex, and geographic region, for baseline GA lesion size and baseline ocular characteristics associated with GA progression that had major imbalances in any of the 3 efficacy studies as described above (GA lesion location, GA lesion focality, the number of intermediate/large drusen category >20/≤20, and LLD). Consistent treatment effects were observed for age, sex and geographic region (US vs. ROW) in both PM and PEOM groups for both pivotal studies. No subgroup analyses were performed by race, because 90% of subjects were white in both studies. No concerns arise from the subgroup analyses regarding demographic characteristics. Concerning GA lesion size, the treatment effect was consistently higher in the >7.5 mm2 subgroup compared to the <7.5 mm2 subgroup and appeared to increase with increasing baseline GA lesion size. Clarification was required regarding these observations. Based on the additionally provided data on that matter, it was shown that larger lesions at baseline showed faster lesion growth compared to smaller lesions, which is in line with the progression of the disease, as evident from literature. Furthermore, the applicant described that the overall mechanism by which pegcetacoplan acts is by reducing inflammation and preventing cell death, irrespective of lesion size. However, due to the overall slower lesion growth of small lesions compared to the faster lesion growth of larger lesions, it can be agreed with the applicant that an absolute treatment difference on reduction of GA progression in smaller lesions is expected to be also lower than in larger lesions.

A numerically greater treatment effect was observed in subjects with baseline GA lesions without subfoveal involvement compared with subjects with baseline GA lesions with subfoveal involvement in study APL2-303 and for the PM group in study APL2-304.

To explore further the relationship between change in GA lesion size and visual function endpoints, the applicant performed post hoc correlation analyses using data through month 24 from study APL2-303 and study APL2-304. Overall, the lesion growth–visual function correlation for NL-BCVA, MRS, FRI Index score, and mean threshold sensitivity was weak, and at best moderate for scotomatous points. Moreover, change in lesion growth (baseline to month 24) was categorised into quartiles to investigate whether the magnitude of lesion growth correlates to the magnitude of visual function changes. In this analysis the strongest association was seen between GA lesion size and number of scotomatous points. Results are shown from pooled data combining all treatment arms from both studies. It was of interest, to perform the same correlation analyses for separated treatment arms (PM, PEOM, SM, SEOM) to further explore the association between GA lesion size and visual function outcomes when comparing sham to pegcetacoplan. Further analyses were requested. Results of these additionally requested analyses have been presented and assessed. The evidence generated for the associations described is considered to be of qualitative nature. The fact that this association can be seen in the study data supports an assumption of sensitive trial settings. However, when it comes to differential assessment of a treatment benefit, no consistent patterns could be identified in the data presented which would give further insight to the question of whether/how/when the slowing of lesion growth would actually manifest in relevant effects in functional outcome.

To further support the claim that pegcetacoplan provides a functional benefit, the applicant elaborated on post-hoc analyses of the microperimetry data. First, it must be remembered that all prespecified microperimetry endpoints (Overall mean threshold sensitivity and Overall number of scotomatous points) showed no effect. Second, even the post-hoc analyses (which are of low evidentiary value because of their post-hoc nature) present inconsistent results, with lack of dose-response further questioning their credibility. Thirdly, this endpoint was measured in only one trial and thereby lacks replication. Moreover, there is no reasonable understanding of the minimum clinically relevant effect size in microperimetry EPs. In addition, as discussed above, these post-hoc results are accompanied by a series of predefined functional data that consistently fail to suggest a treatment benefit for the patient. The applicant performed a refined analysis, detecting the number of scotomatous points in the junctional zone (spanning ±250 µm on either side of the lesion border). Data from the CFB in number of scotomatous points within the junctional zone analyses are suggestive of a possible weak trend favouring both pegcetacoplan treated groups. However, it needs to be reiterated that the more frequent dose (PM) was not nominally significant, while only the less frequent regimen (PEOM) was, and more importantly, the clinical relevance is questionable given an estimated difference (point estimate) of roughly 1 scotomatous point (from approximately 21.4 on average in the junctional zone and from 68 points across the whole microperimetry grid) compared to sham. This, in addition to single trial assessment without replication, increases uncertainty and severely questions the credibility and strength of these results in showing a true treatment effect. In response to one of the major objections, the applicant provided a post-hoc analysis in the subgroup of subjects in whom not all the 4 central stimulus loci (of the microperimetry grid) were scotomatous at baseline. This population was defined as an ‘at-risk population’. The analyses compared the time to conversion of all 4 central points to scotoma between the three treatment groups (PM, PEOM, sham pooled) in the ‘at-risk’ population. From the methodological perspective, several aspects of this analysis setup appear arbitrary and controversial, e.g. the selection of the number of points on the grid (4) as well as the dichotomisation ‘0-3 scotomatous points’ vs ‘4 scotomatous points’ as basis for event-based analyses. Results show that treatment with PM and PEOM corresponded to 34% (hazard ratio [95% CI]: 0.66 [0.46-0.96]) and 36% (hazard ratio [95% CI]: 0.64 [0.44 to 0.92]) reduction in the risk of conversion of all central 4 points to scotoma compared to the sham pooled treatment group within 24 months. Results are acknowledged, however their clinical relevance as well as the post-hoc-nature of the endpoint selection and analysis together with the fact that these represent a selected subgroup of patients only limit their additional value for further assessment. It is understood that the ‘at-risk population’ as defined by the applicant has some interesting correspondence to the subpopulation of subjects with lesions *without foveal involvement* at baseline. Somewhat related to this is the numerical differences in the monocular maximum reading speed (words per minute) between the pegcetacoplan-treated groups vs. the sham-treated group, in the non-subfoveal subpopulation observed within both studies (study APL2-304, baseline to month 24, LS Mean: PM -31.12, PEOM -30.80, sham -36.26; study APL2-303, baseline to month 24, LS Mean: PM -26.92, PEOM -27.71, sham -29.13 [APL2-304, month 24 CSR; APL2-303, month 24 CSR]). Hence, based on the currently available evidence, it could be hypothesised that the subpopulation of subjects without subfoveal lesions could more likely benefit from the treatment compared to patients with already advanced subfoveal lesions and poor vision at baseline. Alternatively, it might be the position of the lesion relative to the fovea (or its distance to it) which could be reasonable predictive for treatment benefit in functional terms. Overall, these observations need however to be understood at best as hypotheses generating at this stage, requiring confirmation from dedicated studies/investigations as described in the *Guideline on the investigation of subgroups in confirmatory clinical trial*, EMA/CHMP/539146/2013, Scenarios 2 and 3). The same analysis, but in central 16 microperimetry points (central 6 degrees) was provided in response to a request, and a similar trend was observed.

In addition, in response to one of the Major Objections the applicant provided post hoc analyses of sustained reduction in NL-BCVA to < 35 ETDRS Letters in the subgroup of subjects in the pooled APL2-304 and APL2-303 studies without severe visual impairment at baseline. Although some delay in progression to severe visual impairment with treatment compared to sham was observed, these results are fraught with uncertainty, given the post-hoc setting in a subgroup of patients and were not even nominally statistically significant when looking at the 95%-CI of the hazard ratios. Moreover, since only 12% of patients in the sham group reached the 35-letter limit within 24M follow-up, mean time-to event analyses were not performed. 9.6% of patients in the PEOM group reached the 35-letter limit within 24M, which represents an estimated difference (point estimate) to the sham group of roughly only 2% at the 24M timepoint, which is considered low and is in line with the nominally non-significant time-to-event analysis. Results are even less convincing in light of the integrated M36 results. M24 results could not be confirmed at integrated M36 after patients on the sham arm were treated with pegcetacoplan for 12 months. In principle, results of this analysis could be an indication that the subgroup of patients with reasonable vision at baseline (above 35 ETDRS letters) might more likely profit from the treatment, compared to subgroup of patients with poor vision. However, further independent confirmation would be needed to substantiate this so far exploratory hypothesis. The ability of pegcetacoplan to delay the progression to <35 ETDRS letters in BCVA, cannot be concluded on the basis of a data driven subgroup selection and would need to be further substantiated. In conclusion, results of these additional analyses are acknowledged, however, as already indicated above, their value is questionable and has methodological limitations. All of the provided additional analyses were performed **post hoc** in certain **subgroups** of patients and – in line with the applicable methodological guidelines and established principles - cannot be considered as confirmatory evidence for the approval for either group for GA secondary to AMD population, but only as hypothesis-generating. In summary, no treatment effect on a functional endpoint that supports clinical patient benefit is demonstrated after a 24M period of treatment with pegcetacoplan.

Post-hoc analyses to predict a treatment effect beyond month 24 are also acknowledged. However besides methodological uncertainties, these analyses mainly refer to pharmacodynamic endpoints (prediction in lesion growth, preservation of retinal tissue), but not to patient benefit. It is not known how visual function (e.g. BCVA, reading speed, FRI index score, quality of life) would evolve over e.g. 5 years and how this correlates to lesion growth, meaning it is still not known what effect in lesion growth would manifest into what effect in functional vision. Anyway, as discussed, after a long period of 24 months of controlled treatment with pegcetacoplan, no patient benefit on functional endpoints is demonstrated.

Ad hoc experts meeting

On 18 June 2024, an ad hoc experts group was convened to discuss on the following points, at the request of CHMP.

What is in the experts view the predictive value of a) size of GA lesions and b) microperimetry endpoints (e.g. retinal sensitivity, number of scotomatous points) on visual function for adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD)?

All agreed that size of GA lesion is an acceptable primary outcome measure for a trial in geographic atrophy; microperimetry (MP) is the best available test for retinal function in this context. Size of GA lesions is correlated with loss of retinal sensitivity as measured in MP with anatomical and functional correlation. GA lesion size is a standard clinical metric to assess severity and progression of GA in patients. It is recognised that lesions also without foveal involvement can cause disability in daily life for patients, and that the condition is usually very slowly progressing.

The heterogeneity of the trial population was recognised and how this could impact the overall perception of the GA lesion change to patients; for example perifoveal GA patients, and rapid GA progressors with impending foveal loss, an impact of 1 mm could have a clinically relevant impact and be perceived by patients. Experts reflected that rapid progressing and perifoveal patients could be identified in clinical practice.

See below for MP further comments on clinical relevance

Do the experts agree that visual function endpoints such as BCVA, maximum reading speed, FRI index are the most relevant endpoints representing a patient benefit in the proposed patient population? What is the experts' opinion on the currently available data on visual function?

Experts do not agree that visual function endpoints such as BCVA, maximum reading speed, FRI index are the most relevant endpoints representing a patient benefit in this context. MP is the mapping of retinal sensitivity and allows correlation of anatomical and functional changes so it will better estimate visual function in GA. BCVA should be taken into account in GA trials, especially when studying population without subfoveal GA lesion at baseline, but not as a primary endpoint. BCVA results can be impacted by confounding factors in patients, e.g. fatigue, cognition.

It would be valuable to see results of sub-populations in GA clinical trials noting that in patients with sub-foveal lesion, changes in BCVA would not be expected; also instead subgroups by other lesion features (Lesion size, multifocality, active fluorescence, location) may help to understand which types of GA patients will benefit most from treatments.

Experts discussed whether small changes in MP could be relevant to patients; will it have impact on visual performance or quality of life? These important outcome parameters are very challenging to measure currently. It is not clear at what stage of MP sensitivity loss patients can perceive changes in their visual function. It would be valuable to gain more information on the correlation between MP sensitivity and patient perceived visual function to better understand the patient benefit of the treatments. Usually, treatment is provided in the worst eye, which also limits testing the impact on visual performance. It was reflected that in other blinding conditions such as glaucoma, nonfunctional measures are considered relevant.

In general terms, reduction in MP sensitivity is clinically relevant to GA patients. Parameters need to be taken into account; the location, parameters and methods. In daily practice, it may be challenging to do MP, with low Visual acuity, elderly patients and difficulties with fixation. Improved MP protocols are in development with learned societies.

2.5.7. Conclusions on the clinical efficacy

Efficacy of Syfovre (pegcetacoplan) for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) in adults has not been sufficiently demonstrated: the effect in the primary anatomical endpoint does not translate into a clinical benefit for the patient. No meaningful differences in prespecified visual function changes over 24 months across treatment groups were observed. It remains also unclear if/when prolonged treatment beyond 24 months could eventually result in meaningful functional patient benefit, and in this case, such benefit can be assumed to be small at best for a reasonably long treatment duration. This lack of demonstrated efficacy on endpoints that represent benefit to the patient, does not allow a positive conclusion on benefit-risk.

2.5.8. Clinical safety

The applicant presented the safety data from 5 clinical studies conducted in patients with GA secondary to AMD (Studies APL2-304, APL2-303, POT-CP121614, APL2-103, and APL2-GA-305) as an integrated safety analysis to support this application. Further, a separate analysis is provided for the pooled safety data from the two phase 3 studies APL2-303 and APL2-304 (pool 1); the latter data are regarded as the pivotal safety data for this submission as they stem from double-masked, controlled, randomised trials.

In pool 1, the following treatment regimen were applied: pegcetacoplan monthly (PM), pegcetacoplan every other month (PEOM), sham monthly (SM), sham every other month (SEOM); for some evaluations data from the two sham-controlled regimen were pooled.

Supportive data are presented from two early-phase studies in subjects with nAMD (Studies POT-CP043014 and APL2-203). This data has less bearing on this assessment, since it has been generated in a patient population that is not in scope for the current submission.

2.5.8.1. Patient exposure

The safety database discussed in the summary of clinical safety comprises over 2000 patient-years of cumulative IVT pegcetacoplan exposure, including approximately 1800 patient-years of phase 3 cumulative exposure using the proposed commercial formulation. Pegcetacoplan years of exposure in IVT studies is summarised below.

Table 70: Pegcetacoplan years of IVT exposure and number of subjects exposed

			Duration of exposure categories					
Population	**Study**	**Number of subjects with at least one pegcetacoplan dose**	**At least 3 mo**	**At least 6 mo**	**At least 12 mo**	**At least 24 mo**	**At least 36 mo**	**Cumulative years on pegcetacoplan exposure**
nAMD	POT-CP043014	13	0	0	0	0	0	1.1
	APL2-203	17	15	12	0	0	0	7.6
	Cumulative (nAMD)	30	15	12	0	0	0	8.7
GA secondary to AMD	APL2-103	19	18	17	12	8	0	25.1
	POT-CP121614	**165**	**159**	**144**	**117**	**0**	**0**	**158.7**
	APL2-303	**414**	**401**	**392**	**356**	**280**	**0**	**698.9**
	APL2-304	**425**	**404**	**384**	**363**	**293**	**0**	**705.4**
	APL2-GA-305	759	661	473	188	0	0	427.1
	Cumulative (GA secondary to AMD)	1281	1205	1098	914	586	118	2037.1
All IVT	Cumulative subjects studies	1311	1220	1110	914	586	118	2045.8

Abbreviation: AMD = age-related macular degeneration; EOM = every other month; GA = geographic atrophy; IVT = intravitreal; mo = months; nAMD = neovascular AMD. **Bold** letters: Sham controlled studies

Notes: For the monthly group, duration of treatment (days) was defined as the minimum (date of last injection + 30 days or discontinuation/completion date) – date of first injection + 1. For the EOM group, duration of treatment (days) was defined as the minimum (date of last injection + 60 days or discontinuation/completion date) – date of first injection + 1. For ongoing Study APL2-GA-305, data up to the data cutoff date 24 June 2022 were included. For other studies (completed), all data were included. Duration of exposure categories are based on having an injection in the study on or after the scheduled visit. Subjects may have participated in more than one study and are presented if they have received at least one dose of pegcetacoplan and are counted once in the cumulative rows.

Source: Month 24 Integrated Summary of Safety Post-Hoc.

Pool 1 Study Drug Exposure

In total, 1256 subjects in pool 1 received at least 1 pegcetacoplan or sham injection through month 24.

Subjects in the pegcetacoplan monthly (PM) and sham monthly (SM) groups were scheduled to have received 24 pegcetacoplan or sham injections; subjects in the pegcetacoplan every other month (PEOM) and sham every other month (SEOM) groups were scheduled to have received 12 pegcetacoplan or sham injections over 24 months. The mean (SD) numbers of injections in the treatment groups were 18.2 (6.80) for the PM group, 9.8 (3.21) for the PEOM group, 18.2 (6.99) for the SM group, and 9.9 (3.18) for the SEOM group.

In the treatment groups that received monthly injections, 48.9% of subjects in the PM group and 49.8% of subjects in the SM group received 22 to 24 pegcetacoplan or sham injections. In the treatment groups that received injections every other month (EOM), 66.0% of subjects in the PEOM group and 66.2% of subjects in the SEOM group received 11 to 12 pegcetacoplan or sham injections.

Mean (SD) duration of treatment for the PM and SM groups was 597.8 (210.00) and 606.7 (213.58) days, respectively. For the PEOM and SEOM groups, duration of treatment was a mean (SD) of 628.4 (193.26) and 631.2 (196.62) days, respectively.

2.5.8.2. Adverse events

AEs summarised by the applicant in the summary of clinical safety were treatment emergent; that is, the AE developed or worsened after the first dose of study medication. Therefore, treatment-emergent AEs are referred to as AEs in this document, and treatment-emergent serious AEs are referred to as SAEs. A summary of the assessment of AEs during the clinical development programme is provided in the following table.

The following safety data were provided:

- the pooled month 24 integrated safety analyses of AEs from Studies APL2-304 and APL2-303 (pool 1);
- supportive safety data from studies including subjects with nAMD (Study POT-CP121614, Study APL2-GA-305, Study APL2-103, Study POT-CP043014, and Study APL2-203) and from pool 2 (comprising pooled safety data from the 5 studies in subjects with GA secondary to AMD [Studies APL2-304, APL2-303, POT-CP121614, APL2-GA-305, and APL2-103]);
- late-breaking AEs, including study eye AEs, SAEs, and AEs leading to discontinuation, from ongoing Study APL2-GA-305 from 24 June 2022 through 21 October 2022.

Pool 1 (Studies APL2-304 and APL2-303)

The following table provides an overall summary of AEs in the safety population of pool 1.

Table 71: Overall summary of AEs in pool 1—safety population

	PM (N = 419)	**PEOM (N = 420)**	**Pegcetacoplan pooled (N = 839)**	**SM (N = 207)**	**SEOM (N = 210)**	**Sham pooled (N = 417)**	**Total (N = 1256)**
All AEs							
n (%)	370 (88.3)	367 (87.4)	737 (87.8)	166 (80.2)	178 (84.8)	344 (82.5)	1081 (86.1)
Total events	2583	2220	4803	1080	1004	2084	6887
Maximum severity of AEs							
Mild, n (%)	90 (21.5)	116 (27.6)	206 (24.6)	49 (23.7)	63 (30.0)	112 (26.9)	318 (25.3)
Moderate, n (%)	156 (37.2)	151 (36.0)	307 (36.6)	68 (32.9)	74 (35.2)	142 (34.1)	449 (35.7)
Mild or moderate, n (%)	246 (58.7)	267 (63.6)	513 (61.1)	117 (56.5)	137 (65.2)	254 (60.9)	767 (61.1)
Severe, n (%)	124 (29.6)	100 (23.8)	224 (26.7)	49 (23.7)	41 (19.5)	90 (21.6)	314 (25.0)
AEs related to treatment							
n (%)	54 (12.9)	40 (9.5)	94 (11.2)	10 (4.8)	9 (4.3)	19 (4.6)	113 (9.0)
Total events	87	69	156	15	19	34	190
AEs related to the injection procedure							
n (%)	110 (26.3)	94 (22.4)	204 (24.3)	46 (22.2)	27 (12.9)	73 (17.5)	277 (22.1)
Total events	240	168	408	91	54	145	553
SAEs							
n (%)	146 (34.8)	107 (25.5)	253 (30.2)	60 (29.0)	52 (24.8)	112 (26.9)	365 (29.1)
Total events	257	212	469	112	80	192	661
AEs leading to treatment discontinuation							
n (%)	47 (11.2)	32 (7.6)	79 (9.4)	19 (9.2)	9 (4.3)	28 (6.7)	107 (8.5)

Total events	58	41	99	21	9	30	129
	PM (N = 419)	**PEOM (N = 420)**	**Pegcetacoplan pooled (N = 839)**	**SM (N = 207)**	**SEOM (N = 210)**	**Sham pooled (N = 417)**	**Total (N = 1256)**
AEs leading to study discontinuation							
n (%)	47 (11.2)	29 (6.9)	76 (9.1)	19 (9.2)	10 (4.8)	29 (7.0)	105 (8.4)
Total events	52	41	93	20	10	30	123
AEs leading to death							
n (%)	28 (6.7)	15 (3.6)	43 (5.1)	11 (5.3)	5 (2.4)	16 (3.8)	59 (4.7)
Total events	29	22	51	12	5	17	68

Abbreviations: AE = adverse event; IP = investigational product; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SAE = serious adverse event; SEOM = sham every other month; SM = sham monthly.

Notes: Pool 1 consists of Studies APL2-303 and APL2-304 and includes data from these studies through month 24. All tabulated AEs had a start date on or after the first dose of IP or, if the AE had a start date before the date of the first dose of IP, increased in severity on or after the date of the first dose of IP. AEs related to treatment had a relationship to study drug of definitely related, possibly related, or not reported. Any AE with a missing or unknown severity was considered as severe.

Source: Month 24 Integrated Summary of Safety.

Through month 24, a slightly greater percentage of subjects in the pegcetacoplan pooled group (87.8%, 737 of 839 subjects) compared with the sham pooled group (82.5%, 344 of 417 subjects) had at least 1 AE during the study.

The maximum severity of AEs in subjects in these treatment groups was generally comparable (61.1% mild or moderate with 26.7% severe in the pegcetacoplan pooled group and 60.9% mild or moderate with 21.6% severe in the sham pooled groups).

No meaningful differences were observed in the percentages of subjects who had SAEs in the PEOM (25.5%) and sham pooled groups (26.9%); in the PM group, a numerically greater percentage of subjects (34.8%) had SAEs.

The percentages of subjects who had AEs leading to treatment discontinuation and study discontinuation were numerically greater in the PM group (11.2% and 11.2%) than in the PEOM group (7.6% and 6.9%) and the sham pooled group (6.7% and 7.0%).

The percentages of subjects who had AEs leading to death were 5.1% and 3.8% in the pegcetacoplan pooled and sham pooled groups. The percentages of subjects who had AEs leading to death was numerically greater in the PM group (6.7%) than in the PEOM and sham pooled groups (3.6% and 3.8%).

Study Eye AEs

The following table provides an overall summary of study eye AEs in pool 1 through month 24.

Table 72: Overall summary of study eye AEs in pool 1—safety population

	PM (N = 419)	**PEOM (N = 420)**	**Pegcetacoplan pooled (N = 839)**	**SM (N = 207)**	**SEOM (N = 210)**	**Sham pooled (N = 417)**	**Total (N = 1256)**
All study eye AEs							
n (%)	258 (61.6)	231 (55.0)	489 (58.3)	96 (46.4)	97 (46.2)	193 (46.3)	682 (54.3)
Total events	753	571	1324	220	200	420	1744
Maximum severity of study eye AEs							
Mild, n (%)	148 (35.3)	147 (35.0)	295 (35.2)	65 (31.4)	69 (32.9)	134 (32.1)	429 (34.2)
Moderate, n (%)	91 (21.7)	76 (18.1)	167 (19.9)	29 (14.0)	25 (11.9)	54 (12.9)	221 (17.6)
Mild or moderate, n (%)	239 (57.0)	223 (53.1)	462 (55.1)	94 (45.4)	94 (44.8)	188 (45.1)	650 (51.8)
Severe, n (%)	19 (4.5)	8 (1.9)	27 (3.2)	2 (1.0)	3 (1.4)	5 (1.2)	32 (2.5)
Study eye AEs related to treatment							
n (%)	51 (12.2)	39 (9.3)	90 (10.7)	10 (4.8)	7 (3.3)	17 (4.1)	107 (8.5)
Total events	78	63	141	12	9	21	162
Study eye AEs related to the injection procedure							
n (%)	109 (26.0)	94 (22.4)	203 (24.2)	45 (21.7)	26 (12.4)	71 (17.0)	274 (21.8)
Total events	231	167	398	85	52	137	535
Study eye SAEs							
n (%)	9 (2.1)	6 (1.4)	15 (1.8)	1 (0.5)	2 (1.0)	3 (0.7)	18 (1.4)
Total events	11	8	19	1	2	3	22
Study eye AEs leading to treatment discontinuation							
n (%)	6 (1.4)	6 (1.4)	12 (1.4)	4 (1.9)	0	4 (1.0)	16 (1.3)

Total events	8	6	14	4	0	4	18
	PM (N = 419)	**PEOM (N = 420)**	**Pegcetacoplan pooled (N = 839)**	**SM (N = 207)**	**SEOM (N = 210)**	**Sham pooled (N = 417)**	**Total (N = 1256)**
Study eye AEs leading to study discontinuation							
n (%)	3 (0.7)	1 (0.2)	4 (0.5)	3 (1.4)	0	3 (0.7)	7 (0.6)
Total events	4	1	5	3	0	3	8
Study eye AEs leading to death							
n (%)	0	0	0	0	0	0	0

Abbreviations: AE = adverse event; IP = investigational product; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SAE = serious adverse event; SEOM = sham every other month; SM = sham monthly.

Notes: Pool 1 consists of Studies APL2-303 and APL2-304 and includes data from these studies through month 24. An AE was considered treatment emergent if it had a start date on or after the first dose of IP or, if the AE had a start date before the date of the first dose of IP, increased in severity on or after the date of the first dose of IP. A treatment-related AE is defined as an AE with a relationship to study drug of definitely related, possibly related, or not reported. Any AE with a missing or unknown severity was considered as severe.

Source: Month 24 Integrated Summary of Safety.

A higher percentage of subjects in the pegcetacoplan pooled group (58.3%) than in the sham pooled group (46.3%) had a study eye AE; this includes 61.6% of subjects in the PM group and 55.0% of subjects in the PEOM group.

The percentage of subjects who had a study eye AE deemed by the investigator to be related to the injection procedure was greater in the pegcetacoplan pooled group (24.2%) than in the sham pooled group (17.0%).

Greater percentages of subjects in the pegcetacoplan pooled group than in the sham pooled group were also observed for:

- severe study eye AEs: 3.2% (PM: 4.5%, PEOM: 1.9%) and 1.2%, respectively
- study eye AEs related to study treatment: 10.7% (PM: 12.2%, PEOM: 9.3%) and 4.1%, respectively
- study eye SAEs: 1.8% (PM: 2.1%, PEOM: 1.4%) and 0.7%, respectively

No meaningful differences were observed in the percentages of subjects who had AEs in the study eye leading to treatment discontinuation (PM, 1.4%; PEOM, 1.4%; and sham pooled, 1.0%) or study discontinuation (PM, 0.7%; PEOM, 0.2%; and sham pooled, 0.7%).

Common Study Eye AEs

The following table summarises pool 1 study eye AEs by PT reported by ≥2% of subjects in any treatment group through month 24.

Table 73: Pool 1 study eye AEs by SOC and PT reported by ≥2% of subjects in any treatment group—safety population

	PM (N = 419) n (%) M	**PEOM (N = 420) n (%) M**	**Pegcetacoplan pooled (N = 839) n (%) M**	**SM (N = 207) n (%) M**	**SEOM (N = 210) n (%) M**	**Sham pooled (N = 417) n (%) M**	**Total (N = 1256) n (%) M**
Number of subjects with ≥1 ocular AE in the study eye	258 (61.6) 753	231 (55.0) 571	489 (58.3) 1324	96 (46.4) 220	97 (46.2) 200	193 (46.3) 420	682 (54.3) 1744
SOC PT							
Eye disorders	250 (59.7) 691	220 (52.4) 513	470 (56.0) 1204	94 (45.4) 208	89 (42.4) 183	183 (43.9) 391	653 (52.0) 1595
Vitreous floaters	41 (9.8) 49	29 (6.9) 37	70 (8.3) 86	3 (1.4) 3	2 (1.0) 2	5 (1.2) 5	75 (6.0) 91
Conjunctival haemorrhage	34 (8.1) 55	34 (8.1) 46	68 (8.1) 101	5 (2.4) 5	10 (4.8) 11	15 (3.6) 16	83 (6.6) 117
Neovascular age-related macular degeneration	41 (9.8) 43	24 (5.7) 25	65 (7.7) 68	4 (1.9) 5	4 (1.9) 4	8 (1.9) 9	73 (5.8) 77
Visual acuity reduced	33 (7.9) 37	27 (6.4) 30	60 (7.2) 67	16 (7.7) 21	12 (5.7) 19	28 (6.7) 40	88 (7.0) 107
Eye pain	30 (7.2) 37	24 (5.7) 27	54 (6.4) 64	13 (6.3) 18	14 (6.7) 15	27 (6.5) 33	81 (6.4) 97
Dry eye	23 (5.5) 25	20 (4.8) 21	43 (5.1) 46	8 (3.9) 8	9 (4.3) 9	17 (4.1) 17	60 (4.8) 63
Vitreous detachment	15 (3.6) 15	25 (6.0) 26	40 (4.8) 41	8 (3.9) 8	6 (2.9) 6	14 (3.4) 14	54 (4.3) 55
Retinal haemorrhage	18 (4.3) 19	21 (5.0) 22	39 (4.6) 41	5 (2.4) 7	7 (3.3) 7	12 (2.9) 14	51 (4.1) 55
Punctate keratitis	23 (5.5) 24	8 (1.9) 8	31 (3.7) 32	2 (1.0) 2	1 (0.5) 1	3 (0.7) 3	34 (2.7) 35
Posterior capsule opacification	15 (3.6) 15	15 (3.6) 15	30 (3.6) 30	5 (2.4) 6	6 (2.9) 6	11 (2.6) 12	41 (3.3) 42
Cataract	16 (3.8) 16	13 (3.1) 14	29 (3.5) 30	8 (3.9) 9	8 (3.8) 8	16 (3.8) 17	45 (3.6) 47
Eye irritation	18 (4.3) 23	10 (2.4) 11	28 (3.3) 34	10 (4.8) 13	10 (4.8) 10	20 (4.8) 23	48 (3.8) 57
Low-luminance best-corrected visual acuity decreased	15 (3.6) 17	13 (3.1) 14	28 (3.3) 31	7 (3.4) 7	8 (3.8) 9	15 (3.6) 16	43 (3.4) 47
Visual impairment	13 (3.1) 15	13 (3.1) 21	26 (3.1) 36	6 (2.9) 6	6 (2.9) 6	12 (2.9) 12	38 (3.0) 48
Blepharitis	9 (2.1) 10	17 (4.0) 17	26 (3.1) 27	4 (1.9) 5	5 (2.4) 5	9 (2.2) 10	35 (2.8) 37
Vision blurred	13 (3.1) 18	10 (2.4) 10	23 (2.7) 28	7 (3.4) 9	9 (4.3) 10	16 (3.8) 19	39 (3.1) 47
Foreign body sensation in eyes	13 (3.1) 15	10 (2.4) 11	23 (2.7) 26	4 (1.9) 4	3 (1.4) 3	7 (1.7) 7	30 (2.4) 33
Choroidal neovascularisation	12 (2.9) 12	4 (1.0) 4	16 (1.9) 16	4 (1.9) 5	1 (0.5) 1	5 (1.2) 6	21 (1.7) 22
Ocular hyperaemia	9 (2.1) 13	5 (1.2) 8	14 (1.7) 21	6 (2.9) 11	1 (0.5) 2	7 (1.7) 13	21 (1.7) 34
Lacrimation increased	6 (1.4) 7	6 (1.4) 6	12 (1.4) 13	5 (2.4) 6	3 (1.4) 3	8 (1.9) 9	20 (1.6) 22
Investigations	9 (2.1) 24	13 (3.1) 26	22 (2.6) 50	0	3 (1.4) 3	3 (0.7) 3	25 (2.0) 53
Intraocular pressure increased	8 (1.9) 23	12 (2.9) 24	20 (2.4) 47	0	3 (1.4) 3	3 (0.7) 3	23 (1.8) 50

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; M = number of events; n = number of subjects; N = number of subjects in group; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; PT = Preferred Term; SEOM = sham injection every other month; SM = sham injection monthly; SOC = System Organ Class.

Notes: Pool 1 consists of Studies APL2-303 and APL2-304 and includes data up to month 24. An AE was considered treatment emergent if it had a start date on or after the first dose of investigational product or if it had a start date before the date of the first dose of investigational product but increased in severity on or after the date of the first dose of investigational product. If a subject had multiple occurrences of an AE, the subject was presented only once in the subject count (n) column and all AEs were counted in total events (M) for a given SOC and PT. AEs were coded to SOC and PT using MedDRA version 23.1.

Across all treatment groups, 682 subjects (54.3%) had 1744 study eye AEs. Most study eye AEs occurred in the SOC of eye disorders (653 subjects [52.0%], 1595 study eye AEs).

A greater percentage of subjects in the pegcetacoplan pooled group (58.3%) than in the sham pooled group (46.3%) had at least 1 study eye AE.

The most common study eye AEs in the pegcetacoplan pooled group by percentage of subjects were vitreous floaters (8.3%), conjunctival haemorrhage (8.1%), nAMD (7.7%), visual acuity reduced (7.2%), and eye pain (6.4%); in the sham pooled group, these events occurred in 1.2%, 3.6%, 1.9%, 6.7%, and 6.5% of subjects, respectively. AEs of vitreous floaters, conjunctival haemorrhage, and eye pain are associated with the IVT injection procedure and are commonly reported in this type of clinical trial.

A greater percentage of subjects in the PM group (61.6%) than in the PEOM group (55.0%) or sham pooled group (46.3%) had at least 1 study eye AE. The study eye AEs with the greatest differences between the percentage in subjects in the PM group and the percentage of subjects in the PEOM group were vitreous floaters (9.8% vs 6.9%), nAMD (9.8% vs 5.7%), and punctate keratitis (5.5% vs 1.9%); vitreous floaters and punctate keratitis are associated with the IVT injection procedure (Ramos et al. 2021).

A greater percentage of subjects in the PM group (7 subjects; 1.7%) had events of optic ischaemic neuropathy compared with the PEOM group (1 subject; 0.2%) and the sham pooled group (0 subjects; 0%). All cases of optic ischaemic neuropathy were reported as not related to treatment or injection procedure. All subjects who had optic ischaemic neuropathy had ocular and/or systemic comorbidities associated with an increased risk of the event.

A greater percentage of subjects in the PM group (1.9%) and the PEOM group (2.9%) compared with the sham pooled group (0.7%) had events of intraocular pressure increased. For more information on changes in intraocular pressure see Section 4.5 of this report.

Common Fellow Eye AEs

Across all treatment groups, 504 subjects (40.1%) had 924 fellow eye AEs. Most fellow eye AEs occurred in SOC eye disorders (489 subjects [38.9%], 860 fellow eye AEs).

There were no meaningful differences in the percentages of fellow eye AEs across treatment groups.

The most common fellow eye AEs in the pegcetacoplan pooled group by percentage of subjects were visual acuity reduced (4.8%), dry eye (4.6%), and nAMD (3.8%). These events were as expected considering that most subjects had ocular history of dry AMD in the fellow eye.

Common Nonocular Adverse Events

Across all treatment groups, 944 subjects (75.2%) had 4219 nonocular AEs.

The most common nonocular SOCs in the pegcetacoplan group by percentage of subjects were in the SOCs infections and infestations (37.1%), musculoskeletal and connective tissue disorders (21.7%), and injury, poisoning and procedural complications (18.7%).

The most common nonocular PTs in the pegcetacoplan pooled group by percentage of subjects were urinary tract infection (9.1%), hypertension (8.2%), and fall (7.5%); these nonocular AEs are common medical conditions in an elderly population.

AEs Related to Treatment

Study Eye

Across all treatment groups, 107 subjects (8.5%) had 162 study eye AEs related to treatment. Most study eye AEs occurred in SOC eye disorders (101 subjects [8.0%], 138 study eye AEs related to treatment).

A greater percentage of subjects in the pegcetacoplan pooled group (10.7%) than in the sham pooled group (4.1%) had at least one study eye AE deemed by the investigator to be related to treatment.

The percentages of subjects with at least 1 study eye AE deemed by the investigator to be related to treatment in the PM and PEOM groups were 12.2% and 9.3%, respectively.

The most common study eye AEs related to treatment in the pegcetacoplan pooled group by percentage of subjects were nAMD (3.1%), vitreous floaters (2.4%), visual acuity reduced (0.8%), vitritis (0.7%), and eye pain (0.7%); in the sham pooled group, these events occurred in 1.0%, 0.2%, 0.7%, 0%, and 0.5% of subjects, respectively.

The incidence of ocular treatment-related AEs was greater in the pegcetacoplan-treated group than in the sham pooled group as expected and includes events commonly reported after IVT procedures.

<u>AEs Related to the Injection Procedure</u>

The following table summarises pool 1 study eye AEs related to the injection procedure reported by ≥1% of subjects in any treatment group through month 24.

Across all treatment groups, 274 subjects (21.8%) had 535 study eye AEs related to the injection procedure.

A higher percentage of subjects in the pegcetacoplan pooled group (24.2%) than in the sham pooled group (17.0%) had a study eye AE deemed by the investigator to be related to the injection procedure. Similar percentages of subjects in the PM (26.0%) and PEOM (22.4%) groups had at least 1 study eye AE deemed by the investigator to be related to the injection procedure.

The most common study eye AEs deemed by the investigator to be related to the injection procedure in the pegcetacoplan pooled group by percentage of subjects were conjunctival haemorrhage (6.2%), eye pain (4.9%), and vitreous floaters (4.4%); in the sham pooled group, these events occurred in 2.9%, 5.3%, and 0.7% of subjects, respectively.

Table 74: Pool 1 study eye AEs related to the injection procedure by SOC and PT reported by ≥1% of subjects in any treatment group—safety population

	PM (N = 419) n (%) M	**PEOM (N = 420) n (%) M**	**Pegcetacoplan pooled (N = 839) n (%) M**	**SM (N = 207) n (%) M**	**SEOM (N = 210) n (%) M**	**Sham pooled (N = 417) n (%) M**	**Total (N = 1256) n (%) M**
Number of subjects with ≥1 study eye AE related to the injection procedure	109 (26.0) 231	94 (22.4) 167	203 (24.2) 398	45 (21.7) 85	26 (12.4) 52	71 (17.0) 137	274 (21.8) 535
SOC PT							
Eye disorders	99 (23.6) 206	83 (19.8) 150	182 (21.7) 356	42 (20.3) 80	24 (11.4) 49	66 (15.8) 129	248 (19.7) 485
Conjunctival haemorrhage	27 (6.4) 47	25 (6.0) 36	52 (6.2) 83	5 (2.4) 5	7 (3.3) 7	12 (2.9) 12	64 (5.1) 95
Eye pain	24 (5.7) 28	17 (4.0) 19	41 (4.9) 47	10 (4.8) 14	12 (5.7) 12	22 (5.3) 26	63 (5.0) 73
Vitreous floaters	17 (4.1) 18	20 (4.8) 27	37 (4.4) 45	3 (1.4) 3	0	3 (0.7) 3	40 (3.2) 48
Eye irritation	13 (3.1) 17	9 (2.1) 10	22 (2.6) 27	9 (4.3) 12	9 (4.3) 9	18 (4.3) 21	40 (3.2) 48
Foreign body sensation in eyes	12 (2.9) 14	8 (1.9) 9	20 (2.4) 23	4 (1.9) 4	2 (1.0) 2	6 (1.4) 6	26 (2.1) 29
Vision blurred	5 (1.2) 7	6 (1.4) 6	11 (1.3) 13	4 (1.9) 6	5 (2.4) 6	9 (2.2) 12	20 (1.6) 25
Ocular discomfort	7 (1.7) 8	3 (0.7) 3	10 (1.2) 11	1 (0.5) 1	2 (1.0) 3	3 (0.7) 4	13 (1.0) 15
Ocular hyperaemia	5 (1.2) 8	4 (1.0) 7	9 (1.1) 15	4 (1.9) 9	1 (0.5) 2	5 (1.2) 11	14 (1.1) 26
Dry eye	2 (0.5) 2	6 (1.4) 6	8 (1.0) 8	3 (1.4) 3	1 (0.5) 1	4 (1.0) 4	12 (1.0) 12
Vitreous detachment	3 (0.7) 3	4 (1.0) 4	7 (0.8) 7	3 (1.4) 3	1 (0.5) 1	4 (1.0) 4	11 (0.9) 11
Vitreous haemorrhage	5 (1.2) 5	1 (0.2) 1	6 (0.7) 6	0	0	0	6 (0.5) 6
Lacrimation increased	3 (0.7) 3	3 (0.7) 3	6 (0.7) 6	4 (1.9) 5	3 (1.4) 3	7 (1.7) 8	13 (1.0) 14
Eye pruritus	3 (0.7) 3	1 (0.2) 1	4 (0.5) 4	3 (1.4) 3	1 (0.5) 1	4 (1.0) 4	8 (0.6) 8
Infections and infestations	3 (0.7) 3	4 (1.0) 4	7 (0.8) 7	1 (0.5) 1	0	1 (0.2) 1	8 (0.6) 8

	PM (N = 419) n (%) M	PEOM (N = 420) n (%) M	Pegcetacoplan pooled (N = 839) n (%) M	SM (N = 207) n (%) M	SEOM (N = 210) n (%) M	Sham pooled (N = 417) n (%) M	Total (N = 1256) n (%) M
Endophthalmitis	2 (0.5) 2	3 (0.7) 3	5 (0.6) 5	0	0	0	5 (0.4) 5
Injury, poisoning and procedural complications	8 (1.9) 13	3 (0.7) 3	11 (1.3) 16	3 (1.4) 3	2 (1.0) 2	5 (1.2) 5	16 (1.3) 21
Corneal abrasion	3 (0.7) 4	2 (0.5) 2	5 (0.6) 6	2 (1.0) 2	2 (1.0) 2	4 (1.0) 4	9 (0.7) 10
Investigations	5 (1.2) 6	7 (1.7) 8	12 (1.4) 14	0	0	0	12 (1.0) 14
Intraocular pressure increased	5 (1.2) 6	6 (1.4) 7	11 (1.3) 13	0	0	0	11 (0.9) 13

Abbreviations: AE = adverse event; IVT = intravitreal; M = number of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the group; n = number of subjects with an event in the SOC or PT; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; PT = Preferred Term; SEOM = sham every other month; SM = sham monthly; SOC = System Organ Class.

Notes: Pool 1 consists of studies APL2-303 and APL2-304 and includes data from these studies through month 24. An AE was considered treatment-related if it had a start date on or after the first dose of IP or, if the AE had a start date before the date of the first dose of IP, increased in severity on or after the date of the first dose of IP. If a subject had multiple occurrences of an AE, the subject was presented only once in the subject count (n) column and all AEs were counted in total events (M) for a given SOC and PT. AEs were coded to SOC and PT using MedDRA version 23.1. An IVT injection–related AE is defined as an AE with a relationship to IVT injection of definitely related, possibly related, or not reported.

Source: Month 24 Integrated Summary of Safety.

Endophthalmitis

Per the study protocols for Studies APL2-304 and APL2-303, all endophthalmitis cases were reported as SAEs.

Study Eye

Five of 839 subjects in the pegcetacoplan pooled group (0.6%) had a study eye SAE of endophthalmitis, corresponding to a rate per injection of 0.04% (5 of 11,736 injections); this includes

- 2 of 419 subjects in the PM group (0.5%) corresponding to a rate per injection of 0.03% (2 of 7600 injections)
- 3 of 420 subjects in the PEOM group (0.7%) corresponding to a rate per injection of 0.07% (3 of 4136 injections)

No subject in the sham pooled group had a study eye SAE of endophthalmitis.

One of the SAEs of endophthalmitis with negative vitreous culture results in the PEOM group appeared to be associated with an impurity in the drug product lots at the beginning of the study, which has been successfully removed by optimisation of the manufacturing process.

Among the 5 subjects who had SAEs of endophthalmitis, culture results were positive for 1 subject in the PM group (*Staphylococcus epidermidis*) and 1 subject in the PEOM group (*Staphylococcus aureus*), negative for 1 subject in the PM group and 1 subject in the PEOM group, and a culture could not be obtained for the remaining 1 subject (PEOM). Four subjects were treated with IVT and topical antibiotics. One subject underwent vitrectomy and was treated with subconjunctival and topical antibiotics. The SAEs of endophthalmitis were resolved (4 subjects) or resolved with sequelae (1 subject). Three subjects (2 in the PM group and 1 PEOM group) completed the study. One subject (PEOM group) discontinued the study because of death, and 1 subject in the PEOM group withdrew from the study. No subjects who had endophthalmitis had a sustained NL-BCVA loss of ≥15 letters from their visual acuity before the endophthalmitis event.

Fellow Eye

Two subjects in the sham pooled group (2 of 417 subjects, 0.5%) had a fellow eye SAE of endophthalmitis; narratives for these subjects, one of whom who had received anti–vascular endothelial growth factor (VEGF) therapy 8 days prior to SAE onset, are provided in Study APL2-304 Month 24 CSR.

Overall, the incidence per subject and rate per injection of AEs of endophthalmitis in pool 1 were low and as expected with an IVT administered product (Rosenfeld et al. 2006; Brown et al. 2009; Holz et al. 2018).

All 5 subjects with endophthalmitis recovered their visual acuity to the level of the visit prior to the onset of the endophthalmitis event.

Intraocular Inflammation

Intraocular inflammation events included PTs of anterior chamber cell, anterior chamber flare, anterior chamber inflammation, anterior chamber fibrin, aqueous fibrin, iridocyclitis, iritis, autoimmune uveitis, uveitis, panophthalmitis, vitritis, vitreal cells, vitreous fibrin, corneal endotheliitis, non-infectious endophthalmitis, cyclitis, immune recovery uveitis, immune-mediated uveitis, Vogt-Koyanagi-Harada disease, autoimmune eye disorder, Behcet’s syndrome, keratouveitis, ocular vasculitis, optic neuritis, chorioretinitis, choroiditis, noninfective chorioretinitis, retinal vasculitis, retinitis, and scleritis.

Studies APL2-304 and APL2-303 were initiated in August 2018. Apellis decided to temporarily halt these trials and Study APL2-203 on 28 September 2018 after 8 subjects enrolled in the 3 trials had transient events of ocular inflammation. Among these events, in Study APL2-203, 4 subjects experienced AEs of uveitis; 2 of these were SAEs. In Study APL2-303, 2 subjects had 1 event each of iridocyclitis and one subject had an AE of vitritis. In Study APL2-304, 1 subject had an SAE of non-infectious endophthalmitis.

Study APL2-103 was initiated to evaluate the safety and tolerability of new drug product lots prior to further dosing in the phase 3 trials. After the initiation of Study APL2-103, 6 subjects developed events of intraocular inflammation, and the study was halted. Chemistry, manufacturing, and controls analyses were performed to determine the root cause of the inflammatory effects in conjunction with nonclinical testing of pegcetacoplan formulations from a different manufacturer. These analyses and further investigations identified an impurity in the active pharmaceutical ingredient as the likely root cause for the events of intraocular inflammation. Additional manufacturing steps were implemented to eliminate this impurity.

IVT pegcetacoplan was reintroduced in Study APL2-103, and no event of intraocular inflammation was observed once the drug product without the impurity was introduced. Apellis then reinitiated the phase 3 studies in March 2019. Study APL2-103 was subsequently terminated to allow subjects to roll over into the ongoing, long-term extension study, Study APL2-GA-305.

The impurity is not present in the drug product currently used in Study APL2-GA-305. Active monitoring is ongoing to review any new cases of intraocular inflammation.

Study Eye

Twenty-four subjects in the pegcetacoplan pooled group (2.9%) had 27 study eye AEs (5 were SAEs) of intraocular inflammation, and the corresponding rate per injection was 0.23%. One study eye AE of intraocular inflammation was observed in sham-treated subjects (0.2%). The incidence and rate per injection for the pegcetacoplan groups was as follows:

- 16 subjects in the PM group (3.8%) who had 17 study eye AEs of intraocular inflammation, corresponding to a rate per injection of 0.22% (17 of 7600 injections)
- 8 subjects in the PEOM group (1.9%) who had 10 study eye AEs of intraocular inflammation, corresponding to a rate per injection of 0.24% (10 of 4136 injections)

The most common study eye AEs of intraocular inflammation in the pegcetacoplan pooled group by percentage of subjects were vitritis (1.0%), vitreal cells (0.7%), iridocyclitis (0.6%), and uveitis (0.4%).

Of the 24 subjects in the pegcetacoplan pooled group who had AEs of intraocular inflammation, 3 subjects had AEs (2 AEs of iridocyclitis and 1 SAE of vitritis) that were associated with a specific lot of pegcetacoplan that contained an impurity in one starting material.

The majority of the intraocular inflammation events were mild to moderate and were treated with topical steroids. One subject (PM group) was treated with intravitreous steroid implant (Ozurdex). One subject (PM group) was treated with oral steroids. Eleven subjects did not require any treatment.

The majority of the subjects who had intraocular inflammation during the study recovered their vision to the pre–intraocular inflammation event onset value. Two subjects in the PM group (1 AE of vitreal cells and 1 SAE of vitritis) had visual acuity loss of ≥15 letters at the last observed value. There was no event of intraocular inflammation that led to permanent severe vision loss (≥30 letters lost).

Among the 24 subjects in the pegcetacoplan pooled group who had AEs of intraocular inflammation:

- 2 subjects in the PM group had SAEs of vitritis, 1 subject in the PEOM group had an SAE of uveitis, and 1 subject in the PEOM group had an SAE of iridocyclitis and uveitis on the same day. These SAEs were deemed by the investigator to be related to treatment. One subject in the PM group with vitritis and 1 subject in the PEOM group with uveitis discontinued from treatment because of the SAE. Both subjects continued in the study.
- The following AEs in the study eye were severe:
  - vitritis (3 subjects in the PM group)
  - uveitis (2 subjects in the PEOM group)
  - iridocyclitis (1 subject in the PEOM group)
- 10 subjects in the pegcetacoplan-treated groups had at least 1 AE of intraocular inflammation that was not resolved at the time of the month 24 reporting time point or last observation.

Fellow Eye

Two subjects in the PM group (0.5%) had mild intraocular inflammation events (PTs of uveitis and iritis), and 1 subject in the PEOM group (0.2%) had a mild intraocular inflammation event of vitreal cells.

No AE of intraocular inflammation in the fellow eye was reported in Study APL2-303.

Overall, the rate per injection of AEs of intraocular inflammation in pool 1 was low and as expected with an IVT administered product (Abraham et al. 2010; Busbee et al. 2013; Goldberg et al. 2014; Ho et al. 2014; Nguyen et al. 2012; Regillo 2008).

The majority of the AEs of intraocular inflammation were mild to moderate and were treated with topical steroids. The majority of subjects who had intraocular inflammation during the study recovered their vision to the pre–intraocular inflammation event onset value. There was no event of intraocular inflammation that led to permanent severe vision loss (≥30 letters lost).

Exudative AMD

Exudative AMD AEs included the PTs of CNV and nAMD.

The following table provides an overall summary of exudative AMD AEs in the study eye in pool 1 through month 24.

A higher percentage of subjects in the pegcetacoplan pooled group (9.4%) than in the sham pooled group (3.1%) had an exudative AMD AE in the study eye.

Subjects in the PM group (12.2%) had a higher incidence of exudative AMD AEs in the study eye than in the PEOM group (6.7%). The majority of the events were mild to moderate.

One event (PEOM group) led to treatment discontinuation and 1 event (sham pooled group) led to treatment and study discontinuation.

No subject had an exudative AMD SAE in the study eye.

Table 75: Overall summary of exudative AMD AEs in the study eye in pool 1—safety population

	PM (N = 419)	**PEOM (N = 420)**	**Pegcetacoplan pooled (N = 839)**	**SM (N = 207)**	**SEOM (N = 210)**	**Sham pooled (N = 417)**	**Total (N = 1256)**
Number of subjects at risk for exudative AMD in the study eye	419	419	838	207	210	417	1255
All AEs							
n (%)	51 (12.2)	28 (6.7)	79 (9.4)	8 (3.9)	5 (2.4)	13 (3.1)	92 (7.3)
Total events	55	29	84	10	5	15	99
Maximum severity of AEs							
Mild, n (%)	24 (5.7)	11 (2.6)	35 (4.2)	2 (1.0)	4 (1.9)	6 (1.4)	41 (3.3)
Moderate, n (%)	22 (5.3)	17 (4.1)	39 (4.7)	4 (1.9)	1 (0.5)	5 (1.2)	44 (3.5)
Mild or moderate, n (%)	46 (11.0)	28 (6.7)	74 (8.8)	6 (2.9)	5 (2.4)	11 (2.6)	85 (6.8)
Severe, n (%)	5 (1.2)	0	5 (0.6)	2 (1.0)	0	2 (0.5)	7 (0.6)
AEs related to treatment							
n (%)	16 (3.8)	12 (2.9)	28 (3.3)	3 (1.4)	2 (1.0)	5 (1.2)	33 (2.6)
Total events	17	12	29	3	2	5	34
SAEs							
n (%)	0	0	0	0	0	0	0
AEs leading to treatment discontinuation							
n (%)	0	1 (0.2)	1 (0.1)	1 (0.5)	0	1 (0.2)	2 (0.2)
Total events	0	1	1	1	0	1	2
AEs leading to study discontinuation							
n (%)	0	0	0	1 (0.5)	0	1 (0.2)	1 (0.1)

	PM (N = 419)	PEOM (N = 420)	Pegcetacoplan pooled (N = 839)	SM (N = 207)	SEOM (N = 210)	Sham pooled (N = 417)	Total (N = 1256)
Total events	0	0	0	1	0	1	1
AEs leading to death							
n (%)	0	0	0	0	0	0	0

Abbreviations: AE = adverse event; AMD = age-related macular degeneration; CNV = choroidal neovascularisation; IVT = intravitreal; N = number of subjects in the group; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; PT = Preferred Term; SAE = serious adverse event; SEOM = sham every other month; SM = sham monthly.

Notes: Pool 1 consists of Studies APL2-303 and APL2-304 and includes data up to month 24. An AE was considered treatment emergent if it had a start date on or after the first dose of investigational product or if it had a start date before the date of the first dose of investigational product but increased in severity on or after the date of the first dose of investigational product. A treatment-related AE was defined as an AE with a relationship to study drug of definitely related, possibly related, or not reported. An IVT injection–related AE was defined as an AE with a relationship to IVT injection of definitely related, possibly related, or not reported. Any AEs with a missing or unknown severity were considered as severe. AMD includes PTs of choroidal neovascularisation and neovascular AMD. Subjects with a medical history of CNV in the study eye were excluded. This includes 1 subject in the PEOM group.

Source: Month 24 Integrated Summary of Safety.

The incidence of exudative AMD AEs in the study eye was higher in subjects with baseline fellow eye CNV than in the subgroup of subjects without baseline fellow eye CNV in the pegcetacoplan pooled (13.9% vs 8.3%) and sham pooled (9.2% vs 1.5%) groups.

In subjects with study eye exudative AMD, the majority of subjects across the treatment groups at baseline had a normal central subfield thickness (CST) and central retinal thickness (CRT), and 6.5% of subjects had presence of cystoid space and 3.3% of subjects had presence of subretinal fluid. At the time of the exudative AMD AE visit, optical coherence tomography (OCT) images showed an increase in CST and CRT, as well as a higher incidence of the presence of cystoid space and subretinal fluid. Spectral domain OCT images showed a significantly greater increase at month 24 in central subfield thickness and in the proportion of patients with presence of cystoid spaces in the pegcetacoplan group compared to the sham pooled group [14.5 microns (PM: 19.9 microns, PEOM: 9.7) vs. 0.3 microns and 9.2% (PM: 15.5%, PEOM: 3.7%) vs. 1.5%, respectively].

Results at month 24 showed an improvement in the retinal anatomical parameters, including a decrease in CST, CRT, and frequency of cystoid spaces and subretinal fluid; this is a standard response to anti-VEGF therapy (Comparison of Age-Related Macular Degeneration Treatments Trials [CATT] Research Group et al. 2016; Rofagha et al. 2013).

Of the subjects with fluorescein angiography (FA) imaging available at the time of the exudative AMD AE visit in the study eye, 51 of 58 subjects in the pegcetacoplan pooled group (87.9%) and 11 of 12 subjects in the sham pooled group (91.7%) showed presence of CNV on FA; the percentage in the PEOM group (22 of 23, 95.7%) was greater than in the PM group (29 of 35, 82.9%). All CNVs were classified as occult or leakage with low likelihood of CNV with the exception of 2 CNV events classified as classic, 1 in the PM and 1 in the PEOM group.

Most subjects with an exudative AMD AE in the study eye received anti-VEGF treatment (i.e., aflibercept, bevacizumab, or ranibizumab).

Mean (SD) NL-BCVA scores decreased from baseline in all treatment groups at the study visit preceding exudation (−3.7 [8.46], −2.4 [9.39], and −1.2 [4.83] letters in the PM, PEOM, and sham pooled groups, respectively). Mean (SD) NL-BCVA scores further decreased in all treatment groups at the study visit at exudation diagnosis, with mean changes from baseline of −6.8 (11.12) letters in the PM group, −5.4 (10.50) letters in the PEOM group, and −10.3 (12.02) letters in the sham pooled group. The mean (SD) change from baseline (CFB) at month 24 was −13.0 (14.78) letters in the PM group, −11.6 (16.72) letters in the PEOM group, and −6.6 (9.41) letters in the sham pooled group. The mean (SD) change from the study visit preceding exudation at month 24 was −8.4 (10.57) letters in the PM group, −9.1 (12.92) letters in the PEOM group, and −5.0 (6.93) letters in the sham pooled group.

Overall, a greater percentage of subjects in the PM and PEOM groups than the sham pooled groups had an AE of exudative AMD in the study eye in pool 1. Exudative AMD was reported in 12.2% of subjects in the PM group and 6.7% of subjects in the PEOM group, demonstrating a posology response.

The events of exudative AMD were more common in subjects with a history of fellow eye CNV. Changes in anatomical features and BCVA score before, at the time of, and after diagnosis correspond with clinical expectation of exudative AMD as well as a generally expected treatment response with anti-VEGF.

<u>AEs Related to Intraocular Pressure</u>

Glaucoma

Through month 24, 17 subjects had 18 study eye AEs of glaucoma (including PTs of open angle, borderline, and normal tension glaucoma) in pool 1: 14 subjects in the pegcetacoplan pooled group

(1.5%) (including 9 subjects in the PM group [1.9%] and 5 subjects in the PEOM group [1.2%]) and 3 subjects in the sham pooled group (0.7%).

In 15 of 16 (94%) subjects, the AE of glaucoma was reported for both the study and fellow eye. Five subjects (3 PM, 1 PEOM, and 1 sham pooled) had prior history of glaucoma in the study eye. Eleven subjects (6 PM, 2 PEOM, and 3 sham pooled) received continuous IOP-lowering medication, and 5 subjects received no medication. All study eye AEs of glaucoma had a maximum severity of mild or moderate. None of the study eye AEs of glaucoma were deemed by the investigator to be related to treatment or the injection procedure. No subject discontinued from treatment or from the study because of an AE of glaucoma.

Ocular Hypertension

Eleven subjects had at least 1 AE of ocular hypertension in the study eye: all were in the pegcetacoplan pooled group (5 subjects in the PM group [1.2%] and 6 subjects in the PEOM group [1.4%]).

Five study eye AEs (in 4 PM subjects) of ocular hypertension resolved within a few days from the onset and did not require chronic treatment with IOP-lowering medication. Nine of 11 (81.8%) subjects received continuous IOP-lowering medication for an event of ocular hypertension. Five of 11 (45.5%) subjects who had study eye AEs of ocular hypertension had a prior history of ongoing glaucoma.

All study eye AEs of ocular hypertension were mild or moderate. One subject in the PM group (0.2%) had a study eye AE of ocular hypertension that was considered related to treatment; 2 subjects in the PM group (0.5%) had a study eye AE of ocular hypertension that was considered related to the injection procedure. One subject in the PM group discontinued from treatment and from the study because of a study eye AE of ocular hypertension.

Intraocular Pressure Increased

Twenty-three subjects (1.8%) had at least 1 study eye AE of intraocular pressure increased through month 24: 20 subjects in the pegcetacoplan pooled group (2.4%) (including 8 subjects in the PM group [1.9%] and 12 subjects in the PEOM group [2.9%]), and 3 subjects in the sham pooled group (0.7%).

All study eye AEs of intraocular pressure increased were transient in duration, and the majority lasted less than 1 day. All study eye AEs of intraocular pressure increased, except for 1, were mild to moderate in severity. Nine subjects had a study eye AE of intraocular pressure increased considered related to treatment (0.7%), and 11 subjects had AEs of intraocular pressure increased considered related to the injection procedure (0.9%).

One subject in the PM group discontinued from treatment at month 18 because of multiple study eye AEs of intraocular pressure increased, which occurred before and after study drug injection and before and after anti-VEGF injections.

Overall, the incidence of glaucoma at month 24 was generally similar across treatment groups in pool 1 (<2%). Five of the 16 subjects with a glaucoma event (3 PM, 1 PEOM, and 1 sham pooled) had prior history of glaucoma in the study eye. Fifteen of the 16 subjects with glaucoma events in the study eye had bilateral glaucoma, suggesting that these events were not associated with pegcetacoplan.

IVT therapies are commonly associated with the risk of increased numbers of IOP events because of increased vitreous volume; these events are usually self-limiting. As expected, nearly all AEs of ocular hypertension and intraocular pressure increased in pool 1 occurred in the pegcetacoplan groups. The majority of the intraocular pressure increased events lasted no more than 1 day, with approximately half receiving treatment and half no treatment. Most glaucoma and ocular hypertension events were managed with IOP-lowering topical medications. Two subjects, both in the PM group, discontinued the study treatment because of safety concerns regarding IOP-related events.

Supportive Safety Data

Study POT-CP121614

Study Eye AEs

Most subjects in the PM (81 of 86 subjects; 94.2%), PEOM (71 of 79 subjects; 89.9%), and sham pooled (71 of 81 subjects; 87.7%) groups experienced at least 1 AE during the on-treatment period, the majority of which were nonocular in each group. Higher percentages of pegcetacoplan-treated subjects (70.9% in the PM group [61 of 86 subjects] and 53.2% in the PEOM group [42 of 79 subjects]) than subjects in the sham pooled group (46.9%; 38 of 81 subjects) experienced on-treatment study eye events in the SOC eye disorders.

A higher percentage of subjects in the pegcetacoplan pooled group (69.7%) than in the sham pooled group (58.0%) had at least 1 study eye AE.

The most common study eye AEs (PTs) in the pegcetacoplan pooled group by percentage of subjects were vitreous floaters (15.8%), conjunctival haemorrhage (15.2%), and nAMD (12.1%); in the sham pooled group, these events were occurred in 2.5%, 11.1%, and 1.2% of subjects, respectively. AEs of vitreous floaters and conjunctival haemorrhage are commonly reported after IVT procedures. AEs of vitreous floaters were more frequent in Study POT-CP121614 than in pool 1 of Studies APL2-304 and APL2-303 most likely because of the use of a lyophilised formulation in Study POT-CP121614 compared to a liquid formulation in Studies APL2-304 and APL2-303.

The most frequent AEs in a higher percentage of subjects in the PM group compared with the PEOM group were vitreous floaters (22.1% vs 8.9%), nAMD (15.1% vs 8.9%), and conjunctival haemorrhage (18.6% vs 11.4%).

Endophthalmitis

Endophthalmitis was an AE of special interest in Study POT-CP121614, but there was no study requirement to report it as an SAE. However, all endophthalmitis AEs in Study POT-CP121614 were reported as SAEs. Three of 165 subjects in the pegcetacoplan pooled group (1.8%) had a study eye SAE of endophthalmitis, corresponding to a rate per injection of 0.21% (3 of 1397 injections); this includes

- 2 of 86 subjects in the PM group (2.3%) corresponding to a rate per injection of 0.22% (2 of 904 injections)
- 1 of 79 subjects in the PEOM group (1.3%) corresponding to a rate per injection of 0.20% (1 of 493 injections).

Two subjects from the PM group had 1 case of moderate and 1 case of severe SAE endophthalmitis, respectively, and 1 subject from the PEOM had a mild SAE of endophthalmitis. All 3 subjects were treated with IVT antibiotics, and 1 subject underwent pars plana vitrectomy (severe SAE from the PM group). Two subjects recovered to their pre-endophthalmitis BCVA levels, but 1 subject (the severe SAE from the PM group) had lost vision to light perception and exited the study.

No subject in the sham pooled group had a study eye SAE of endophthalmitis. No subject had a fellow eye SAE of endophthalmitis in Study POT-CP121614.

Intraocular Inflammation

No study eye AEs of intraocular inflammation were observed in sham-treated subjects.

Ten subjects in the pegcetacoplan pooled group (6.1%) had 10 study eye AEs of intraocular inflammation, corresponding to a rate per injection of 0.72% (10 of 1397 injections); this includes

- 6 subjects in the PM group (7.0%) who had 6 study eye AEs of intraocular inflammation, corresponding to a rate per injection of 0.66% (6 of 904 injections)
- 4 subjects in the PEOM group (5.1%) who had 4 study eye AEs of intraocular inflammation, corresponding to a rate per injection of 0.81% (4 of 493 injections)

In Study POT-CP121614, the incidence and rate per injection of AEs of intraocular inflammation were higher than expected potentially because a lyophilised formulation was used that required additional manipulation during its reconstitution.

Exudative AMD

Study eye exudative AMD is presented from baseline through month 18 (i.e., 12 months of treatment and 6 months of follow-up) for the safety population.

The incidence of study eye exudative AMD was higher in the PM (20.9%) and PEOM (8.9%) groups than in the sham pooled group (1.2%), corresponding to rates per 100 patient-years of 17.24 in the PM group, 6.57 in the PEOM group, and 0.89 in the sham pooled group.

The incidence of exudative AMD AEs in the study eye was greater in the subgroup of subjects with baseline fellow eye CNV in the PM and PEOM groups (33.3% and 17.9%, respectively) than in the subgroup of subjects without baseline fellow eye CNV (12.0% and 3.9%, respectively).

The majority of the exudative AMD were mild to moderate in severity and 92.3% of the subjects were treated with anti-VEGF therapy per investigator discretion. Rates of exudative AMD in Study POT-CP121614 were higher than in pool 1 perhaps because of a higher prevalence of CNV in the fellow eye, a known risk factor for development of exudative AMD in the study eye, in Study POT-CP121614 compared with pool 1.

The impact of exudative AMD on visual acuity was minor as indicated by changes from the visit prior to exudative AMD diagnosis to the visit at which exudative AMD was diagnosed.

Any appreciable vision loss appeared to be due to the natural progression of GA as indicated by changes from the baseline visit to the visit prior to exudative AMD diagnosis.

Study APL2-GA-305

Study Eye AEs

In the pegcetacoplan pooled group, 190 subjects (25.0%) had 324 study eye AEs. Most study eye AEs occurred in SOC eye disorders (179 subjects [23.6%], 287 study eye AEs).

The most common study eye AEs (PTs) in the pegcetacoplan pooled group by percentage of subjects were vitreous floaters (3.8%), conjunctival haemorrhage (2.8%), eye pain (2.2%), nAMD (1.6%), cataract (1.4%), visual acuity reduced (1.3%), and retinal haemorrhage (1.3%); these events are commonly reported after IVT procedures.

A higher percentage of subjects in the PM group (31.3%) than in the PEOM group (19.1%) had at least 1 study eye AE.

Treatment is ongoing for most subjects in the PM (94.3%) and PEOM (94.1%) groups of Study APL2-GA-305 as of the data cut date for this report.

Endophthalmitis

No subject had a study eye SAE of endophthalmitis.

Intraocular Inflammation

Fourteen subjects in the pegcetacoplan pooled group (1.8%) had 14 study eye AEs of intraocular inflammation as of the data cut date of this report.

The most common study eye AEs (PTs) of intraocular inflammation in the pegcetacoplan pooled group by percentage of subjects were vitritis (0.7%), vitreal cells (0.4%) and iridocyclitis (0.4%). One PM subject had an SAE of vitritis.

A higher percentage of subjects in the PM group (2.7%) than in the PEOM group (1.0%) had an intraocular inflammation AE.

Exudative AMD

As of the data cut date, 12 subjects in the PM group (3.6%) and 4 subjects (1.1%) in the PEOM group had 12 and 4 exudative AMD AEs in the study eye, respectively. Three subjects (0.9%) in the PM group and 2 subjects (0.5%) in the PEOM group had an exudative AMD AE in the study eye deemed by the investigator to be related to treatment. No exudative AMD SAEs in the study eye or exudative AMD AE in the study eye leading to treatment or study discontinuation were reported.

Study APL2-103

The study was initiated to evaluate the safety of a new lot of drug product in subjects with GA secondary to AMD who had low vision in response to study eye AEs of intraocular inflammation reported in other IVT pegcetacoplan studies. After the initiation of the APL2-103 study, 6 subjects developed intraocular inflammation and the study was halted.

Chemistry, Manufacturing, and Controls analyses were performed to determine the root cause of the inflammatory effects in conjunction with nonclinical testing of pegcetacoplan formulations from the different manufacturer. These analyses and further investigation by GMP QA of the manufacturing process identified an impurity in the active pharmaceutical ingredient as the likely root cause for the intraocular inflammation events. Additional manufacturing steps to eliminate this impurity were implemented and Study APL2-103 study was reinitiated.

Summary of Safety Findings

Safety results for Study APL2-103 are provided in the Study APL2-103 CSR. Key safety findings are the following:

- IVT injection of pegcetacoplan was well tolerated.
- No AEs of endophthalmitis were reported during the study.
- The incidences of intraocular inflammation after study resumption were within acceptable limits. Of the 19 subjects who received pegcetacoplan on or after study resumption, 6 subjects had 6 events of intraocular inflammation. The incidence of intraocular inflammation events was within the expected range after the optimisation of the pegcetacoplan manufacturing process.
- Two subjects (18.2%) developed choroidal neovascularisation in the study eye and were treated with anti-VEGF treatment.

- Ten subjects (52.6%) had 15 SAEs. These included 14 nonocular SAEs and 1 ocular SAE of uveitis.
- Two subjects withdrew from the study because of AEs: one for worsening heart failure and the other for acute coronary syndrome.
- One subject died of congestive heart failure unrelated to pegcetacoplan treatment after withdrawing from the study.
- No clinically meaningful changes were observed in IOP; any clinical chemistry, haematology, or urinalysis laboratory assay; vital signs; or physical examination after IVT pegcetacoplan treatment.

Late-breaking AEs

The late-breaking period was 24 June 2022 through 21 October 2022. At this time, only Study APL2-GA-305 was ongoing. Late-breaking data are provided for study eye AEs, AEs of interest (endophthalmitis, intraocular inflammation, exudative AMD, and AEs related to IOP), SAEs, ocular AEs leading to treatment and/or study discontinuation, and deaths.

In the pegcetacoplan pooled group, 106 subjects (14.2%) had 151 study eye AEs during the late-breaking period.

The most common study eye AEs by PT in the pegcetacoplan pooled group were conjunctival haemorrhage (1.3%), cataract and nAMD (1.2% each), and CNV (1.1%).

In the PM group, 15.0% of subjects had at least 1 study eye AE, and in the PEOM group 13.4% of subjects had at least 1 study eye AE.

No subject had a study eye SAE of endophthalmitis during the late-breaking period.

One subject in the PM group (0.3%) had 1 study eye AE of uveitis, and 1 subject in the PEOM group (0.3%) had 1 study eye AE of vitritis.

Ten subjects in the PM group (3.1%) and 7 subjects in the PEOM group (1.9%) had an exudative AMD AE in the study eye during the late-breaking period. Five subjects (1.5%) in the PM group and 2 subjects (0.5%) in the PEOM group had exudative AMD AEs that were deemed by the investigator to be related to treatment.

During the late-breaking period, one subject in the PEOM group had 2 ocular study eye SAEs reported as retinal artery occlusion and afferent pupillary defect with an onset on the same day. Neither SAE was deemed by the investigator to be related to treatment or the injection procedure.

No subject had a fellow eye SAE during the late-breaking period.

In the pegcetacoplan pooled group, 56 subjects (7.5%) had 76 nonocular SAEs during the late-breaking period. More subjects in the PM group (9.5%) than in the PEOM group (5.7%) had nonocular SAEs. The most common nonocular SAEs (SOC) were infections and infestations (1.7%), injury, poisoning, and procedural complications (1.5%), and cardiac disorders (1.3%). This was consistent across both treatment groups.

AEs Leading to Treatment and Study Discontinuation

Two subjects in the PM group (0.6%) had a study eye AE (verbatim terms: dot haemorrhages and infection right eye) leading to treatment/study discontinuation during the late-breaking period.

No subject had a fellow eye AE leading to treatment and study discontinuation during the late-breaking period.

Deaths

Four subjects (1.0%) in the PEOM group had a nonocular SAE leading to death during the late-breaking period (PTs: acute myocardial infarction, COVID-19 pneumonia, respiratory failure; verbatim term: urosepsis with cardiovascular collapse).

Overall, the safety findings reported in the late-breaking period were consistent with those of Study APL2-GA-305 and pool 1, and no new safety signals were identified.

2.5.8.3. Serious adverse events, deaths, and other significant events

Pool 1

Study Eye SAEs

Ocular SAEs in the study eye were infrequent. Across all treatment groups, 18 subjects (1.4%) had 22 study eye SAEs. Most study eye SAEs occurred in the SOC of eye disorders (14 subjects [1.1%], 16 study eye SAEs).

Table 76: Pool 1 study eye SAEs—safety population

	PM (N = 419) n (%) M	PEOM (N = 420) n (%) M	Pegcetacoplan pooled (N = 839) n (%) M	SM (N = 207) n (%) M	SEOM (N = 210) n (%) M	Sham pooled (N = 417) n (%) M	Total (N = 1256) n (%) M
Number of subjects with ≥1 study eye SAE	9 (2.1) 11	6 (1.4) 8	15 (1.8) 19	1 (0.5) 1	2 (1.0) 2	3 (0.7) 3	18 (1.4) 22
SOC PT							
Eye disorders	8 (1.9) 8	3 (0.7) 5	11 (1.3) 13	1 (0.5) 1	2 (1.0) 2	3 (0.7) 3	14 (1.1) 16
Optic ischaemic neuropathy	3 (0.7) 3	0	3 (0.4) 3	0	0	0	3 (0.2) 3
Vitritis	2 (0.5) 2	0	2 (0.2) 2	0	0	0	2 (0.2) 2
Retinal detachment	1 (0.2) 1	1 (0.2) 1	2 (0.2) 2	0	0	0	2 (0.2) 2
Uveitis	0	2 (0.5) 2	2 (0.2) 2	0	0	0	2 (0.2) 2
Papilloedema	1 (0.2) 1	0	1 (0.1) 1	0	0	0	1 (0.1) 1
Retinal tear	1 (0.2) 1	0	1 (0.1) 1	0	0	0	1 (0.1) 1
Visual acuity reduced	0	1 (0.2) 1	1 (0.1) 1	0	1 (0.5) 1	1 (0.2) 1	2 (0.2) 2
Iridocyclitis	0	1 (0.2) 1	1 (0.1) 1	0	0	0	1 (0.1) 1
Dry age-related macular degeneration	0	0	0	1 (0.5) 1	0	1 (0.2) 1	1 (0.1) 1
Macular hole	0	0	0	0	1 (0.5) 1	1 (0.2) 1	1 (0.1) 1
Infections and infestations	2 (0.5) 2	3 (0.7) 3	5 (0.6) 5	0	0	0	5 (0.4) 5
Endophthalmitis	2 (0.5) 2	3 (0.7) 3	5 (0.6) 5	0	0	0	5 (0.4) 5
Injury, poisoning and procedural complications	1 (0.2) 1	0	1 (0.1) 1	0	0	0	1 (0.1) 1
Hyphaema	1 (0.2) 1	0	1 (0.1) 1	0	0	0	1 (0.1) 1

Abbreviations: AE = adverse event; IP = investigational product; M = number of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the group; n = number of subjects with an event in the SOC or PT; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; PT = Preferred Term; SAE = serious adverse event; SEOM = sham every other month; SM = sham monthly; SOC = System Organ Class.

Notes: Pool 1 consists of Studies APL2-303 and APL2-304 and includes data up to month 24. An AE was considered treatment emergent if it had a start date on or after the first dose of investigational product or if it had a start date before the date of the first dose of investigational product but increases in severity on or after the date of the first dose of investigational product. If a subject had multiple occurrences of an AE, the subject is presented only once in the subject count (n) column and all AEs are counted in total events (M) for a given SOC and PT. AEs were coded to

SOC and PT using MedDRA version 23.1.
Source: Month 24 Integrated Summary of Safety.

Higher percentages of subjects in the PM group (2.1%) than in the PEOM group (1.4%) and sham pooled group (0.7%) had at least 1 study eye SAE.

The most common study eye SAEs in the pegcetacoplan pooled group by percentage of subjects were endophthalmitis (0.6%), optic ischaemic neuropathy (0.4%), and vitritis, retinal detachment, and uveitis (0.2% each); these SAEs are commonly reported after IVT procedures or are related to an elderly study population with many comorbidities (optic ischaemic neuropathy). No subject in the sham pooled group had an SAE for any of these PTs.

Seven subjects (0.6%) had 9 SAEs that were deemed by the investigator to be related to treatment; this included

- 4 subjects in the PM group who had SAEs of vitritis (2 subjects), papilloedema, and retinal tear
- 3 subjects in the PEOM group who had SAEs of uveitis (2 subjects), iridocyclitis, visual acuity reduced, and endophthalmitis

Further information about the subjects who had study eye SAEs of endophthalmitis is provided in Section 4.3 of this AR.

Fellow Eye SAEs

Across all treatment groups, 5 subjects (0.4%) had 5 fellow eye SAEs. Three subjects in the pegcetacoplan pooled group had a fellow eye SAE (cataract, choroid melanoma, retinal detachment), and 2 subjects in the sham pooled group had a fellow eye SAE of endophthalmitis.

No meaningful differences were observed in the percentages of subjects who had fellow eye SAEs across treatment groups. No fellow eye SAEs were deemed by the investigator to be related to treatment.

Nonocular SAEs

Across all treatment groups, 349 subjects (27.8%) had 634 nonocular AEs.

There were no meaningful differences in the percentages of nonocular SAEs across treatment groups.

The most common SOCs for nonocular SAEs in the pegcetacoplan pooled group by percentage of subjects were SOCs infections and infestations (8.1%), cardiac disorders (6.4%), and injury, poisoning and procedural complications (5.5%).

The most common nonocular SAEs in the pegcetacoplan pooled group by percentage of subjects were pneumonia (2.9%), COVID-19 (1.8%), atrial fibrillation (1.5%), cerebrovascular accident (1.3%), and cardiac failure congestive (1.2%); these nonocular SAEs are common medical conditions in an elderly population, and in the context of the ongoing COVID-19 pandemic.

One subject (0.2%) in the PM group had a nonocular SAE of enterococcal bacteraemia that was deemed by the investigator to be related to treatment.

AEs Leading to Treatment or Study Discontinuation

The percentage of subjects who had at least 1 study eye AE leading to treatment discontinuation was 1.4% in the pegcetacoplan pooled group and 1.0% in the sham pooled group. There were no meaningful differences in the percentages of subjects who had at least 1 study eye AE leading to treatment discontinuation across treatment groups.

The percentage of subjects who had at least 1 study eye AE leading to study discontinuation was 0.5% in the pegcetacoplan pooled group and 0.7% in the sham pooled group. There were no meaningful differences in the percentages of subjects who had at least 1 study eye AE leading to study discontinuation across treatment groups.

One subject in the PM group had a fellow eye AE of choroid melanoma leading to study treatment and study discontinuation; this event was deemed by the investigator to be not related to treatment.

Across all treatment groups, 90 subjects (7.2%) had 110 nonocular AEs leading to treatment discontinuation through month 24, and 97 subjects (7.7%) had 114 nonocular AEs leading to study discontinuation.

The most common nonocular AEs leading to treatment discontinuation or study discontinuation in the pegcetacoplan pooled group by percentage of subjects were COVID-19 (0.8%) and cardiac failure congestive (0.6%). The AE cerebrovascular event led to treatment discontinuation and study discontinuation in 0.6% and 0.8% of subjects, respectively.

The percentages of nonocular AEs leading to treatment discontinuation were 9.5%, 6.2%, and 5.8% in the PM, PEOM, and sham pooled groups, respectively, and the percentages of nonocular AEs leading to study discontinuation were 10.3%, 6.7%, and 6.2% in the PM, PEOM, and sham pooled groups, respectively. There were no meaningful differences in the nonocular AEs leading to treatment or study discontinuation.

Deaths

Across all treatment groups, 59 subjects (4.7%) had 68 nonocular AEs leading to death. All were deemed by the investigator to be not related to treatment. No subject had an ocular AE leading to death

In pool 1, there was a higher percentage of deaths in the PM group (6.7%) than in the PEOM group (3.6%) and sham pooled group (3.8%). The higher percentage of deaths in the PM group is accounted for by the Study APL2-304 PM group (PM group 9.4%; PEOM group 4.2%; sham pooled group 3.8%). In Study APL2-303, these percentages were PM group 3.9%; PEOM group 2.9%; and sham pooled group 3.9%.

In pool 1, the most common SOCs for nonocular AEs leading to death in the pegcetacoplan pooled group by percentage of subjects were SOCs infections and infestations (1.4%); cardiac disorders (1.3%); and neoplasms benign, malignant and unspecified (including cysts and polyps) (1.1%). The most common PT for nonocular AE leading to death in the pegcetacoplan pooled group by percentage of subjects was COVID-19 (0.7%), followed by cardiac failure (including congestive) (0.6%), cardiac arrest, and death (not otherwise specified) (0.4% each).

The causes of death between the PM and PEOM groups compared with the sham pooled group were consistent with age group, medical history, intercurrent condition, and time to onset.

No causal or contributory association with the study treatment was revealed in pool 1 nonocular AEs leading to death through month 24.

Supportive Safety Data

Study POT-CP121614

Study Eye SAEs

Across all treatment groups, 7 subjects (2.8%) had 8 study eye SAEs. Study eye SAEs most commonly occurred in SOC infections and infestations (3 subjects [1.2%], 3 study eye SAEs).

Higher percentages of subjects in the PM (4.7%) and PEOM (2.5%) groups had at least 1 study eye SAE than in the sham pooled group (1.2%).

Study eye SAEs (PTs) in the pegcetacoplan pooled group were endophthalmitis (1.8%), intraocular pressure increased (1.2%), and retinal detachment (0.6%); these SAEs are commonly reported after IVT procedures. No subject in the sham pooled group had an SAE that coded to any of these 3 PTs.

Two subjects had 2 SAEs that were deemed by the investigator to be related to treatment; this included

- 1 subject in the PM group who had an SAE of endophthalmitis
- 1 subject in the PEOM group who had an SAE of intraocular pressure increased

Nonocular SAEs

Overall, 51 of the 246 study subjects (20.7%) reported 88 nonocular SAEs during the on-treatment period. A greater percentage of subjects had on-treatment nonocular SAEs in the PEOM group (29.1%; 23 of 79 subjects) than in the PM (14.0%; 12 of 86 subjects) and sham pooled (19.8%; 16 of 81 subjects) groups.

No on-treatment nonocular SAEs were considered treatment-related.

The most common on-treatment nonocular SAEs by subject were atrial fibrillation, cardiac failure congestive, and pneumonia (each occurring in 4 subjects [1.6%]).

Discontinuations

A higher percentage of subjects in the pegcetacoplan pooled group (14.5%) than in the sham pooled group (3.7%) had at least 1 study eye AE leading to treatment discontinuation.

The most common study eye AEs (PTs) leading to treatment discontinuation in the pegcetacoplan pooled group by percentage of subjects were neovascular age-related macular degeneration (9.1%), choroidal neovascularisation (1.8%), and vitreous floaters (1.2%). The study design stipulated that pegcetacoplan treatment be discontinued following an AE of neovascular age-related macular degeneration or choroidal neovascularisation.

A higher percentage of subjects in the PM group (22.1%) than in the PEOM (6.3%) and sham pooled (3.7%) groups had at least 1 study eye AE leading to treatment discontinuation.

Similar percentages of subjects in the pegcetacoplan pooled (3.6%) and sham pooled (2.5%) groups had at least 1 study eye AE leading to study discontinuation.

The most common study eye AE (PT) leading to study discontinuation in the pegcetacoplan pooled group by percentage of subjects was neovascular age-related macular degeneration (1.2%).

A higher percentage of subjects in the PM group (5.8%) than in the PEOM (1.3%) and sham pooled (2.5%) groups had at least 1 study eye AE leading to study discontinuation.

Deaths

Three subjects died because of nonocular SAEs during the on-treatment period that were deemed by the investigator to be not related to pegcetacoplan or sham. These nonocular SAEs were PTs of multiple organ dysfunction syndrome, post-procedural sepsis, and subdural haemorrhage.

Two subjects had fatal nonocular SAEs during the on-treatment period that continued into the off-treatment period. These events were deemed by the investigator to be not related to pegcetacoplan. These nonocular SAEs were PTs of coronary artery disease and pneumonia staphylococcal.

Three subjects had fatal nonocular SAEs during the off-treatment period. These events were deemed by the investigator to be not related to pegcetacoplan or sham. These nonocular SAEs were PTs of respiratory failure (2 events) and atrial fibrillation.

Study APL2-GA-305

Five subjects had 5 study eye SAEs through the data cut date, one of which (vitritis) was deemed by the investigator to be related to treatment. Brief narrative summaries for the 5 subjects who had study eye SAEs are provided in the clinical AR.

One subject in the PEOM group had a fellow eye SAE of visual impairment, which was deemed by the investigator to be not related to treatment. One subject (0.3%) in the PEOM group had a fellow eye SAE of blindness transient that was deemed by the investigator to be not related to treatment.

In the pegcetacoplan pooled group, 93 subjects (12.3%) had 136 nonocular SAEs through the data cut date. The most common nonocular SAEs in the pegcetacoplan pooled group by percentage of subjects were in the SOCs of cardiac disorders (2.5%); injury, poisoning and procedural complications (2.5%); and infections and infestations (2.5%).

The most common nonocular SAEs in the pegcetacoplan pooled group by percentage of subjects were atrial fibrillation, pneumonia, and cerebrovascular accident (0.7% each); these nonocular AEs are common medical conditions in an elderly population.

No meaningful difference was observed in the percentages of subjects in the PM group (11.7%) and PEOM group (12.8%) who had nonocular SAEs.

One subject in the PEOM group had a nonocular SAE of oedema peripheral, and 1 subject in the PEOM group had a nonocular SAE of headache; both were deemed by the investigator to be related to treatment.

AEs Leading to Treatment and Study Discontinuation

In the PM group, 1 subject (0.3%) had a study eye AE of iridocyclitis, and 1 subject (0.3%) had a study eye AE of vitritis leading to treatment and study discontinuation.

No subject had a fellow eye AE leading to treatment and study discontinuation as of the data cut date.

As of the data cut date, 18 subjects (2.4%) in the pegcetacoplan pooled group had 20 nonocular AEs leading to treatment and study discontinuation: 8 subjects in the PM group had 9 AEs (atrial fibrillation, coronary artery disease, myocardial infarction, death, COVID-19, COVID-19 pneumonia, acute myeloid leukaemia, embolic stroke, and chronic respiratory failure). Ten subjects in the PEOM group had 11 AEs (acute myocardial infarction, cardiac arrest, cardiac failure acute, cardiac failure congestive, ischaemic cardiomyopathy, death [2 events], pneumonia, urinary tract infection, craniocerebral injury, and cerebrovascular accident).

Deaths

In the pegcetacoplan pooled group, 13 subjects (1.7%) had 15 nonocular AEs leading to death: 5 subjects (1.4%) in the PM group (cardiac failure congestive, myocardial infarction, death, COVID-19, COVID-19 pneumonia, and chronic respiratory failure); and 8 subjects (2.0%) in the PEOM group (cardiac failure congestive, acute myocardial infarction, cardiac arrest, cardiac failure acute, ischaemic cardiomyopathy, death [2 subjects], pneumonia, and craniocerebral injury). Brief narrative summaries for the 13 subjects who had nonocular AEs leading to death are provided in this section.

2.5.8.4. Laboratory findings

In Study APL2-303 and Study APL2-304, laboratory evaluations did not reveal clinically relevant trends suggestive of a safety signal. Overall, the laboratory findings were consistent with those expected in patients with GA secondary to AMD.

Pool 1

Haematology

Baseline was defined as the last available non-missing observation prior to first study drug administration. Post baseline was defined as any assessment after first study drug administration.

No meaningful differences in potentially clinically significant (PCS) haematology values were observed in the PM, PEOM, and sham pooled groups through month 24.

One haematology SAE (haemoglobin decreased) in the SOC of investigations was reported in 1 subject (0.2%) in the PM group (see previous section).

No haematology AE related to treatment in the SOC of investigations was reported in the PM or PEOM group.

Clinical Chemistry

Across all treatment groups through month 24, no meaningful differences in the following clinical chemistry values that were PCS at baseline were observed in the PM, PEOM, and sham pooled groups:

No clinical chemistry SAE in the SOC of investigations was reported in the PM or PEOM group.

No clinical chemistry AE related to treatment in the SOC of investigations was reported in the PM or PEOM group. One clinical chemistry AE (blood creatine phosphokinase increased) related to treatment in the SOC of investigations was reported in 1 subject (0.2%) in the sham pooled group.

Urinalysis

No urinalysis SAE in the SOC of investigations was reported in the PM or PEOM group.

One subject in the PM group had an AE of urine leukocyte esterase that was deemed related to treatment by the investigator. One subject in the sham pooled group had 5 AEs (protein urine present, urinary sediment present, urine analysis abnormal, urine leukocyte esterase positive, and urobilinogen urine increased) that were deemed related to treatment by the investigator.

Vital Signs

No meaningful differences were observed between postbaseline PCS vital signs values through month 24 in the PM, PEOM, and sham pooled groups.

No vital signs SAE in the SOC of investigations was reported in the PM or PEOM group.

No vital signs AE related to treatment in the SOC of investigations was reported in the PM or PEOM group.

Physical Examination Findings

No SAE of physical examination findings in the SOC of investigations was reported in the PM or PEOM group. One SAE of breath sound abnormal was reported in 1 subject in the sham pooled group.

No AE of physical examination findings related to treatment in the SOC of investigations was reported in the PM or PEOM group.

Supportive Safety Data

In Study POT-CP121614, overall, no safety signals were identified on the basis of the nature, frequency and severity of reported AEs and mean changes in haematology, clinical chemistry, or laboratory values over time.

No clinically meaningful changes in systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, or body temperature were observed in any treatment group during the study.

No physical examination findings SAE or AE related to treatment in the SOC of investigations was reported in the PM or PEOM group.

2.5.8.5. In vitro biomarker test for patient selection for safety

2.5.8.6. Safety in special populations

Subgroup analyses of ocular AEs were performed for intrinsic factors (age, sex, race) and extrinsic factor (region). Extrinsic factors, such as alcohol and tobacco use, were not considered relevant and were not included in the design of the clinical trials.

Interpretation of these individual analyses is limited given the small number of subjects within certain subgroups. No clinically meaningful findings were observed.

Pregnancy

There are no data on IVT pegcetacoplan use in pregnant women. Studies in animals at high systemic exposures have shown reproductive toxicity.

Breastfeeding

It is not known whether pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal IVT treatment is minimal.

Fertility

There are no fertility data in humans or animals. There were no microscopic abnormalities in male or female reproductive organs in toxicity studies in rabbits and monkeys indicative of an impact of pegcetacoplan on fertility.

To date, there are insufficient data on pegcetacoplan use in pregnant women to fully inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or foetal outcomes. Therefore, had pegcetacoplan been approved, it would not have been recommended to be taken by pregnant women. Women of childbearing potential and non-vasectomised men with female partners of childbearing potential would have needed to use effective contraception methods to prevent pregnancy during treatment with pegcetacoplan and for at least 8 weeks after the last dose of pegcetacoplan.

2.5.8.7. Immunological events

The applicant has developed at the beginning of its clinical development at BioAgilytix a two-tiered (screening and confirmation) approach based on a two-step ELISA to detect antibodies against PEG in human serum. In brief, the assay is a direct immunogenicity assay, with a bead pre-extraction, to purify PEG specific ADAs. Anti-PEG bead pre-extracted samples are bound to the immobilised PEG, captured by a direct bind ELISA method and detected with goat anti-human IgG-HRP. The presence of anti-drug antibodies (ADA) that bind to PEG is determined by comparing the signal in the sample or control to a statistically derived threshold, the assay cut point. Critical reagents were listed and CoA's were provided. Negative and positive controls (human and murine) and well as assay matrix were carefully selected, and are considered representatives. Cut-point evaluation of the screening and the confirmation assay were described and found acceptable. The assay was validated according to respective guidance documents, and all validation parameters met target acceptance criteria. A subsequent validation study demonstrated that C3 complement does not interfere with detection of anti-PEG antibodies, and a further one that lipemia, and haemolysis did not interfere with the confirmatory method for the detection of anti-PEG antibodies. Thus the assay is suitable for detection of anti-PEG antibodies with a sensitivity of approximately 9-10 ng/mL in both the screening and confirmatory assays. For the assessment of clinical samples, sample receipt and handling was documented, details regarding critical reagents and raw-data were provided. Taken together, the assay and respective analysis data seem valid in the setting presented by the applicant.

The applicant later on developed and validated at Q2 Solutions a tiered approach based on a bead based sandwich ELISA to screen, confirm and titre anti-PEG antibodies in human serum samples. Positive and negative controls were well selected, and assay cut-points correctly determined. Validation was conducted in accordance with acceptance criteria described in a Method Validation Plan provided by the applicant, and according to applicable guidelines. All raw-data were provided, deviations were well described, and their impact well discussed. Taken together, the assay as described by the applicant seems suitable for the intended application.

The applicant developed and validated first at BioAgilytix and then at Q2 Solutions a tiered chemiluminescence based assay to screen, confirm, and titre human serum samples for the presence of anti-APL-2 antibodies. In brief, screening was performed in duplicates, and samples with mean raw signal values equal to or above the assay screening cut point were reported as positive and continued to Tier 2. 340 out of 3260 samples screened positive, confirming that the assay cut-point was correctly set. To confirm the presence of specific anti-APL2 antibodies, samples that screened positive were spiked with 100 μg/mL APL2. APL2 inhibited samples should demonstrate inhibition ≥ confirmation cut point to be considered confirmed positive. Positive samples were reported as containing APL2 specific antibodies and continued to titre (Tier 3). To obtain assay titres, samples were diluted using a two-fold dilution series in pooled human serum, and the titre was identified as the highest dilution where the RLU signal was greater than or equal to the titration cut point. Critical reagents were described and CoA's included. Assay controls were well selected, and the assay was validated according to respective guidance documents, based on pre-defined acceptance criteria defined in a validation plan. Raw-data and reports were provided, and the impact of deviations was discussed. Sample receipt and handling was documented. The assay and respective clinical results seem valid in the setting presented by the applicant.

The applicant built up and validated at BioAgilytix an ECL based competitive ligand binding assay that to detect neutralizing antibodies against APL-2 in Human Serum in the presence of large quantities of complement C3, the target of APL-2. Complement is depleted in a first step by capturing immunoglobulins using protein A/G/L Sepharose. After elution and neutralisation, samples are transferred on an APL-2 coated MSD standard bind plate. Any NAb present will bind APL-2 and compete with a Sulfo-Tagged human complement C3 protein. The more NAb present, the less Sulfo-tagged human complement C3 will bind and the less ECL signal will be produced. Assay cut-point was defined by a non-Parametric method (1% Quantile) to target a 1% false positive rate. The assay was validated for its sensitivity, specificity, cut point, drug tolerance, selectivity and matrix interference, haemolysis and lipemia, precision, stability and robustness. Target (C3 complement up to 2,45 mg/ml) interference was studied in a subsequent validation study. Assay setup seems appropriate, and validation was performed in accordance with respective guidance documents. Critical reagents, provenience and lot numbers were provided. Controls were described and seem representatives. The applicant demonstrated that functionality of neutralising antibodies was maintained during the sample pre-treatment (affinity extraction and neutralisation) step. Taken together, the assay seems appropriate for the intended application.

Immunogenicity data were provided from all clinical pharmacology studies (APL2-203, POT-CP121614, APL2-303, and APL2-304).

To understand the potential impact of immunogenicity on pegcetacoplan exposure and clinical response, ad hoc population analyses were performed using data from the 4 clinical studies outlined in this section. In all studies, ADA responses were defined as

- treatment-emergent if the subject had a negative antibody result at baseline and a positive antibody result postdose,
- persistent treatment-emergent if positive evaluations occurred at the last 2 available time points,
- transient treatment-emergent if only a single positive evaluation occurred that was not the last assessment,
- treatment-boosted if the subject had a positive antibody result postdose with ≥4-fold increase in titre from baseline.

For Studies APL2-304 and APL2-303, subjects who were evaluable for ADA response had at least 1 postdose sample with reportable results (positive or negative) during the treatment or follow-up periods.

Of the 17 subjects enrolled in Study APL2-203, 16 subjects were assessed for immunogenicity. All subjects received 15 mg IVT pegcetacoplan. Baseline samples were not collected in this study; therefore, subjects are reported as having either a positive or negative ADA result. No subject was positive for anti–pegcetacoplan peptide antibodies in this study. Eight subjects were positive for an anti-PEG antibody response postdose; the highest titre reported among these subjects was 1:640.

In Study POT-CP121614, 3 of 246 subjects had treatment-emergent responses for anti–pegcetacoplan peptide antibodies (1.2%), all of whom were in the pegcetacoplan pooled group (1.8%). Positive samples were further tested for neutralizing capability. One sample was confirmed positive with the neutralizing antibody (NAb) assay; however, serum samples from the subject's subsequent visits tested negative in the NAb assay. Twelve of 246 subjects had treatment-emergent responses for anti-PEG antibodies (4.9%): 4 subjects in the pegcetacoplan pooled group (2.4%) and 8 subjects in the sham pooled group (9.9%). Five of 246 subjects had treatment-boosted responses for anti-PEG antibodies (2.0%), all of whom were in the sham pooled group (6.2%).

In Study APL2-303, 14 subjects of 598 evaluable subjects had a positive anti–pegcetacoplan peptide antibody response: 10 of 404 subjects in the pegcetacoplan pooled group (2.5%) and 4 of 194 subjects were in the sham pooled group (2.1%). Of the subjects who had ≥1 postdose positive sample for anti–pegcetacoplan peptide antibodies, only 1 subject in the PEOM group was positive for NAb response (9 subjects were negative and 5 were unevaluable).

Sixty-five subjects of 598 evaluable subjects had a treatment-emergent anti-PEG antibody response: 36 of 404 subjects in the pegcetacoplan pooled group (8.9%) and 29 of 194 subjects in the sham pooled group (14.9%). Forty subjects of 598 evaluable subjects had a treatment-boosted anti-PEG response: 21 of 404 subjects in the pegcetacoplan pooled group (5.2%) and 29 of 194 subjects in the sham pooled group (14.9%).

In Study APL2-304, 27 subjects of 622 evaluable subjects had a positive anti–pegcetacoplan peptide antibody response: 18 of 415 subjects in the pegcetacoplan pooled group (4.3%) and 9 of 207 subjects in the sham pooled group (4.3%). Of the subjects who had ≥1 postdose positive sample for anti–pegcetacoplan peptide antibodies, 2 subjects in the sham pooled group were positive for NAb response (32 subjects were negative and 14 were unevaluable).

Fifty-four subjects of 618 evaluable subjects had a treatment-emergent anti-PEG antibody response: 27 of 412 subjects in the pegcetacoplan pooled group (6.6%) and 27 of 206 subjects in the sham pooled group (13.1%). Twenty-nine subjects of 618 evaluable subjects had a treatment-boosted anti-PEG antibody response: 15 of 412 subjects in the pegcetacoplan pooled group (3.6%) and 14 of 206 subjects in the sham pooled group (6.8%).

A medical review of pool 1 AEs was performed for subjects who had an antidrug antibody (ADA)-positive or undefined ADA response for anti–pegcetacoplan peptide antibodies or anti-PEG antibodies. There were no meaningful differences in the percentages of subjects who had at least 1 AE and a positive or undefined ADA response for anti–pegcetacoplan peptide antibodies or anti-PEG antibodies across treatment groups.

In addition, a medical review of pool 1 AEs was performed to assess whether subjects with a positive or undefined ADA response for anti–pegcetacoplan peptide antibodies or anti-PEG antibodies also had a non-ocular AE of hypersensitivity or anaphylaxis to study treatment or an ocular AE of intraocular inflammation or endophthalmitis. No non-ocular AEs of hypersensitivity or anaphylaxis to study treatment were observed in subjects with a positive or undefined anti-pegcetacoplan peptide antibody or anti-PEG antibody response. There were no meaningful differences in the subjects who had endophthalmitis or intraocular inflammation with an overall positive or undefined response compared to a negative response to anti-pegcetacoplan peptide antibodies or anti-PEG antibodies.

2.5.8.8. Safety related to drug-drug interactions and other interactions

Results of the in vitro studies related to DDI are discussed in more detail in the preclinical assessment report. In brief, no systemic DDI effects are expected by IVT administration of Syfovre. DDI with systemic therapeutics is in general not expected for Syfovre given the local administration into the eye and the resulting low systemic exposure.

Potential DDI effects by concomitant or prior ophthalmologic medication with local administration on or into the eye have not been discussed by the applicant.

2.5.8.9. Post marketing experience

Syfovre has been authorised by the US FDA on 17 February 2023. With the answers to questions from the CHMP, the applicant provided the following information:

Apellis has received reports of intraocular inflammation, specifically reported cases of retinal vasculitis from post-authorisation use in the US. No events of retinal vasculitis have been reported in the intravitreal (IVT) pegcetacoplan clinical studies (Studies APL2-304 and APL2-303) by investigators or identified by the reading centre. A summary of the cases is provided below.

Retinal vasculitis is a sight-threatening inflammatory eye condition that involves the retinal vessels accompanied by intraocular inflammation. The term retinal vasculitis is used to describe a combination of characteristic clinical presentations, which may include perivascular sheathing or cuffing, vascular leakage, and/or occlusion. It may be associated with signs of retinal ischemia, including cotton-wool spots and intraretinal haemorrhage (Walton and Ashmore 2003; Abu El-Asrar et al. 2005). Retinal vasculitis has been observed in other intravitreal treatments, for example, ranibizumab, aflibercept, faricimab, brolucizumab (FDA Adverse Event Reporting System July 2023).

As of 15 January 2024, 22 potential cases of retinal vasculitis have been identified by the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) vasculitis (broad). Of these 22 potential cases, Apellis safety monitoring committee and external retina/uveitis experts have adjudicated 12 cases as non-occlusive/occlusive vasculitis and 3 cases as suspected retinal vasculitis. Three additional cases of suspected vasculitis are awaiting adjudication and included as suspected vasculitis for purposes of these analyses. Four cases are excluded from the analysis as 3 were adjudicated to be intraocular inflammation with absence of retinal vasculitis and 1 case was adjudicated as presumed vasculitis (not drug related) secondary to suspected endogenous endophthalmitis. Case details are shown in the table below.

As of 15 January 2024, 18 cases have 19 confirmed or suspected vasculitis events (one case had bilateral vasculitis reported and was counted as 2 events). Of the 18 cases (12 confirmed and 6 suspected), 2 patients had their first Syfovre injection in April 2023, 3 patients in May 2023, 3 patients in June 2023, 3 patients in August 2023, 2 patients in September 2023, 2 patients in October 2023, 2 patients in November 2023, and 1 patient in December 2023. All cases were serious, confirmed by a reporting physician, and from different physicians/sites. Eight of the 12 confirmed cases were adjudicated as retinal occlusive vasculitis, 3 cases adjudicated as non-occlusive retinal vasculitis, and 1 case adjudicated as unknown occlusive or non-occlusive vasculitis. The patients ranged in age from 43 to 96 years; 10 were female patients and 8 were male patients.

Medical history was remarkable for 4 patients with preexisting autoimmune diseases (1 patient with a history of Hashimoto's thyroiditis, 1 patient with hypothyroidism, 1 patient with diabetes mellitus, and 1 patient with ulcerative colitis), 3 patients with glaucoma/ocular hypertension, 2 patients with recent COVID infection, 1 patient with preexisting genetic disease of Stargardt, and 1 patient with a complex history of a prior retinal vein occlusion, cystoid macular oedema/uveitis, and status post pars plana vitrectomy. Three patients had prior anti–vascular endothelial growth factor treatment and 1 patient received Eylea and Syfovre via separate injection at the same visit in the same eye. Clinical presentations at event onset included diabetic retinopathy, optic disc cupping, elevated IOP, decreased visual acuity, visual impairment, eye redness, eye irritation, eye pain, eyelid swelling, retinal haemorrhages, vascular leakage, and in some cases, retinal vascular occlusion.

All confirmed vasculitis patients received only a single dose of Syfovre. One suspected patient experienced suspected vasculitis after the second injection in one eye. One confirmed patient received a single dose of Syfovre in both eyes and experienced retinal vasculitis events in both eyes. One suspected vasculitis patient received a single dose of Syfovre in both eyes and experienced suspected retinal vasculitis in 1 eye. One patient experienced confirmed retinal vasculitis (left eye) after receiving a single dose of Syfovre in their left eye for the diagnosis of Stargardt disease (off-label use). Subsequently, the same patient experienced retinal vasculitis in their right eye after receiving their first dose of another complement inhibiting drug, avacincaptad pegol, in their right eye. Event onset ranged from 8 to 18 days (1 case unknown) after Syfovre with a mean of 11.3 days and median of 10.5 days for confirmed vasculitis cases. Most of the patients received treatment with steroids.

As of 15 January 2024, the 12 confirmed and 6 suspected retinal vasculitis outcomes were as follows: 4 cases were reported as resolved, 5 cases as resolving, and 9 cases as not resolved/not reported. The visual acuity outcomes for each patient of the 18 confirmed and suspected cases include: 6 patients have vision impairment including 2 patients who underwent enucleation, 1 patient recovered their vision back to baseline, 4 patients have partially recovered, 1 patient's vision was unchanged from baseline, for 4 patients the outcomes of visual acuity are ongoing, and 2 patients the outcome of visual acuity was not reported.

As outlined above, the confirmed cases of retinal vasculitis have a broad spectrum of clinical presentation. Some cases presented with focal intraretinal haemorrhages and vascular leakage, while other cases presented with peripheral non-perfusion. One case presented with fibrin in the anterior chamber similar to an endophthalmitis clinical presentation, although culture from aqueous humour was negative. In addition, the cases have different potential contributing factors (e.g., medical history, concomitant use with anti-VEGF). One case that was originally reported by the physician as suspected vasculitis, was later adjudicated to not be vasculitis, but rather a peripapillary choroidal neovascularisation (CNV) and intraocular inflammation. This demonstrates the complexity of these cases and the fact that the diagnosis of retinal vasculitis might be difficult.

Table 77: Retinal vasculitis cases in patients who received Syfovre in the post-approval setting (as of 15 January 2024)

No.	Event PT (verbatim)	Event time from dose to onset	Dose data (OD, OS, OU)	Outcome of vasculitis event	Outcome of visual acuity and most current VA (baseline VA)	Treatment	Relevant medical history and con-meds	External retinal expert adjudication	MAH comments
Confirmed (n = 12)									
1	Retinal occlusive vasculitis (vaso-occlusive vasculitis post-Syfovre)	11 days	OS	Resolved	Partial recovery, 20/400 (baseline VA: 20/200)	Moxifloxacin drops and Polytrim drops OS; prednisolone drops; glaucoma drops; IVT Eylea; Cyclogel drops; prednisone PO; azithromycin PO; IVT ceftazidime and subconjunctival dexamethasone; Ozurdex.	Ocular hypertension; Hashimoto's thyroiditis, hypothyroidism; COVID (Mar 2023), cataract surgery Con-meds included Synthroid	Vasculitis, occlusive	Apellis assessed retinal occlusive vasculitis as related to Syfovre.
2	Retinal vasculitis (bilateral vasculitis)	12 days	OU	Resolved in both eyes	Partial recovery 20/70 OU (baseline VA: 20/30)	Oral prednisone, atropine drops, ophthalmic Durezol drops.	Wet AMD Con-meds included Eylea (OS since May 2019 and OD since Apr 2020, last injection OU on 02 May 2023)	Vasculitis, non-occlusive	Apellis assessed the retinal vasculitis (bilateral) as related to Syfovre.
3	Retinal occlusive vasculitis (retinal artery vein occlusion with vasculitis)	Unknown	OD	Not resolved	Partial recovery; 20/100 (baseline VA: 20/30)	Topical steroids, then Avastin.	Prostate cancer, skin cancer, cataract surgery, glaucoma, prior retinal vein occlusion, pars plana vitrectomy for epiretinal membrane OD with cystoid macular oedema and cells following surgery. Con-meds not reported.	Vasculitis, occlusive	Apellis assessed retinal occlusive vasculitis as related to Syfovre.
4	Ocular vasculitis (notable vasculitic findings)	8 days	eye not specified	Resolving	Visual impairment; no light perception (baseline VA: 20/150)	Topical steroid drops; IVT dexamethasone; IVT vancomycin and ceftazidime; Subtenon Kenalog.	Skin cancer s/p local excision, cataract surgery, hypertension. Con-meds included diuretic and beta-blocker	Vasculitis, non-occlusive	Apellis assessed ocular vasculitis as related to Syfovre.

No.	Event PT (verbatim)	Event time from dose to onset	Dose data (OD, OS, OU)	Outcome of vasculitis event	Outcome of visual acuity and most current VA (baseline VA)	Treatment	Relevant medical history and con-meds	External retinal expert adjudication	MAH comments
5	Retinal occlusive vasculitis (worsening occlusive retinal vasculitis)	9 days	OS	Not resolved	Visual impairment, light perception prior to excision of the eye (baseline VA: 20/100)	Oral prednisone and topical prednisolone, topical Durazol, Ozurdex IVT, Cosopt.	Wet AMD in fellow eye treated with Eylea, active smoker. Con-meds included Eylea (started 2020), sertraline, and trazodone. History of Lucentis (2018) and Avastin (2017)	Vasculitis, occlusive	Apellis assessed retinal occlusive vasculitis as related to Syfovre.
6	Retinal vasculitis (vasculitis, non-occlusive)	~2 weeks	OS	Resolved	Recovery to baseline 20/50 (baseline VA: 20/60)	Topical prednisolone, Cyclogyl and Combigan. Later oral prednisolone, subtenon injection of methylprednisolone	Bilateral cataract (extractions), posterior vitreous detachment, vitreous floaters. Con-meds included carvedilol, hydrochlorothiazide, losartan, Xarelto (rivaroxaban).	Vasculitis, non-occlusive	Apellis assessed retinal vasculitis as related to Syfovre.
7	Haemorrhagic occlusive retinal vasculitis (HORV)	10 days	OS	Not reported	Visual impairment; light perception (baseline VA: 20/40)	Q2 hours topical steroids, glaucoma gtts, Tap and inject abx (vancomycin / cetfazidime), PO moxifloxacin, acetazolamide, valacyclovir	Medical history not reported Con-meds: included Eylea (given at same time as Syfovre)	Vasculitis, occlusive	Apellis assessed the causal relationship between haemorrhagic occlusive retinal vasculitis and Syfovre as related. Concurrent injection of Eylea in the same eye is a confounding factor.
8	Retinal occlusive Vasculitis (occlusive vasculitis)	18 days	OS	Not resolved	No change from baseline vision (baseline VA: 20/150)	Topical corticosteroids, Ozurdex	Narrow angle glaucoma, cataract surgery Con-meds included glaucoma drops for levothyroxine, lisinopril, meloxicam, metformin, sertraline, Maxzide-25 (hydrochlorothiazide, triamterene).	Vasculitis, occlusive	Apellis assessed the events of retinal occlusive vasculitis as related to Syfovre.
9	Retinal occlusive vasculitis (occlusive vasculitis)	~11 days	OS	Resolving	Partial recovery, 20/250 (baseline VA: 20/50)	Subtenon Kenalog, topical polytrim, cyclogyl, and brimonidine as well as continued on prednisolone and cosopt gtts.	Cataract surgery OU, Lucentis: 8 injections, Vabysmo: (×2), ulcerative colitis, COVID vaccine (16 Mar 2021), hyperlipidaemia	Vasculitis, occlusive	Apellis assessed retinal occlusive vasculitis as related to Syfovre.

No.	Event PT (verbatim)	Event time from dose to onset	Dose data (OD, OS, OU)	Outcome of vasculitis event	Outcome of visual acuity and most current VA (baseline VA)	Treatment	Relevant medical history and con-meds	External retinal expert adjudication	MAH comments
10	Retinal vasculitis (vasculitis)	10 days	OD	Not resolved	Ongoing, counting fingers at 2'-4' (baseline VA: 20/30)	Ozurdex, PO prednisone, prednisolone eye drops, Tylenol	High blood pressure, hypothyroidism, seizures, GERD, dry AMD OU, no history of wet AMD or anti-VEGF usage Con-meds included Dilantin, Synthroid, PreserVision, AcipHex	Vasculitis, occlusive	Apellis assessed retinal vasculitis as related to Syfovre.
11	Haemorrhagic occlusive retinal vasculitis (HORV)	14 days	OD	Not resolved	Ongoing Hand motion Baseline VA: 20/125	Durezol, atropine, Brimonidine, Muro 128 drops and ointment, oral prednisone, Ozurdex	Hypertension, sleep apnoea, deep vein thrombosis, and atrial fibrillation Allergies to penicillin. Con-meds included atorvastatin, metoprolol, losartan, omeprazole	IOI (Intraocular Inflammation) with vasculitis, unknown if occlusive or not.	Apellis assessed HORV as related to Syfovre.
12	Retinal vasculitis [Diagnosed with vasculitis in the left eye (OS)] Retinal vasculitis [Vasculitis in the right eye (OD)]	9 days 12 days	OS Co-suspect product OD	Not resolved	Ongoing No light perception OS; Hand motion OD Baseline VA: OS: Count Fingers OD: 20/100	PO Prednisone, Atropine, Pred Forte Cosopt, Vyzulta, Diamox, Alphagan, Ozurdex, Valtrex, Kenalog	Recent COVID infection, off-label use of Syfovre in left eye (OS) for the diagnosis of Stargardt disease. On 26 Sep 2023, patient received avacincaptad pegol in right eye (OD)	Vasculitis, presumed occlusive (OS)	Apellis assessed retinal vasculitis (OS) as related to Syfovre. Apellis assessed retinal vasculitis (OD) as not related to Syfovre.
Suspected cases (n = 6)									
13	Retinal vasculitis (vasculitis primarily of retinal veins)	9 days	OS	Resolved	Ongoing, VA 20/200; (baseline VA: 20/100)	Cosopt, topical prednisolone hourly for inflammation, brimonidine BID added on 27 Aug 2023, 1 mg/kg oral prednisone started on 28 Aug 2023	Partial thickness corneal transplant OU (2016), cataract surgery OU (2009), Fuchs' endothelial dystrophy OS. Mitral valve prolapse, osteoporosis, HTN, hyperlipidaemia, no prior IVT injection or immunosuppression therapy. COVID vaccine (2021), no recent infection, history of autoimmune disease, malignancy, and implants	Vitritis, possible vasculitis (non-occlusive)	Apellis assessed suspected retinal vasculitis as related to Syfovre. Apellis agrees with the external experts' adjudication that this case is a possible vasculitis (non-occlusive) with an alternative diagnosis of vitritis

No.	Event PT (verbatim)	Event time from dose to onset	Dose data (OD, OS, OU)	Outcome of vasculitis event	Outcome of visual acuity and most current VA (baseline VA)	Treatment	Relevant medical history and con-meds	External retinal expert adjudication	MAH comments
14	Retinal vasculitis (Unexpected Vasculitis)	~12 days	2nd injection	Not reported	Ongoing, 20/200 (baseline VA 20/30)	oral steroids	Not reported	Presumed vasculitis	Apellis has assessed this case as presumed vasculitis
15	Retinal vasculitis (Vasculitis OD)	35 days	OD OS	Resolving	Ongoing, 20/400 OD; Baseline VA OD (20/250)	prednisolone acetate QID for 3 weeks then tapered	Type 2 diabetes mellitus with non-proliferative diabetic retinopathy OU, hyperlipidaemia, hypertension, hypothyroidism, allergy to IOP lowering eye drops Con-meds included: atorvastatin, HCTZ, levothyroxine, glimepride, losartan, rybelsus, testosterone, Coq10, vitamin D3	Suspected vasculitis possible/ indeterminate (not enough clinical information provided to date) OD. The left eye had IOI without evidence of vasculitis.	Apellis has assessed this case as suspected vasculitis in the right eye only.
16	Retinal vasculitis (Retinal vasculitis)	19 days	OD	Resolving	Not reported	triamcinolone 4mg and Ofloxacin 0.3% four times daily	anaemia, arthritis, hypertension, thyroid disease, anxiety Con-meds included: pantoprazole, amlodipine, levothyroxine. losartan, ranitidine, teal ophthalmic drops, Lotemax ophthalmic gel, Preservision, vitamin D	None	Pending adjudication
17	Retinal Vasculitis	34 days	OU	Resolving	Not reported	Faricimab (unspecified eye) steroid eye drops	Not reported	None	Pending adjudication
18	Vasculitis (vasculitis)	9 days	OD	Not reported	Ongoing NLP (baseline VA 20/50)	topical prednisolone hourly, eye pressure lowering agents (not specified)	Not reported	None	Pending adjudication
Excluded cases (n = 4)									

No.	Event PT (verbatim)	Event time from dose to onset	Dose data (OD, OS, OU)	Outcome of vasculitis event	Outcome of visual acuity and most current VA (baseline VA)	Treatment	Relevant medical history and con-meds	External retinal expert adjudication	MAH comments
19	Retinal vasculitis (bilateral) (bilateral IOI-suspected non-occlusive vasculitis)	~10 days	OU	Resolved	Back to baseline 20/60 OD 20/80 OS (baseline VA: 20/70 OD, 20/100 OS)	Topical steroids; oral prednisone; Benadryl, prednisone gtt; cycloplegic; glaucoma drops	No medical history or con-meds reported. History of treatment with Lucentis OD (last injection 4 weeks prior to Syfovre and 6 weeks prior to onset of current symptoms)	Non-vasculitis	Apellis assessed the relationship between Syfovre and the event as related to Syfovre. Recent administration of Lucentis (ranibizumab) is a confounding factor. Apellis agrees with the external experts' adjudication that this case is a non-vasculitis case and is consistent with a diagnosis of IOI with retinal haemorrhage.
20	Retinal vasculitis (suspected vasculitis)	~2 weeks	OD	Resolving	Back to baseline (VA 20/80) (baseline VA: 20/80)	Topical, subtenon, and oral steroids, prednisone (60 mg) and Kenalog (triamcinolone acetonide) subtenon, Diamox, Cosopt	Cataract surgery, autoimmune disease (rheumatoid arthritis) Con-med included Rinvoq (upadacitinib)	Non-vasculitis	Apellis assessed the event as related to Syfovre. Apellis agrees with the external experts' adjudication that this case is a non-vasculitis case.
21	Retinal vasculitis (non-occlusive vasculitis uveitis OD)	~2 weeks	OD	Resolved	Partial recovery, 20/100 (baseline VA: 20/50)	Prednisolone QID OD	Hypertension, vertigo, tinnitus, depression/anxiety (duloxetine), cataract surgery Con-meds included Duloxetine.	Non-vasculitis	Apellis assessed the event as related to Syfovre. Apellis agrees with the external experts' adjudication that this case is a non-vasculitis case.
22	Retinal vasculitis (Retinal vasculitis)	~ 6 weeks	OD	Resolving	Ongoing, LP OD (baseline VA: 20/100)	IVT antibiotics (Vancomycin, ceftazidime), difluprednate OD Q2HRS, combigan OD 1 ggt BID, and atropine OD 1 ggt BID, durezol q2	Long term neutropenia (unk aetiology), cerebral meningioma, hypertension, osteoarthritis stroke, hyperlipidaemia, allergy to codeine and aspirin, cataract extraction Con-meds included: PreserVision	Presumed vasculitis (not drug related) secondary to suspected endogenous endophthalmitis	Apellis received an external expert assessment for this case which contributed to Apellis' presumed vasculitis secondary to suspected endogenous endophthalmitis

Abbreviations: AMD = age-related macular degeneration; BID = twice per day; con-meds = concomitant medications; F = female; GERD = gastroesophageal reflux disease; gtt = drop; HORV = haemorrhagic occlusive retinal vasculitis; HTN = hypertension; IOI = intraocular inflammation; IVT = intravitreal; LP= light perception

M = male; MAH = marketing authorisation holder; NLP = No light perception; OD = right eye; OS = left eye; OU = both eyes; PO = orally; PT = Preferred Term; Q2 hours = every 2 hours; QID = 4 times per day; VA = visual acuity.

Estimation of Retinal Vasculitis in the Post-approval Setting

Retinal vasculitis is an intraocular inflammatory condition that includes the involvement of the retinal vessels and is a form of severe intraocular inflammation (IOI). Although retinal vasculitis was not observed in the combined month 24 results of Studies APL2-303 and APL3-304, similar injection rates of severe IOI were observed in phase 3 studies (5 cases/11,736 injections [0.04%]) and in the post-approval setting 38 cases/152,000 injection [0.02%]), which includes the post-approval retinal vasculitis cases.

As of 15 January 2024, 18 patients have 19 confirmed or suspected vasculitis events (one patient had bilateral vasculitis reported and was counted as 2 events in the calculation) relative to an estimated over 176,000 total injections (152,000 post-approval, 24,000 clinical trials).

As of 15 May 2024 (submitted with the responses to list of outstanding issues), 25 patients have 26 confirmed or suspected vasculitis events relative to an estimated over 277,000 total injections (253,000 post-approval and 24,000 clinical trials).

Although it is not always possible to reliably estimate the frequency as adverse events are reported voluntarily from a population of uncertain size, in the post-approval setting an estimated rate per injection of approximately 0.01% (26 events/253,000 injections) corresponds to a rare event (≥1/10,000 to <1/1,000).

Overview of Retinal Vasculitis Investigation

Apellis has initiated an investigation to evaluate informative factors that may be relevant to the occurrence of these events. The components of the investigation and their statuses are outlined in the following table.

Table 78: Components and status of the investigation

	Components of investigation	**Completed**	**Ongoing**
Mechanism of action of intravitreal pegcetacoplan	Review of the pegcetacoplan mechanism of action and association with retinal vasculitis	X	
Chemistry, manufacturing, and controls and product quality	Review of lot genealogy, manufacturing and testing changes, major and critical deviations, and product quality attributes	X	
	Product stability programme; monitoring of commercial lots through the end of product shelf life		X
Intravitreal pegcetacoplan clinical programme	Review of pegcetacoplan clinical programme	X	
	Review of antidrug antibody data in pegcetacoplan clinical programme	X	
	Monitoring of the long-term extension, Study APL2-GA-305		X
	Evaluation of the immunogenicity profile of Syfovre patients who experienced retinal vasculitis and serious intraocular inflammation in postmarketing setting		X

Drug preparation and administration	Investigation into drug preparation and administration by the health care providers in the postmarketing setting, including comparison of the clinical study, the structure of the devices, and subvisible particles in the supplies used for Syfovre administration		X

Summary of Completed Investigation Activities:

Mechanism of Action of IVT Pegcetacoplan: No Biological Plausibility Between Pegcetacoplan and Retinal Vasculitis Events

Pegcetacoplan is a complement inhibitor composed of 2 identical pentadecapeptides covalently bound to the ends of a linear PEG40. The peptide moieties are derivatives of compstatin and retain its ability to inhibit human classical and alternative pathway complement activation by binding to C3 and C3b, components of both C3 and C5 convertases (serine-proteases that cleave complement C3 and C5 proteins).

Pegcetacoplan was shown to inhibit complement activity in both the classical pathway and alternative pathway following 84 mg/kg intravenous doses of pegcetacoplan administered to cynomolgus monkeys on days 1 and 2 (2 IV doses). CH50 results (mainly driven by the classical pathway), AH50 results measured by enzyme-linked immunosorbent assays, and C3a concentrations decreased, with the effect on AH50 results and C3a persisting up to 7 days postdose.

The pharmacology of pegcetacoplan, inhibiting the complement cascade, is anti-inflammatory as the complement activation and its biological consequences (formation of C3a and C5a, interacting with their respective receptors C3aR and C5aR on immune cells activating those cells, opsonisation with C3b and iC3b, and production of the membrane attack complex) are inflammatory (Johnson et al. 2001; Mullins et al. 2001; Hageman et al. 2001). Based on this, there is no plausible pharmacologic relationship between an inflammatory event such as retinal vasculitis and the inhibition of the complement system, a part of the innate immune system.

As outlined in the Study APL2-304 Month 24 Clinical Study Report and the Study APL2-303 Month 24 Clinical Study Report, medical review was performed for subjects who had responses for anti–pegcetacoplan peptide or anti-polyethylene glycol antibodies from Studies APL2-304 and APL2-303. None of the antidrug antibody responses were linked to events of intraocular inflammation (IOI), indicating that these events are not related to an immunogenic reaction to the drug.

The observation that the retinal vasculitis events in the post-approval setting all occurred after the first injection precludes the conclusion that these events are immune-mediated reactions to the drug. This differentiates Syfovre from other intravitreal therapies that have been associated with retinal vasculitis (Karle et al. 2023; Kearns et al. 2023).

Despite the fact that there is no evidence suggesting an immunogenicity response, and that the time course and presentation of postmarket vasculitis is inconsistent with an immunogenicity reaction, antidrug antibodies are continuing to be collected in the extension study. Study APL2-GA-305 and possible immunogenetic responses will be further evaluated as additional data becomes available.

Chemistry, Manufacturing, and Controls and Product Quality:

The investigation evaluated clinical and commercial chemistry, manufacturing, and controls (CMC) throughout the entire supply chain, including but not limited to review of lot genealogy, manufacturing and testing changes, major and critical deviations, and product quality attributes. This review was comprehensive of the overall process from drug substance intermediates to finished goods distribution and included review for potential CMC activities that were different between clinical and commercial and might correlate to the adverse events (AEs). There has been no observed correlation between the reported events of retinal vasculitis with the drug product lot in the commercial setting. No CMC-related root cause could be determined for the identified events of retinal vasculitis associated with administration of Syfovre.

Review of Pegcetacoplan Clinical Programme

An analysis was conducted to identify any indication of retinal vasculitis in the pegcetacoplan clinical programme. Data from Studies POT-CP121614, APL2-304, and APL2-303 (all completed) and Study APL2-GA-305 (ongoing; data cut 11 August 2023) were reviewed.

The following analyses were performed during study conduct:

- review of all AEs reported by investigators for subjects enrolled in the studies
- review of all fluorescein angiography images by the independent reading centre

After the initial report of retinal vasculitis in the postmarketing setting, Apellis performed a comprehensive case review, including different imaging modalities, in subjects who experienced any events of IOI, endophthalmitis, or retinal vascular occlusion in the pegcetacoplan clinical Studies APL2-304, APL2-303, and APL2-GA-305. In addition, cases of severe IOI from Studies APL2-304 and APL2-303 were reviewed by external retinal/uveitis experts.

The clinical investigation further confirmed no events of retinal vasculitis in the pegcetacoplan clinical programme, evidenced by no reports of retinal vasculitis events by the investigators, no retinal vasculitis identified by the reading centre, and no suggestion of retinal vasculitis according to case review.

Ongoing Investigation Activities:

An in-depth examination of other possible causal factors associated with these rare events is ongoing.

CMC and Product Quality

The commercial lots associated with the postmarketing cases of vasculitis are part of the product stability programme. The results generated to date for the commercial lots are consistent with the drug product stability profile established with the clinical product. No out-of-trend or out-of-specification results have been observed for the commercial lots through the most recent time point (6 months on stability). In addition, it is also worth noting that the commercial lots in distribution were tested for sterility as part of the stability programme, and no growth was observed. The commercial lots will continue to be monitored through the end of product shelf life per the stability protocols detailed in the NDA post-approval stability commitment.

Pegcetacoplan Clinical Programme

Study APL2-GA-305 is an ongoing extension study designed to evaluate the long-term safety and efficacy of pegcetacoplan in subjects with geographic atrophy. To date, no events of retinal vasculitis have been reported in Study APL2-GA-305. Apellis will continue to monitor this study to further characterise the safety profile of intravitreal pegcetacoplan.

Drug Preparation and Administration Supplies

An investigation into drug preparation and administration supplies used by the health care providers in the postmarketing setting is ongoing. Based on the interim results, non-preferred structural variations were identified in the B. Braun 19 G filter needles. Out of an abundance of caution, Apellis initiated a field correction of the injection kits containing the B. Braun 19 G filter needles. The interim findings from the investigation and potential clinical relevance of the observed filter needle structural variations are detailed in the following section.

Interim Results From the Drug Preparation and Administration Investigation

Intravitreal injection kits containing B. Braun 19 G and BD 18 G filter needles were provided to support the preparation and administration of the drug product. The following evidence compelled a close examination of the B. Braun 19 G filter needles provided in certain lots of the injection kit:

1. The focus of the investigation in this area has been the difference of administration supplies used in a post-approval commercial setting vs those used in phase 3 clinical trials since there were no vasculitis cases in the clinical trials. The key difference is the use of filter needles in the former and a vial adapter in the latter. Information provided to Apellis by the manufacturers of both Vial Adapter and BD 18 G indicate they are made with the same filter element specification and materials of construction, while the B. Braun 19 G filter is uniquely comprised of a nylon woven structure.
2. While conducting the investigation, Apellis became aware of internal structural variations in the B. Braun 19 G filter needle included in certain injection kits supplied by Apellis. The structural variants were discovered during visual inspection and confirmed by x-ray computed tomography (CT) scans of aberrant forms manifesting in certain lots of B. Braun 19 G filter needles. Those forms included devices with 2 or 3 filter elements instead of a single filter element, variability in the remelt form which is created during the manufacturing operation that forms the seal between the filter element and the luer hub, and filter edges exposed to the fluid path which could impact the particulate load entering the syringe for injection.
3. Based on data from supply chain analysis, Apellis was able to make a singular determination in 5 of 9 confirmed cases of vasculitis that the only filter needle provided to the site at the time of injection was B. Braun 19 G. In the other 4 confirmed cases, both BD 18 G and B. Braun 19 G filter needles were provided, and a singular determination could not be reached at this time.

Potential Clinical Relevance of Findings from the Drug Preparation Investigation

A causal relationship has not been established between the structural variations in the B. Braun 19 G filter needle and the rare events of retinal vasculitis in the real-world environment; however, it is plausible that the nonpreferred characteristics observed in the filter needles could contribute to these events. For instance, the exposed part of the filter needle could potentially introduce nylon or other particles into the drug product during the drug extraction from the vial. Additionally, the incomplete seals observed in units with multiple filter membranes could potentially allow particles into the administration syringe. The response to the presence of nylon or other particles in the vitreous cavity is not well understood, but it is possible that this could lead to an inflammatory reaction.

Conclusion

Retinal vasculitis is an intraocular inflammatory condition that includes the involvement of the retinal vessels and is a form of severe IOI. Rates of severe IOI reported in the phase 3 studies (5 cases/11,736 injections [0.04%]) and in the post-approval setting (38 cases/152,000 injections [0.02%]), which includes the retinal vasculitis cases) were similar. Retinal vasculitis was observed in the post-approval setting at an estimated rate per injection of 0.01% (19 events/152,000 injections) and an estimated rare frequency. Retinal vasculitis was not observed in the combined month 24 results of Studies APL2-303 and APL2-304. Since there does not seem to be an association between MoA and vasculitis, the investigation of these rare events of retinal vasculitis is ongoing. Apellis has taken actions related to the injection procedure to reduce the possibility of these events and is currently evaluating the clinical presentation of retinal vasculitis cases, including the immunogenicity profile.

Overall, the safety profile of Syfovre in the post-approval setting is generally consistent with what has been reported in the clinical trials. Based on the rarity of these events and the outcomes observed to date, the overall safety profile of Syfovre remains manageable.

Rate Per Injection by the Filter Needle Type (as of 15 January 2024)

Following the findings from investigation of filter needles, Apellis assessed the rate of vasculitis associated with B. Braun 19 G and BD 18 G needles. Since B. Braun 19 G filter needles were only used post-approval, the rate by needle type is evaluated based on post-approval data only, excluding clinical trial data. Out of the approximated 152,000 injections, it was estimated (based on the shipment data) that approximately 47,000 (30.9%) injections used B. Braun 19 G filter needles and 105,000 (69.1%) used BD 18 G filter needles. Apellis was able to determine that a B. Braun 19 G filter needle was used for 6 of 18 patient cases. For 5 cases the filter needle use could not be determined because both types of needles could have been available at the sites according to supply chain records. For the 7 cases with injection dates 22 August 2023 onward (i.e., following the 22 August 2023 issuance of the Class 2 Device Recall of 19 G B. Braun injection kits) it is assumed that the filter needle used in drug preparation was from the 18 G BD injection kit.

To estimate the rate of retinal vasculitis by filter needle type, 2 approaches were used to estimate the probability of either a B. Braun 19 G or a BD 18 G filter needle used for the undetermined cases (see Table below). Approach 1 assumes the risk for retinal vasculitis to be the same for B Braun 19 G and BD 18 G, and the probability that a B. Braun 19 G or BD 18 G was used is then simply estimated by the proportion of each filter needle type available at the site or at the distribution centre when the site information is not available. Approach 2 was based on Bayesian predictive probabilities. In the Bayesian approach, a neutral noninformative Jeffreys prior was applied to the risk (i.e., probability) per injection for both B. Braun 19 G and BD 18 G needles, and the probabilities were updated including the determined cases and injections with non-cases, based on which the probability that a B. Braun 19 G needle was actually used was predicted for each of the undetermined case. Cases with injection dates post-issuance of the field correction are assumed to have been prepared with the BD 18 G filter needle. The rate per injection by needle type is calculated as the sum of the probabilities for all cases divided by the total injections for each needle type.

The following table presents the rate of retinal vasculitis by type of filter needle for Syfovre injection as of 15 January 2024.

Table 79: Rate of retinal vasculitis by type of filter needle for Syfovre injection (as of 15 January 2024)

		B. Braun 19 G (N=47000)			**BD 18 G (N = 105000)**		
		Estimated number of cases	Rate per injection (%)	NNT**	Estimated number of cases	Rate per injection (%)	NNT[a]
Approach 1[b]	Confirmed case	10.10	0.021	4655	2.90	0.003	36158
	Confirmed and pending case	10.76	0.023	4367	8.24	0.008	12747
Approach 2[c]	Confirmed case	10.82	0.023	4342	2.18	0.002	48256
	Confirmed and pending case	11.75	0.025	4000	7.25	0.007	14484

Abbreviation: N = estimated number of injections with each type of needle; NNT = number needed to treat.
a Number of injections needed to treat to observe 1 case.
b Approach 1 estimated the probability of each needle type being used based on frequency of needles shipped for undetermined cases.
c Approach 2 estimated the probability of B. Braun 19 G or BD 18 G being used for each undetermined case based on Bayesian predictive probabilities with a non-informative prior.

Notes: Based on cutoff of 30 December 2023 for total number of injections and 15 January 2024 for PM reported events. One patient had an event on both eyes and was counted as 2 events in the calculation.

Using the conservative Approach 1 based on frequency of the needles available:

- The estimated rate per injection for B. Braun 19 G was between 0.021% for a confirmed event and 0.023% for a confirmed or suspected event.
- The estimated rate per injection for BD 18 G was between 0.003% for a confirmed event and 0.008% for a confirmed or suspected event.

Using the modelling Approach 2:

- The estimated rate per injection for B. Braun 19 G was between 0.023% for confirmed event and 0.025% for a confirmed or suspected event.
- The estimated rate per injection for BD 18 G was between 0.002% for a confirmed event and 0.007% for a confirmed or suspected event.

Based on these evaluations, the rate per injection, i.e., the risk for retinal vasculitis, was estimated to be much lower for the BD 18 G filter needle than for the B. Braun 19 G filter needle.

2.5.9. Discussion on clinical safety

Overview and patient exposures

The applicant presented the safety data from 5 clinical studies conducted in patients with GA secondary to AMD (Studies APL2-304, APL2-303, POT-CP121614, APL2-103, and APL2-GA-305). The safety database discussed in the summary of clinical safety comprises over 2000 patient-years of cumulative IVT pegcetacoplan exposure, including approximately 1800 patient-years of phase 3 cumulative exposure.

Supportive data are presented from two early-phase studies in subjects with nAMD (Studies POT-CP043014 and APL2-203). This data has less bearing on this application, since it has been established in a different patient population.

Immunogenicity data are presented and assessed from all clinical pharmacology studies, including one study in subjects with nAMD (APL2-203, POT-CP121614, APL2-303, and APL2-304).

A separate analysis is provided for the pooled safety data from the two phase 3 studies APL2-303 and APL2-304 (pool 1). This data are regarded as the pivotal safety data for this submission as they stem from double-masked, controlled, randomised trials.

In pool 1, the following treatment regimen were applied: pegcetacoplan monthly (PM), pegcetacoplan every other month (PEOM), sham monthly (SM), sham every other month (SEOM); for most evaluations, data from the two sham-controlled regimen were pooled.

In total, 839 patients in pool 1 received at least one administration of study drug, and 624 completed treatment through month 24. Overall, the safety database is considered large enough to judge on the safety of Syfovre.

Fewer patients completed treatment in the PM group as compared to the PEOM group (70.2% versus 78.6%). Subjects in the PM and SM groups were scheduled to have received 24 pegcetacoplan or sham injections; subjects in the PEOM and SEOM groups were scheduled to have received 12 pegcetacoplan or sham injections over 24 months. The mean (SD) numbers of injections in the treatment groups were 18.2 (6.80) for the PM group, 9.8 (3.21) for the PEOM group, 18.2 (6.99) for the SM group, and 9.9 (3.18) for the SEOM group. In the treatment groups that received monthly injections, 48.9% of subjects in the PM group and 49.8% of subjects in the SM group received 22 to 24 pegcetacoplan or sham injections. In the treatment groups that received injections every other month (EOM), 66.0% of subjects in the PEOM group and 66.2% of subjects in the SEOM group received 11 to 12 pegcetacoplan or sham injections. These figures show that treatment adherence was much lower in the groups with monthly injection compared to the every other month groups. Within each regimen, though, treatment adherence was comparable between patients receiving study drug and sham control.

The general baseline characteristics were mostly well balanced. Numerical imbalances in baseline characteristics relevant to safety were minor between treatment groups, and were mostly not considered of medical significance. However, imbalances are noted in the rate of subjects using any concomitant ocular medication as well as the rate of subjects using aflibercept between the study groups in the two phase 3 studies. In response to a question raised during assessment, the applicant provided details on concomitant ocular medication including IVT treatments and compared the safety findings in patients with and without additional treatment. In pool 1 (Studies APL2-303 and APL2-304 combined), there was a higher incidence of subjects who experienced study eye AEs and received concomitant ocular medication in the pegcetacoplan groups (72.9% and 65.9% in the PM and PEOM, respectively) compared with the sham pooled group (61.9%). This seems reasonable, since the majority of study eye AEs was treated with concomitant ocular medication. In the pegcetacoplan pooled group the incidences of ocular AEs in the study eye were 73.2% and 54.0% for subjects with and without concomitant anti-VEGF treatment, respectively. Excluding the events of exudative AMD, for which most of the IVT treatment were given, the most prevalent AEs were comparable between the 2 groups. The percentage of subjects who received any concomitant IVT treatment in the study eye was 12.9%, 7.9%, and 2.6% in the PM, PEOM, and sham, respectively. The majority of the IVT treatments were anti-VEGF medications for exudative AMD (i.e., 10.0%, 4.8%, and 1.9% of subjects in the PM, PEOM, and sham pooled groups in pool 1, respectively). This correlates to the incidences of exudative AMD in pool 1, which occurred in 12.2%, 6.7%, and 3.1% of subjects in the PM and PEOM and sham pooled groups, respectively. Other IVT treatments included medications given for endophthalmitis, including 1 subject in the PM group and 3 subjects in the PEOM group in Study APL2-304, as well as 1 subject in Study APL2-303.

These data further demonstrate that pegcetacoplan treatment is related to severe eye disorders, which require concomitant ocular medication. Although the applicant argued that their product’s safety profile would be manageable by concomitant treatment, it needs to be stressed that a substantial part is administered intravitreal which adds to the burden of the treatment and increases the risk for additional serious adverse events related to IVT treatment. Besides this increased risk of additional procedural complications with associated AEs, also potential unwanted effects of these concomitant medications have to be anticipated. It is acknowledged that the overall compliance was considered acceptable during the clinical study setup as no relevant posology-related imbalances between sham and pegcetacoplan groups were observed. Still, considering also absence of benefit perceivable by patients and the advanced age of subjects that are intended for treatment (average life expectancy of 6.4 years; Colijn et al. 2021) the cumulative treatment burden of pegcetacoplan together with potentially required concomitant medication is expected to affect treatment compliance in the real-world setting.

In terms of baseline disease characteristics, such as bilateral GA, NL-BCVA score and history of CNV in the fellow eye, the groups were generally well balanced.

Specific data for the safe use of Syfovre in special populations have not been provided. This is acceptable, since the patient population in the phase 3 studies had a mean age of >78 years, and paediatric patients are not in scope of this MAA.

Subgroup analysis of ocular AEs in the study eye were performed for intrinsic factors (age, sex, race) and an extrinsic factor (region). Due to the low number of patients included within certain subgroups, limited conclusions about differences in the safety profile with regard to AEs in the study eye can be drawn. However, no trends or patterns were observed that could be considered clinically meaningful. Upon request also subgroup analysis of non-ocular AEs by age, sex, race and geographic region have been provided. Due to the low number of patients included within certain subgroups, limited conclusions about differences in the safety profile with regard to non-ocular AEs can be drawn. However, no trends or patterns were observed that could be considered clinically relevant.

Adverse events

In the pool 1 safety evaluation (that included data from the two phase 3 studies through month 24) 86.1% of all subjects had at least one treatment emergent adverse event (AE). Most of the subjects had mild or moderate AEs (61.1%) and 25.0% had severe AEs. Overall, only 9.0% of subjects had AEs reported as treatment-related and 22.1% of subjects had AEs related to the injection procedure. Both of these categories are considered crucial for the assessment of safety and risk benefit.

The overall percentage of subjects with at least one treatment emergent adverse event (AE) across the two phase 3 studies (evaluated as pool 1 safety data) was 87.8% in the pegcetacoplan pooled group and 82.5% in the sham pooled group. Whereas the percentage of subjects with AEs was comparable between the PM and PEOM group (88.3% versus 87.4%), the overall number of events was distinctly higher in the PM compared to the PEOM group (2583 versus 2220).

No relevant differences were observed in the percentages of subjects who had AEs of severity grade 3 (severe) in the PEOM (23.8%) and sham pooled groups (21.6%), whereas in the PM group, a numerically greater percentage of subjects (29.6%) had severe AEs.

The same trend was observed for subjects who had SAEs (25.5% and 26.9% in the PEOM and sham pooled group, respectively, compared to 34.8% in the PM group), subjects with AEs leading to treatment discontinuation (7.6% and 6.7% in the PEOM and sham pooled group, respectively, compared to 11.2% in the PM group), subjects with AEs leading study discontinuation (6.9% and 7.0% in the PEOM and sham pooled group, respectively, compared to 11.2% in the PM group), non-ocular AEs (73.1% and 71.9% in the PEOM and sham pooled group, respectively, compared to 80.4% in the PM group), AEs leading to death (3.6% and 3.8% in the PEOM and sham pooled group, respectively, compared to 6.7% in the PM group), and AEs leading to treatment interruption (6.0% and 5.8% in the PEOM and sham pooled group, respectively, compared to 12.4% in the PM group).

The percentage of subjects with AEs related to the injection procedure was higher in the PEOM group compared to the sham pooled group (22.4% and 17.5%, respectively), but the highest percentage was observed in the PM group (26.3%).

The percentage of subjects with AEs related to treatment was higher in the PEOM group compared to the sham pooled group (9.5% and 4.6%, respectively), but the highest percentage was observed in the PM group (12.9%).

The data demonstrate that, in general, the number and severity of AEs was higher in the pegcetacoplan treated groups compared to the sham controls, and also increased with treatment frequency.

The same trend was observed for study eye AEs:

In total, there were 753 study eye AEs in the PM group compared to 571 in the PEOM group. In both groups the % subjects with study eye AEs was higher than in the sham control (61.6%, 55.0% and 46.3% in the PM, PEOM and sham pooled groups, respectively).

Greater percentages of subjects in the pegcetacoplan groups than in the sham pooled group were also observed for the following categories (in the order PM, PEOM and sham pooled):

- study eye AEs related to injection procedure: 26.0%, 22.4% and 17.0%
- severe study eye AEs: 4.5%, 1.9% and 1.2%
- study eye AEs related to study treatment: 12.2%, 9.3% and 4.1%
- study eye SAEs: 2.1%, 1.4% and 0.7%

No meaningful differences were observed in the percentages of subjects who had AEs in the study eye leading to treatment discontinuation or study discontinuation.

The most common study eye AEs in the pegcetacoplan pooled group by percentage of subjects were vitreous floaters (8.3% compared to 1.2% in the sham pooled group), conjunctival haemorrhage (8.1% compared to 3.6%), nAMD (7.7% compared to 1.9%), visual acuity reduced (7.2% compared to 6.7%), and eye pain (6.4% compared to 6.5%). The study eye AEs with the greatest differences between the percentage of subjects in the PM group and the percentage of subjects in the PEOM group were vitreous floaters (9.8% vs 6.9%), nAMD (9.8% vs 5.7%), and punctate keratitis (5.5% vs 1.9%).

Differences were also detected for Choroidal neovascularisation (2.9%, 1.0% and 1.2% in the PM, PEOM and sham pooled groups, respectively), Optic ischaemic neuropathy (1.7%, 0.2% and 0% in the PM, PEOM and sham pooled groups, respectively) and Intraocular pressure increased (1.9%, 2.9% and 0.7% in the PM, PEOM and sham pooled groups, respectively). For Intraocular pressure increased, the affected subjects in the PM and PEOM groups experienced on average 2-3 cases of this AE, whereas the 3 subjects in the sham pooled group had one case each.

In the process of the assessment it has been discussed if **intraocular inflammation** could – at least partly – be ascribed to a rebound phenomenon. In this aspect the applicant pointed out that TEAEs of intraocular inflammation in the study eye were observed more frequently in the pegcetacoplan monthly (PM) group than in the pegcetacoplan every other month (PEOM) or sham groups (in 3.8%, 1.9%, and 0.2% of subjects in the PM, PEOM and sham group, respectively). The corresponding rates per injection were comparable in the PM (17 of 7600 injections or 0.22%) and the PEOM group (10 of 4136 injections or 0.24%) in the combined 24 month results of Studies APL2-303 and APL2-304. Similarly, the overall incidences of study eye TEAEs and study eye TEAEs related to study treatment were higher in the PM group as compared to the PEOM and sham groups. Significant differences in C_{trough} were observed between the PM and PEOM groups as reported above. As pointed out by the applicant, clinical implications of a possible rebound would be most significant in patients dosed every other month or a less frequent interval, where C_{trough} levels of pegcetacoplan would be at their lowest. The greater rate of overall study eye TEAEs and intraocular inflammation per patient observed in the PM group rather than PEOM group is thus concluded to be mainly caused by the greater number of injections rather than a possible rebound effect.

Altogether, the results show that the monthly administration of intravitreal pegcetacoplan appears to be associated with a worse safety profile than the every other month regimen. With the responses to list of outstanding issues, the applicant proposed to change and limit the dosing regimen to once every other month (PEOM regimen). This is agreed to from a safety perspective.

Three times more patients in the pegcetacoplan group had an **exudative AMD** AE (PTs CNV and nAMD) in the study eye compared to the sham pooled group, with an even larger difference when comparing the PM and sham groups [9.4% vs. 3.1%]. This is consistent with the results reported by a study that showed that mice lacking C3 or C5 had increased neovascularisation in a laser injury-induced model compared with control mice, suggesting that complement deficiency may be proangiogenic[6], although not all animal studies have reached the same conclusions. To explain why new onset exudative AMD was more frequent in patients treated with IVT pegcetacoplan, the applicant has provided two possible scientific explanations. One possibility is that by inhibiting C3 cleavage and slowing the progression of GA, the viable endothelium in the choriocapillaris adjacent to the GA lesion may sprout new vessels, which would manifest as exudative AMD. Another possibility is that the complement system plays a role in maintaining a prophagocytic state of macrophages in eyes with GA, and the inhibition of C3 cleavage may lead to a transient phase of proangiogenic macrophages when prophagocytic macrophages transition to a resting state (Cao et al. 2011; Tarique et al. 2015). Both potential mechanisms that could lead to new onset exudative AMD are linked to the mechanism of action of pegcetacoplan, but only the latter (involving pro-angiogenic macrophages) is supported by literature references. In conclusion, new-onset exudative AMD appears as a relevant risk of intravitreal treatment with pegcetacoplan.

Most patients with an exudative AMD AE in the study eye received an anti-VEGF for the treatment of exudative AMD (97.5% in the pegcetacoplan pooled group vs. 84.6% in the sham pooled group). At month 24, NL-BCVA reduction was greater in the exudative AMD pegcetacoplan-treated patients than in the sham group [-12.4 letters (PM: −13.0 letters, PEOM: −11.6 letters) vs. −6.6 letters], showing that despite anti-VEGF treatment, pegcetacoplan-treated patients lost more vision than those who received sham injections. An analysis of BCVA decline in patients with exudative AMD from the time of exudative AMD diagnosis to the end of studies has also been performed by the applicant. Differences between treatment groups in mean BCVA change between the pre-exudation visit and the end of studies (PM: −8.4, PEOM: −9.1, sham: −5.0) is driven by five outlier subjects (2 in PM, 3 in PEOM) who lost 30 or more letters. OCT and FAF imaging data were further reviewed for these patients in order to investigate the reasons for their vision loss. Four of these 5 patients had a mild clinical presentation of exudative AMD with some fluid accumulation in the retina that was resolved after anti-VEGF therapy. In the absence of other findings, the vision loss is likely due to natural disease progression of GA with involvement of the foveal area (either further progression of existing subfoveal GA or transformation from nonsubfoveal to subfoveal GA). The additional subject who experienced severe vision loss had a 4-month delay in the initiation of anti-VEGF therapy, which is typically associated with poorer visual outcomes. The 5 patients were responsive to anti-VEGF therapy. In addition, the applicant states that there are no known biological mechanisms that would result in a poorer anti-VEGF response in the presence of C3 inhibition. Taken together, these data do not suggest that patients treated with intravitreal pegcetacoplan are at risk of developing an untreatable (or less-treatable) form of exudative AMD.

AEs related to **intraocular pressure**, including glaucoma, ocular hypertension, and intraocular pressure increased were more common in the pegcetacoplan groups than in the sham groups. The majority of the events were mild to moderate and were treated with topical IOP-lowering medication. Two subjects, both in the PM group, discontinued the study treatment because of safety concerns regarding IOP-related events. Fifteen of the 16 subjects with glaucoma events in the study eye had bilateral glaucoma, suggesting that these events were not associated with pegcetacoplan.

Across all treatment groups, 75.2% of subjects had non-ocular AEs. The most common non-ocular SOCs in the pegcetacoplan group by percentage of subjects were in the SOCs infections and infestations (37.1%), musculoskeletal and connective tissue disorders (21.7%), and injury, poisoning and procedural complications (18.7%). The most common non-ocular PTs in the pegcetacoplan pooled group by percentage of subjects were urinary tract infection (9.1%), hypertension (8.2%), and fall

[6] Poor SH, Qiu Y, Fassbender ES, et al. Reliability of the mouse model of choroidal neovascularization induced by laser photocoagulation. Invest Ophthalmol Vis Sci. 2014;55: 6525.

(7.5%); these non-ocular AEs are common medical conditions in an elderly population and were comparable between groups.

Endophthalmitis occurred in 5 subjects in the pegcetacoplan pooled group (0.6%) in pool 1, 2 in the PM and 3 in the PEOM group; this corresponds to a rate per injection of 0.04% (5 of 11,736 injections). No event of endophthalmitis occurred in the sham pooled group. As pointed out by the applicant, the observed rate per injection in the pool 1 safety data is consistent with literature data from other trials with IVT administration. Of note, two subjects in the sham pooled group had a fellow eye SAE of endophthalmitis; one of them had received intravitreal anti–VEGF therapy 8 days prior to SAE onset. In Study POT-CP121614, endophthalmitis occurred in 3 of 165 subjects in the pegcetacoplan pooled group (1.8%); 2 (2.3%) in the PM group and 1 (1.3%) in the PEOM group. Endophthalmitis was not recorded in the sham control groups or in a fellow eye. The endophthalmitis rate per injection was 0.21% (3 of 1397 injections) in this study. This is approximately 5-times higher than the rate per injection reported for pool 1. In response to the LoQ the applicant discussed the differences in endophthalmitis rate per injection between studies and provided literature data comparable to the rate observed in the pool 1 safety data (0.04% in the phase 3 Chroma and Spectri trials of IVT lampalizumab (Holz et al. 2018) and 0.05% in the MARINA and ANCHOR trials (Rosenfeld et al. 2006; Brown et al. 2009)). The more elevated rate encountered in Study POT-CP121614 might be due to the utilisation of a lyophilised formulation requiring additional manual handling – which is not the commercial formulation. It is acknowledged, that the commercial formulation is apparently associated with a lower frequency of the respective AEs. Still, some uncertainty remains in this aspect.

Non-ocular SAEs

In pool 1, 349 subjects (27.8%) had 634 non-ocular SAEs. The most common SOCs for non-ocular SAEs in the pegcetacoplan pooled group by percentage of subjects were SOCs infections and infestations (8.1%), cardiac disorders (6.4%), and injury, poisoning and procedural complications (5.5%). Only one of the events (enterococcal bacteraemia) was reported as related to treatment.

Important imbalances were noted in the SOC Cardiac disorders [6.4% (PM: 8.1%, PEOM: 4.8%) versus 4.6% in the sham pooled group], and the PTs pneumonia [2.9% (PM: 3.3%, PEOM: 2.4%) vs. 1.4%] and transient ischaemic attack [0.7% (PM: 1.0%, PEOM: 0.5%) vs. 0.2%]. Upon request the applicant has provided an analysis of the frequency of the SOC cardiac disorders and the PTs pneumonia and transient ischaemic attack separated for studies APL2-303 and APL2-304, which shows that the imbalances in the individual studies were not as marked as for the pooled data. Furthermore, a thorough review of the individual cases responsible for the imbalances demonstrated that most subjects had risk factors and confounders (advanced age and baseline medical conditions) that may have contributed to the adverse events. Also, none of the SAEs of pneumonia, the SAEs of transient ischemic attack, or the reviewed cardiac events were assessed as related to treatment by the investigators. Also considering the low systemic exposure of intravitreally administered pegcetacoplan, the available data does not suggest a link between intravitreal pegcetacoplan and cardiac disorders, pneumonia or transient ischemic attacks.

In Study POT-CP121614, 51 of the 246 study subjects (20.7%) reported 88 non-ocular SAEs during the on-treatment period. None of these SAEs were considered treatment-related. The most common on-treatment non-ocular SAEs by subject were atrial fibrillation, cardiac failure congestive, and pneumonia (each occurring in 4 subjects [1.6%]).

In Study APL2-GA-305, 93 subjects (12.3%) had 136 non-ocular SAEs through the data cut date in the pegcetacoplan pooled group. The most common non-ocular SAEs in the pegcetacoplan pooled group by percentage of subjects were in the SOCs of cardiac disorders (2.5%); injury, poisoning and procedural complications (2.5%); and infections and infestations (2.5%).

Overall, most non-ocular SAEs were related to common medical conditions in the elderly patient population, or the ongoing COVID-19 pandemic.

Deaths

In pool 1, 59 subjects (4.7%) had 68 non-ocular AEs leading to death across all treatment groups.

There was a higher percentage of non-ocular AEs leading to death in the pegcetacoplan group (especially in the PM group) than in the sham pooled group [5.1% (PM: 6.7%, PEOM: 3.6%) 3.8%].

An overview of AEs leading to death in studies APL2-303 (month 24 data), APL2-304 (month 24 data), APL2-GA-305 (month 6 interim data) and POT-CP121614 showed that the greatest imbalance between treatment groups was registered in study APL2-304 (PM: 9.4%, PEOM: 4.2%, sham pooled group: 3.8%). Consequently, an in-depth review of the deaths in the study APL2-304 PM group was performed (N=20). Risk factors/confounders (advanced age and previous/concurrent medical conditions) were present in all 20 cases. Out of the 20 deaths, 18 were assessed as not related to pegcetacoplan and 2 were assessed as unlikely related to pegcetacoplan by the investigator. These conclusions can be followed and are also in line with the low systemic exposure of intravitreally administered pegcetacoplan.

In Study POT-CP121614, eight subjects died because of non-ocular SAEs. In Study APL2-GA-305, 13 subjects (1.7%) in the pegcetacoplan pooled group had 15 non-ocular AEs leading to death.

Across all studies, all of the (S)AEs leading to death were of non-ocular nature and none of them was considered related to treatment. This is not unexpected due to the presence of comorbidities in this relatively old patient population.

Laboratory findings

Overall, there were no meaningful differences in laboratory parameters and changes from baseline were well balanced between groups in pool 1.

One haematology SAE (haemoglobin decreased) in the SOC of investigations was reported in 1 subject (0.2%) in the PM group but it was not considered related to treatment.

No meaningful differences were observed between postbaseline vital signs values through month 24 in the PM, PEOM, and sham pooled groups. No vital signs SAE in the SOC of investigations was reported in the PM or PEOM group.

In Study POT-CP121614, no safety signals were identified on the basis of the nature, frequency and severity of reported AEs and mean changes in haematology, clinical chemistry, or laboratory values over time.

Postinjection intraocular pressure (IOP) of >30 mm Hg was observed in more frequently in the PM and PEOM groups (6.4% of and 5.2% of subjects, respectively) compared to the sham pooled group (0.2%) in pool 1. Only a minor fraction of these events were reported as adverse and all but one AE resolved on the same day; however, all subjects with AEs required treatment for at least one event. For the subject whose event did not resolve in one day, an AE of worsened ocular hypertension was reported and the subject discontinued the study because of safety concerns about this event.

Shift from baseline in slitlamp examination results in the study eye and fellow eye at month 24 did not reveal clinically meaningful differences in the eyelids, conjunctiva/sclera, cornea, iris, or pupil in any treatment group. Worsening of lens opacity occurred in up to 3.9% of subjects per group but no meaningful differences were observed between groups.

Indirect ophthalmoscopy examination results in the study eye macula showed that more patients in the PM group (2.8%) than in the PEOM group (1.2%) or sham pooled group (0.9%) had a shift from ‘normal’ or ‘abnormal not clinically significant’ findings at baseline to ‘abnormal clinically significant’ findings at month 24. Similar results were found for the study eye optic nerve (PM: 2.9%, PEOM: 0.9%, sham pooled group: 0.9%). Upon request the applicant clarified that the types of reported AEs that can lead to a change in the ocular examination of the macula and the optic nerve, respectively, were more frequent in the PM group than the PEOM or sham pooled groups, which can explain the greater number of shifts from baseline of “normal” or “abnormal not clinically significant” to “abnormal clinically significant” at month 24 in the macula and in the optic nerve observed in the PM group compared to the PEOM and sham groups.

No clinically meaningful differences were observed in the peripheral retinal, choroid, or vitreous cells in the study eye at month 24.

In the study eye, more patients in the pegcetacoplan pooled group [9.6%, (PM: 11.6%, PEOM: 7.6%)] than the sham pooled group (6.0%) had a CNV detected by the reading centre. Spectral domain optical coherence tomography images showed a significantly greater increase at month 24 in central subfield thickness and in the proportion of patients with presence of cystoid spaces in the pegcetacoplan pooled group compared to the sham pooled group [14.5 microns (PM: 19.9 microns, PEOM: 9.7) vs. 0.3 microns and 9.2% (PM: 15.5%, PEOM: 3.7%) vs. 1.5%, respectively]. The applicant argued that exudative AMD and GA are overlapping clinical manifestations of the same disease (AMD) and that the changes observed in the CST and cystoid spaces were likely due to the ongoing or potential exudative AMD subjects in the study, which can be followed.

The majority (80.4%) of the patients in pool 1 had bilateral GA. However, intravitreal administration of pegcetacoplan in both eyes in these patients has not been studied. A discussion regarding the potential for an increase in adverse events with bilateral treatment has been provided by the applicant. Results from a 9-month repeat-dose ocular toxicity non-clinical study where male and female cynomolgus monkeys were administered IVT pegcetacoplan bilaterally showed no safety signals. Bilateral administration of pegcetacoplan is expected to result in systemic exposures that are below those anticipated to result in meaningful systemic complement inhibition. Additionally, the systemic exposure of intravitreally administered pegcetacoplan corresponds to approximately 0.3% of the values observed with systemically administered pegcetacoplan (Aspaveli, authorised in the EU for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria), which is reassuring. An analysis of AEs in the fellow eye shows that there were no meaningful differences in the frequency of these AEs across treatment groups. Based on these data, no major safety issues are anticipated after bilateral treatment.

Post-marketing data

During the assessment the applicant provided additional information on cases of **retinal vasculitis** from post-authorisation use in the US. It was reported that as of 15 January 2024, 22 potential cases of retinal vasculitis have been identified. Of these 22 potential cases, Apellis safety monitoring committee and external retina/uveitis experts have adjudicated 12 cases as non-occlusive/occlusive vasculitis, 3 cases as suspected retinal vasculitis, and 3 additional cases of suspected vasculitis are awaiting adjudication and included as suspected vasculitis for purposes of these analyses. The 18 adjudicated cases (12 confirmed/3 suspected/3 awaiting adjudication) were all serious, confirmed by a reporting physician, and from different physicians/sites. Eight of the 12 confirmed cases were adjudicated as retinal occlusive vasculitis, 3 cases adjudicated as non-occlusive retinal vasculitis, and 1 case adjudicated as unknown occlusive or non-occlusive vasculitis. At the time of reporting, 4 cases were reported as resolved, 5 cases as resolving, and 9 cases as not resolved/not reported. The visual acuity outcomes for each patient of the 18 confirmed and suspected cases include: 6 patients have vision impairment including 2 patients who underwent enucleation, 1 patient recovered their vision back to baseline, 4 patients have partially recovered, 1 patient’s vision was unchanged from baseline, for 4 patients the outcomes of visual acuity are ongoing, and 2 patients the outcome of visual acuity was not reported. As of 15 May 2024, 25 patients have 26 confirmed or suspected vasculitis events relative to an estimated over 277,000 total injections (253,000 post-approval and 24,000 clinical trials).

In the post-approval setting an estimated rate per injection of approximately 0.01% (26 events/253,000 injections) corresponds to a rare event (≥1/10,000 to <1/1,000).

However, it is not always possible to reliably estimate the frequency as adverse events are reported voluntarily from a population of uncertain size, as pointed out by the applicant. Thus, it must be assumed that potentially more cases of retinal vasculitis occurred that were not correctly identified or not reported.

The applicant has conducted the following root-cause analyses to further investigate the unexpected findings of retinal vasculitis in the postmarketing setting.

MoA/Biological plausibility

There is no plausible pharmacologic relationship between an inflammatory event such as retinal vasculitis and Syfovre's mechanism of action as pegcetacoplan acts by inhibiting the complement cascade, thereby exhibiting is anti-inflammatory effects.

Further investigation of the clinical trials for subjects who had responses for anti–pegcetacoplan peptide or anti-polyethylene glycol antibodies showed that none of the antidrug antibody responses were linked to events of intraocular inflammation, indicating that these events are not related to an immunogenic reaction to the drug. The observation that the retinal vasculitis events in the post-approval setting all occurred after the first injection renders an immune-mediated reaction to the drug highly unlikely.

Thus, the observed events of retinal vasculitis cannot be explained by pegcetacoplan's MoA or primary pharmacology.

Review of Pegcetacoplan Clinical Programme

Further, the applicant performed a comprehensive case review, including different imaging modalities, in subjects who experienced any events of IOI, endophthalmitis, or retinal vascular occlusion in the phase 3 clinical studies. This investigation further confirmed the absence of events of retinal vasculitis in the pegcetacoplan clinical programme.

Drug Preparation Investigation

Lastly, the applicant investigated the potential impact of structural variations in the filter needle included in the injection kits in the commercial setting. It was concluded that these variations could lead to the introduction of nylon or other particles into the drug product during the drug extraction from the vial. Though not confirmed, it was postulated that the presence of nylon or other particles in the vitreous cavity could lead to an inflammatory reaction. Based on these evaluations, the rate per injection for retinal vasculitis was estimated to be much lower for the BD 18 G filter needle used in the clinical trials than for the B. Braun 19 G filter needle used in the postmarketing setting. However, with the overall small number of events accounted for in those evaluations, firm conclusions on an impact of the needle type on the development of retinal vasculitis cannot be drawn.

In conclusion, a specific trigger for the development of retinal vasculitis after pegcetacoplan administration could not be assigned by the time of the opinion.

Immunogenicity

No anti-pegcetacoplan peptide antibodies were detected in Study APL2-203 in subjects with nAMD. Eight of 16 subjects were positive for post-dose anti-PEG antibodies. However, predose samples were not collected in this study. Thus, it is not conclusive to what extent pre-existing antibodies present at baseline contributed to the high percentage of subjects with positive anti-PEG antibodies.

In study POT-CP121614, three of 165 subjects in the pegcetacoplan pooled group (1.8%) had anti-pegcetacoplan peptide antibodies; one of the samples was also positive for NAb but only at one time point. Twelve of 246 subjects had treatment-emergent responses for anti-PEG antibodies (4.9%): 2.4% of subjects in the pegcetacoplan pooled group and 9.9% in the sham pooled group.

In study APL2-303, 14 of 598 evaluable subjects had a positive anti–pegcetacoplan peptide antibody response: 10 of 404 subjects in the pegcetacoplan pooled group (2.5%) and 4 of 194 subjects in the sham pooled group (2.1%). Thirty-six of 404 subjects in the pegcetacoplan pooled group (8.9%) and 29 of 194 subjects in the sham pooled group (14.9%) had treatment-emergent anti-PEG antibodies. Treatment-boosted anti-PEG antibodies were detected in 5.2% of subjects in the pegcetacoplan pooled group and 14.9% of subjects in the sham pooled group.

In study APL2-304, 27 of 622 evaluable subjects had a positive anti–pegcetacoplan peptide antibody response: 18 of 415 subjects in the pegcetacoplan pooled group (4.3%) and 9 of 207 subjects in the sham pooled group (4.3%). Two subjects tested positive for NAb, both in the sham control group. 6.6% of subjects in the pegcetacoplan pooled group and 13.1% of subjects in the sham pooled group had treatment-emergent anti-PEG antibodies. Treatment-boosted anti-PEG antibodies were detected in 3.6% of subjects in the pegcetacoplan pooled group and 6.8% of subjects in the sham pooled group.

In summary, the incidence of anti-pegcetacoplan peptide antibodies was low across all studies, ADA were mostly transient and neutralizing antibodies were only detected sporadically. The incidence of anti-pegcetacoplan peptide antibodies was comparable between the pegcetacoplan and sham-control groups in the phase 3 studies APL2-303 (2.5% and 2.1%, respectively) and APL2-304 (4.3% and 4.3%, respectively). Moreover, neutralizing antibodies were detected in two subjects in the sham-control group in Study APL2-304. As pointed out by the applicant, the ADA rates observed in Study APL2-303 and APL2-304 most likely represent the false positive rate within the study populations, based on a 1% false positive rate established as a floating cut point in the assay validation. The same is assumed for the NAb-positive subjects in the sham-control group in Study APL2-304, since also the NAb assay was validated with a 1% false positive rate. Thus, no concern arises from the immunogenicity findings in the pivotal phase 3 studies.

Slightly higher, but overall also low incidences of treatment-emergent or treatment-boosted anti-PEG antibody response were observed, and many of those responses were transient. There was no apparent relationship between incidence of anti-PEG antibodies and treatment group.

In pool 1, no non-ocular AEs of hypersensitivity or anaphylaxis to study treatment were observed in patients with a positive or undefined anti-pegcetacoplan peptide antibody or anti-PEG antibody response. Among pegcetacoplan-treated patients, the frequency of intraocular inflammation AEs was similar between anti-pegcetacoplan antibody positive/undefined patients and anti-pegcetacoplan antibody negative patients and between anti-PEG antibody positive/undefined patients and anti-PEG antibody negative patients. Two patients with anti-PEG antibody positive/undefined response had a SAE of endophthalmitis, but both cases were of infectious origin (bacterial), whereas immunogenicity has been associated with cases of sterile endophthalmitis. Therefore, no apparent effect of ADA response on safety was observed, acknowledging the limitation in the assessment due to the low number of ADA-positive patients.

Safety related to drug-drug interactions

Based on the results of in vitro assessments conducted with pegcetacoplan, which suggested that the risk of drug-drug interactions was low, no clinical drug-drug interaction studies have been performed with pegcetacoplan. In order to assess potential interactions between pegcetacoplan and intravitreal anti-VEGF therapies, an analysis of ocular AEs in the study eye in subjects with and without concomitant anti-VEGF treatment in the study eye has been provided. Overall, study eye AEs were reported more frequently in patients who received anti-VEGF concomitantly with pegcetacoplan than patients who received only pegcetacoplan (73.2% vs. 54.0%). This imbalance is mainly due to the AEs associated with exudative AMD (PTs of neovascular age related macular degeneration and choroidal neovascularisation), which were frequent (40.2% and 14.6%, respectively) and were only reported in patients treated concomitantly with pegcetacoplan and anti-VEGF. For other ocular AEs, no significant differences were observed between patients treated concomitantly with pegcetacoplan and anti-VEGF and patients treated only with pegcetacoplan. In summary, with the available data, there is no evidence of any interaction between pegcetacoplan and intravitreal anti-VEGF therapies that could lead to safety issues.

Discontinuation due to adverse events

Overall, the percentage of patients in the pegcetacoplan pooled group who had AEs leading to treatment discontinuation (9.4%) was higher than in the sham pooled group (6.7%). In addition, the rate of discontinuation was higher in the PM group (11.2%) than in the PEOM group (7.6%). A higher proportion of patients discontinued treatment due to non-ocular AEs than due to study eye AEs (7.2% vs. 1.3%). The most common non-ocular AEs leading to treatment discontinuation in the pegcetacoplan pooled group were COVID-19 (0.8%), cardiac failure congestive and cerebrovascular accident (0.6% each). The most common study AEs leading to treatment discontinuation in the pegcetacoplan pooled group were optic ischaemic neuropathy and retinal detachment (0.2% each).

2.5.10. Conclusions on the clinical safety

The available data characterises the safety of Syfovre to a sufficient extent to conclude on the benefit/risk. The data clearly demonstrate higher rates of ocular adverse events in pegcetacoplan treated patients as compared to sham control. In most cases, an association with treatment frequency was present, i.e., more events occurred in subjects treated every month as compared to subjects treated every other month. With the responses to list of outstanding issues, the applicant proposed to change and limit the dosing regimen to once every other month (PEOM regimen). From a safety perspective, this is accepted. However, also with the PEOM regimen, significant safety findings need to be considered.

An important proportion of the events was regarded as related to the intravitreal injection procedure, while a smaller part was considered related to pegcetacoplan itself. All of these events are regarded as important for the risk-benefit assessment as the injection is part of the treatment regimen and related events may also lead to severe impact on visual acuity and negatively impact the quality of life.

Important (serious) adverse events that need to be taken into account in the risk-benefit assessment are endophthalmitis, exudative AMD, and inflammation including vitritis, uveitis and retinal vasculitis (from the post-marketing setting), all of which may lead to a worsening or complete loss of eye-sight. While endophthalmitis and intraocular inflammation are known risks of intravitreal injections, new-onset exudative AMD is an unexpected risk of intravitreal pegcetacoplan.

No non-ocular adverse events were identified that would pose a significant risk to patients receiving Syfovre.

2.6. Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP and PRAC, having considered the data submitted by the applicant, were of the opinion that, due to the concerns identified with this application, as above outlined, the pharmacovigilance system summary cannot be agreed at this stage.

2.7.2. Periodic Safety Update Reports submission requirements

Not applicable

2.8. Product information

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Syfovre (pegcetacoplan) is intended to be indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) in adults.

GA is an advanced form of AMD and is characterised by thinning and loss of the retinal pigment epithelium (RPE) and concurrent atrophy of photoreceptors and the choriocapillaris that leads to progressive and irreversible loss of visual function.

3.1.2. Available therapies and unmet medical need

There are currently no medicinal products licensed in Europe for the use in GA and no standard of care treatment is available. Natural disease progression appears devastating for the individual and the progressing GA manifests a major threat to a patient´s eyesight as well as general well-being. GA represents a significant unmet medical need because it leads to significant visual impairment.

3.1.3. Main clinical studies

The main evidence of the efficacy submitted is based on two Phase III studies of very similar design: APL2-303 (DERBY) and APL2-304 (OAKS).

Both studies were randomised, double-masked, sham-controlled and investigated the efficacy and safety of intravitreal pegcetacoplan therapy (15 mg/0.1 mL monthly or every other month) compared to sham injections in subjects with geographic atrophy secondary to age-related macular degeneration.

The primary outcome in both studies was the change from baseline to month 12 in total area of GA lesions, and the change in visual function was studied as secondary outcome until month 24. In each study a total of 600 subjects were planned to be assigned on a 2:2:1:1 basis to receive either pegcetacoplan monthly (PM) or every other month (PEOM) or sham monthly (SM) or every other month (SEOM).

Data from the ongoing 36-months open-label extension study APL2-305 are also presented.

3.2. Favourable effects

Two pivotal studies were aimed at showing a reduction of GA lesion growth at month 12. In the pivotal Phase III study APL2-304, the change from baseline in total area of GA lesion is statistically significant. Its magnitude (least-square mean, mm2) at month 12 compared to sham pooled (sham monthly SM + sham every other month SEOM) is –0.4114mm2 with 95% CI (–0.6397mm2 to –0.1831mm2; p=0.0004) for the PM (pegcetacoplan monthly) group, and –0.3180mm2 with 95% CI (–0.5423mm2 to –0.0937mm2; p=0.0055) in the PEOM (pegcetacoplan every other month) group. The other Phase III study (APL2-303) did not meet its primary efficacy endpoint and revealed an effect size estimate being smaller than expected at the planning stage, and smaller as compared to the outcome seen in study APL2-304. In study APL2-303, the change from baseline in total area of GA lesion (least-square mean, mm2) at month 12 compared to sham pooled (SM + SEOM) is –0.2296mm2 with 95% CI (–0.4703mm2 to 0.0111mm2; p=0.0615) for the PM group, and –0.2077mm2 with 95% CI (–0.4444mm2 to 0.0290mm2; p=0.0854) in the PEOM group, but was not statistically significant. In study APL2-304 the change from baseline in total area of GA lesion at month 24 compared to sham pooled is –0.9015 mm2 with 95% CI (–1.3026mm2 to –0.5004mm2; p=<.0001) for the PM group, and –0.7426 mm2 with 95% CI (–1.1282mm2 to –0.3570mm2; p=0.0002) in the PEOM group. In study APL2-303, the change from baseline in total area of GA lesion at month 24 compared to sham pooled is –0.7451 mm2 with 95% CI (–1.1539mm2 to –0.3362mm2; p=0.0004) for the PM group, and –0.6331 mm2 with 95% CI (–1.0508mm2 to –0.2153mm2; 0.0030) in the PEOM group. Results from the interim analysis (month 24 – 30) in the ongoing study APL2-305 continue to demonstrate a sustained treatment effect of pegcetacoplan in reduction of GA lesion growth.

3.3. Uncertainties and limitations about favourable effects

There are concerns in the two pivotal studies with regards to unbiasedness of the data. Information on patients withdrawing from treatment reveals that all 10 patients from both pivotal trials who stated withdrawal reasons related to (lack of) treatment effect are either PM or PEOM. None of the sham treated patients withdrew for that reason. This constitutes an imbalance which contributes as noteworthy uncertainty in relation to the treatment benefit.

Inconsistencies were identified regarding the effect size in PM compared to PEOM groups. Whilst the primary outcome effect is consistently higher in the PM groups vs. the PEOM groups when comparing to sham pooled, in some analyses a higher treatment effect is observed in the PEOM treated group than in the PM treated group, when both are compared to their corresponding individual sham control.

The GA lesion growth reducing effect (morphological changes) measured by FAF was confirmed by SD-OCT imaging. This measure relates to specific aspects of lesion growth and are as such per se a correlate measure of the primary analyses. Consequently, strong correlation with results on the primary lesion growth endpoint are not surprising and can therefore only provide little additional evidence.

The surrogacy level of change in GA growth rate for visual function is unknown. As stated by the experts in the ad hoc expert group and as post-hoc correlation analyses suggest, there is reason to hypothesise that an effect on GA growth rate could eventually translate into an effect on visual function. However, no corresponding trend was observed in any of the pre-specified key-secondary endpoints measuring visual function over the two-year period investigated in the submitted studies. Neither meaningful differences nor positive trends in any key secondary functional endpoints (reading speed, FRI index score, NL-BCVA, microperimetry measures) were observed for visual function changes or quality of life over 24 months. It is not possible to estimate whether and to what extent an effect on lesion growth of treatment beyond the two-year period may eventually translate into a clinically relevant benefit. In the experts' opinion, visual function endpoints such as BCVA, maximum reading speed, FRI index are not the most relevant endpoints representing a patient benefit in this context. Microperimetry of especially foveal areas were considered to better quantify visual function in GA. However, also results in the corresponding pre-specified key-secondary microperimetry endpoint "Mean Threshold Sensitivity of All Points" did not show a positive trend in favour of treatment. Estimates in favour of treatment with pegcetacoplan were only observed in microperimetry analyses that followed as other secondary endpoints or were only defined once failure to demonstrate a positive trend in the pre-specified key-secondary endpoints was apparent. Importantly, while the sensitivity to quantify an effect is acknowledged, microperimetry measures effects on the morphological level. Moreover, it was the experts' opinion that it is not clear at what stage of MP sensitivity loss patients can perceive change in visual function.

Considering the progressive worsening in functional key-secondary endpoints like Maximum Monocular Reading Speed, Functional Reading Independence Index and BCVA compared to baseline, with little fluctuation over time, as demonstrated within both pivotal studies, at least some effect of treatment on these outcomes would have been expected to be observed. However, in both of the two replicated trials corresponding treatment group differences in fact numerically favour sham across all key-secondary endpoints, thus not supporting a trend in favour of pegcetacoplan. This implies, that the demonstrated reduction in lesion growth by about 20% (i.e. implying that the additional lesion growth in the treatment group was still around 80% of the growth observed in the control group) in the every other month dosing regimen compared to sham was not sufficient to translate to a measurable benefit on vision in the 24 months of treatment. Microperimetry measurements were only performed in study APL2-304, which imposes an uncertainty with regards to lack of replication. Moreover, and in addition to the secondary and post-hoc character of these analyses there is no reasonable understanding of the minimum clinically relevant effect size for microperimetry EPs. The prespecified key-secondary microperimetry endpoint (overall mean threshold sensitivity) did not show a positive trend in favour of treatment within 24 months (results numerically favour sham). While results with respect to the increase in the number of scotomatous points, do numerically favour treatment, corresponding results are of questionable reliability considering the endpoint was selected only after the fact of failure to demonstrate a trend for favourable results in any of the higher ranked endpoints (i.e. that were originally considered of higher priority or relevance). Even the performed post-hoc analyses (which are of even lower evidentiary value because of their post-hoc nature) present inconsistent results with lack of dose-response, further questioning their credibility. This, in addition to the single trial assessment, increases uncertainty and severely questions the strength and robustness of these results in demonstrating a true treatment effect.

The potential for observing in the longer term a clinically relevant benefit (if any) is further compromised by the level of compliance that can be expected in practice, in a population with comorbidities and the treatment burden of Syfovre. Lastly, the population recruited in the development programme was enriched for factors predicting relatively fast progression, hence an even longer time to develop a meaningful benefit to the patient (if any) would be needed on average in the general population affected.

The applicant also reports further post-hoc analyses and subgroup analyses, that are however only hypothesis-generating at this stage.

3.4. Unfavourable effects

Important (serious) adverse events with imbalances between groups in the pool 1 safety data were Exudative AMD (12.2%, 6.7% and 3.1% in the PM, PEOM and sham pooled group, respectively), Intraocular inflammation (3.8%, 1.9% and 0.2%), Endophthalmitis (0.5%, 0.7% and 0) and Intraocular pressure increased (1.9%, 2.9% and 0.7%). For the latter, the affected subjects in the PM and PEOM groups experienced more occurrences of this AE compared to the subjects in the sham pooled group.

The per-injection rates of Intraocular Inflammation - PM group: 0.22% and PEOM group: 0.24% - are overall low and as expected in an IVT administered product. However, it needs to be taken into account that patients would in practice be treated with Syfovre 6 times per year with the PEOM treatment regimen so that the individual patient incidence will increase with treatment duration, and currently, no end of treatment has been defined. The same considerations concern the endophthalmitis rate per injection, which ranged from 0.04% to 0.22% across studies.

3.5. Uncertainties and limitations about unfavourable effects

Limited long-term data is available, leading to an uncertainty concerning the long-term safety of Syfovre. The applicant has not defined criteria for an end of treatment with Syfovre. This means that the risks associated with intravitreal injection will gradually increase with treatment duration. Moreover, pegcetacoplan administration has thus far only been studied in one eye per patient and there is a potential for increase in ocular and non-ocular adverse events with bilateral treatment.

Concomitant ocular medication, especially when administered by IVT injection, may add to the injection related AEs observed for Syfovre. Of note, pegcetacoplan treated patients may develop neovascular or exudative AMD, which is often treated by intravitreal anti-VEGF medication. This means that the risk of endophthalmitis and intraocular inflammations, amongst others, will further increase in patients developing wet AMD.

Differences in the percentage of subjects with certain AEs (e.g., Endophthalmitis, Intraocular inflammation) were noted between studies. According to the applicant this may be explained by the utilisation of a non-commercial lyophilised formulation requiring additional manual handling in the earlier studies. Even though the commercial formulation is apparently associated with a lower frequency of the respective AEs, some uncertainty remains in this aspect.

In addition to the specific observations made with respect to identified safety events, it is noted that the withdrawal of consent occurred more frequently in patients treated with the most frequent posology of Syfovre.

As of 15 May 2024, 25 patients have 26 confirmed or suspected retinal vasculitis have been reported from post-authorisation use in the US. No events of retinal vasculitis have been reported in the intravitreal (IVT) pegcetacoplan clinical studies (Studies APL2-304 and APL2-303) by investigators or identified by the reading centre. A specific trigger for the development of retinal vasculitis after pegcetacoplan administration cannot be identified at this time. The estimated rate per injection of these events is 0.01%. The estimated frequency of retinal vasculitis based on estimated number of patients exposed in the US post-approval setting is rare (≥1/10,000 to <1/1,000), however, it is not always possible to reliably estimate the frequency as adverse events are reported voluntarily from a population of uncertain size, as pointed out by the applicant. Thus, it must be assumed that potentially more cases of retinal vasculitis occurred that were not correctly identified or not reported.

3.6. Effects Table

Table 80: Effects table for Syfovre (pegcetacoplan) for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) in adults.

Effect	Short Description	Unit	Treatment	Control[1]	Uncertainties/ Strength of evidence	References
Favourable Effects						
Total area of GA lesion	Change from baseline in total area of GA lesion, least-square mean (SE)	mm2	PM: 3.175 PEOM: 3.131	3.999	Uncertainties: - No clinical relevant in itself and surrogacy not shown. Strength of evidence: - Effect estimation for anatomical EP established and robust from statistical perspective.	Month 24 Integrated Summary of Efficacy
Unfavourable Effects						
Exudative AMD	Included the terms neovascular age-related macular degeneration and choroidal neovascularisation	%	PM: 12.2 PEOM: 6.7	3.1	839 patients in pool 1 safety set, of whom 624 completed treatment through month 24	Section on clinical safety
Intraocular inflammation		%	PM: 3.8 PEOM: 1.9	0.2		
Endophthalmitis		% subjects with ≥1 event	PM: 0.5 PEOM: 0.7	0		
Increase in intraocular pressure		% subjects with ≥1 event	PM: 1.9 PEOM: 2.9	0.7		

[1]) Sham groups were pooled (every month EM + every other month EOM) in both studies (APL2-303 and APL2-304).
Abbreviations: AEs: adverse events, *EOM: every other month, PM: pegcetacoplan monthly, SE: Standard Error.

3.7. *Benefit-risk assessment and discussion*

3.7.1. Importance of favourable and unfavourable effects

The observed reduction of the GA growth rate is not in itself a clinically relevant benefit and has not translated into an observable clinically meaningful benefit in terms of patient relevant visual function after 24 months of treatment. While it is possible that such might develop after long-term treatment, this has not been demonstrated. It remains unknown when, to which extent and whether at all the slowing of anatomical progression will manifest in a functional benefit for the patient.

The potential risks of regular intravitreal injections with pegcetacoplan, which include the development of exudative AMD, intraocular inflammation (including serious cases of retinal vasculitis, as reported in the postmarketing setting), or endophthalmitis - all of which may lead to a worsening or complete loss of eye-sight - are considered significant.

3.7.2. Balance of benefits and risks

Overall, there are no demonstrated clinical benefits that could outweigh the risks associated with the treatment. Even if considering only the PEOM regimen, due to the lack of demonstrated clinical benefit to the patient with this regimen, a positive benefit-risk balance cannot be concluded for PEOM.

Hence, the benefit-risk of pegcetacoplan in the treatment of GA secondary to AMD in adults is negative.

3.7.3. Additional considerations of benefits-risk balance

Ad-hoc expert group (AHEG)

An AHEG was convened on 18th June 2024. The expert's comments and expertise are fully acknowledged. All agreed that size of GA lesion is an acceptable primary outcome measure for a trial in geographic atrophy. However, in the Rapporteurs' opinion, the assumption that any effect in GA lesion growth will at some point translate into a functional benefit and will become clinically relevant is not supported by the data provided by the applicant. It could not be answered when and to what extent a certain lesion size reduction would turn into perceivable patient benefit. Also with regards to microperimetry, the experts expressed that it is not clear at what stage of MP sensitivity loss patients can perceive changes in their visual function. In fact, and on the contrary, no differences at all in the key secondary endpoints (reading speed, FRI index score, NL-BCVA, threshold sensitivity) were observed for visual function changes over 24 months across the 3 treatment groups in both pivotal studies and thus not any effect at all with respect to the patient functioning is indicated by these data. The experts did not agree that visual function endpoints such as BCVA, maximum reading speed, FRI index are the most relevant endpoints representing a patient benefit in this context. Microperimetry especially foveal areas were considered to better quantify visual function in GA. However, also the predefined microperimetry (secondary) EPs did not show a convincing trend, only post-hoc analyses appeared to be better, but were also inconsistent with doses. Microperimetry was conducted only in a limited number of patients and positive trends in this post-hoc analyses are not convincing. Also, the estimated size (if any) was around 1 scotomatous point (point estimate) improvement, with equally unknown predictive value.

Of note, the experts state in their discussion an effect of $1mm^2$ lesion size reduction. However, the primary outcome effect actually observed in the double-blind, sham-controlled phase after 24M was only $-0.6868mm^2$ (both studies pooled, compared to sham pooled). Thus the discussed $1mm^2$ is around 46% larger than what was indeed estimated after 2 years of treatment with the proposed every other month dosing regimen.

In addition, it needs to be considered that the safety profile of Syfovre is not benign. This adds even more doubts to the use of a product whose clinical efficacy is uncertain and thus not supporting a positive benefit-risk balance.

Third party intervention during the evaluation of Syfovre

The CHMP received, during the assessment of this application, several interventions from third parties expressing, amongst others, views about the efficacy of Syfovre, the difficulty to demonstrate functional benefit in GA, and the unmet medical need of GA patients.

The CHMP acknowledged and considered those interventions in the context of its assessment and concluded that the observations put forward were already known by CHMP. An evaluation and assessment of all information has been conducted and considered for the overall assessment of the benefit-risk.

Post-authorisation study

With the responses to the List of Outstanding Issues, the applicant proposes a post-authorisation study that aims to address specific uncertainties raised regarding the post hoc nature of some analyses (i.e. microperimetry) and the lack of replication of these findings. However, a post-authorisation study would only be an adequate measure to address remaining uncertainties in a scenario where a positive benefit-risk balance is concluded, which is currently not the case, and which is precluded by the lack of demonstration of a clinically relevant benefit for patients.

3.8. Conclusions

The overall benefit/risk balance of Syfovre is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Syfovre in the treatment of geographic atrophy secondary to age-related macular degeneration in adults, the CHMP considers by majority that the efficacy of the above-mentioned medicinal product is not sufficiently demonstrated,

and therefore, recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

- Efficacy of Syfovre has not been sufficiently demonstrated. While an effect on slowing GA lesion growth with every other month pegcetacoplan treatment for up to 24 months was observed, this anatomical effect did not translate into a patient-relevant clinical benefit. At this stage, with the data provided it cannot be answered when and to what extent a certain lesion size reduction (and specifically that achieved by pegcetacoplan administered every other month; PEOM) would turn into perceivable patient benefit.

  In absence of a clinically relevant benefit to the patient and together with the risks of regular intravitreal injections of Syfovre, which include the development of exudative AMD, intraocular inflammation, or endophthalmitis, the benefit-risk balance of Syfovre in the indication applied for is negative.

Due to the afore-mentioned concerns, a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

New active substance

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP is of the view that pegcetacoplan is not to be qualified as a new active substance. The detailed position of the CHMP is reflected in Appendix.

5. Re-examination of the CHMP opinion of 27 June 2024

On 27 June 2024, the CHMP adopted a negative opinion recommending the refusal of the granting of the marketing authorisation for Syfovre (pegcetacoplan).

The concluding grounds for CHMP's refusal were based on the following key point:

"Efficacy of Syfovre has not been sufficiently demonstrated. While an effect on slowing GA lesion growth with every other month pegcetacoplan treatment for up to 24 months was observed, this anatomical effect did not translate into a patient-relevant clinical benefit. At this stage, with the data provided it cannot be answered when and to what extent a certain lesion size reduction (and specifically that achieved by pegcetacoplan administered every other month; PEOM) would turn into perceivable patient benefit. In absence of a clinically relevant benefit to the patient and together with the risks of regular intravitreal injections of Syfovre, which include the development of exudative AMD, intraocular inflammation, or endophthalmitis, the benefit-risk balance of Syfovre in the indication applied for is negative.".

The applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

Summary

The applicant, Apellis, respectfully disagrees with CHMP's conclusions and maintains that the treatment with Syfovre does bring a clinically meaningful patient-relevant benefit and that Syfovre has a positive benefit-risk profile (as also expressed in the divergent position). Apellis respectfully requested a re-examination of the initial CHMP opinion, highlighting their belief that the data previously submitted in support of the MAA for Syfovre were not fully recognized in their entirety. Apellis suggests that the comprehensive body of clinical evidence demonstrates the clinical efficacy of Syfovre for the treatment of adults with GA secondary to AMD. The applicant's intentions in the grounds for re-examination were to emphasize the substantial evidence and its clinical relevance, which Apellis believes warrants a positive re-assessment of Syfovre's benefit-risk profile. Treatment with Syfovre in patients with GA secondary to AMD has been demonstrated to result in a clear and unequivocal treatment benefit on GA lesion growth translating to changes in functional endpoints relevant for the commonly reported symptoms of GA. The applicant believes that the requirements to demonstrate a reduction in lesion growth with associated trends in functional benefit as outlined by CHMP during the 2018 Scientific Advice have been met.

GA is an irreversible, progressive form of advanced AMD with currently no approved therapy in Europe. Under Article 70 of the proposed Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the EMA, GA would be considered as an orphan disease due to its high unmet medical need and there being no medicinal product authorised in the Union for such condition. It leads to severe visual impairment and legal blindness. Patients experience symptoms of functional vision loss such as difficulties in recognizing objects and faces, scotoma (i.e., a loss of field of vision that is typically surrounded by a field of normal—

or well preserved—vision), distorted images, as well as difficulty in reading, driving, and night vision (Sadda et al. 2016; Taylor et al. 2018; Taylor et al. 2017; Caswell et al. 2021). It is characterized by thinning and loss of the retinal pigment epithelium (RPE) and concurrent atrophy of PRs, the cells in the retina responsible for vision (Holz et al. 2014; Sunness et al. 1999a; Sunness et al. 1999b).

The CHMP agreed with Apellis' position that the Studies APL2-304 and APL2-303, both randomised, double-masked, sham-controlled phase 3 studies, demonstrated a reduction in lesion growth but did not consider the magnitude of the effect as clinically relevant, whereas the divergent position did consider this magnitude as clinically relevant. In the applicant's opinion, the treatment effect on lesion growth with Syfovre reached a clinically meaningful amount of area saved, a viewpoint supported by the amount of lesion area saved the AHEG considers as clinically relevant.

The CHMP and Apellis did not agree on whether the reduction of the lesion growth with Syfovre translates to a patient-relevant clinical benefit. The final CHMP assessment report concluded that based on the evidence to date, it cannot be answered when and to what extent a certain lesion size reduction would turn into a perceivable patient benefit. This conclusion was principally based on the endpoints of BCVA, maximum reading speed, and FRI, because, as stated in the final CHMP assessment report, at least some effect of treatment on these outcomes would have been expected to be observed. This is contradictory to the consensus position of the AHEG that these are not the most relevant endpoints representing patient benefit in patients with GA secondary to AMD. Furthermore, evidence from analyses of scotoma was considered of questionable reliability for demonstrating a patient benefit despite the consensus AHEG position that this endpoint will better estimate visual function in patients with GA secondary to AMD. It is the applicant's position that the results based on scotomatous areas as assessed by microperimetry provide reliable evidence of a patient-relevant benefit in slowing the lesion growth and should be more prominently considered in the benefit-risk discussion. These analyses and results are scientifically and medically sound, represent the most up-to-date knowledge in GA research, which the AHEG acknowledges as a better estimate of visual function in GA. The divergent position also took a contrasting view to the final CHMP assessment report on this important topic concluding that microperimetry analyses show that the preserved retina retains light sensitivity and is thus functional. They also noted that establishing clinical benefit within the placebo-controlled phase of the clinical trials may not have been possible due to the disease. Apellis agrees with the divergent position.

In the applicant's opinion, Syfovre showed a consistent and clinically meaningful treatment benefit in pathological and functional hallmarks relevant for the commonly reported symptoms of GA, as set out in the 2018 Scientific Advice.

Specifically, Syfovre treatment (according to the applicant):

- meaningfully reduces the growth of GA lesion as analysed by the change from baseline in lesion size that is quantified by FAF and OCT imaging modalities;
- reduces the growth of the scotoma as analysed by the number of new scotomatous points from baseline over time in the macula and junctional, which also indicates that the preserved retina retains light sensitivity;
- reduces the risk of progression to severe vision impairment as analysed by the time to complete loss of light sensitivity in the central field of the fovea;
- an early trend in reducing the risk of progression to severe vision impairment as analysed by the time to a sustained BCVA at or below 35 letters.

Based on the 2018 Scientific Advice, the applicant believes the negative opinion from CHMP requested more evidence than initially intended. While the 2018 Scientific Advice indicated that a "positive trend of treatment on visual function parameters” would be sufficient, the negative opinion called for a higher level of proof. The applicant contends that the submitted data, including post hoc analyses, demonstrate the necessary “positive trend.” Studies APL2-304 and APL2-303 showed a robust effect on slowing GA lesion growth, with further confirmation from RPE and PR loss endpoints using SD-OCT. Microperimetry assessments also supported that preserved retina remains functional. The applicant proposes a PAS to address remaining concerns by replicating the microperimetry findings. The PAS will be a multicentre, randomised, double-masked, sham-controlled phase 3b study to compare the efficacy of Syfovre to sham in patients with GA secondary to AMD.

At the time of the original MAA submission, the safety database contained more than 2000 patient-years of cumulative Syfovre exposure, including approximately 1800 patient-years of phase 3 cumulative exposure (data cutoff date of 24 June 2022) using the proposed commercial formulation. The safety profile of Syfovre is well characterized and acceptable, based on the current (data cutoff date of 30 June 2024) cumulative IVT exposure in both the clinical and real-world setting estimated to be more than 44,000 patient-years and 334,000 injections (306,000 injections post-approval and 28,000 injections in clinical studies). Notwithstanding the demonstrated positive benefit-risk profile with both monthly and EOM dosing, EOM demonstrates a more favourable safety profile and reduced treatment burden compared to monthly. Apellis continues to seek authorisation for the PEOM dosing regimen only and requests the review to be principally focused on the benefit-risk of EOM. Whereas the majority of CHMP members did not yet conclude on the safety profile of EOM dosing, the CHMP members with the divergent opinion acknowledged the acceptability of the proposed EOM dosing regimen.

During the initial assessment of the MAA, Conditional Marketing Authorisation or Exceptional Circumstances Authorisation was not considered since a positive benefit-risk balance was not established. The applicant asserts that the efficacy and safety results provided do demonstrate a positive benefit-risk balance for Syfovre in treating GA secondary to AMD. Insights from the 18 June 2024, AHEG meeting supported the positive benefit-risk profile of Syfovre, with experts unanimously agreeing on the clinical relevance of GA lesion size and microperimetry for retinal function assessment. If CHMP agrees with the view from AHEG and conclude the benefit-risk is positive but finds that the application is not ”comprehensive,” the applicant believes Syfovre meets the criteria for conditional marketing authorisation. This pathway is justified by the substantial evidence demonstrating Syfovre's efficacy in slowing GA lesion growth, its consistent and meaningful reduction of pathological and functional hallmarks of GA, and an acceptable safety profile. Syfovre's immediate availability is essential to address the high unmet medical need in GA, offering significant public health benefits by preserving vision in a vulnerable population while additional data is gathered through a proposed PAS.

The June 2024 AHEG meeting advanced the understanding of assessing and treating GA secondary to AMD by highlighting the limitations of traditional endpoints like BCVA and reading speed in capturing GA's progression. Experts emphasized microperimetry as a more accurate and patient-relevant measure, agreeing that GA lesion size is an acceptable primary outcome due to its correlation with retinal sensitivity loss and disease severity. They noted that even small reductions in lesion size could be clinically relevant, especially in specific subgroups. The applicant requests that the CHMP reconsider the AHEG meeting outcomes during re-examination, factoring this into the totality of evidence for Syfovre's benefit-risk profile.

Many third-party interventions support the potential approval of Syfovre, highlighting the substantial medical need for a GA treatment. Professional retina societies and patient advocacy organizations have unanimously endorsed Syfovre's efficacy in reducing GA lesion progression, despite the limitations of current instruments for measuring visual function. Sixteen interventions communicated via the EMA emphasize this support, noting the US Food and Drug Administration (FDA) approval based on

Syfovre's efficacy, which has led to widespread use in the US. These organizations stress the urgent need for effective GA treatments, highlighting the therapeutic inequity for EU patients.

Apellis' assessment is that the efficacy and safety data demonstrate a positive benefit-risk assessment for approval of Syfovre 150 mg/mL IVT injection EOM in patients with GA secondary to AMD. This view is also strongly supported by the third-party interventions by reputable Retina Societies in EU states and patient organizations, as well as by 8 divergent positions that dissented with the June 2024 CHMP opinion for Syfovre.

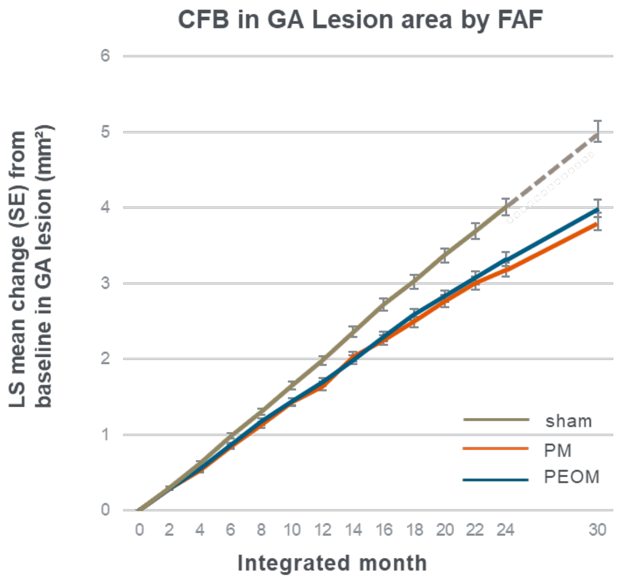
I. Positive Benefit Demonstrated with Syfovre Treatment

II. Clinically Meaningful Reduction in Growth of GA Lesions With Syfovre

Unequivocal Evidence Syfovre Slows the Growth of the Lesion With Increasing Effects Over Time

Lesion growth is the hallmark of disease progression in GA leading to RPE and PR cell death.
A treatment resulting in a substantial reduction of lesion growth is clinically meaningful as it is clinically and biologically evident that GA lesion growth, leading to RPE and PR cell death, causes an inevitable and irreversible loss of visual function (Sunness et al. 1999a; Schmitz-Valckenberg et al. 2016a; Schmitz-Valckenberg et al. 2016b; Heier et al. 2020). This was also endorsed by the AHEG convened for Syfovre, as they noted "*size of GA lesions is correlated with loss of retinal sensitivity as measured in MP with anatomical and functional correlation*." Preserving the retinal structure can therefore serve the basis for preserving the visual function as it is biologically impossible to preserve function without first preserving structure.

The effectiveness of Syfovre has been clearly demonstrated in 2 phase 3 clinical trials, which provided robust and unequivocal evidence that the drug slows lesion growth. Additionally, the trials also demonstrated treatment effects that increased over 24 months; the longer patients received treatment, the greater their protection against lesion growth. This has been demonstrated across PM and PEOM groups using 2 independent imaging technologies (graph shown on right in Figure 28). Initial data from the phase 3 extension Study APL2-GA-305 demonstrated a sustained treatment effect with Syfovre treatment in slowing the lesion growth through month 30 as well as provided evidence that the increased treatment effect was sustained after month 24 (graph shown on left in Figure R28 and Figure R29). The preserved area of PR loss after 2 years of treatment reaches the size of the blind spot (approximately 2 mm^2), the largest area without light perception that can be compensated by the fellow eye and any loss of retinal tissue of this size is clinically relevant. Continuous treatment with Syfovre beyond 24 months is expected to also preserve an area of RPE of this magnitude. Therefore, the applicant considers the observed reduction in lesion growth as clinically relevant.



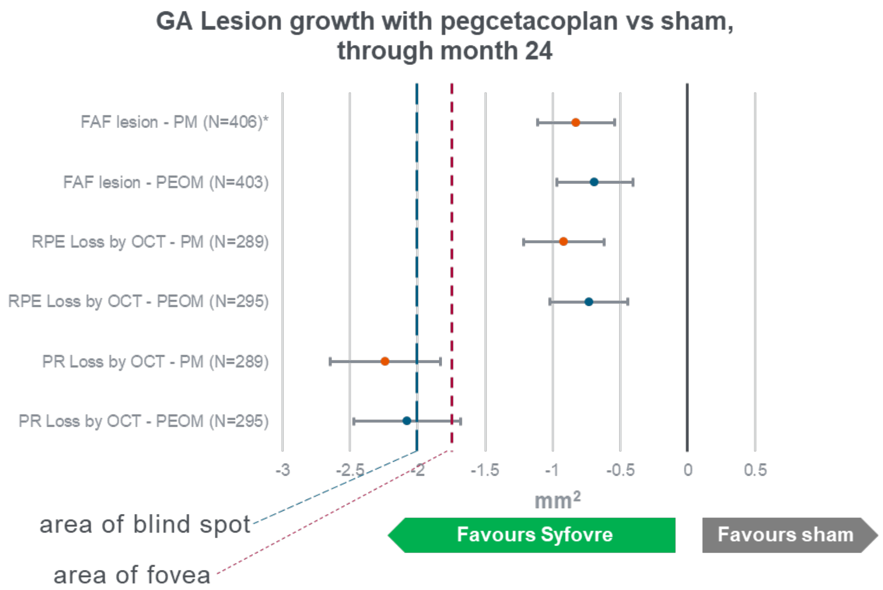


Figure 28: Anatomical treatment benefit observed with Syfovre

Abbreviations: CFB = change from baseline; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measure; OCT = optical coherence tomography; PEOM = Syfovre (pegcetacoplan) every other month; PM = Syfovre (pegcetacoplan) monthly; PR = photoreceptor; RPE = retinal pigment epithelium.

Notes: LS means estimated from MMRM analyses. For analyses of FAF, the mITT population was used for the analysis, defined as all randomised patients who received at least 1 injection of Syfovre or sham and have a baseline and ≥1 postbaseline value of GA lesion area in the study eye. For analyses of OCT, the Retinsight mITT population was used for the analysis, defined as the mITT population with ≥1 quantifiable RPE/PR loss area measurement from a Spectralis HRA+ OCT image. For the graph on the left, a projected sham was used for the month 24 to month 30 sham pooled group growth. The projected sham was estimated by extending LS mean change from baseline to month 24.

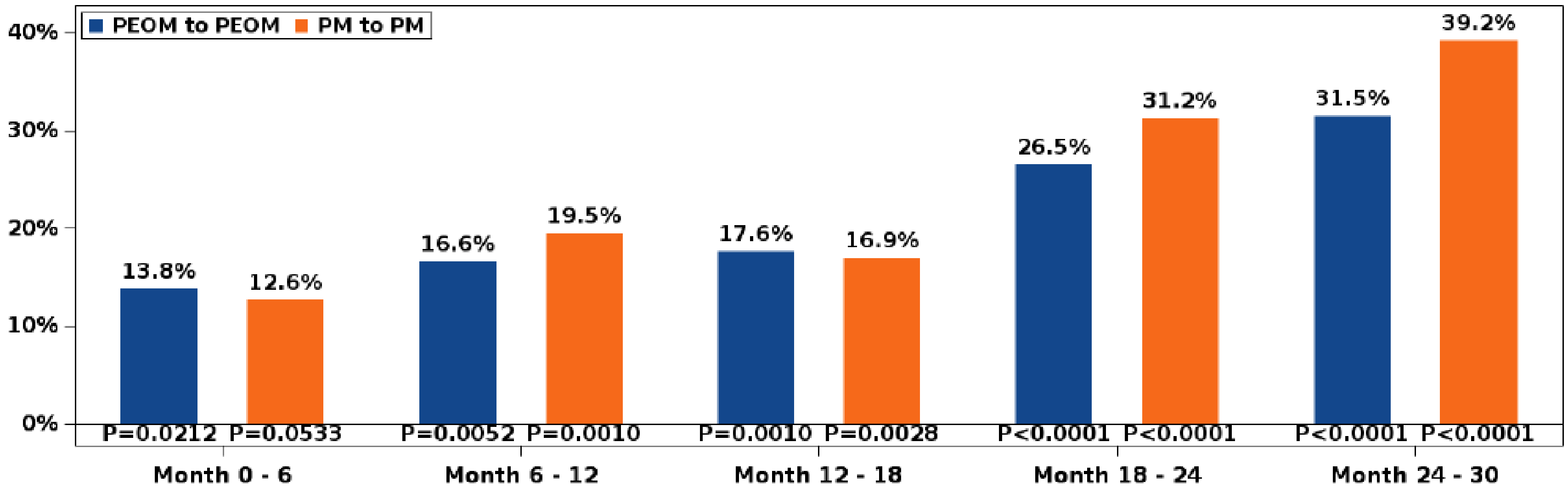


Figure 29: Increased treatment effects on rate of GA lesion growth sustained through month 30

Abbreviations: PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Note: Treatment effects for each 6 month period estimated from an analysis of the rate of GA lesion growth for PM to PM and PEOM to PEOM compared to the sham pooled group though month 24 and the projected sham from month 24 to month 30. The projected sham was based on the average of the 6-month sham pooled group rates through month 24.

III. Lesion Area Saved Reaches Size the AHEG Considered as Clinically Relevant

It was acknowledged by the AHEG that "*perifoveal GA patients, and rapid GA progressors with impending foveal loss, an impact of 1 mm^2 could have a clinically relevant impact and be perceived by patients.*" When commenting on the feedback from the AHEG, the CHMP final assessment report referenced that the 1 mm^2 lesion size reduction is around 46% larger than what was indeed estimated after 2 years of treatment with the proposed every other month dosing regimen during the double-blind, sham-controlled phase: only −0.6868 mm^2 (both studies pooled, compared to sham pooled). Despite the end of the sham-controlled portion at 24 months, data from Study APL2-GA-305 for the objective anatomical endpoint is useful for understanding the growth in the preserved retinal area with continued treatment. The applicant would like to emphasize that they did provide the CHMP the estimated lesion size reduction after 30 months:

- Compared to the projected sham rate at month 30 for the Pooled APL2-304 and APL2-303 mITT population – Study APL2-GA-305 Month 6 Interim Analysis (a linear extrapolation of the sham growth through 24 months as the growth of GA lesion in the pooled sham group through month 24 was approximately linear and the approximate linear behaviour was also observed in the untreated fellow eye through month 24 and month 30):
    - PM: 1.19 mm^2 and PEOM: 1.02 mm^2 (graph shown on left in Figure 28)
- Compared to the untreated fellow eye in bilateral patients with fellow eyes meeting key inclusion criteria at month 30 for the Study APL2-GA-305 mFAS population – Study APL2-GA-305 Month 6 Interim Analysis (a likely conservative estimate of the amount of lesion area saved with treatment considering sham study eyes grew 0.07 mm^2 faster than sham fellow eyes at month 24 in both studies pooled and that if both eyes met criteria the worse eye was selected):
    - PM: 0.99 mm^2 and PEOM: 0.93 mm^2

While an estimate of the lesion size reduction compared to sham was not able to be directly obtained because of the crossover of sham subjects to Syfovre treatment, the results above show retinal tissue preserved with Syfovre reaches or, conservatively, nearly reaches the size that the AHEG considered as clinically relevant by 30 months in this heterogenous patient population as recognized by the divergent position. Furthermore, the amount of PR area preserved after 2 years of treatment with Syfovre was already double the size that the AHEG considered as clinically relevant. With steady GA lesion growth if left untreated and the sustained and increased treatment effect of both PM and PEOM, larger retinal tissue area is expected to be saved with continued treatment.

IV. Syfovre Reduces the Growth of the Scotoma Demonstrating That Preserved Retina is Functional

GA disrupts normal vision and affects daily activities such as reading, driving, and recognizing faces. These impairments can be attributed to:

- the development and expansion of retinal areas of PR death, resulting in impaired sensitivity as lesion progresses, and
- ultimately to scotoma, which is an area of total loss of visual sensitivity.

Microperimetry is a functional test that measures patient-reported perception of light stimuli of variable intensity at defined retinal locations. Changes in the number of topographical test areas without light perception (i.e., scotomatous points) quantify changes in the area of scotoma. During the review process, the CHMP did not recognize the growth of the scotomatous area quantified by microperimetry as a patient-relevant functional endpoint stating that "microperimetry measures effects on the morphological level." The applicant respectfully disagrees with this assessment as a scotoma is a commonly reported symptom by GA patients and would like to point to the AHEG which was of the consensus view that microperimetry will better estimate visual function in GA than BCVA, maximum reading speed, and FRI index endpoints: *"MP is the mapping of retinal sensitivity and allows correlation of anatomical and functional changes so it will better estimate visual function in GA."*

Scotoma measured by microperimetry was also acknowledged by the German Health Technology Assessment (HTA) body, Gemeinsamer Bundesausschuss (G-BA) in an early advice meeting in 2023, to be an appropriate functional and patient-relevant outcome measure. Of note, G-BA had originally not viewed microperimetry as a suitable measure and had not considered scotoma and macular sensitivity to be patient-relevant in a scientific advice meeting in 2018, entirely revising its initial opinion in 2023. This also serves to highlight the evolving science around endpoint measurements in GA and their general acceptance. G-BA also considered the extension of central visual field defect to be a patient-relevant outcome. Lastly, microperimetry was recommended by the CHMP in scientific advice as a functional endpoint to quantify treatment benefit.

A signal of a functional benefit was observed with Syfovre treatment on the prespecified change from baseline in the total number of scotomatous points among the 68 points of the grid at month 24. This finding was revealed through the totality of data from several longitudinal timepoints and as well as additional sensitivity analyses. To confirm the functional benefit with Syfovre treatment finding, Apellis conducted analyses targeting the highest risk area for developing new scotoma (ie, the junctional zone). The totality of analyses demonstrated a positive treatment effect with both Syfovre treatment groups in the reduction of new scotomatous points in the junctional zone (Figure R30). While post hoc, the positive trend observed here is biologically plausible (Pfau et al. 2019) based on the demonstrated reduction in GA lesion growth leading to reduced retinal cell death, consistently observed in both PM and PEOM and thereby corroborates the signal of a functional benefit in the prespecified endpoint covering all 68 points of the grid. The functional benefit observed in the junctional zone also indicates that the preserved retina retains light sensitivity. Therefore, reduction in lesion growth corresponds to a reduction in the number of new areas of a complete loss of retinal sensitivity providing patient-relevant clinical evidence of the benefit of slowing GA lesion growth rate. Overall summary of the scotomatous points analyses is presented in Figure R30.

In conclusion, scotoma is a commonly reported and relevant symptom of GA that affects daily activities of patients. A clear, robust, and consistent trend in treatment benefit of Syfovre on growth of the scotoma as quantified by the number of scotomatous points across the entire macula or within the junctional zone of the lesion was observed.

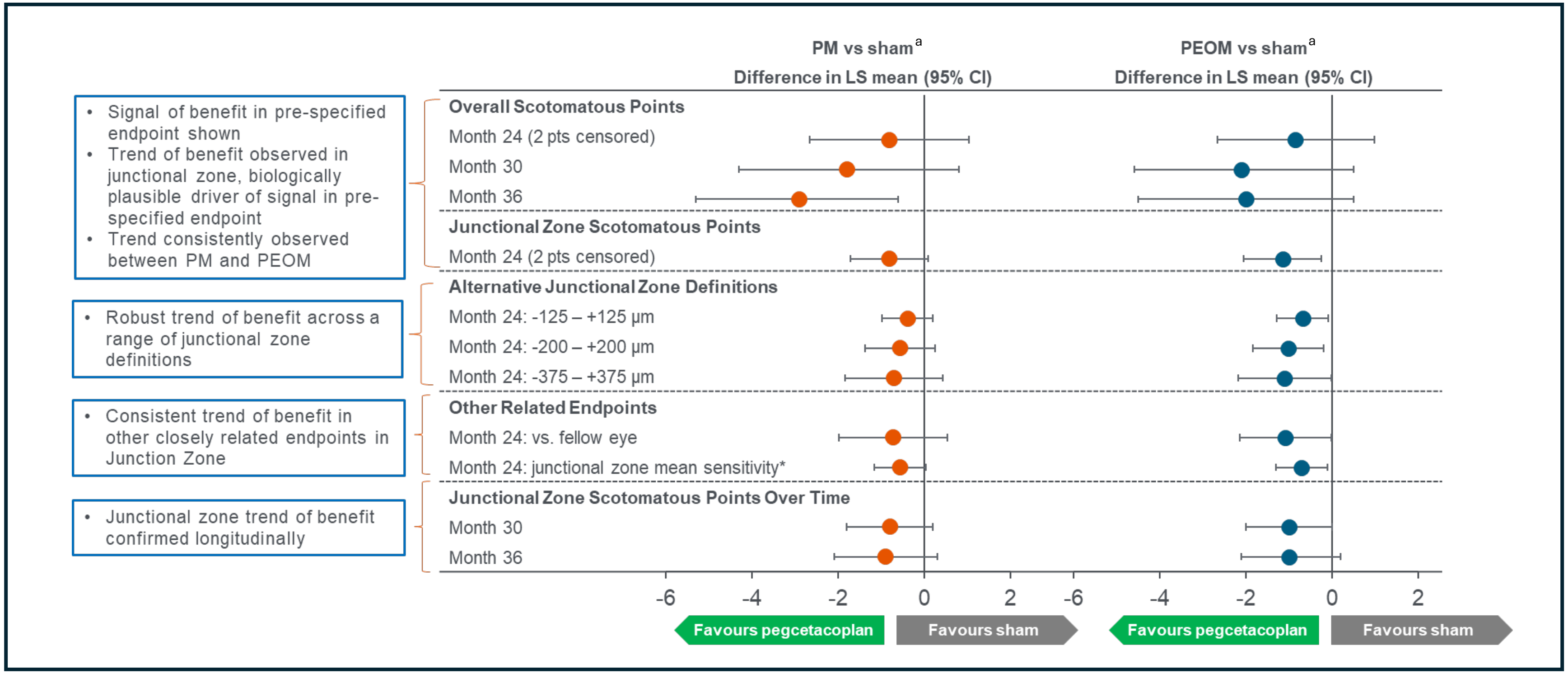


Figure 30: Overview of treatment benefit with Syfovre on the reduction in the development of new scotomatous points

Abbreviations: LS = least-square; MMRM = mixed-effect model for repeated measure; PEOM = Syfovre (pegcetacoplan) every other month; PM = Syfovre (pegcetacoplan) monthly.

[a] Through month 24, sham refers to the sham pooled group. For months 30 and 36, sham refers to the sham pooled to Syfovre group where subjects crossed over to Syfovre and received 6 and 12 months of treatment.

*Junctional zone mean sensitivity reversed to present forest plot interpretation (favors Syfovre or sham) in a single direction.

Notes: LS means estimated from MMRM analysis. Patients in the modified intent-to-treat population who had a baseline and ≥1 postbaseline value through the corresponding visit for corresponding endpoint were included in the analysis. The fellow eye analysis includes subjects with bilateral GA with the fellow eye meeting key inclusion criteria. Two patients censored refers to the sensitivity analyses with 2 spurious month 24 assessments in the PM group censored. Junctional zone was defined as −250 µm inside baseline atrophy border to +250 µm outside atrophy border.

Source: Study APL2-304; Microperimetry Statistical Report APL2-304EFF02 Post Hoc; Integrated APL2-304 and APL2-GA-305 Month 30 Analysis; Integrated APL2-303, APL2-304, and APL2-GA-305 Month 36 Report.

V. Syfovre Delays Disease Progression to Severe Visual Impairment

Scotomas in central visual field, severe visual impairment and blindness have a profound impact on the quality of life. In the case of older adults, vision impairment can contribute to social isolation, difficulty walking, and a higher risk of falls and fractures. This leads to a greater dependency on supportive care and an increased likelihood of early entry into nursing or care homes (Ehrlich et al. 2021).

Severe visual impairment occurs when the scotoma encroaches the centre of the fovea, ie, when light perception is lost in the central 2 or 6 degrees of the visual field (Sunness et al. 1997). The event of loss of light perception in the central 2 or 6 degrees of the visual field, the area responsible for the sharpest vision, results in a profound reduction in visual function. For example, patients with loss of central light perception are more likely to report an inability to recognize faces (Wallis et al. 2014).

The occurrence of these events was associated with a greater vision loss compared to cases where these events did not occur (6.8 and 6.4 ETDRS letters of BCVA, respectively). The ability of Syfovre to prevent the progression of severe visual impairment was shown by reduction in the risk for treated patients to lose light sensitivity in the central 2 degrees (central 4 points) and 6 degrees (central 16 points) of the retina using microperimetry. Syfovre treatment with PM and PEOM regimen corresponded to a 34% and 36% risk reduction in the central fovea (central 4 points) and to a 43% and 48% risk reduction in the fovea (central 16 points) compared to the sham-pooled treatment group after 24 months, respectively (Figure R29). Similar results were observed 12 months later at integrated month 36 showing the robustness of Syfovre to reduce the risk of developing severe visual impairment.

In addition, a combined analysis of patients from Studies APL2-304 and APL2-303 showed trend of a reduced risk of developing sustained visual acuity of less than 35 letters, the WHO definition of severe visual acuity impairment, for subjects treated with Syfovre vs sham (Figure 31), although not confirmed beyond month 24 after subjects in the sham treatment group were treated with Syfovre for 12 months.

In conclusion, severe visual impairment has a profound impact on the quality of life in older patients. Syfovre has shown a reduction in the risk of progression to loss of light perception in the central area of the fovea most relevant for visual function as well as an early trend in reducing the risk of progression to severe vision loss (35 letters in BCVA).

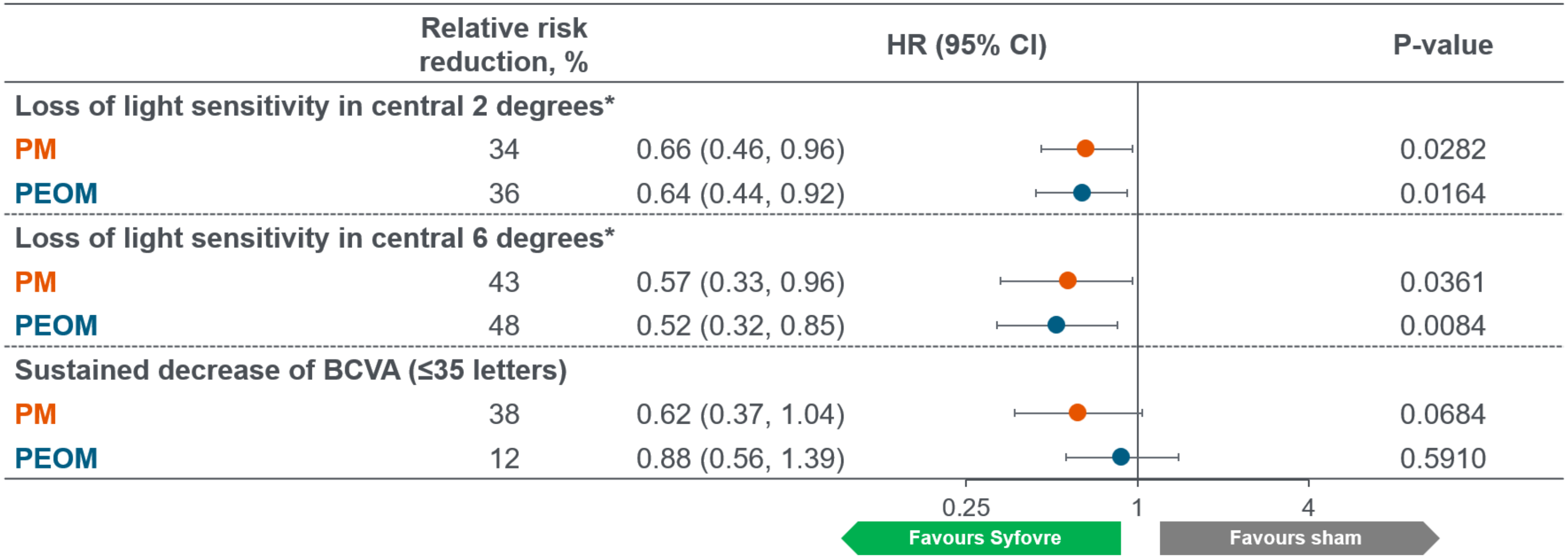


Figure 31: Reduction of risk of progression to severe vision impairment

Abbreviations: BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; HR = hazard ratio; PEOM = Syfovre (pegcetacoplan) every other month; PM = Syfovre (pegcetacoplan) monthly

* Defined as a complete loss of light sensitivity in the 4/16 assessed microperimetry points in the central 2/6 degrees of the fovea.

Notes: Post hoc analysis *P* values are nominal. Hazard ratio estimated from Cox proportional hazards model, including patients in the modified intent-to-treat population at risk for the event with ≥1 postbaseline assessment. Analyses of the central 2/6 degrees are in Study APL2-304 and the analysis of sustained BCVA ≤35 ETDRS letters is in the pooled Studies APL2-304 and APL2-303. The first observed postbaseline assessment with 4/16 central scotomatous points is counted as the event in the analyses of loss of light sensitivity. For sustained BCVA ≤35 ETDRS letters, an event was defined as the first time a subject experienced a sustained reduction below 35 ETDRS letters for at least 4 months postbaseline (including both scheduled and unscheduled visits) and without a later recovery to ≥40 ETDRS letters at a subsequent assessment.

Source: Study APL2-304, Pooled APL2-304 and APL2-303.

VI. Why did the Pre-Specified Key Secondary Functional Endpoints Not Demonstrate a Treatment Benefit

The applicant acknowledges that in studies APL2-304 and APL2-303, no meaningful differences were observed in the prespecified key secondary functional endpoints of mean change from baseline in normal luminance BCVA, maximum reading speed, FRI score, and mean threshold sensitivity through month 24 for the Syfovre treatment groups compared to sham.

However, in the applicant's view, an analysis of the mean changes in these secondary endpoints does not take into account the heterogeneity of the GA patient population recruited in the 2 pivotal studies, as recognized by the AHEG, and the established weak correlation between lesion size and measures of central vision such as BCVA, maximum reading speed (MRS), and FRI. At the time these studies were designed, there was limited understanding of functional endpoints relevant to GA clinical trials.
The weak correlations between GA lesion growth and change from baseline in NL-BCVA, MRS and FRI observed in these studies along with acknowledged variability inherent in these measurements indicates that these endpoints are not the most predictive or relevant. The AHEG convened in June stated that "Experts do not agree that visual function endpoints such as BCVA, MRS, FRI index are the most relevant endpoints representing a patient benefit in this context…BCVA results can be impacted by confounding factors in patients, e.g. fatigue, cognition." In spite of this feedback from the AHEG, the final CHMP assessment report still insisted that "at least some effect of treatment on these outcomes would have been expected to be observed."

As noted, lesion growth and change in BCVA are not well correlated. It is known that functional vision loss in GA patients is complex and that central vision, which BCVA measures, is often only impacted when the lesion encroaches partially or fully on the central fovea. For this reason, and others mentioned below, the applicant would not expect to see a treatment effect on the difference in mean change from baseline in BCVA. This was also the position of the June AHEG. Because BCVA is a valid measure of central vision, its use in understanding and quantifying the impact on visual function of conversion to scotoma of the central 2 degrees of the retina (i.e., the central fovea) is meaningful and informative. The applicant found that those patients who converted to complete scotoma lost on average 6.8 more letters BCVA than those patients who did not. A similar difference was observed for those patients who converted to complete scotoma in the central 6 degrees (ie, the full fovea).

Therefore, it is the position of the applicant that despite these limitations the risk/benefit of Syfovre can be evaluated and remains positive.

VII. Limitations of BCVA Change as an Endpoint to Assess Treatment Benefit in GA

BCVA is a measure of central vision and is used as a key functional assessment of efficacy and safety for multiple ophthalmic treatments. It reflects in retinal diseases mainly the functional integrity of the fovea. However, as discussed extensively above, GA impacts a broader region of the retina resulting in scotoma and other visual disturbances and the fovea is often only impacted very late in the disease (foveal spearing), hence central vision as assessed by BCVA cannot be considered as a comprehensive method to capture the impact of GA on visual function.

The fovea has the highest optical resolution and is the original preferred retinal locus (PRL) for high resolution tasks. When the fovea is impacted by GA lesion growth, patients have the ability to develop a new (or alternative) PRL therefore adapting to the disease progression. Once the new preferred locus is assigned, the BCVA findings are now determined by the functional state and concentration of healthy PRs in the new PRL (Li et al. 2021; Sunness et al. 1996). However, the BCVA at the new PRL remains modifiable: first, lesion growth can affect the new PRL leading to functional loss and second, the vision originating from the new PRL can be significantly improved through training. This latter part is commonly used in low vision training, in which patients frequently experience an improvement of up to 3 lines of BCVA (Zaky et al. 2020).

Therefore, this metric of mean change in BCVA in a broad heterogeneous population presenting with variable disease states is inadequate to fully capture vision loss in GA and is not sensitive to detect a therapeutic effect even though such an effect was observed in lesion growth, microperimetry endpoints as well as sustained loss of visual acuity (severe visual acuity impairment).

Particularly, the 2 Studies APL2-304 and APL2-303 recruited a heterogenous population representing patients presenting at different stages of lesion growth and with different lesion types. In Studies APL2-304 and APL2-303, the patient population was broadly similar to real-world presentation where GA lesion size is variable, could be subfoveal (involving the fovea) or nonsubfoveal, unifocal, or multifocal. Lesions involving the fovea or close to the fovea may show changes in BCVA while lesions sparing the fovea or patients changing their PRL may not have a significant change. As shown in Figure 32 (A) below, although mean BCVA decreases with increasing lesion size, in heterogenous populations, it is variable for the same GA lesion size and large change in lesion growth is required to observe a mean change in BCVA. The mean difference between lesions that are <2.5 mm^2 in size and lesions that are 2.5 to 7.5 mm^2 is about 10 letters. However as can be seen from the box plots, the variability within each lesion size is greater than the mean difference.

Similarly, the mean difference between lesions that are 2.5 to 7.5 mm^2 and lesions that are 7.5 to 12.5 mm^2 is 7 letters with greater difference within each lesion size. The change in BCVA reaches a plateau after lesion size of 12.5 to 25 mm^2 possibly illustrating the effects of foveal sparing or alternate PRL. Figure 5 B illustrates the change in BCVA in individual patients with GA over time. Although there is a mean decrease over time, there is a significant difference among patients reflecting the heterogeneity of GA. Some patients show rapid decline in BCVA while others show little or no change even after 96 months of follow-up. After 24 months of follow-up, the mean change in BCVA was 0.181 logMAR or 9 letters which is in the same range as that observed in the sham treatment group of Studies APL2-304 and APL2-303 (pooled).

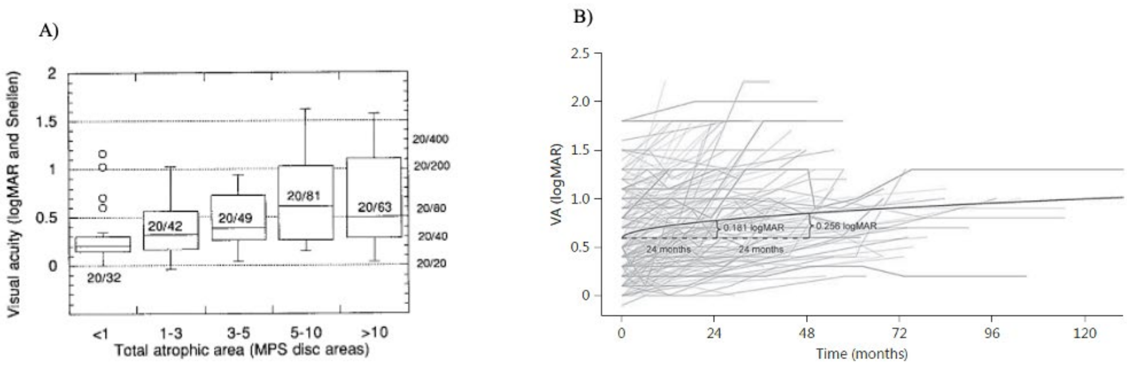


Figure 32: High variability in BCVA assessment within and between lesions of different sizes

A) Mean change in BCVA with increasing lesion sizes (Sunness et al. 1999a).
B) Change in BCVA in individual patients over time (Schmitz-Valckenberg et al. 2016b).

Therefore, the metric of mean change in BCVA in a broad heterogenous population presenting with variable disease state may not be able to detect a therapeutic effect even though such an effect is observed in lesion growth.

In Studies APL2-304 and APL2-303, BCVA and GA lesion size correlated weakly (spearman partial correlation −0.1494, *P* <.001) and this was in agreement with several previous studies that showed similarly weak correlation between BCVA and GA lesion growth, and a high intra-subject test-retest variability of up to 11 to 15 letters between tests in patients with GA (Patel et al. 2008; Heier et al. 2020). GA lesion CFB (Mean ±SE) in the Geographic Atrophy Progression Study (Schmitz-Valckenberg et al. 2016a) was 1.85 ± 0.1 mm^2 and the mean decrease in BCVA was 6.2 ± 15.6 letters at 12 months. Schmitz-Valckenberg and colleagues (2016a) modelled VA in GA based on the FAM study (Holz et al. 2007; Fleckenstein et al. 2011) and noted an association between lesion growth and VA with an average of 1 to 4.5 letters decrease for each millimeter of square root transformed GA size depending on foveal involvement.

Mean BCVA showed an expected general trend of decline over time from baseline. The CFB in BCVA in the pooled data from Studies APL2-304 and APL2-303 was (mean ± SE) −7.889 (0.7355), −8.830 (0.7365) and −6.940 (0.7373) letters for PM, PEOM, and sham pooled, respectively. The decline of only 2.6 letters after 12 months of follow-up and 6.94 letters after 24 months in sham pooled group was mild in this elderly patient population especially compared to other interventional and natural history studies. In the Chroma and Spectri trials (Heier et al. 2020), the mean decline in NL-BCVA in the sham group after 12 months was 4.9 letters. In the Proxima A clinical trial, which was a prospective, noninterventional, observational study (Holekamp et al. 2020), the adjusted mean (SE) decline in BCVA at 24 months was 13.88 (1.40) letters.

These limitations were evident in Studies APL2-304 and APL2-303 where a lack of mean BCVA decline in the first 5 to 6 months in sham pooled group were shown while there was lesion growth during this time. There were also fluctuations in mean BCVA between months 22 and 24 in the sham pooled group.

Due to these limitations, mean BCVA change is not a valid endpoint to assess treatment effect on function in GA. In contrast to GA, wet AMD is exudative and leads to disruption of central retinal architecture, showing a significant decline in BCVA and consequently significant transient therapeutic effect with treatment because it restores retinal architecture by removing the fluid. Therefore, GA and wet AMD must be viewed distinctly in terms of disease pathophysiology, treatment goals and suitable endpoint measurements.

Such observations led a panel of experts in ophthalmology clinical research discussing clinical trial design and endpoints to conclude that slowing GA lesion growth is an optimal endpoint for therapy because it can be measured using objective and reliable measures from retinal imaging (Csaky et al. 2008; Csaky et al. 2017). BCVA is valuable for monitoring significant vision changes over time, especially related to central vision loss, but it is less suitable for detecting small or early changes in lesion size or disease status due to its inherent variability and the nature of GA progression. The AHEG convened in June stated that "Experts do not agree that visual function endpoints such as BCVA, MRS, FRI index are the most relevant endpoints representing a patient benefit in this context…BCVA results can be impacted by confounding factors in patients, e.g. fatigue, cognition." In spite of this feedback from the AHEG, the final CHMP assessment report still insisted that "at least some effect of treatment on these outcomes would have been expected to be observed."

It should be noted that within the 2018 Scientific Advice procedure (EMEA/H/SA/3633/2/2018/SME/II), the CHMP noted the limitations of BCVA due to a lack of sensitivity in assessing disease progression within a suitable timeframe. In this Scientific Advice, the CHMP said itself that "It is acknowledged that best -corrected visual acuity (BCVA) may not be sensitive enough to assess disease progression within a reasonable time frame." Also, there are a number of publications that reference the lack of sufficient sensitivity in clinical endpoints such as BCVA and visual field, once again citing the long duration of trials and the high number of patients who would be required to evaluate efficacy (Wickström and Moseley 2017; Csaky et al. 2017). This is in agreement with the AHEG feedback.

In consultation with patient representatives, Apellis has repeatedly been advised that BCVA change is considered a too narrow definition of patient benefit, and that a broader consideration of visual function would be desired (Apellis Patient Expert Advisory Council, July 2021 and September 2023, notes on file). In agreement with the need for the development of additional clinical endpoints for GA, the EMA has published a letter of support for the MACUSTAR programme for biomarker and novel clinical endpoint development in intermediate AMD; of note, microperimetry is highlighted as one of these candidate clinical endpoints (Rasi 2018). In their scientific advice, the CHMP supported the fact that microperimetry provides a sensitive measure of visual function in GA.

In agreement with obtained advice and experts' statements, it is the applicant's opinion that the impact of Syfovre on central vision can be best captured by assessing the risk of progressing to severe visual impairment of <35 ETDRS letters, however this event is rare during a 2-year clinical trial period and has limited opportunity to show separation between arms. This assessment based on an absolute, clinically meaningful and widely accepted threshold of BCVA avoids the variability in how vision is lost by lesion growth and rather quantifies benefit in the form of preventing severe visual impairment as an outcome.

In summary:

1. Mean change in BCVA is not appropriate to assess treatment effect in GA patients. This was affirmed by the AHEG and is the reason FDA considers lesion growth alone sufficient.
2. In Studies APL2-303 and APL2-304 the sham pooled group only lost 6.94 letters after 24 months. This is far less than would have been expected based on other observational and

interventional studies where the loss ranged from 4.9 letters after 12 months (Heier et al. 2020) and 13.88 letters after 24 months (Holekamp et al. 2020).

3. There was a lack of mean BCVA decline in the first 5 to 6 months in sham pooled group while there was lesion growth during this time. This is a surprisingly unexpected result in a progressive disease and based on natural disease progression.
4. In addition, it is not explainable why the mean change in BCVA in the sham arm improved from month 22 to 24.
5. GA lesion growth is weakly correlated with the change in BCVA after 24 months (spearman partial correlation = −0.1494). This means change in the growth of the lesion after 2 years explains roughly 20% of the BCVA change or approximately 2 letters in the sham pooled group. It is difficult to ascertain the cause for the decline of the remaining 5 letters. Therefore, it is not surprising that no treatment effect may be observed when the signal we can potentially impact is approximately 2 letters of BCVA after 24 months.

In conclusion, mean CFB in BCVA is not an appropriate metric to assess treatment benefit in a broad heterogeneous GA population. BCVA is effective in detecting sustained severe visual impairment, eg, 35 letters.

An in-depth discussion of the limitations of MRS, FRI and other prespecified microperimetry endpoints can be found in the LoOI.

VIII. Observed Effects on Functional Endpoints by Syfovre are Clinically Meaningful, Patient-Relevant, and Reliable

As stated in the Negative Opinion, the CHMP concluded that while an effect on slowing GA lesion growth was demonstrated with Syfovre, this effect did not translate into a patient-relevant clinical benefit. The applicant respectfully disagrees with the CHMP and maintains that an effect on slowing GA lesion growth with Syfovre does bring a clinically meaningful patient-relevant benefit on functional endpoints.

IX. Evidence of a Benefit in Slowing the Lesion Growth on Functional Endpoints

GA patients experience symptoms of functional vision loss such as scotoma, difficulties in recognizing objects and faces, distorted images, as well as difficulty in reading, driving, and night vision (Sadda et al. 2016; Taylor et al. 2018; Taylor et al. 2017; Caswell et al. 2021). These symptoms are consequences of the developing area of scotoma, ie, an area of the visual field with no light perception that eventually leads to severe visual impairment.

Across the totality of analyses, treatment with both Syfovre monthly and every other month resulted in a positive trend in the reduction in the number of new areas of a complete loss of retinal sensitivity providing patient-relevant clinical evidence of the benefit of slowing GA lesion growth rate. This trend was observed across both the prespecified area of the macula as well as the most pathophysiological active area of the macula, the junctional zone.

Development of scotoma in the fovea is a vision impairment that eventually progresses to severe vision impairment and blindness. The ability of Syfovre to prevent the progression of severe vision impairment was shown by reduction in the risk for treated patients to lose light sensitivity in the central 2 degrees and 6 degrees of the retina using microperimetry as well as in developing sustained visual acuity of less than 35 letters, although the latter was not confirmed beyond month 24 after subjects in the sham treatment group were treated with Syfovre for 12 months.

The applicant acknowledges that a continuous change compared to baseline was observed on BCVA, reading speed, FRI, and microperimetry mean sensitivity, but no treatment benefit was demonstrated with these prespecified key secondary endpoints between PM, PEOM, and sham pooled after 24 months.

However, the lack of a treatment effect on these measures is not a conclusion of lack of patient-relevant benefit, but rather a reflection of variability and neurological plasticity that render subjective assessments of changes in these measures in the totality of a heterogenous population difficult. This was acknowledged by the AHEG as they noted that BCVA results can be impacted by confounding factors (eg, fatigue, cognition) in patients. The literature describes these measures as noisy outcomes that lack sensitivity to detect small changes from baseline in this population that is slowly progressing with islands of visual loss and foveal sparing (Sunness et al. 2008; Patel et al. 2008; Subramanian and Pardhan 2009; Holz et al. 2014; Csaky et al. 2019; Dunbar et al. 2022). The AHEG did not agree that visual function endpoints such as BCVA, MRS, and FRI index are the most relevant endpoints representing a patient benefit in the GA secondary to AMD population.

Topographical evaluation of complete loss of light sensitivity with microperimetry and the risk to severe, sustained vision impairment appear to be more appropriate measures of assessing the treatment benefit of a therapy in GA.

X. Reliability of the Benefit in Slowing the Lesion Growth on Functional Endpoints

Evidence of a benefit on functional endpoints with Syfovre was primarily based on scotomatous areas assessed with microperimetry, which was measured in a single study. In the negative opinion the main concern raised by CHMP on this evidence was the questionable reliability of the results from analyses based on scotomatous areas in demonstrating a true treatment effect. The applicant believes the results provide reliable evidence of a patient-relevant benefit in slowing the lesion growth and the rationale is explained below.

- **Biologically plausibility of results**

GA lesion growth represents RPE and PR death. These cell deaths result in formation of scotoma and loss of visual field. The area where lesion grows into is at risk for developing scotoma due to GA progression. The area outside lesion growth is less active and less likely to develop scotoma, and therefore is of less interest clinically.

It is reasonable to expect that a treatment reducing GA lesion growth and preserving functional retinal tissue will reduce the number of new scotomatous points, particularly in the junctional zone area. A reduction in lesion growth did lead to a signal of a functional benefit observed in the prespecified endpoint of the number of scotomatous points across all 68 points with the confirmation of a functional benefit coming from more refined post hoc analyses of the junctional zone showing an enhanced benefit of treatment.

When junctional zone overlaps with the central areas of the fovea, it is also reasonable to expect that a treatment reduces the number of new scotomatous points in the central areas of the fovea. A treatment benefit that favours Syfovre in delaying the progression of all points to scotomatous was observed in both the central 2 and central 6 degrees of the fovea.

In addition, GA lesion growth showed the highest correlation with the number of scotomatous points in this study, and the finding is consistent with those observed in prior large clinical trials that evaluate

IVT lampalizumab in GA (Heier et al. 2020; Chang et al. 2023), providing further rationale why it is plausible to expect changes with reduced lesion growth.

Overall, the biological plausibility of the treatment benefit in the reduction of the areas of scotoma with the slowing of lesion growth supports the conclusion that this positive benefit of PM and PEOM treatment with Syfovre is credible.

- **Robust across multiple analyses**

The signal of a positive benefit on scotoma across all 68 points in the PEOM group in the prespecified analysis was supported by the results from the analysis where 2 clinically spurious points in the PM group were censored and by additional analyses that investigate the impact of outliers, which show that there is a signal of functional benefit in both PM and PEOM groups at month 24. The treatment effects on scotoma in the junctional zone with both PM and PEOM were shown across multiple sensitivity analyses including different definitions of the junctional zone, in a comparison to the fellow eye, as well as the closely related endpoint, junctional zone mean sensitivity. For severe visual impairment as assessed by microperimetry, treatment effects were shown across different areas of the centre of the fovea (central 2 degrees and central 6 degrees) for both PM and PEOM. Similar findings across multiple sensitivity analyses showed the robustness of the finding of a positive benefit with Syfovre for both PM and PEOM treatment.

- **Confirmed longitudinally**

Treatment effects on scotoma and severe visual impairment as assessed by microperimetry were shown across multiple time points in the extension study, confirming the finding of a positive benefit with Syfovre for both PM and PEOM treatment at month 24.

- **Consistent across posologies**

Treatment effects observed across the totality of the analyses on visual function were generally consistent between PM and PEOM treatment posologies, providing credibility that a patient benefit was observed.

It is acknowledged that a clear dose-response signal was not observed and, in some analyses, results numerically favored PEOM compared to PM. First, given the numerically small differences between PM and PEOM treatment on slowing lesion growth, an objective anatomical endpoint without patient input, a clear dose-response signal should not be expected on patient-perceived functional endpoints nor should a clear dose-response be expected on a discrete endpoint measuring a complete loss of light sensitivity. Second, the confidence intervals for the estimates of treatment difference for PM and PEOM compared to sham pooled overlapped considerably showing a similarity in the estimate of the treatment effect of the functional benefit. Third, for the number of scotomatous points analyses at month 24, this is arguably the longitudinal timepoint with the largest dose-response inconsistency between PM and PEOM. The applicant believes the magnitude of the treatment effect estimate in the PM group was impacted by clinically spurious assessments which was supported by an investigation into the impact of all outlier assessments as presented in Table R84 and Table R85 of the EMA Summary of Additional Sensitivity Analyses (29 May 2024) report. In these analyses, the estimate of the magnitude of treatment benefit is nearly the same for both PM and PEOM providing support that there is a consistent finding across both posologies. Overall, the consistent treatment effect observed between PM and PEOM across analyses support the credibility of the positive benefit with Syfovre for both PM and PEOM treatment.

- **Conclusiveness of treatment benefit**

At the time of study design, microperimetry was not widely available and due to logistical reasons, microperimetry was only included in the APL2-304 study. Despite the fact that only APL2-304 measured microperimetry, the effect on lesion growth with Syfovre was demonstrated across both PM and PEOM treatment frequencies and replicated in both APL2-304 and APL2-303. Given the established effect on lesion growth with both PM and PEOM treatment, microperimetry that was assessed in 2 separate Syfovre treatment frequencies within the single study, the moderate correlation between lesion growth and the number of scotomatous points, and the finding of a consistent and robust favorable effect on function with both PM and PEOM treatment across multiple analyses over several longitudinal time points, the finding of a beneficial functional effect with a slowing of lesion growth has been shown with the available data.

In conclusion, the applicant believes the results provide reliable evidence of a patient-relevant benefit in slowing lesion growth. While the evidence comes from analyses of a lower ranked endpoint than BCVA, reading speed, FRI, and mean sensitivity as well as post hoc analyses, the analyses and results are scientifically and medically sound, represent the most up-to-date knowledge in GA research, and come from microperimetry which the AHEG acknowledges as a better estimate of visual function in GA.

XI. Meaningfulness of a Benefit in Slowing the Lesion Growth on Functional Endpoints

The general impact of GA progression on quality of life has been studied (Caswell et al. 2021; Künzel et al. 2020); however, the applicant is not aware of a study that specifically assesses the impact of the scotoma progression on patient wellbeing. However, such studies have been conducted in glaucoma in which the location and extent of damage to the visual field was found to correlate with the quality of life (Moghimi et al. 2023; Chun et al. 2019). It is therefore the applicant’s position that preventing any loss of visual field, defined as new area or growth of existing area of scotoma, is considered clinically meaningful as the new area of scotoma represents loss of corresponding visual field and expansion of dark regions in patient’s vision, further affecting their quality of life.

The CHMP concluded that there is no reasonable understanding of the minimum clinically relevant effect size for microperimetry endpoints. The June 2024 AHEG also expressed the desire for further information on the correlation between microperimetry sensitivity and patient-perceived visual function: “*It is not clear at what stage of MP sensitivity loss patients can perceive changes in their visual function. It would be valuable to gain more information on the correlation between MP sensitivity and patient-perceived visual function to better understand the patient benefit of the treatments.”* As such, CHMP questioned the clinical meaningfulness of the magnitude of the amount of new area of scotoma (roughly 1 scotomatous point compared to sham after 24 months). The applicant believes the challenge with establishing a minimum clinically relevant effect size is the heterogeneity of the disease based on the location of the lesion with respect to the fovea and the cumulative accumulation of the area of scotoma. To best demonstrate the impact of location and cumulative accumulation, microperimetry points in the foveal areas can be used.

When considering the central 4 points that represents the central 2 degrees, it was observed at baseline that NL-BCVA decreases systematically with increasing number of scotomatous points among the central 4 with each additional scotomatous point corresponding to approximately 5 fewer Early Treatment Diabetic Retinopathy Study (ETDRS) letters , which is clinically meaningful. In addition, participants who progress to have 4 central scotomatous points on study have a worse visual function outcome over 2 years than subjects who did not, losing, on average, an additional 6.8 ETDRS letters. These analyses show that the effect of an additional scotomatous point in the central 2 degrees is greater than the magnitude of difference that was established as non-inferiority margin of 4 letters in anti-VEGF studies for nAMD (Dugel et al. 2020).

When considering the central 16 points that represents the central 6 degrees, it was observed at baseline that NL-BCVA generally decreases with an increasing number of scotomatous points among the central 16, with accelerating decline in NL-BCVA after loss of 13 points, indicating a "cliff effect." The range of difference in means among subjects with 0-13 scotomatous points was 12.2 ETDRS letters whereas the range of means among subjects with 13 to 16 scotomatous points was 19 ETDRS letters. In addition, participants who progress to have 16 central scotomatous points on study have a worse visual function outcome over 2 years than subjects who did not, and lose on average an additional 6.4 ETDRS letters. These analyses show that an additional scotomatous point in the central 6 degrees may not be correlated with a meaningful difference in BCVA until the number of scotomatous points accumulate. As such, it does not allow for a clear definition of the minimum clinically meaningful difference for this endpoint. A more interpretable approach for quantifying the magnitude of benefit with microperimetry could be the progression to severe visual impairment in the areas of the fovea.

As stated above, participants who progress to have 4 and 16 central scotomatous points on study lose on average an additional 6.8 and 6.4 ETDRS letters than subjects who did not. Additional support that events are patient-relevant can be observed based on the NEI VFQ-25 composite score. At month 24, subjects with a central 4/16 event lost, on average, an additional 0.4/4.0 points of NEI VFQ-25 composite score than subjects without the event.

In addition, subjects with a central 4/16 event were more likely to experience a drop of at least 15 points (15% of the NEI VFQ-25 scale), a noticeable change per IQWiG 2023 after 24 months than subjects without the event (central 4 with event/without event: 27.7%/19.6%; central 16 with event/without event 34.8%/21.3% [Study APL2-304]).

Treatment with PM and PEOM corresponded to 34% (hazard ratio [95% CI]: 0.66 [0.46-0.96]) and 36% (hazard ratio [95% CI]: 0.64 [0.44-0.92]) reduction in the risk of conversion of all central 4 points in the study eye to scotoma when compared to the sham-pooled treatment group after 24 months. In addition, treatment with PM and PEOM corresponded to 43% (hazard ratio [95% CI]: 0.57 [0.33 to 0.96]) and 48% (hazard ratio [95% CI]: 0.52 [0.32 to 0.85]) reduction in the risk of conversion of all central 16 points in the study eye to scotoma when compared to the sham-pooled treatment group during the same timeframe. It is the applicant's belief that the percent reductions observed with Syfovre treatment in the risk of these consequential events is considered clinically meaningful.

XII. Conclusion on Clinical Relevance of Functional Benefit

In conclusion, the applicant maintains that an effect on slowing GA lesion growth with Syfovre does bring a clinically meaningful patient-relevant benefit. A signal of a functional benefit was observed in the prespecified endpoint of the number of scotomatous points covering all 68 points of the grid. Post hoc analyses in the junctional zone and fovea confirmed the patient-relevant benefit of slowing lesion growth. The applicant believes the results from the totality of the analyses of scotomatous areas provide reliable evidence of a patient-relevant benefit in slowing lesion growth. While the evidence comes from analyses of a lower ranked endpoint than BCVA, reading speed, FRI, and mean sensitivity as well as post hoc analyses, the analyses and results are scientifically and medically sound, represent the most up-to-date knowledge in GA research, and are based on microperimetry assessments which the AHEG acknowledges as a better estimate of visual function in GA. With regards to the magnitude of benefit, it is the applicant's belief that the percent reductions observed with Syfovre treatment in the risk of the consequential events of severe visual impairment as assessed by loss of foveal sensitivity (central 4 and central 16 points becoming scotomatous) is considered clinically meaningful.

XIII. Adequate Evidence Provided to Reach Conclusion of a Positive Benefit with Syfovre

To support the grounds for re-examination, Apellis would like to recall regulatory guidance provided by the CHMP during the 2018 Scientific Advice as it is relevant to the clinical data and analyses presented in support of the initial dossier, the responses to the CHMP's List of Questions, LoOI, and in both Oral Explanation meetings (December 2023 and June 2024). In response to the CHMP's scientific advice and considering the evolving scientific landscape surrounding the treatment of GA, the applicant wishes to highlight that it met the regulatory expectations outlined in the 2018 Scientific Advice (EMEA/H/SA/3633/2/2018/SME/II). The below summary describes that based on the scientific advice given there was no expectation to see statistically significant differences in the prespecified secondary endpoint outcomes, simply put, the expectation was that an effect on lesion growth reduction would translate into some effect/trend on visual function parameters. In the advice, the CHMP stated that:

> "*the use of GA area (as measured with FAF, see the following question) as a primary efficacy variable could be acceptable, provided it can be justified that it represents a valid surrogate measure for visual function, or prevention of progression of AMD. This justification could be based partly on literature demonstrating the prognostic value of GA area on visual function. In addition, to support the prognostic value and relevance of the change of the lesion, evidence from the pivotal studies showing at least a positive trend of treatment on visual function parameters would be needed. In a future MAA, a dedicated and profound discussion on the clinical relevance of the morphological improvement needs to be provided.*"

With this advice, the CHMP did not express an expectation that statistically significant results be shown, but rather that an effect on the growth of GA lesions should translate into a trend on visual function parameters, without a specification of which parameter.

Within the 2018 Scientific Advice, the CHMP agreed that the primary endpoint for the studies, change from baseline in GA lesion area, would be appropriate "*if Apellis justified in the MAA that this represents a valid surrogate measure for visual function or AMD progression.*" With respect to the visual function surrogate, the CHMP noted that this "*justification could be based on*

- *literature demonstrating the prognostic value of GA area on visual function, or*
- *evidence from the studies showing at least a positive trend of treatment on visual function parameters"*

XIV. Lesion Area as "Valid Surrogate Measure for Visual Function"

With respect to justifying that the lesion growth represents a "valid surrogate measure for visual function," the 2018 Scientific Advice (as described above) required the applicant to draw upon both relevant literature and data from pivotal studies demonstrating a treatment-induced positive trend in visual function parameters.

The CHMP thus clearly envisaged a possibility of granting approval based on the treatment effect on the GA lesion growth, provided that the prognostic value of GA area on visual function is partly supported by literature and partly supported by a positive trend of treatment on visual function.

For the avoidance of doubt, the applicant would like to mention here that the 2018 Scientific Advice expressly did not limit the source of evidence with respect to showing a positive trend. And it furthermore did not exclude the possibility of providing such data alternatively from either of the pivotal studies, by not expressly asking for evidence from both studies cumulatively.

Within the 2018 Scientific advice, microperimetry was acknowledged by the CHMP as a functional measure and secondary study endpoint, emerged as a key focus in Study APL2-304 due to its sensitivity to detect the local impact of changes in GA lesion growth on retinal light (in) sensitivity in addition to the limitations (in GA) of more traditional visual function endpoints such as BCVA, FRI, and reading speed. Microperimetry parameters have been shown to have a moderate correlation with GA lesion growth in a previous clinical study (Heier et al. 2020). Apellis undertook a comprehensive literature review as requested by the 2018 Scientific Advice and provided a profound analysis of microperimetry data, aiming to fulfil the CHMP's criteria for demonstrating the prognostic value and clinical relevance of lesion changes. As the applicant explained in detail in Section IV and Section V, the pre-specified analysis, change from baseline (CFB) in the number of scotomatous points assessed by mesopic microperimetry over time and the entire grid of 68 points, shows a signal for functional benefit with PM and PEOM treatment, which became more apparent at longitudinal assessments.

Further to the pre-specified endpoint, the applicant's findings from post hoc microperimetry assessments support evidence of a trend, presenting a nuanced understanding of the treatment's beneficial and meaningful impact on visual function, especially in junctional zones and central vision, areas critical for daily living. These analyses supported a consistent trend favouring patient-relevant treatment efficacy in reducing risks for the development of scotomatous points, thereby underscoring the functional benefits of treatment in GA and addressing the CHMP's request for evidence showing a positive treatment trend on visual function.

However, during MAA evaluation, the subsequent request from the CHMP for a definition or justification of a clinically relevant effect size for microperimetry endpoints appeared to represent a shift from the original guidance, focusing on showing a "trend" towards functional improvement. Of note, within the 2018 Scientific Advice, the CHMP did not request confirmatory evidence of a relationship between treatment and visual function to be demonstrated. The CHMP also did not ask for a specific measure of visual function (but did support the choice of secondary visual function endpoints used in Studies APL2-304 and APL2-303) or a minimal effect size, or that the benefit of treatment should be perceptible to the patient. The objective of a treatment of GA with a complement inhibitor is to slow down the degenerative progression, not to revert the process. Indeed, a patient-perceptible benefit of treatment in a chronically degenerative disease such as GA is in principle challenging to demonstrate as the patient cannot know how their disease would evolve without treatment. Scotoma as measured by microperimetry can be viewed as a lack of patient perception of light stimuli and thus as a measure of light insensitivity, as also confirmed by German HTA body, the G-BA in 2023, to further solidify the applicant's understanding of Syfovre's impact on patient-relevant outcomes. Similarly, the CHMP also explicitly characterized microperimetry as a functional measure and encouraged Apellis to use it as a secondary study endpoint in the 2018 Scientific Advice.

Apellis remains committed to addressing these scientific inquiries and emphasize the clinical significance of the applicant's findings and the role of microperimetry in showing the preservation of visual function, as seen in the proposed PAS. Whilst acknowledging the perceived shift in regulatory expectations, Apellis proposes this PAS and aims to engage in further scientific advice to clarify and align on the criteria for further replicating the clinical relevance of the applicant's treatment in the context of GA management.

XV. Applicant's Conclusion: The Scientific Advice Requirement for a Positive Trend on Visual Function Parameters was Shown

Based on the above guidance from the 2018 Scientific Advice with respect to the data required to show a functional "trend," the applicant believes that the negative opinion requested a higher bar or more evidence from the applicant than the intention of the original Scientific Advice request.

While the 2018 Scientific Advice gave guidance to the applicant that a "positive trend of treatment on visual function parameters" would be sufficient, the negative opinion (as summarised in the CHMP Day 210 Assessment Report) with respect to functional benefits asked for "a demonstration of efficacy," for a "true treatment effect," for "confirmation from dedicated studies/ investigations," for "confirmatory evidence," and concluded that all these were not fulfilled by the data submitted by the applicant.

However, the key purpose of a scientific advice meeting is to guide an applicant through the requirements, which need to be fulfilled for successful MA proceedings. In the applicant´s opinion, the submitted data and in particular the post hoc analyses are sufficient to show the "positive trend" as requested in the 2018 Scientific Advice.

Specifically, regarding the point of GA lesion growth representing a valid surrogate measure for visual function; a robust, unequivocal effect on slowing GA lesion growth with increased treatment effects over 24 months with Syfovre has been demonstrated across PM and PEOM groups in Studies APL2-304 and APL2-303. Further confirmation of a treatment effect with Syfovre was shown on RPE and PR loss endpoints using SD-OCT. Microperimetry assessments of overall scotomatous points as well as the junctional zone demonstrate that the preserved retina remains functional. A moderate correlation of 0.5116, ($p < 0.0001$, Spearman partial correlation) between number of scotomatous points and lesion growth was also observed. Given the biological relationship between preservation of retinal cells and visual function and the evidence provided of treatment effects on lesion size, treatment effects on areas of scotoma, as well as their correlation, the CHMP requested evidence of trial level surrogacy has been provided and lesion size can therefore be used to assess the benefit of treatment in this application.

In addition, the applicant is offering to initiate a Post-authorization in order to address any remaining concerns around data replication of microperimetry findings in Study APL2-304.

This concept of generating data (in the context of efficacy) in the post-authorisation setting from the 2018 Scientific Advice, has not been taken into account in the MAA proceedings so far.

In the opinion of the applicant and taking into consideration the requirements of the 2018 Scientific Advice, it would therefore not be reasonable and also not consistent with the previous guidance of CHMP in 2018, to ask for more evidence of functional benefit at this stage of the proceedings.

XVI. Applicant's Conclusion on Clinical Efficacy of Syfovre for the Treatment of GA Secondary to AMD

GA is an irreversible, progressive, bilateral, vision-threatening advanced form of AMD with currently no approved therapy in Europe and represents a high unmet medical need. According to a meta-analysis of observational studies, the prevalence of late AMD in Europeans aged 60 years or older was estimated to be 2.4% (95% CI, 1.8%-3.3%). By 2040, the prevalence of late AMD is estimated to be more than 18 million people globally (Wong et al. 2014) and between 3.9 and 4.8 million people in Europe (Colijn et al. 2017).

GA is a progressive disease that eventually leads to severe visual impairment and legal blindness. Patients experience symptoms of functional vision loss such as difficulties in recognizing objects and faces, scotoma, distorted images, as well as difficulty in reading, driving, and night vision (Sadda et al. 2016; Taylor et al. 2018; Taylor et al. 2017; Caswell et al. 2021). It is characterized by thinning and loss of the RPE and concurrent atrophy of PRs, ie, cells in the retina responsible for vision (Holz et al. 2014; Sunness et al. 1999a; Sunness et al. 1999b).

Clinical Studies APL2-304 and APL2-303, both being randomised, double-masked, sham-controlled phase 3 studies, unequivocally demonstrated a treatment benefit in the reduction of GA lesion growth from both monthly and every other month Syfovre injections. Syfovre showed a consistent and clinically meaningful positive trend in treatment benefit in regards to pathological and functional hallmarks relevant for the commonly reported symptoms of GA, as set out by CHMP in the 2018 Scientific Advice.

Specifically, Syfovre treatment:

- meaningfully reduces the growth of GA lesion as analysed by the CFB in lesion size that is quantified by FAF and OCT imaging modalities
- reduces the growth of the scotoma as analysed by the number of new scotomatous points from baseline over time in the macula and junctional zone, which also indicates that the preserved retina retains light sensitivity
- reduces the risk of progression to severe vision impairment as analysed by the time to complete loss of light sensitivity in the central field of the fovea
- an early trend in reducing the risk of progression to severe vision impairment as analysed by the time to a sustained BCVA at or below 35 letters (definition of severe visual impairment by WHO)

In summary, a positive benefit has been demonstrated with Syfovre treatment with unequivocal evidence of Syfovre slowing GA lesion growth with increasing effects over time. The lesion area preserved by Syfovre treatment is the size that was considered as clinically relevant by the AHEG. Additionally, the preserved retina retains light sensitivity and hence Syfovre treatment reduces growth of scotoma. Syfovre treatment also delays progression to severe visual impairment.

Apellis is proposing to conduct a PAS to replicate the microperimetry findings. The PAS will be a multicentre, randomised, double-masked, sham-controlled phase 3b study to compare the efficacy of Syfovre to sham in patients with GA secondary to AMD.

XVII. Acceptable Safety Profile with IVT Syfovre Treatment

The safety profile of Syfovre is well characterized and acceptable, based on over 44,000 patient-years of cumulative IVT exposure in the clinical and real-world setting (306,000 estimated injections post-approval and 28,000 injections clinical) as of 30 June 2024. Syfovre has demonstrated to be well tolerated and manageable in subjects with GA secondary to AMD through 24 months of treatment (and preliminary data in the long-term extension Study APL2-GA-305). The table below summarises the notable and overall adverse event (AE) differences between treatment groups through 24 months in the pooled Studies APL2-304 and APL2-303. The procedure-related AEs are in line with other IVT-administered drugs.

Table 81: Summary of notable and overall adverse events between treatment groups through 24 months, pool 1—safety population

	PM	**PEOM**	**Sham pooled**
	N = 419 **n (%)**	**N = 420** **n (%)**	**N = 417** **n (%)**
Notable AEs			
Endophthalmitis	2 (0.5)	3 (0.7)	0
Exudative age-related macular degeneration*	51 (12.2)	28 (6.7)	13 (3.1)
Intraocular inflammation*	16 (3.8)	8 (1.9)	1 (0.2)
Optic ischaemic neuropathy	7 (1.7)	1 (0.2)	0
Intraocular pressure increased	**8 (1.9)**	**12 (2.9)**	**3 (0.7)**
Overall			
Study eye AEs	258 (61.6)	231 (55.0)	193 (46.3)
Study eye SAEs	9 (2.1)	6 (1.4)	3 (0.7)
Study eye severe AEs	19 (4.5)	8 (1.9)	5 (1.2)
Study eye AEs related to injection procedure	109 (26.0)	94 (22.4)	71 (17.0)
Study eye AEs related to treatment	51 (12.2)	39 (9.3)	17 (4.1)
Study eye AEs leading to discontinuation	6 (1.4)	6 (1.4)	4 (1.0)

Abbreviations: PEOM = Syfovre (pegcetacoplan) every other month; PM = Syfovre (pegcetacoplan) monthly.
* The following reported terms were combined: exudative age-related macular degeneration (included neovascular age-related macular degeneration and choroidal neovascularization); intraocular inflammation (included vitritis, iridocyclitis, iritis, uveitis, anterior chamber cell, anterior chamber flare, and vitreal cells).

The majority of intraocular inflammation (IOI) events were mild to moderate and were treated with topical steroids. Patients resumed Syfovre once the events resolved. No endophthalmitis events or IOI led to severe vision loss (>30 letters). Most executive AMD (eAMD) events were mild to moderate in severity and no cases were reported as serious. Overall, eAMD patients responded as expected to anti-VEGF treatment with a corresponding decrease in central subfield thickness and central retinal thickness. Changes in BCVA from pre-exudative event to month 24 were similar among patients who developed eAMD. There were no reports of occlusive or nonocclusive retinal vasculitis during the course of the clinical trials. Rare events of retinal vasculitis were observed in the postauthorisation setting in the US. Detailed discussion of safety results was presented.

XVIII. Every Other Month Dosing Regimen Presents a More Favorable Benefit-Risk Profile

The results from Studies APL2-304 and APL2-303 demonstrated that Syfovre administered monthly or EOM provided substantial evidence of clinically meaningful reduction in GA lesion growth as well as benefits in visual function. Syfovre administered monthly and EOM was well tolerated and AEs were manageable. However, patients in the monthly arm experienced higher rates of AEs, including exudative AMD and AEs related to injection procedures, when compared to EOM. Since Syfovre will be given as a chronic therapy for an undetermined period (eg, until the patient and physician believe the therapy is no longer providing clinical benefit), a treatment posology with a lower manageable rate of AEs would be preferable. It would also lead to a lower burden on patients and health systems.
In addition, there are no robust patient-specific criteria to recommend change in posology (eg, switching from EOM to monthly dosing).

In order to address concerns from the CHMP on the higher rate of AEs (eg, exudative AMD) with the monthly use of Syfovre, within the responses to the LoOI, Apellis narrowed the proposed dosing regimen for authorisation to Syfovre 15 mg every other month only, and requests the review to be principally focused on the benefit/risk of EOM. Safety outcomes between the Syfovre EOM group versus the monthly group show a more favorable profile for EOM, particularly concerning the key AE of eAMD. The incidence of eAMD was notably lower in the EOM group (6.7%) than the incidence in the monthly group (12.2%), with the sham treatment showing a 3.1% occurrence over 24 months.
This lower eAMD incidence with EOM dosing also contributes to a decreased overall risk of IVT injection-related AEs, including from additional anti-VEGF therapy. Additionally, the EOM regimen showed a lower incidence of IOI and other injection-related AEs due to the reduced number of injections, further enhancing its safety profile compared to monthly dosing. EOM dosing resulted in a lower incidence of IOI (1.9%) versus monthly dosing (3.8%). Compared to sham-treated subjects (0.2%), where such events are expected to be minimal due to the absence of globe puncture, this data underlines the lower risk with EOM dosing.

Other injection-related AEs were overall lower in subjects treated EOM versus subjects treated monthly, but higher in Syfovre-treated subjects than in sham-treated ones.

The current risk management plan (RMP v0.4) reflects the totality of safety data observed at all Syfovre doses; however, in line with the proposed PEOM dosing regimen, RMP v0.4 focuses on pooled (PM and PEOM) and PEOM safety data. The change to the PEOM posology did not change the important (identified and potential) risks of this therapy, or the risk minimization measures. These remain described in detail in the RMP.

Overall, limiting the administration frequency to the EOM dosing regimen significantly lowers the overall risk of AEs, particularly eAMD and IOI, compared to the previous option to use EOM or monthly dosing. With only 6 injections of Syfovre per year, the EOM regimen presents a more favorable benefit-risk profile by reducing the incidence of key AEs and injection-related risks whilst maintaining similar efficacy. It also represents a lower treatment burden on the elderly patient population and health care systems. This proposal is aligned with real-world experience in the US. The US label of Syfovre allows for a flexible dosing regimen; however, the dosage is mostly EOM in clinical practice. This suggests that the proposed posology is in line with clinical practice.

Applicant's assessment of the specific criteria for the granting of a CMA

3.5.1 The Benefit-risk Balance of the Product is Positive

GA condition is characterised by the thinning and loss of the RPE and the concurrent atrophy of PRs, which are essential cells for vision. Clinical studies APL2-304 and APL2-303, both being randomised, double-masked, sham-controlled phase 3 studies, unequivocally demonstrated the benefit of Syfovre in reducing GA lesion growth when injected both monthly and every other month. Syfovre showed a consistent and clinically meaningful positive trend in reducing pathological and functional hallmarks relevant to GA symptoms. Specifically, Syfovre treatment significantly reduced the growth of GA lesions and the development of new scotomatous points, decreased the risk of progression to severe vision impairment, and preserved areas of the RPE and PR. The safety profile of Syfovre, well characterised with over 44,000 patient-years of cumulative IVT exposure as of 30 June 2024has demonstrated tolerability and manageability in subjects with GA through 24 months of treatment and is acceptable. Notably, dosing every other month further reduces the risk of AEs, such as eAMD and IOI, compared to monthly dosing. This regimen aligns with real-world practices in the US, suggesting that Syfovre offers a favorable benefit-risk profile for treating GA secondary to AMD.

3.5.2 It is Likely That the Applicant Will be Able to Provide Comprehensive Data

Apellis's application for the marketing authorisation of Syfovre is grounded in substantial evidence demonstrating its efficacy in slowing the progression of GA lesion growth, a claim further supported by additional microperimetry analyses conducted in Study APL2-304. These results, particularly those obtained from the microperimetry assessments, demonstrate Syfovre's capacity to decelerate scotoma progression and preserve visual function. In response to the CHMP's concerns regarding the post hoc nature of some microperimetry analyses and the necessity for replication, Apellis acknowledges the need to further substantiate Syfovre's impact on patient-relevant outcomes. Consequently, Apellis proposes a PAS designed not only to address these specific issues, but also to enhance the robustness of the existing findings.

This prospective study will employ the latest advancements in microperimetry technology to replicate and extend the insights gained from Study APL2-304, thereby affirming the initial results and providing additional evidence of Syfovre's clinical benefits.

The primary objective of the study is to evaluate the functional benefit of Syfovre compared to sham injection in participants with GA secondary to AMD in the most pathophysiologically active area of the macula as assessed by mesopic microperimetry. Currently, the Applicant is proposing the primary endpoint in CFB in the number of scotomatous points in the junctional zone, as well as key secondary endpoints that include CFB in the total area of GA lesion(s) and time to conversion of assessed points in the central 2 degrees to scotomatous. Through these carefully designed endpoints and robust study methodologies, Apellis hopes to provide comprehensive and replicable data for the microperimetry endpoint, thereby addressing the CHMP's concerns and affirming the clinical benefits of Syfovre.

In Section 3.7.1 the Applicant has discussed and demonstrated the feasibility of the potential PAS to provide comprehensive data in support of a conditional marketing authorization for Syfovre. This is based on the conclusions around the Applicants robust enrollment rate and operational capacity. In Studies APL2-304 and APL2-303, Apellis recruited 405 patients across 100 international sites within 9 months, with an enrollment rate of 0.45 patients per site per month. Given Syfovre's established safety and efficacy profile, its approval in the US, and increased awareness and understanding of the treatment within the retina community, Apellis anticipates an increased enrollment rate of 0.55 patients per site per month for the proposed PAS study. Apellis has identified 220 sites in Europe and other regions outside of US. The PAS study design, which includes EOM dosing and a simplified schedule of assessments, is expected to enhance patient recruitment and retention by reducing patient and site burden. Additionally, the inclusion of mesopic microperimetry as a noninvasive, patient-relevant test, is anticipated to increase the desirability of participation. This well-structured approach ensures that Apellis can effectively gather the necessary comprehensive data to support a conditional marketing authorization for Syfovre.

3.5.3 Fulfilment of Unmet Medical Need

GA represents a high unmet medical need due to its irreversible, progressive, and bilateral nature, posing a significant threat to vision in advanced AMD patients. Currently, there are no approved therapies for GA in Europe. The prevalence of late AMD in Europeans aged 60 and older is estimated at 2.4%, with projections indicating that by 2040, more than 18 million people globally, and between 3.9 and 4.8 million people in Europe, will be affected. Patients with GA experience severe functional vision loss, including difficulties in recognizing objects and faces, scotomas, distorted images, and challenges in reading, driving, and night vision.

This debilitating condition is marked by the thinning and loss of the RPE and concurrent atrophy of PRs, which are crucial for vision. Unlike neovascular AMD, which has approved treatments aimed at restoring retinal structure and function, the primary therapeutic goal for GA is to slow disease progression by reducing the growth rate of GA lesions. This approach aims to contain the atrophy and preserve the remaining retinal cells, rather than improving BCVA. Therefore, the key benefit for GA patients is the slowing down of disease progression, as evidenced by reduced lesion growth rates, addressing a critical unmet need in this patient population.

3.5.4 The Benefits to Public Health of the Immediate Availability of the Medicinal Product Outweigh the Risks Inherent in the Fact That Additional Data Are Still Required

The immediate availability of Syfovre can significantly benefit public health by addressing the high unmet medical need as described above. The observed reduction in lesion growth with Syfovre is clinically meaningful and relevant to patients. The loss of PRs and RPE cells directly impacts visual function, making the preservation of these critical retinal cells essential. Despite the CHMP's view that GA lesion growth rate is an anatomical endpoint, extensive research and expert consensus support its clinical relevance (see AHEG feedback in Section 3.8). Observational and interventional studies have shown that increasing GA lesion size leads to deterioration in various visual function parameters. Experts unanimously agree that GA lesion size is a critical anatomical parameter reflecting PR and RPE loss, which has high clinical significance due to its direct link to essential visual structure loss.

Syfovre treatment has demonstrated significant retinal preservation, with treatment effects comparable to the size of the optic disc, an area without PRs and no light perception. Over 2 years, Syfovre preserved retinal tissue equivalent to approximately 41% and 35% of the blind spot size and an area of PRs of the same magnitude as the blind spot. Continuous treatment is expected to preserve even more retinal tissue over time as shown by the month 30 data, which shows the amount of retinal tissue preserved with Syfovre reaching, or conservatively, nearly reaching the size the AHEG considered as clinically relevant by this timepoint. Given this preservation of critical visual structures and the alignment with CHMP’s guidance, the immediate availability of Syfovre outweighs the inherent risks of requiring additional supportive data in a PAS. This approach ensures that patients benefit from the treatment without delay while ongoing studies continue to gather further evidence. Visual function loss in GA is nonreversible due to the permanent death of the retinal RPE and PRs. Thus, the positive benefit-risk profile of Syfovre justifies its immediate use, offering significant public health benefits by slowing the progression of GA and preserving vision in a vulnerable population. GA is a relentlessly progressive disease and once vision is lost it will never be restored. Waiting for the completion of the proposed PAS before granting of a marketing authorization would result in patients having to wait several years for an effective treatment and for many GA patients this would constitute an irreversible loss of vision within this time period.

3.6 Exceptional Circumstances Authorisation was not Considered During the Initial MAA Evaluation

In a setting where the CHMP feel the totality of evidence does support a positive benefit-risk assessment but still require demonstration of a patient-perceived benefit measured by the key secondary functional endpoints (reading speed, FRI index score, NL-BCVA) in Studies APL2-304 and APL2-303, the Applicant notes that no trends were observed at 24 months for these endpoints or quality of life changes.

Given the slowly progressing nature of GA, caused by growing atrophic lesions in the retinal tissue leading to visual function decreases over time, and considering that the fovea is often spared late into the disease, thereby retaining central vision in patients, the data remain inconclusive. As a long-term investigation of these functional endpoints in a randomised controlled trial would take a significant period of time, coupled with the statistical considerations for an adequate cohort size to show an effect and the need for a sham control, the study likely becomes unfeasible and even unethical to have patients on sham treatment for an extended period of time. The AHEG also agreed that that visual function endpoints such as BCVA, maximum reading speed, FRI index are not the most relevant endpoints representing demonstration of a patient benefit. Based on this consideration and in the present state of scientific knowledge, comprehensive information on these endpoints cannot be provided. In this scenario, an exceptional circumstances authorisation would be the most appropriate to ensure that patients have access to an effective treatment to slow the growth of GA lesions.

3.7 A Randomised, Controlled Postauthorization Study will Provide Insights into Uncertainties Raised, and Enhance the Validity of Existing Findings

Apellis’s submission for MA of Syfovre is underpinned by robust evidence that demonstrate its efficacy in reducing GA lesion growth, and the evidence is further substantiated within Study APL2-304 via additional microperimetry analyses. These findings, notably those derived from the microperimetry assessments, present a compelling narrative of Syfovre's capacity to decelerate scotoma progression and preserve visual function. However, in response to CHMP's perspectives on the post hoc nature of some analyses and the lack of replication of these findings, the Applicant recognizes the opportunity to further solidify our understanding of Syfovre's impact on patient-relevant outcomes.

Accordingly, Apellis proposes a PAS that aims not only to address the specific uncertainties raised, but also to enhance the validity of our existing findings. This prospective study, utilizing the latest disease relevant advancements and learnings in microperimetry technology, seeks to replicate and extend the insights gained from Study APL2-304. By doing so, we aim to affirm the robustness of the initial results and provide additional evidence of Syfovre's clinical benefits. Furthermore, a prospective investigation using the latest available technology would serve to enhance the scientific validity of the conclusions discussed in this MAA and would provide further certainty on the magnitude of the treatment effects to improve information provided to prescribers whilst also advancing the field's knowledge on effective GA management.

Specifically, Apellis is already collaborating with centralized reading centers and experts that have expertise in microperimetry to implement customized microperimetry assessment. Customized or patient tailored microperimetry is a recent advancement in the field that modifies the microperimetry stimulus points based on the lesion (Pfau et al 2020). When APL2-304 was designed, a standard grid pattern centered on the fovea was the only available option. With customized pattern, the density of points can be increased in the fovea and in the lesion border to better capture functional changes in the most pathophysiologically active regions without negatively impacting testing duration. Based on the learnings from APL2-304, Apellis will develop a microperimetry procedure manual to incorporate improved procedural safeguards such as implementation of training regimen before each assessment, improvements in fixation monitoring and rigorous quality checks to improve data quality.

Apellis seeks to collaborate with the CHMP to ensure the PAS is effectively designed and implemented. As part of this collaboration, Apellis proposes engaging in a round of scientific advice with the CHMP. This dialogue will focus on aligning the specifics of the endpoints, particularly the secondary endpoints that will support the primary endpoint of the study.

Furthermore, Apellis aims to align on the scientific aspects of the trial design, including study objectives and inclusion/exclusion criteria, to ensure the study's success and relevance. Apellis is actively pursuing collaboration with patient representatives and organizations to integrate patient perspectives into the study design, with specifics to be provided in the Scientific Advice Briefing Document.

A detailed study outline of the PAS is included in Annex III. Below is a high-level summary of the key points of the proposed study design. These aspects can be further discussed during scientific advice, and as described above, the Applicant would welcome the input and feedback from the Scientific Advice Working Party/CHMP during such a procedure. The primary objective of the study is to evaluate the functional benefit of Syfovre compared to sham injection in participants with GA secondary to AMD in the most pathophysiological active area of the macula as assessed by mesopic microperimetry. Currently, the Applicant is proposing the following primary endpoint and key secondary endpoints:

Primary endpoint:

• CFB in the number of scotomatous points in the junctional zone (−250 μm to 250 μm of the baseline atrophy border) in the study eye assessed by mesopic microperimetry at month 24

Key secondary endpoints:

• CFB in total area (mm2) of GA lesions(s) in the study eye as measured by FAF images at month 24

• Time to conversion of assessed points in the central 2 degrees to scotomatous in the study eye as assessed by mesopic microperimetry at month 24

The applicant is proposing the following initial key milestones for the PAS development and execution (based on a positive CHMP opinion in September 2024 and EC Decision in November 2024):

• Initial Scientific Advice Procedure Application: 13 January 2025

• Scientific Advice Procedure Start: 10 February 2025

• Procedure with meeting (70 day), CHMP Adoption of advice: 25 April 2025

• Applicant protocol finalization: 23 May 2025

3.7.1 PAS Additional Feasibility Information

Results of a recent PAS feasibility assessment gives confidence in the operational plan to recruit up to 600 randomized subjects over a 12–24 month enrollment window. In this section, Apellis summarizes feasibility of the proposed PAS, focusing on operational considerations, a patient-centric study design, including acceptability of IVT injections, and impact of local approvals/launch of Syfovre on feasibility.

3.7.1.1 Enrolment Rate and Operational Feasibility

• For Studies APL2-304 and APL2-303, the enrollment rate of 0.45 patients per sites per month resulted in a total of 405 patients were recruited within approximately 9 months across 100 sites outside of the US. These sites were in Argentina, Australia, Brazil, Canada, Czechia, France, Germany, Israel, Italy, Netherlands, New Zealand, Poland, Spain, and the UK.

• Given that the inclusion/exclusion criteria for the proposed PAS study are similar to the I/E criteria from the phase 3 Studies APL2-304 and APL2-303, increased awareness and understanding of Syfovre within the global retina community, and Syfovre's approval in the US, Apellis anticipates a higher enrollment rate of approximately 0.55 patients per site per month in the proposed PAS.

• Apellis has completed a PAS feasibility assessment leveraging a site database and identified a pool of 220 sites in Europe and other regions outside of the US (Canada, New Zealand, India, South Africa, Argentina, Brazil, Peru, Chile Columbia, and Mexico). Approximately 100 sites will be sufficient to obtain the proposed sample size of 600 randomized subjects over an anticipated 12–24 month enrollment window.

• To further de-risk the PAS study enrollment timeline, Apellis proposes to: o Assess feasibility of incorporating additional site feasibility globally, including the US

o Once Apellis and CHMP have agreed on the PAS protocol, Apellis will generate a final patient recruitment plan and submit to CHMP to ensure confidence with study enrollment and execution timelines. This recruitment plan will consider country specific launch dates and enrollment windows to ensure target enrollment rates are feasible, as well as retention.

o In the event commercialization negatively impacts enrollment rates, Apellis will consider incorporation of fellow eye control for subjects with Bilateral GA disease.

• Furthermore, the proposed PAS includes dosing of patients with Syfovre EOM. In Studies APL2-304 and APL2-303, a higher dropout rate was observed in the monthly treatment groups as compared to the EOM treatment groups (8.8% improvement). Additionally, Studies APL2-304 and APL2-303 included an extensive schedule of assessments, whereas the PAS will focus on core questions of interest, which will reduce the patient and site burden. Limiting dosing to EOM along with a simplified schedule of assessments are expected to support both recruitment and retention of patients in the proposed PAS.

• Finally, the inclusion of mesopic MP as a noninvasive patient-relevant psychophysical test that complements traditional visual function tests and facilitates co-registration of the retinal sensitivity map to standard imaging is an important differentiation factor in the proposed clinical study. To our knowledge, only one other active GA clinical program includes microperimetry assessments (clinicaltrials.gov NCT05811351). Given the recent interest and advancements in microperimetry testing, the emphasis on microperimetry testing in the proposed study is expected to increase desirability of participation in this trial.

• Apellis has also considered inclusion of only patients with bilateral GA with one eye randomised to treatment and the other randomised to control group. Such a strategy would have the impact of reducing the total number of patients required and could potentially improve recruitment timelines. However, there are also several challenges to using fellow eyes as controls:

o The GA phenotype would have to be similar in both eyes as defined by inclusion/exclusion criteria, which could significantly affect recruitment

o Fellow eye comparator study designs have methodological limitations, eg. fully masking, which is why they are not typically used

3.7.2 GA Patient and Caregiver Perspectives

Apellis will consider the patient and caregiver perspective into the PAS study design, and will perform the following activities to seek patient input:

• Apellis will collaborate with the Apellis GA Patient Expert Advisory Council to seek input regarding patient perspectives on the protocol development and outcomes, as well as insights from patients who have received commercially available Syfovre in the US. In addition, Apellis plans to initiate exit interviews with patients upon completion of their participation in the ongoing Study APL2-GA-305 to gather feedback regarding their experience with long-term treatment with pegcetacoplan during the study.

• Apellis will conduct a Scientific Advisory Board to seek feedback from key opinion leaders regarding the PAS design to reduce patient burden while maintaining scientific integrity of the study endpoints. This feedback will be included in the Scientific Advice Briefing Document.

The approach outlined above will ensure a patient-centric study, which will ensure adequate patient recruitment and retention.

3.7.3 Acceptability of IVT Injections

Apellis's experience in Studies APL2-GA-304, APL2-GA-303, and APL2-GA-305 (the long-term extension study) demonstrates acceptability of IVT injections in GA. Of the 790 patients who participated in Study APL2-GA-305, 621 patients averaged 23.4 completed study months as of March 2024. Combined with the 2 years of the antecedent studies, this is equivalent to 4 years of continual IVT Syfovre therapy.

Acceptability of IVT injection in GA is further demonstrated in publications by Enoch and colleagues (2023) and Dinah and colleagues (2024). In these publications, there was a large rise of patient acceptability when injections were offered EOM compared to every month.

Apellis's clinical trial experience along with patient feedback suggests that IVT therapy will not play a significant role in patient participation in clinical trials.

3.7.4 Approval and Reimbursement

Potential approval and reimbursement of Syfovre will be completed in "waves" and the timelines for approval and reimbursement globally will be considered in the selection of countries for the PAS conduct and in the enrollment projections. Apellis will prioritize countries where approval and reimbursement timelines are expected to be appropriate/facilitatory for execution of the PAS study.

In summary, drawing upon Apellis's extensive experience with Studies APL2-GA-304, APL2-GA-303, and Study APL2-GA-305, along with patient and caregiver experience, and considering the study design for the proposed PAS, Apellis expects an enrollment rate between 0.45 and 0.55 patients per site per month. Apellis has pre-identified sites within countries where Syfovre will not be commercially available during the enrollment of this study. The patient-centric study design of the PAS, including EOM treatment, is expected to support patient retention and maintaining sufficient statistical power.

Apellis conservatively expects enrollment to take 18 months, with a projected study completion of 42 months (based on a 24-month primary endpoint).

3.7.5 PAS Summary

This commitment to further research GA underscores Apellis's dedication to providing health care professionals with the most accurate and comprehensive data possible. By enhancing the certainty around the magnitude of Syfovre's treatment effects, Apellis strives to ensure that prescribers are equipped with reliable information to make informed treatment decisions. The proposed PAS represents an integral component of Apellis's ongoing efforts to address the unmet needs of patients with GA and reinforces our commitment to advancing care in this very challenging and evolving therapeutic area.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant.

There is a high-unmet medical need for the treatment of geographical atrophy, which is a manifestation of advanced stage dry age-related macular degeneration (AMD). Currently no medicinal products licensed in Europe for the use in GA and no standard of care treatment (medical or surgical) is available that can halt or reverse the progression of geographic atrophy. Therefore, meaningful, well-defined outcomes that are relevant to patients, clinicians and policy-makers are essential for regulatory consideration.

The applicant considers that the provided primary endpoint's results in the study APL2-304 (OAKS) as well as the pooled data from both pivotal studies APL2-303 (DERBY) and APL2-304 (OAKS) demonstrate a meaningful reduction in lesion growth with associated trends in functional benefit. Therefore, according to the applicant, they provide reliable evidence of a patient-relevant benefit in slowing the lesion growth and should be more prominently considered in the benefit-risk discussion. The applicant's point of view is that the effectiveness of Syfovre has been clearly demonstrated in 2 phase 3 clinical trials, which provided robust and unequivocal evidence that the drug slows lesion growth.

Efficacy

The applicant's argumentation that efficacy has been demonstrated is based on the data submitted in the application as well as during the assessment process, and already described above. The pivotal data comes from two phase 3 studies: APL2-303 (DERBY) and APL2-304 (OAKS). In the APL2-303 (DERBY) and APL2-304 (OAKS) studies, the subjects were randomised to receive treatment with pegcetacoplan once monthly (PM), pegcetacoplan every-other-month (PEOM), sham injection monthly and sham injection every-other month, 2:2:1:1, respectively. The null hypotheses in both studies for the primary efficacy endpoint were the same:

•H1a: There is no difference between PM and Sham in mean change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm2) based on FAF for the mITT set.

•H1b: There is no difference between PEOM and Sham in mean change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm2) based on FAF for the mITT set.

The statistical plan required the successful rejection of both primary hypotheses in each of two pivotal trial to enable statistical testing of key-secondary hypotheses. Both primary hypotheses were rejected only in the study APL2-304 (OAKS), while they were not rejected in the APL2-303 (DERBY), the *P* values were above pre-specified level. The primary endpoint analysis was done at month 12, but also at month 24 together with pre-specified secondary endpoints. According to the Scientific Advice given, it was strongly recommended to conduct primary study analysis not earlier than at the month 24. Moreover, it was advised to the applicant that the studies should be ongoing at the time of the MAA. However, the applicant stated that continuing the studies in a randomised, masked fashion past month 24 was considered unfeasible and potentially unethical because it would have either withheld treatment with IVT pegcetacoplan having demonstrated beneficial effect on GA lesions or prolonged futile treatment. This could be acknowledged, but only if the reduction in the rate of progression of the lesion achieved would have translated into a delayed significant impairment in visual function, as normally expected in case of seeking an approval. It should be noted that the use of GA area (as measured with FAF) as a primary efficacy variable was endorsed, provided it could be justified that it represents a valid surrogate measure for visual function, or prevention of progression of AMD.

It is agreed that the data analysis performed at month 24 provides the evidence that IVI of pegcetacoplan either monthly or every other month reduces the growth of GA lesion based on the change from baseline in lesion size that is quantified by FAF and OCT compared with sham-pooled group. These results of the main analysis are generally supported by the sensitivity analyses. Based on the primary outcome data analysis the effect of pegcetacoplan is numerically bigger when it is administered as a monthly IVI compared with the every other month IVI, if both groups are compared to the sham pooled group. However, when comparing the corresponding individual sham control groups (monthly and every other month), the bigger effect of pegcetacoplan on lesion size is observed in patients administered every other month IVI vs. monthly IVI. The magnitude of the reduction in the lesion growth was estimated -22.4% for monthly IVI of pegcetacoplan and -18.4 % for EOM IVI of pegcetacoplan (APL2-304 study through 24 months). From two pivotal studies, only the APL2-304 study met the primary endpoint: a reduction of GA lesion – a change from the baseline - was statistically significant in favour of pegcetacoplan (both type of administrations) compared to sham pooled group at month 12. However, no pre-specified threshold for this primary endpoint was foreseen. The study APL2-303 did not met the primary endpoint in both PM and PEOM groups compared with sham-pooled group: a reduction of GA lesion did not reach a statistically significance. Nevertheless, the Applicant believes that treatment with pegcetacoplan brings consistent and clinically meaningful benefit. As the supportive evidence, the applicant makes reference to the secondary endpoint – macular functional response as assessed by microperimetry.

However, the APL2-304 study pre-specified analysis of change from baseline in number of scotomatous points at month 24-m in ITT population showed inconsistent results in PM and PEOM treated patients. At month 24, the difference in least-square (LS) mean (95% CI) of change from baseline between PM and sham pooled groups was close to zero: 0.027 points (−2.137 to 2.192 points)], while the difference between PEOM and sham pooled groups was −0.803 points (−2.623 to 1.017 points). According to the applicant, the most likely explanation for the unexpected finding in number of scotomatous points in the PM group at month 24 is a technical error (e.g., a faulty clicker). Outliers were identified in 4 PM subjects and 3 PEOM subjects, no outlier was identified in the sham polled group. Consequently, after excluding two samples corresponding to two different subjects in the PM group at month 24, a sensitivity analysis showed a point estimate similar to that observed in the PEOM group. However, a post-hoc removal of suspected outliers on the basis of inconsistent results is not considered appropriate. Therefore, the reviewed results need to be interpreted with a caution, as it raises doubts regarding the robustness of the provided results due to the *post hoc* adjustment.

Post hoc analysis on the number of prevented scotomatous points in **junctional zone** (±250 µm on either side of lesion border) showed a potential trend favouring pegcetacoplan-treated groups (PM, PEOM). However, again there were inconsistencies for the types of administration of pegcetacoplan: nominally significant among patients with PEOM, but not among those with PM Of note, microperimetry measurements were only performed in study APL2-304, which imposes an uncertainty regarding the replication of the results. The consistency across ways of defining the junctional zone and with the analysis versus the contralateral eye does not represent independent replication as the results are expected to be correlated.

In the open label phase after the 24 months' period of the randomised observation, data focused on microperimetry results (mean threshold sensitivity overall/junctional zone, number of scotomatous points overall/junctional zone, number of scotomatous points in central 2/6 degrees) overall compared to M24 were similar or numerically larger at integrated M36, others showed numerically smaller effects. Despite the comparison to the sham-to-pegcetacoplan group, additional treatment with pegcetacoplan up to M36 seems did not shown additional effects. The refined analysis performed by the applicant demonstrated that in both groups of patients treated with pegcetacoplan there was a trend in reduction of the number of new scotomatous points from baseline compared with sham-pooled group. It could be agreed that the provided evidence demonstrates that pegcetacoplan slows down the lesion growth, which is probably associated with the reduction in the development of new scotomatous points. These data indicate the potential of pegcetacoplan to preserve the photoreceptors, however, this potential was not reflected a clinically relevant benefit, as demonstrated by the lack of treatment effect of pegcetacoplan in regards of sustaining the visual function parameters (e.g. FRI index, LLVA etc.) compared to sham pooled group trough 24 months of the studies. It is possible that the MP endpoints in the post-hoc analysis were selected to highlight a correlation with a lesion growth (e.g. loss of light sensitivity in areas of lesion growth), whereas microperimetry endpoints that capture overall light sensitivity showed no treatment effect.

It should be noted that there is no doubt that GA lesion size and pattern are the benchmark quantitative measurements in evaluating GA progression, but sustaining visual function due to the slowing the lesion growth rate is the clinically important outcome to achieve. Based on the literature, repeated VA testing over time is used to help monitor disease progression (e.g. BCVA and low-luminance VA, LLVA). It is considered that LLVA may identify visual changes in response to AMD earlier than BCVA. Similarly, a decrease in reading speed may also indicate lesion growth into the central macula and, therefore, it has been utilised as a metric to assess disease progression. The applicant argues that central vision as assessed by BCVA cannot be considered as a comprehensive method to capture the impact of GA on visual function. It is considered that in GA patients VA can be maintained earlier in the disease course, particularly if the fovea is spared from atrophy. Indeed, it is not until GA progresses to include the fovea that severe and irreversible vision loss typically occurs. Furthermore, visual decline can be gradual and variable. Moreover, patients can adapt via eccentric fixation to optimise their VA (Sunness JS et al, 2005; Sunness JS et al., 1999). Therefore, it may not be deemed feasible to demonstrate a clinical benefit of a therapeutic intervention for GA using VA (Guymer RH, 2018; Abidi M et al., 2022). Notably, this was acknowledged in the scientific advice (EMA/CHMP/SAWP/151552/2018) that best-corrected visual acuity (BCVA) may not be sensitive enough to assess disease progression within a reasonable time frame due to the potential foveal-sparing pattern until late in the course of the disease. On the other hand, the study population was slightly enriched by "fast-progressors", therefore some positive trends in the visual function are expected to be based on the chosen key secondary endpoints. Other functional indicators of vision like reading speed could be considered reflective of retinal function beyond BCVA and may therefore be more suitable to acquire less correlated data than reading acuity (Krezel Ka et al, 2019; Sunness et al, 2005). It should be highlighted that the key secondary endpoints were not met in either APL2-303 (DERBY) or APL2-304 (OAKS) studies (Table R85). The key secondary endpoints were 1) change from baseline in monocular maximum reading speed (study eye) as assessed buy MNREAD or Radner reading charts at month 24; 2) change from baseline in functional reading independence index score, at month 24; 3) change from baseline in normal luminance best corrected visual acuity score (NL-BCVA) at month 24 (by ETDRS chart). Based on literature, it considered that increase in the GA lesion size lead to dense scotomas over the atrophy area that can influence activities of daily living, especially reading, independent of central visual acuity (Csaky K et al., 2024; Krezel Ka et al, 2019; Sunness JS et al, 2005). The maximum reading rate in AMD patients with GA is highly correlated with the size of the atrophic area, regardless of whether GA is fovea- involving or not (Sunness JS et al, 1996). It should mentioned that the maximum reading speed is a functional indicator, that showed a relevant change from baseline in the trial period (which is an argument against the concept that it could not have been sensitive to a treatment effect). However, there were no difference in changes from baseline to month 24 for maximum reading speed when comparing pegcetacoplan treatment groups with sham group (Table R85). The low correlation between GA lesion area size and the measures of visual acuity – also reported by the applicant including at the Oral Explanation – and the individual case reports where such low correlation manifests to different degrees, do not offer support to the surrogacy of GA area, and similarly does not demonstrate that a benefit that is perceivable to patients cannot be demonstrated, if it exists.

Table 82: The key secondary endpoints: analysis of CFB in mean With MMRM model at month 24 in study APL2-304 and study APL2-303 (simplified, sources: the CHMP AR, June 2024, data from the application)

	APL2-304			APL2-303		
	PM (N=202)	PEOM (N=205)	Sham pooled (N=207)	PM (N=201)	PEOM (N=201)	Sham pooled (N=195)
CFB in Monocular Maximum Reading Speed of the Study Eye, LS mean (95% CI), wpm	-22.446 (-28.404 to -16.488	-17.533 (-23.993 to -11.072)	-16.211 (-23.701 to -8.721)	-22.897 (-30.986 to -14.808)	-25.355 (-30.970 to - 20.094	- 22.355 (-28.120 to -16.590)
Difference (95% CI) in LS mean CFB in maximum readng speed (vs. Sham pooled), wpm	-6.235 (-15.182 to 2.712)	-1.322 (-10.562 to 7.918)	NA	-0.542 (-19.922 to 8.838)	-3.177 (-10.619 to -4.265)	NA
P value (vs. Sham pooled)	**0.1716**	**0.7788**	NA	**0.9096**	**0.4002**	NA
CFB in Mean FRI Index Score, LS mean (95% CI)	-0.287 (-0.398 to -0.177	-0.379 (-0.484 to -0.274)	-0.273 (-0.382 to -0.164)	-0.408 (-0.520 to -0.296)	-0.371 (-0.481 to -0.260)	-0.360 (-0.478 to -0.242)
Difference in LS mean CFB in FRI (vs. Sham pooled),	-0.015	-0.106	NA	-0.048	-0.011	NA
P value (vs. sham pooled)	**0.8450**	**0.1508**	NA	**0.5483**	**0.8921**	NA
CFB in NL-BCVA score, LS mean, EDTRS letters	-7.477 (-9.541 to -5.412)	-8.526 (-10.593 to -6.459)	-7.660 (-9.768 to 5.552)	-8.126 (-10.126 to -6.126)	-8.947 (-10.975 to - 6.920)	-6.217 (-8.214 to -4.220)
Difference (95% CI) in LS mean CFB in NL-BCVA score (vs. Sham pooled),	0.183	-0.866	NA	-1.909	-2.730	NA
P value (vs. sham pooled)	**0.9015**	**0.5615**	NA	0.1799	0.059	NA
LS mean CFB in meaan threshold sensitivity, dB (95% CI)	-3.319 (-3.903 to -2.736)	-3.064 (-3.522 to -2.606)	-2.954 (-3.377 to -2.530)	NA	NA	NA
Difference in LS men CFB in mean threshold sensitivity vs. shaam pooled group, dB	-0.365	-0.110	NA	NA	NA	NA
P value (vs. sham pooled)	**0.2998**	**0.7106**	NA	NA	NA	NA

The applicant claims that there was a trend of a reduced risk of developing sustained visual acuity of less than 35 letters. However, the HR for every other month IVI of pegcetacoplan did not show any favourable trend in reducing the risk of progression to severe vision loss (35 letters in BCVA; HR =0.88; 95% CI 0.56-1.39; p=0.5910). In general, the total share of patients with ≤ 35 letters in BCVA was relatively small (11%), the inclusion criteria allowed to include patients even with ≥ 24 letters in BCVA. The applicant's interpretation on a positive trend in reducing the risk of progression to severe vision loss (35 letters in BCVA) is not supported for any of the treated groups.

Decline in VA is difficult to measure if already poor. According to the ad-hoc expert meeting conducted during the initial MAA, the experts do not agree that BCVA, maximum reading speed, FRI index are the most relevant endpoints representing a patient benefit. Notably, the experts were not categorical, they mentioned that in patients with sub-foveal lesion, changes in BCVA would not be expected, while BCVA should be taken into account in GA trials, when studying population without subfoveal GA lesion at baseline, but not as a primary endpoint. This expert statement actually did not contradict with scientific advice and the CHMP first opinion. In fact, as stated above, the CHMP already agreed that BCVA may not be the most suitable measure, since it may not capture the full extent of visual function loss or its progression in GA, due to the phenomenon of foveal sparing.

Some recent publications have also discussed that the relationship between GA and functional outcomes varies by lesion characteristics, including location of the GA lesion (Chakravarthy U. et al, 2023). It is highlighted that the lesions with different GA growth rates demonstrated separation in the trajectory of visual acuity loss in subjects with unifocal but not multi- focal lesions. Interestingly, the most significant correlation between GA expansion rates and visual acuity loss was seen in eyes with subfoveal unifocal lesions (Csaky K et al, 2024).

According to the data from both pivotal studies, at baseline there were 63.2% patients with subfoveal involvement and 36.8% patients w/o subfoveal involvement. While there were only around 30% patients with unifocal lesion of GA and 70% patients with multifocal lesions of GA. However, there was no available data, which would allow comparing the visual acuity loss in subjects with subfoveal unifocal lesions. The results of two pivotal studies, therefore, raises the question, which GA patients will benefit more from the treatment with pegcetacoplan. Probably, the patients subgroups based on the location of the lesion and lesion characteristics (lesion uni- or multi-focal) as well as VA status of patients at the baseline should be considered in this regard. It seems that the targeted population of two pivotal studies is too broad and the treatment with pegcetacoplan for 24 months does slow the rate of the lesion growth, but the magnitude of the effect is not enough to bring a visual benefit to the patients.

The applicant does not agree with the conclusion in the CHMP assessment report of the initial opinion that based on the current evidence, it cannot be answered when and to what extent a certain lesion size reduction would turn into a perceivable patient benefit. According to the applicant, this conclusion was principally based on the endpoints of BCVA, maximum reading speed, and FRI. This is not supported. The conclusion was based on the totality of the data provided by the applicant in the application and during the assessment procedure. It should be mentioned that only one confirmatory study met the primary endpoint at month 12, the second study did not show a significant difference between sham pooled group and treated with either monthly or every other month IVI of pegcetacoplan groups. Referring to the AHEG discussion, the experts stated that "an impact of 1mm could have a clinically relevant impact and be perceived by patients". However, referring to the results of the primary endpoint analysis, the reduction in growth rate difference did not reach 1 mm^2 either at month 12 or month 24. The difference of $1mm^2$ at 30 months is based on assumption on what the trajectory of sham-treated eyes would have been, had they stayed untreated. The study APL2-304 (OAKS) demonstrated the -0.32 mm^2; 95% CI (−0.54 mm^2 to −0.09 mm^2; p=0.0055) difference between sham pooled group and every other month IVI of pegcetacoplan in favour of pegcetacoplan at month 12. At month 24, the difference in lesion growth was doubled between pool sham group and every other month IVI of pegcetacoplan (−0.74 mm^2, 95% CI (−1.13 mm2 to −0.36 mm2; p=0.0002). In conclusion, based on the overall results from the pivotal studies, it is considered that the evidence for surrogacy of reduction in GA growth rate is not sufficient to demonstrate clinical benefit for the targeted patients' population. No difference in change from baseline to 24 month in for reading speed, FRI index score, LLVA and NL-BCVA between treatment groups and sham pooled group has been demonstrated.

Results from the interim analysis (month 24-30) in the ongoing study APL2-305 demonstrates a sustained treatment effect of pegcetacoplan in reduction of GA lesion growth. However, that additional data from the APL2-305 long-term extension study did not show any significant or meaningful differences between early vs. late initiation of pegcetacoplan from month 24 to integrated month 30.

Safety

Data analysis demonstrates that there were higher rates of ocular adverse events in pegcetacoplan treated patients as compared to sham control. There were more events in patients treated with monthly IVI of pegcetacoplan than in those treated every other month of IVI. Compared with sham pooled group of patients the exudative AMD incidence was approximately 4 times higher in the PM pooled group and 2 times higher in PEOM group. While intraocular inflammation mostly occurred in the pegcetacoplan groups, no case of endophthalmitis in sham group was observed (Table 83).

Table 83: Most prominent adverse events (data from the two pivotal studies APL2-303 (DERBY) and APL2-304 (OAKS))

Adverse event	Monthly IVI of pegcetacoplan	Every other month IVI of pegcetacoplan	Sham pooled
Exudative AMD, %	12.2	6.7	3.1
Intraocular inflammation, %	3.8	2.1	0.2
Endophthalmitis, %	0.5	0.6	0

There was a higher incidence of subjects who experienced AEs in the study eye and received concomitant ocular medication in the pegcetacoplan groups (72.9% and 65.9% in the PM and PEOM, respectively) compared with the sham pooled group (61.9%). The majority of the IVT treatments were anti-VEGF medications for exudative AMD (i.e., 10.0%, 4.8%, and 1.9% of subjects in the PM, PEOM, and sham pooled groups in pool 1, respectively). This correlates to the incidences of exudative AMD in pool 1, which occurred in 12.2%, 6.7%, and 3.1% of subjects in the PM and PEOM and sham pooled groups, respectively.

Because there was the association of ocular adverse events with the frequency of IVI (monthly and every other month), the applicant proposed to limit the dosing regimen of pegcetacoplan to once every other month (i.e. PEOM regimen), as monthly based regimen generated relatively more frequent AEs (eAMD and intraocular inflammation). From the safety point of view the choice of PEOM regimen could be supported, however, it should be considered together with efficacy results and in the regards with benefit/risk balance, which is considered negative for all posologies (see below).

The new-onset exudative AMD, unexpected risk of intravitreal pegcetacoplan, raises a safety concern. No end of treatment has been defined, which can increase risk of the unknown or unexpected adverse events, i.e. observed in the randomised clinical studies. Such a safety concern could be expressed regarding retinal vasculitis. As mentioned in the CHMP assessment report of the initial opinion, up to 15 May 2024, 25 patients have 26 confirmed or suspected retinal vasculitis reported from post-authorisation use in the US. No events of retinal vasculitis have been either reported in the pivotal clinical studies (APL2-304 and APL2-303) by investigators or identified by the reading centre. A specific trigger for the development of retinal vasculitis after pegcetacoplan administration cannot be identified at this time. The estimated rate per injection of these events is 0.01%. The estimated frequency of retinal vasculitis based on estimated number of patients exposed in the US post-approval setting is rare (≥1/10,000 to <1/1,000), however, it is not always possible to reliably estimate the frequency as adverse events are reported voluntarily from a population of uncertain size, as pointed out by the applicant. Thus, it must be assumed that potentially more cases of retinal vasculitis occurred that were not correctly identified or not reported.

Historically, larger injection volumes (0.1 mL vs 0.05 mL) have been associated with higher IOP levels and with more common and severe pressure spikes following intravitreal injections, when compared with other IVT injections with less volume. There is no clear explanation for the fact that the frequency of increased IOP AEs was lower than expected. This adds to uncertainties regarding the reported safety results, namely AEs due to the intravitreal procedure. Together with the significant risk of inducing wet AMD and the risk of retinal vasculitis it can be concluded that the risk profile is not acceptable in the context of the non-clinically relevant efficacy results.

Considering the possibility of a conditional marketing authorisation (CMA)

In the context of this re-examination, the applicant proposes a CMA, with a post-authorisation study that aims to address specific uncertainties raised regarding the post hoc nature of some analyses (i.e. microperimetry) and the lack of replication of these findings. However, this study would not address the key uncertainty (of whether these replicated findings would translate into a patient-relevant benefit) and more generally the conditions for the granting of a CMA are not met: (i) as explained in the benefit-risk section in this document, the benefit-risk balance is negative, in absence of a benefit relevant to patients; (ii) the proposed PAES does not address the key uncertainty therefore it is considered the applicant has not demonstrated that comprehensive data is likely to be generated; in absence of a demonstrated benefit, the (iii) fulfilment of the (undisputed) unmet need and (iv) the benefit of immediate availability cannot be supported. See also section 6.7.3 of this report.

In addition, in view of the negative benefit-risk balance, it is considered that the MA application for Syfovre is not eligible for a marketing authorisation under exceptional circumstances.

Overall conclusion on the grounds for re-examination

Having considered the arguments presented in writing and in an Oral Explanation by the applicant, as well as third party interventions expressing views on the unmet need and on the relevance of the observed effects, the CHMP concludes that the grounds for refusal adopted in the initial opinion are still valid.

5.1. Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

Geographic Atrophy (GA) is an advanced form of Age-Related Macular Degeneration (AMD) and is characterised by thinning and loss of the retinal pigment epithelium (RPE) and concurrent atrophy of photoreceptors (PRs) and the choriocapillaris that leads to progressive and irreversible loss of visual function. It starts typically in the perifoveal region and expands to involve the fovea with time, leading to central scotomas and permanent loss of visual acuity.

GA represents a chronic progressive condition and is usually bilateral in nature. Patients with GA experience severe functional vision loss, including difficulties in recognizing objects and faces, distorted images, and challenges in reading, driving, and impaired night vision.

6.1.2. Available therapies and unmet medical need

There are currently no treatments available for GA. Natural disease progression appears devastating for the individual and the progressing GA manifests as a major threat to a patient's eyesight as well as general wellbeing.

GA therefore represents a condition with a high unmet medical need.

6.1.3. Main clinical studies

The clinical development programme of Syfovre is composed of 6 completed studies (Studies APL2-304, APL2-303, APL2-103, and POT-CP121614 in subjects with GA and Studies POT-CP043014 and APL2-203 in subjects with nAMD) and 1 ongoing study (Study APL2-GA-305 in subjects with GA).

The main evidence of the efficacy submitted is based on two phase 3 studies of very similar design: Studies APL2-304 (OAKS) and APL2-303 (DERBY).

Both phase 3 studies were randomised, double-masked, and sham-controlled, and they investigated the efficacy and safety of IVT pegcetacoplan therapy (15 mg/0.1 mL monthly or every other month) compared to sham injections in subjects with GA secondary to AMD.

The primary outcome in both studies was the CFB to month 12 in total area of GA lesions, and the change in visual function was studied as secondary outcome until month 24. In each study, a total of 600 subjects were planned to be assigned on a 2:2:1:1 basis to receive PM, PEOM, sham monthly, or sham every other month (SEOM). Data from the ongoing 36 months open-label extension study APL2-GA-305 of these two pivotal studies are also presented.

While every month (EM) and every other month (EOM) treatment regimens have been evaluated in the clinical studies, the applicant, Apellis, now seeks authorisation for Syfovre for only the EOM dosing regimen and requests the review to be principally focused on the benefit/risk of pegcetacoplan EOM (PEOM).

6.2. *Favourable effects*

IVT pegcetacoplan, administered EOM, demonstrated a reduction in GA lesion growth at month 12 compared with sham in both phase 3 studies (Studies APL2-304 and APL2-303) as well as in the phase 2 Study POT-CP121614.

Results from the interim analysis (month 24 – 30) in the ongoing study APL2-305 continued to demonstrate a sustained treatment effect of pegcetacoplan in reduction of GA lesion growth. It appears that a monthly reduction of 0.030-0.032 mm^2 in the total area of GA lesion was maintained from month 12 until month 30.

However, the study (APL2-303) did not meet its primary efficacy endpoint and demonstrated effect size estimate was smaller than expected at the planning stage, and smaller as compared to the outcome seen in study APL2-304.

In the pivotal Phase 3 study APL2-304, the change from baseline in total area of GA lesion was statistically significant. Its magnitude (least-square mean, mm^2) at month 12 compared to sham pooled (sham monthly SM + sham every other month SEOM) was –0.3180 mm^2 with 95% CI (–0.5423 mm^2 to –0.0937 mm^2; p=0.0055) in the **PEOM** (pegcetacoplan every other month) group.

In Study APL2-304, at 24 months, the difference in least-square (LS) mean CFB in total area of GA lesions between the **PEOM** group and the sham pooled group was −0.7426 mm^2 (95% CI, −1.1282 to −0.3570 mm^2; P = .0002), corresponding to a percentage difference of −18.4% from the sham pooled group.

In Study APL2-303, at 24 months, the difference in LS mean CFB in total area of GA lesions between the **PEOM** group and the sham pooled group was −0.6331 mm^2 (95% CI, −1.0508 to −0.2153 mm2; P = .0030), corresponding to a percentage difference of −15.9% from the sham pooled group.

Results from the interim analysis (month 24 – 30) in the ongoing study APL2-305 continue to demonstrate a sustained treatment effect of pegcetacoplan in reduction of GA lesion growth. Extrapolation of the linear lesion growth of sham-treated eyes observed through month 24 up to month 30 led to an estimated mean reduction of 1.02 mm^2 with PEOM compared to the projected sham rate and of 0.93 mm^2 compared to the untreated fellow eye, respectively. These values are in accordance with a rough estimation of the monthly rate of reduction of -0.030 to -0.032 mm^2.

In Study APL2-304, the difference in LS mean CFB in total area of RPE loss at month 24 between the **PEOM** group and the sham pooled group was less than PM group but statistically significant −0.7094 mm^2 (95% CI, −1.0822 to −0.3365 mm^2; P = .0002), corresponding to a percentage difference of −19.7% from the sham pooled group.

In the same study, at 24 months, the difference in LS mean CFB in total area of PR loss between the **PEOM** group and the sham pooled group was −2.0608 mm^2 (95% CI, −2.5738 to −1.5478 mm^2; P < .0001), corresponding to a percentage difference of −46.0% from the sham pooled group.

In Study APL2-303, the difference in LS mean CFB in total area of RPE loss at month 24 between the **PEOM** group and the sham pooled group was less than PM group but again statistically significant −0.7839 mm^2 (95% CI, −1.2213 to −0.3464 mm^2; P = .0005), corresponding to a percentage difference of −20.6% from the sham pooled group.

In the same study, at 24 months, the difference in LS mean CFB in total area of PR loss between the **PEOM** group and the sham pooled group was −2.0715 mm^2 (95% CI, −2.6700 to −1.4731 mm^2; P < .0001), corresponding to a percentage difference of −46.4% from the sham pooled group.

In the prespecified secondary endpoint of overall number of scotomatous points among the 68 points of the grid in Study APL2-304 using microperimetry, at month 24, the difference in LS mean between **PEOM** and sham pooled groups was −0.803 points (95% CI, −2.623 to 1.17 points; P = .3863). A numerical reduction in mean sensitivity lost for PEOM compared to sham pooled was observed (difference in LS mean [95% CI, P value] CFB: 0.406 [−0.318 to 1.131, P = .2711] in the perilesional points (0-500 µm). These endpoints were only included in study APL2-304.

In a post-hoc analysis, a nominally statistically significant difference was observed in the development of new scotomatous points in the junctional zone defined as a -250 µm to +250 µm ring surrounding the region of atrophy in Study APL2-304. At month 24, the difference in LS mean between **PEOM** and sham pooled groups was −1.138 points (95% CI, −2.045 to −0.231 points; P = .0140). At month 24, the difference in LS mean (95% CI, *P* value) CFB in mean threshold sensitivity at month 24 for **PEOM** compared to sham pooled in the junctional zone was 0.707 (0.111 to 1.303, *P* = .0202), supporting what was observed for new scotomatous points.

Further post-hoc time to event analyses in Study APL2-304, at 24 months, showed that treatment with **PEOM** corresponded to 36% (hazard ratio [95% CI], HR value: 0.64 [0.44 to 0.92], P = .0164) reduction in the risk of conversion of all central 4 points in the study eye to scotoma, compared to the sham-pooled treatment group. Treatment with **PEOM** also corresponded to 48% (hazard ratio [95% CI], HR value: 0.52 [0.32 to 0.85], P = .0084) reduction in the risk of conversion of all central 16 points in the study eye to scotoma, compared to the sham-pooled treatment group.

6.3. Uncertainties and limitations about favourable effects

The APL-303 study did not meet the statistical significance at the pre-specified ɑ level at month 12, therefore the results achieved in the APL2-304 could not be considered fully replicated in the second trial.

There were inconsistencies in results when comparing treatment effect from monthly and every other month IVI administrations of pegcetacoplan with the sham individual groups and with the sham pooled group. The effect was consistently higher in the group with PM than in PEOM when comparing to the sham pooled group. However, when the comparison of primary endpoint results was done for each treatment group with individual sham control, the higher effect was observed for PEOM type administration. While only one posology is proposed by the applicant, these inconsistencies lower the overall quality of evidence.

Regarding the key secondary endpoints (maximum reading speed, FRI score or NL-BCVA) neither meaningful differences nor positive trend in favour of treatment with pegcetacoplan was observed through 24 months in both pivotal studies, despite presence of change from baseline on these measures in the placebo arms.

There was a mean difference at month 24 in change from baseline of -0.7426 mm^2 between PEOM and sham pooled groups, however the slower progression of the GA lesion size was not translated into visual benefit of clinical relevance to patients in the treatment group over the relevant time period. The postulated relevance of a 1 mm^2 difference has not been demonstrated, and in any case this threshold has not been reached in the main phase of the study, but only at month 30 with analyses that rely on unverifiable assumptions. The demonstrated reduction in lesion growth by ~ 20% in the every other month dosing regimen compared to sham is also considered by CHMP to be modest.

The analysis detecting the number of scotomatous points in the junctional zone (spanning ±250 μm on either side of the lesion border) suggests a possible weak trend favouring both pegcetacoplan treated groups. However, the more frequent dose (PM) was not nominally significant, while only the less frequent regimen (PEOM) was. Again, while only the latter regimen is now proposed, this inconsistency lowers the overall quality of evidence. While, as mentioned by the applicant, this is a functional and not an anatomical test, it does not measure a benefit that the patient can directly perceive in their functioning, and its translation into a clinical relevant benefit was not demonstrated, also taking into account an estimated difference (point estimate) of roughly 1 scotomatous point (from approximately 21.4 on average in the junctional zone and from 68 points across the whole microperimetry grid) compared to sham. These findings, in addition to single trial assessment without replication, increase uncertainty and severely questions the credibility and strength of these results in showing a true treatment effect for a functional measure. The post hoc nature of some of the analyses presented further lowers the credibility of these results.

The estimates of effect at 30 months suffer from additional weaknesses, as they rely on assumptions about what the course of disease would have been had untreated patients stay untreated.

The totality of the provided evidence has not demonstrated that the slowing of GA lesion growth with pegcetacoplan would actually manifest into relevant visual benefit to patients. Lastly, the population recruited in the development programme was enriched for factors predicting relatively fast progression, hence an even longer time to develop a meaningful benefit to the patient (if any) would be needed on average in the general population affected.

6.4. Unfavourable effects

Over 44,000 patient-years of cumulative Syfovre exposure in the clinical and real-world setting are available, including approximately 3,000 patient-years of phase 3 cumulative exposure using the proposed commercial formulation as of 30 June 2024.

Important (serious) AEs with imbalances between groups in the clinical trials (through 24 months) pool 1 safety data comparing PEOM and sham pooled groups were exudative AMD (eAMD) (6.7% and 3.1%), intraocular infections (IOI) (1.9% and 0.2%), endophthalmitis (0.7% and 0), and intraocular pressure increased (2.9% and 0.7%). The per-injection rates for the PEOM group were 0.24% for IOI and 0.07% for endophthalmitis, which are overall low and expected in an IVT-administered product. The endophthalmitis rate per injection ranged from 0.04% to 0.22% across studies.

6.5. Uncertainties and limitations about unfavourable effects

Despite that the 44,000 patient-years and more of cumulative IVT exposure in the clinical and real-world setting, the safety profile is not fully characterised.

Increased intraocular pressure (IOP) had a higher percentage in the PEOM group compared to the PM group. This requires continuous monitoring and special attention during the post-approval setting.

Treatment with pegcetacoplan for GA is expected to be a continuous treatment. Limited long-term safety data of IVT pegcetacoplan beyond 24 months was available at the time of the submission.

The limited long-term data available leads to an uncertainty concerning the long-term safety of Syfovre. The applicant has not defined criteria for an end of treatment with Syfovre. This means that the risks associated with intravitreal injection will gradually increase with treatment duration.

Moreover, pegcetacoplan administration has thus far only been studied in one eye per patient and there is a potential for increase in ocular and non-ocular adverse events with bilateral treatment.

Concomitant ocular medication, especially when administered by IVT injection, may add to the injection related AEs observed for Syfovre. Of note, pegcetacoplan treated patients may develop neovascular or exudative AMD, which is often treated by intravitreal anti-VEGF medication. This means that the risk of endophthalmitis and intraocular inflammations, amongst others, will further increase in patients developing wet AMD.

Differences in the percentage of subjects with certain AEs (e.g., Endophthalmitis, Intraocular inflammation) were noted between studies. In addition to the specific observations made with respect to identified safety events, it is noted that the withdrawal of consent occurred more frequently in patients treated with the most frequent posology of Syfovre.

As of 15 May 2024, 25 patients have 26 confirmed or suspected retinal vasculitis have been reported from post-authorisation use in the US. No events of retinal vasculitis have been reported in clinical studies (Studies APL2-304 and APL2-303) by investigators or identified by the reading centre. A specific trigger for the development of retinal vasculitis after pegcetacoplan administration cannot be identified at this time. The estimated rate per injection of these events is 0.01%. The estimated frequency of retinal vasculitis based on estimated number of patients exposed in the US post-approval setting is rare (≥1/10,000 to <1/1,000), however, it is not always possible to reliably estimate the frequency as adverse events are reported voluntarily from a population of uncertain size, as pointed out by the applicant. Thus, it must be assumed that potentially more cases of retinal vasculitis occurred that were not correctly identified or not reported.

6.6. Effects Table

Table 84: Effects table for [Syfovre every other month for the treatment of GA secondary to AMD in adults] (data cut-off: 30 June 2024)

Effect	Short Description	Unit	PEOM	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Total area of GA lesion (prespecified) at month 24	Percentage difference and difference compared with sham in LS mean CFB in total area of GA lesion at month 12 and month 24 (95% CI)	mm^2	−0.7426 mm^2 [−1.1282 to −0.3570 mm^2]	NA	Strength: The primary efficacy endpoint is an anatomical endpoint, which is objective and reproducible and can be reliably assessed in a standardised manner to track the progression of GA lesion growth. Effect was replicated using OCT to quantify RPE and PR loss. Uncertainties: no demonstration of surrogacy for visual function	**APL2-304**

Effect	Short Description	Unit	PEOM	Control	Uncertainties/ Strength of evidence	References
Scotomatous points across all 68 points (pre-specified)	Difference compared with sham in LS mean CFB in number of overall scotomatous points at month 24 (95% CI)	Count of scotomatous points	APL2-304 −0.803 points (−2.623 to 1.0117 points)	NA	Strengths: Supports a signal of functional benefit in prespecified endpoint Uncertainties: Low spatial resolution of the microperimetry testing grid	APL2-304
Scotomatous points in the junctional zone (post-hoc)	Difference compared with sham in LS mean CFB in number of junctional zone (250 µm on either side of the GA lesion border) scotomatous points at month 24 (95% CI)	Count of scotomatous points	−1.144 (−2.052 to −0.237)	NA	Strengths: Support the presence of a protective treatment effect at the junctional zone which is at risk of progression to overt GA (region of no sensitivity to light), indicating a trend toward visual benefit. Uncertainties: Low spatial resolution of the microperimetry testing grid Region-specific **post-hoc analyses** The findings have not been replicated No direct clinical benefit	APL2-304
Unfavourable Effects						
Exudative AMD	Included the terms neovascular age-related macular degeneration and choroidal neovascularisation	%	PEOM: 6.7	3.1	839 patients in pool 1 safety set, of whom 624 completed treatment through month 24	Section on clinical safety
Intraocular inflammation		%	PEOM: 1.9	0.2		
Endophthalmitis		% subjects with ≥1 event	PEOM: 0.7	0		
Increase in intraocular pressure		% subjects with ≥1 event	PEOM: 2.9	0.7		

Abbreviations: AE = adverse event; AMD = age-related macular degeneration; eAMD = exudative age-related macular degeneration; ETDRS = Early Treatment Diabetic Retinopathy Study; FRI = functional reading independence; IOI = intraocular inflammation; IOP = intraocular pressure; IVT = intravitreal; LS = least-square; MRS = maximum reading speed; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SAE = serious adverse event

6.7. *Benefit-risk assessment and discussion*

6.7.1. Importance of favourable and unfavourable effects

The observed reduction of the GA growth rate is not in itself a clinically relevant benefit and has not translated into an observable clinically meaningful benefit in terms of patient relevant visual function after 24 months of treatment. While it is possible that such might develop after long-term treatment, this has not been demonstrated. It remains unknown when, to which extent and whether at all the slowing of anatomical progression will manifest in a functional benefit for the patient.

The potential risks of regular intravitreal injections with pegcetacoplan, which include the development of exudative AMD, intraocular inflammation (including serious cases of retinal vasculitis, as reported in the postmarketing setting), or endophthalmitis - all of which may lead to a worsening or complete loss of eye-sight - are considered significant.

6.7.2. Balance of benefits and risks

Overall, there are no demonstrated clinical benefits that could outweigh the risks associated with the treatment. Even if considering only the PEOM regimen, due to the lack of demonstrated clinical benefit to the patient with this regimen, a positive benefit-risk balance cannot be concluded for PEOM.

Hence, the benefit-risk of pegcetacoplan in the treatment of GA secondary to AMD in adults is negative.

6.7.3. Additional considerations on the benefit-risk balance

Third-Party Interventions

Third party interventions have been received, submitted by professional societies and patient advocacy organisations. They have intervened at the CHMP with statements in support of a marketing authorisation. In this context, interveners have generally pointed out the unmet medical need and the burden on patients and have supported the importance of the reduction of GA lesion progression, also expressing views on the unsuitability of current instruments to measure visual function, the risk profile of Syfovre, and the importance of microperimetry and of light sensitivity in GA.

The CHMP has taken the third-party interventions into account.

Conditional marketing authorisation

A conditional marketing authorisation was requested by the applicant as part of the re-examination.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating disease

The CHMP considers that the product cannot be recommended for a conditional marketing authorisation as the benefit-risk balance is negative (as discussed), the applicant is unlikely to be able to provide comprehensive data after authorisation, it has not been demonstrated that the product will address an unmet medical need, and the benefits to public health of the immediate availability do not outweigh the risks inherent in the fact that additional data are still required. Detailed for each of the reasons are given below for each of the CMA criteria.

The positive benefit-risk balance of the product.

The demonstrated reduction in lesion growth by ~ 20% (i.e. implying that the additional lesion growth in the treatment group was still around 80% of the growth observed in the control group) in the every other month dosing regimen compared to sham is considered to be modest. The effect of pegcetacoplan to slow the growth of GA lesion (i.e. 0.7mm^2 retinal tissue preserved thorough 24 months and prevention of roughly 1 scotomatous point (uncertain PE in post hoc)) was not sufficient to demonstrate a vision function benefit in the treated patients. There was no trend at all in clinical efficacy endpoints (e.g. maximum reading speed, FRI) at month 24 and a benefit perceived by patients could be only hypothesised. Together with the significant risk of inducing wet AMD and the risk of retinal vasculitis it can be concluded that the risk profile is not acceptable in the context of the non-clinically relevant efficacy results. Therefore, it is considered that based on the provided evidence the benefit risk balance is negative.

It is likely that the applicant will be able to provide comprehensive data

The study proposed by the applicant, aiming at replicating the post-hoc results on the microperimetry parameters, is not expected to address the outstanding uncertainties regarding efficacy. Moreover, if a marketing authorisation would be granted for pegcetacoplan, it will be challenging to conduct a sham/placebo-controlled study. It is therefore considered the applicant has not demonstrated that comprehensive data is likely to be generated.

Fulfilment of unmet medical need

There is a high-unmet medical need for the treatment of geographical atrophy, which is a manifestation of advanced stage dry age-related macular degeneration (AMD). Currently no medicinal products licensed in Europe for the use in GA and no standard of care treatment (medical or surgical) is available that can halt or reverse the progression of geographic atrophy. However, in absence of a demonstrated benefit, Syfovre would not fulfil that unmet need.

The benefits to public health of the immediate availability of the medicinal product outweigh the risks inherent in the fact that additional data are still required

As above, lacking a demonstrated benefit to patients, this criterion cannot be considered fulfilled.

In addition, in view of the negative benefit-risk balance, the CHMP considers that the MA application of Syfovre is not eligible for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004.

6.8. Conclusions

The overall benefit/risk balance of Syfovre is negative.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and therefore recommends the refusal of the granting of the conditional marketing authorisation for the above-mentioned medicinal product.

The CHMP considers that:

- Efficacy of Syfovre has not been sufficiently demonstrated. While an effect on slowing GA lesion growth with every other month pegcetacoplan treatment for up to 24 months was observed, this anatomical effect did not translate into a patient-relevant clinical benefit. At this stage, with the data provided it cannot be answered when and to what extent a certain lesion size reduction (and specifically that achieved by pegcetacoplan administered every other month; PEOM) would turn into perceivable patient benefit. In absence of a clinically relevant benefit to the patient and together with the risks of regular intravitreal injections of Syfovre, which include the development of exudative AMD, intraocular inflammation, or endophthalmitis, the benefit-risk balance of Syfovre in the indication applied for is negative.
- Taking into account the negative benefit-risk balance of Syfovre, a conditional marketing authorisation cannot be granted.

Due to the afore-mentioned concerns, a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures cannot be agreed.

Divergent positions

Divergent positions to the majority recommendation are appended to this report.

8. Appendix

8.1. Divergent position(s) to the majority recommendation

The undersigned members of the CHMP did not agree with the CHMP’s negative opinion recommending the refusal of the granting of the marketing authorisation of Syfovre indicated for Geographic Atrophy (GA).

The reason for divergent opinion was the following:

Geographic atrophy (GA) secondary to age-related macular degeneration (AMD) is a usually slowly progressing disease caused by growing atrophic lesions in the retinal tissue leading to visual function decreases over time. The fovea is often spared late into the disease, thereby retaining central vision in patients. However, vision loss can happen rapidly once the GA lesions reach the fovea.

Currently, no medicinal products or other therapeutic options are available for the treatment of GA in the European Union, emphasizing the high unmet medical need.

The undersigned consider that the B/R of pegcetacoplan in the treatment of GA secondary to AMD is favourable for the following reasons:

- Compelling evidence has been provided that Syfovre reduces the growth of GA lesions with the effect becoming larger over time. This effect is considered clinically meaningful.
- Microperimetry analyses show that the preserved retina retains light sensitivity and is thus functional. Since these analyses were performed post-hoc, the applicant has agreed to confirm the preservation of retinal function in another randomised controlled trial post-approval.

- GA secondary to AMD is slowly progressing with foveal sparing in most patients. Therefore establishing clinical benefit within the placebo-controlled phase of the clinical trials may not have been possible.
- The safety profile of the proposed every-other-month intravitreal injections is acceptable.

CHMP Member(s) expressing a divergent opinion:

Robert Pórszász

Lyubina Racheva Todorova

Helena Panayiotopoulou

Jan Mueller-Berghaus

Anastasia Mountaki

Andreja Kranjc

Janet Koenig

Hrefna Gudmundsdottir

Paolo Gasparini

Frantisek Drafi

Margareta Bego