



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/503729/2024
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Izelvay

International non-proprietary name: avacincaptad pegol

Procedure No. EMEA/H/C/006153/0000

Note

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



List of abbreviations

4 MSU	4 Month Safety Update
ADR	adverse drug reaction
AE	adverse event
AMD	age-related macular degeneration
BCVA	best-corrected visual acuity
C3	complement component 3
C5	complement component 5
CI	confidence interval
C _{max}	maximum concentration
CNV	choroidal neovascularization
CSR	clinical study report
ECG	electrocardiogram
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	fundus autofluorescence
FDA	Food and Drug Administration
GA	geographic atrophy
IND	Investigational New Drug
IOP	intraocular pressure
IPCV	idiopathic polypoidal choroidal vasculopathy
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IVT	intravitreal
KD	dissociation constant
MAC	membrane attack complex
MMRM	mixed-effects model for repeated measures
MRHD	maximum recommended human dose
NAION	non-arteritic anterior ischemic optic neuropathy
nAMD	neovascular age-related macular degeneration
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire 25
NDA	New Drug Application

PEG	polyethylene glycol
PK	pharmacokinetics
PopPK	population pharmacokinetics
PRO	patient-reported outcome
PT	preferred term
RMP	Risk Management Plan
RNA	ribonucleic acid
RPE	retinal pigment epithelium
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SPA	Special Protocol Assessment
TEAE	treatment-emergent adverse event
TEAEI	treatment-emergent adverse event of interest
tmax	time to maximum concentration
US	United States
VEGF	vascular endothelial growth factor

1. CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Izelvay in the treatment of adults with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section VI).>

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Clinical:

- 4. The clinical benefit was not established because it has not been demonstrated whether the reduction in GA lesion growth observed will result in a functional benefit for the patient in terms of visual acuity, furthermore, the safety profile of avacincaptad pegol treatment, including the potential risks associated with the regular IVT injection, adds uncertainty to the B/R balance of the product

1.1. Inspection issues

1.1.1. GMP inspection(s)

Evidence of GMP compliance for all manufacturing and testing sites is available. A GMP inspection is not required.

1.1.2. GCP inspection(s)

Not applicable

1.2. New active substance status

Based on the review of the data, it is considered that the active substance avacincaptad pegol contained in the medicinal product Izelvay is qualified as a new active substance.

1.3. Similarity with authorised orphan medicinal products

Not applicable

1.4. Derogation(s) from market exclusivity

Not applicable

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Izelvay (avacincaptad pegol) is intended to be indicated for the treatment of adults with GA secondary to AMD.

Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD) that leads to progressive and irreversible loss of visual function.

2.1.2. Epidemiology

An estimated 973,000 people in the United States and approximately 5 million globally have GA in at least one eye. In the United Kingdom, GA is estimated to account for 26% of legal blindness. The incidence of advanced AMD increases exponentially with age, with the two forms of advanced AMD, GA and neo-vascular AMD, occurring with roughly equal prevalence. As the population ages, the prevalence of advanced AMD is expected to rise from 9.64 million to 11.26 million in 2020 and 18.57 million in 2040 (Boyer, 2017).

Factors potentially prognostic for an individual's progression rate include lesion features in affected and fellow eyes; genetic, environmental, and demographic factors may also contribute.

2.1.3. Biologic features and pathogenesis

Geographic atrophy secondary to AMD is currently defined by the presence of sharply demarcated atrophic lesions of the outer retina, resulting from loss of photoreceptors, RPE, and underlying choriocapillaris, leading to irreversible loss of visual function and blindness. Although atrophic lesions typically appear first in the perifoveal macula, sparing the foveal center, over time these lesions often expand and coalesce to include the fovea (Fleckenstein, 2018).

By FAF (Fundus Autofluorescence), GA lesions appear as areas of decreased autofluorescence (hypoautofluorescence) due to loss of RPE cells containing intrinsic fluorophores such as lipofuscin. Fundus autofluorescence imaging using a blue excitation wavelength (488 nm) and confocal scanning laser ophthalmoscopy is the predominant modality for assessing GA lesion size and progression. Flood-illuminated and green-wavelength widefield FAF systems also are available (Fleckenstein, 2018).

The pathogenesis of GA is multifactorial and is generally thought to be triggered by intrinsic and extrinsic stressors of the poorly regenerative RPE, particularly oxidative stress caused by the high metabolic demand of photoreceptors, photo-oxidation, and environmental stressors such as cigarette smoke. With aging, the damage caused by these stressors accumulates, resulting in the appearance of drusen (extracellular) and lipofuscin (intracellular) deposits. Components of drusen (cellular debris, lipids, lipoproteins, amyloid deposits) and lipofuscin (by-products of photoreceptor outer-segment degradation, A2E), as well as other products of oxidative stress such as advanced glycation end products, are thought to trigger inflammation via multiple pathways, such as the complement cascade and the NLRP3 inflammasome. When the regulatory components in these pathways are compromised, as is the case with several GA-linked genetic risk factors in the complement cascade, this inflammation can ultimately lead to the retinal cell death characteristic of GA (Boyer, 2017).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Geographic atrophy is a progressive disease, and progression rates can vary depending on baseline size, atrophy location, and the patterns of autofluorescence surrounding atrophic areas on FAF images. Geographic atrophy lesions are often multifocal, and the total atrophic area in eyes with multifocal lesions has been reported to grow faster than in eyes with unifocal lesions (Boyer, 2017).

As GA impacts the visual field to varying degrees depending on lesion location, tasks dependent on full-field central vision such as reading may be impaired to a greater extent than is apparent from BCVA. Patients with early/intermediate AMD and GA experience increased visual impairment under

low-light conditions. Deficits in visual acuity under reduced illumination (low luminance visual acuity; LLVA) may precede and be larger than losses in BCVA under normal illumination (Boyer, 2017).

2.1.5. Management

There are currently no drugs 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.

CHMP early contact with patient and consumer organisations

In August 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 and depression, non-compliance in comorbidities, becoming a burden, erosion of independence, isolation and inclusion. 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

Avacincaptad pegol is a chemically synthesized oligonucleotide that is covalently bound to a branched 40 kDa PEG molecule.

It functions by specifically binding to human C5 with high affinity, inhibiting cleavage of C5 into C5a, and preventing C5b from joining with C6. The ribonucleic acid (RNA) aptamer is polyethylene glycol (PEG)ylated to confer stability to the molecule against biodegradation and delayed clearance in vivo without diminishing its activity, ultimately contributing to its efficacy in patients with GA.

The claimed indication is the treatment of adults with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

2.3. The development programme/compliance with guidance/scientific advice

There was no scientific advice.

There is no guideline in the claimed indication.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

A valid QP declaration for all drug substance manufacturing sites is provided. Evidence of GMP compliance for all drug product manufacturing and testing sites is available.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.5.2. PRIME

Not applicable.

2.5.3. Accelerated assessment

Not applicable.

2.5.4. Conditional marketing authorisation

Not applicable

2.5.5. Marketing authorisation under exceptional circumstances

Not applicable

2.5.6. Biosimilarity

- Not applicable

2.5.7. Additional data exclusivity/ marketing protection

- Not applicable

2.5.8. New active substance status

The applicant requested the active substance avacincaptad pegol contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union. Assessment of this claim is appended.

2.5.9. Orphan designation

Not applicable.

2.5.10. Similarity with orphan medicinal products

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.

2.5.11. Derogation(s) from orphan market exclusivity

Not applicable.

2.5.12. Information on paediatric requirements

Not applicable

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

Avacincaptad pegol is a chemically synthesised ribonucleic acid aptamer conjugated with polyethylene glycol (PEG). Avacincaptad pegol drug product (DP) is formulated at a nominal concentration of 20 mg/mL (oligonucleotide basis) in phosphate buffered saline. The finished DP is a preservative-free, sterile, aqueous solution compounded with compendial excipients such as dibasic sodium phosphate heptahydrate and monobasic sodium phosphate monohydrate, sodium chloride and water for injection, intended for single-dose intravitreal (IVT) injection. The commercial DP is packaged in a 2R (ISO) vial. Each vial contains a slight overfill to permit administration of a 0.1 mL (100 µL) IVT dose.

The final commercial presentation of avacincaptad pegol includes a co-packaged, sterile, 18 Gauge 1½ inch filter needle, a 1 mL Luer-Lok™ empty syringe, and the DP vial. Both intended devices, filter needle and syringe, are commercially available with CE marks and are used in the ongoing clinical studies (OPH2005 and ISEE2009). Each medical device is in its own primary packaging (sterile barrier) within the kit.

3.1.2. Active substance

General Information

International non-proprietary name (INN):	Avacincaptad pegol
United States Adopted Name (USAN):	Avacincaptad pegol sodium
Chemical names:	Poly(oxy-1,2-ethanediyl), α-hydro-ω-methoxy-, 5'-ether with RNA ((2'-deoxy-2'-fluoro)C-Gm-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-G-(2'-deoxy-2'-fluoro)C-Gm-Gm-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-Am-Gm-Gm-(2'-deoxy-2'-fluoro)C-G-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-Gm-Am-Gm-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-Gm-Am-Gm-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-A-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-Gm-(2'-deoxy-2'-fluoro)C-Gm-(3'→3')-dT) 5'-[6-[[[(2,3-dihydroxypropoxy)carbonyl] amino]hexyl hydrogen phosphate], sodium salt (2:1:39).
Molecular formula:	non-PEGylated aptamer, free acid form: C ₃₈₉ H ₄₈₂ N ₁₄₂ O ₂₅₈ P ₃₉ F ₂₁ Avacincaptad pegol, free acid form: C ₃₉₅ H ₄₉₂ N ₁₄₂ O ₂₆₂ P ₃₉ F ₂₁ ((CH ₂) ₂ O) _n where n~970
Relative molecular mass:	non-PEGylated avacincaptad pegol: 12,882 Da average mass (free acid form) Avacincaptad pegol: 12,882 Da + ~43,000 Da PEG = ~55,882 Da

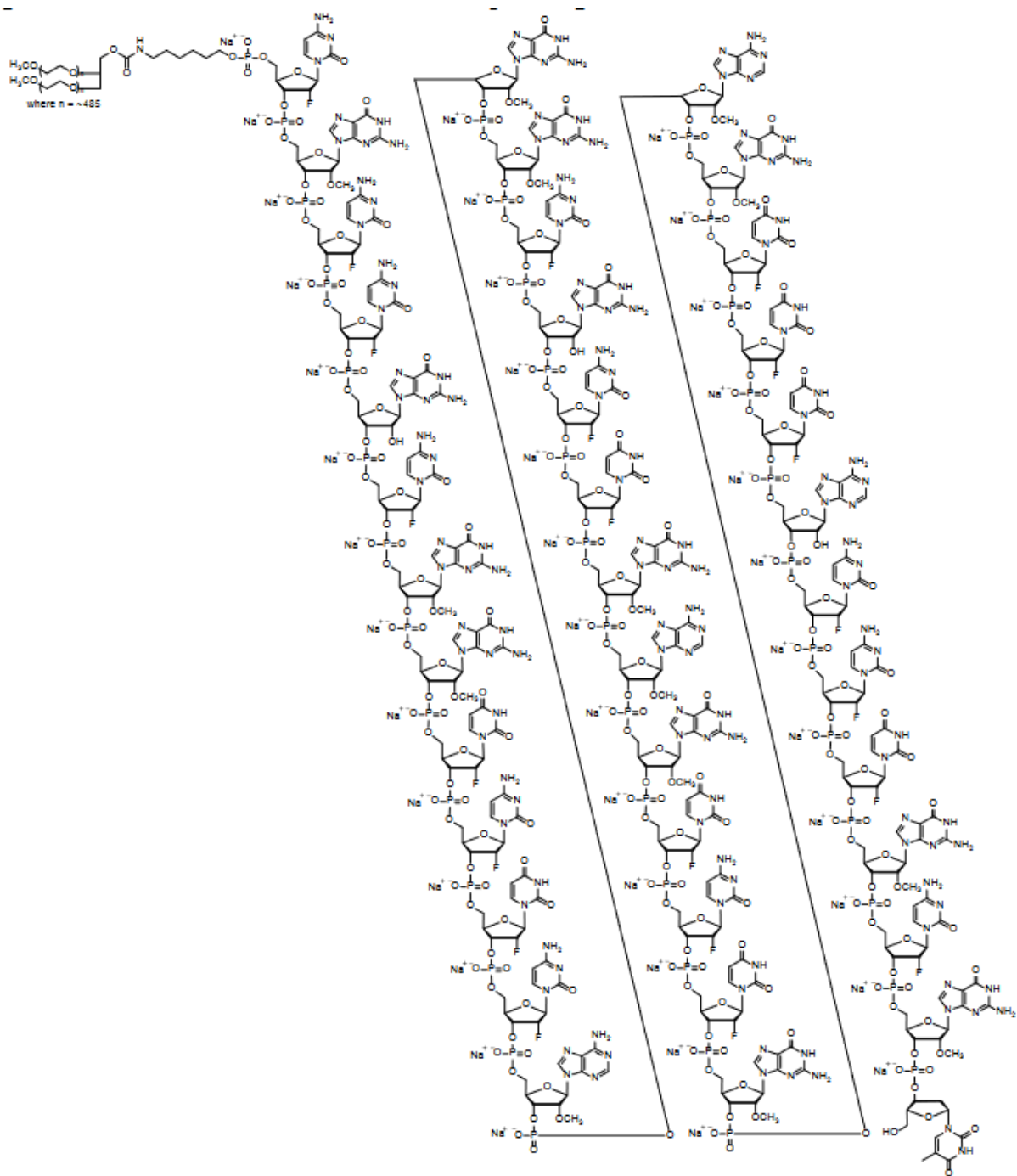


Figure 1: Chemical Structure of Avacincaptad Pegol Sodium

Avacincaptad pegol is a PEGylated 39-mer oligonucleotide having the following sequence:

5'-[43 kDa PEG]-NH₂ C6-fC-mG-fC-fC-rG-fC-mG-mG-fU-fC-fU-fC-mA-mG-mG-fC-rG-fC-fU-mG-mA-mG-fU-fC-fU-mG-mA-mG-fU-fU-fU-rA-fC-fC-fU-mG-fC-mG-idT-3'

Legend:

rA, rG = 2'-ribonucleotides (Adenosine, Guanosine)

fC, fU = 2'-fluoronucleotides (Cytidine, Uridine)

mA, mG = 2'-O-Methyl nucleotides (Adenosine, Guanosine)

idT = inverted 2'-deoxyribonucleotide (Thymidine)

NH₂ C6 = Hexylamino Linker

43 kDa PEG = 2,3-Bis(methylpolyoxyethylene-oxy)-1-yl propyl carbonate

Length: 39mer + linker+ PEG

Backbone: Phosphodiester

The sugar nucleotides are all 2-modified (fluoro or methoxy) except for three unmodified ribose residues. The 5' terminus is occupied by an aliphatic chain linker (hexylamino) at the end of which a glycerol residue is attached; the other two hydroxyls of the glycerol are replaced by two long polyethylene glycol (PEG) chains. Overall the PEG moiety constitutes the vast majority of the molecule mass and only ~ 24% is the oligonucleotide.

Manufacture, process controls and characterisation

Description of Manufacturing Process and Process Controls (CTD section: S.2.2)

Manufacture of avacincaptad pegol starts with synthesis of the non-PEGylated avacincaptad pegol (non-PEGylated ACP). Non-PEGylated ACP is then purified and concentrated prior to PEGylation. After PEGylation, the crude avacincaptad pegol is purified, concentrated, and lyophilized to produce the final drug substance.

The manufacturing process is a classical solid phase supported assembly of the oligonucleotide chain using conventional 5'-DMT protected phosphoramidites. A description of manufacturing process and process controls, which also includes a Flow diagram, is provided and is sufficiently detailed but certain significant process parameters are missing from the description (OC). Other elements of the control strategy, i.e. in-process controls & control of critical parameters as well as control of starting materials, also appear deficient.

Control of materials (CTD section: S.2.3)

ACP is synthesised using well defined starting materials with acceptable specifications. One of the initially proposed starting materials (A) was not considered acceptable by CHMP resulting in a major objection (MO). In response, the applicant re-defined A as an intermediate and tightened its specification. An earlier material was defined as a starting material which was considered acceptable by CHMP.

Critical Process Parameters

The criticality of quality attributes and process parameters for the manufacturing process of ACP was examined by risk assessment. The critical quality attributes (CQAs) that have an impact on the quality of ACP and critical and non-critical process parameters have been identified. No design space is declared. PARs and NORs have been studied and established for the relevant process parameters and in-process parameters. All operating ranges proposed in the finalised manufacturing process have been sufficiently justified. An adequate control strategy is in place for all critical quality attributes. Impurity specifications and limits were amended during the procedure in response to a MO and are considered acceptable. The limits proposed have been qualified in non-clinical studies.

Manufacturing Process Development (CTD section: S.2.6)

A technical risk assessment using FMEA was conducted for the avacincaptad pegol drug substance manufacturing process. The risk assessment was performed to identify and score each processing risk and/or process parameter based on the impact to the quality of the drug substance and consistency of

the manufacturing process. The risk assessment process was also used to identify the scope of needed characterization activities (studies and assessments).

Following the conclusion of the risk assessment, studies were performed to characterize process parameters associated to actionable risks. Those process parameters identified were evaluated using Design of Experiments (DoE) and/or One-Factor-at-A-Time (OFAT) studies.

After performing what appears to be an "initial" FMEA risk assessment of the process, several process parameters were selected for further "characterisation studies". Details of the "Characterisation Studies" mentioned in section S.2.6 were provided. The applicant presents in section S.2.6 several PARs for the same process steps. However, the applicant claims that PARs are not intended to be used during routine manufacture but only at set-point. (OC)

Elucidation of structure and other characteristics (CTD section: S.3.1)

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. The methods used for characterisation appear adequate for establishing the correct nucleotide sequence and correct linkage for conjugation of the PEG chains; however, insufficient information is provided in the dossier to establish full characterisation in particular regarding nucleotide sequence confirmation and secondary structure (OC). Information is provided regarding the 3-dimensional structure which is essential for the biological activity of the aptamer. Information about the aggregation potential & the stereochemistry of the active substance were provided.

Impurities (CTD section: S.3.2)

Potential and actual impurities, including small molecules, truncated/deletion oligos/insertion/base modifications, PEG-derived, solvent and elemental impurities, were well discussed with regards to their origin and characterised.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification (CTD section: S.4.1)

The active substance specification includes tests for appearance (visual), oligonucleotide content, identification, purity, impurities, polydispersity, pH of a 1% solution, residual solvents, elemental impurities, sodium content, moisture, bacterial endotoxin, and bioburden. Analytical procedures were described in sufficient detail.

Validation of analytical procedures is generally in accordance with ICH.

Batch analysis results were provided; these confirm consistency & uniformity of the product within the analytical capabilities of the used analytical methods. The provided batch data justified the proposed specification limits.

The current reference standard for Avacincapted Pegol has been adequately qualified.

The choice of the container/closure appears justified. The containers proposed for routine storage are those which have been used in the stability studies supporting the re-test period. The specifications for the CCS are provided and include an identification test.

Stability

The stability studies are carried out in accordance with ICH guidelines. The batches included in the stability study are representative of the commercial manufacturing process and are in sufficient number. The parameters tested in the studies are those in the proposed specifications.

The retest period is considered justified based on the real time data presented.

3.1.3. Finished medicinal product

3.1.3.1. Description of the product and pharmaceutical development

The composition is summarised in section 3.1.1. (Introduction). The drug product is a preservative-free, sterile, aqueous solution intended for single dose intravitreal administration.

No overage is added but overfill has been proposed.

The drug product is manufactured by the following process –dissolution of different compounds, sterile filtration, aseptic filling and packaging.

The development approach is based on an understanding of the relationship between formulation inputs and manufacturing process parameters on the critical quality attributes (CQAs) of the drug product.

The critical quality attributes (CQAs) for drug product were defined based on an appropriate quality target product profile.

The functional relationships and process understanding gained were utilized in constructing the control strategy for the drug product which consists of control of material attributes (drug substance related), control of the critical process parameters, critical in process controls and release testing.

A liquid formulation (solution for injection) of drug product was developed and utilized in all clinical studies. The drug product concentration, the pH and the buffer strength have been sufficiently justified.

The finished/commercial drug product contains the drug product vial and two medical devices (a sterile, 1 mL - from 0.1 ml to 1.0 ml for the main graduation (with an intermediate graduation of 0.01 ml), Luer-LokTM empty syringe BD, and a sterile, 18 Gauge, 1½ inch filter needle BD) in a secondary carton with a package insert. Both medical devices are CE-marked and seem adequate to sample the solution from the vial and to deliver an accurate dose.

A detailed overview of the drug product manufacturing process development history is presented summarizing the main changes and the rationale of change as well as a comparability between the different processes.

The optimization and robustness of the proposed manufacturing process was conducted according to “ICHQ8 principle” and a classical approach to establish PARs and/or NORs. However, the manufacturing process flexibility sought by the applicant is unclear and compliance with Q&A Improving the understanding of NORs, PARs, DSP and normal variability of process parameters” should be confirmed.

Besides, based on the development results and batch analysis, the proposed control strategy may be considered as adequate for the type of dosage form and drug product.

The primary closure system of the drug product is a glass vial with a rubber stopper which may be also considered as suitable. Moreover, the integrity of the co-packaged kit is considered as demonstrated to ensure the whole sterility of different compounds of the kit.

In order to demonstrate the compatibility between the drug product and the different devices (syringes and needles) intended for the market, an in use stability study was carried out. All results in terms of quality attributes comply with drug product specifications and the drug product may be considered as compatible with the different devices (syringe, filter needle and injection needle). Nevertheless, regarding the in use stability study, few information has been provided on the number of samples used, the age of samples and the batch number, batch size, manufacturing process used and manufacturing site. That information should be properly provided.

3.1.3.2. Manufacture of the product and process controls

The drug product manufacturing process consists of a Phosphate Buffer Preparation, a Drug Substance (DS) Equilibration and Pooling, a Compounding followed by a Sterile Filtration and an Aseptic Filling, Stoppering and Crimping, Storage and Shipping and Labeling. IPCs are adequate for the drug product and the manufacturing process.

Validation data have been presented and are considered adequate.

3.1.3.3. Product specification, analytical procedures, batch analysis

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), clarity, colour, oligonucleotide content, biological activity, identification, purity, impurities, polydispersity, pH, osmolality, viscosity, content uniformity, particulate matter, extractable volume, bacterial endotoxin, sterility, CCI.

Moreover, several OC remain not solved regarding unspecified impurities and total impurities, as well as sterility testing.

Globally, the analytical methods are sufficiently detailed.

In terms of characterization, the section is at this stage considered as satisfactory regarding the evaluation of all components and possible sources of elemental impurities and the evaluation of potential risk for nitrosamine impurity on the finished drug product.

3.1.3.4. Stability of the product

Registration batches were packed in 2 mL (ISO 2R), clear, USP Type I glass vial, closed with a FluroTec® coated, chlorobutyl rubber stopper and over sealed with an aluminum crimp seal. Results have been provided for stability studies performed according to ICH conditions (at long term conditions (5 ± 3 °C) and accelerated conditions (25 ± 2 °C / $60 \pm 5\%$ RH)) for those batches (up to 24 months). Moreover, supporting stability data have also been presented up to 48 months under long term conditions in order to support the proposed 36 months shelf life.

3.1.3.5. Post approval change management protocol(s)

N/A

3.1.3.6. Adventitious agents

No raw materials from animal or human origin are utilized in the manufacturing of the drug substance and drug product.

3.1.3.7. GMO

N/A

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Quality sections of the dossier cover the general and specific attributes of the proposed drug substance and drug product. Three major objections were resolved following the receipt of the Day 180 list of outstanding issues: the synthetic scheme was modified, the specifications for specified impurities were changed, and a test was added to the specifications.

3.2. Non-clinical aspects

3.2.1. Introduction

Izelvay, is a polyethylene glycol (PEG)-conjugated RNA aptamer intended for the treatment of adults with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). GA is associated with AMD and causes progressive and irreversible loss of retinal tissue (photoreceptors, retinal pigment epithelium [RPE], and choriocapillaris) leading to a permanent loss of visual function and blindness.

The complement pathway and C5 have been identified as important mediators of inflammation in AMD with complement proteins detected in the subretinal drusen deposits characteristic of GA.

Dysregulation of the complement system is thought to be a central and underlying cause leading to the pathogenesis of GA. C5 activation and C5a formation may serve as the link between lipofuscin accumulation, photo-oxidative damage, inflammasome formation, and cell lysis that causes RPE and photoreceptor degeneration in AMD.

Avacincaptad pegol is a novel inhibitor of complement activation that acts by binding to human complement component 5 (C5) with high affinity and specificity.

Avacincaptad pegol drug product is a sterile, aqueous solution for intravitreal injection. It is formulated at a concentration of 20 mg/mL (oligonucleotide mass) in a phosphate-buffered saline. The recommended dose is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal (IVT) injection once monthly (approximately 28 ± 7 days) for up to 12 months.

The nonclinical program for avacincaptad pegol has been focused on compound potency, target engagement, selectivity, PK, safety pharmacology, and toxicology, as suitable animal models of GA that are both relevant to human disease phenotype and predicted to be responsive to avacincaptad pegol are not available.

Pharmacodynamics of avacincaptad pegol was assessed throughout in vitro and in vivo studies. Toxicological studies were conducted after IV or IVT injections in various species. Genotoxic potential of ARC1905 was investigated throughout a standard battery for genotoxicity testing in line with the ICH recommendations.

Carcinogenicity studies with avacincaptad pegol were not conducted based on the rationale provided by the applicant.

Reproductive toxicology evaluation of avacincaptad pegol included preliminary and definitive EFD studies in S-D rats and NZW rabbits. Other developmental and reproductive toxicity (DART, i.e., fertility and early embryonic developmental and pre- and post-natal developmental) studies were not conducted based also on rationale provided by the applicant.

Local tolerance was assessed during the course of IV and IVT toxicity studies in the respective selected species as previously indicated.

No European scientific advice from EMA/CHMP has been requested by the company prior to submission.

A pre-submission meeting with the (Co)-Rapporteurs was conducted via videoconference on the 28th of April 2023, where the applicant was advised to justify the relevance of the species used for the nonclinical assessment in the MAA.

3.2.2. Pharmacology

A comprehensive series of nonclinical pharmacology studies was conducted to characterize the mechanism of action, primary and secondary pharmacologic effects, and safety pharmacology profile of avacincaptad pegol, consistent with International Council for Harmonisation (ICH) guidelines S7A and S7B. The nonclinical pharmacology program included both in vitro and ex vivo studies designed to characterize the effect of avacincaptad pegol on complement function and confirm inhibition of C5 cleavage. The primary pharmacology studies included binding assays, complement activity inhibition assays and radioligand binding assays, while the secondary pharmacology studies investigated potential "off-target" effects of avacincaptad pegol.

Pharmacology studies were also conducted using a bioequivalent compound identical to avacincaptad pegol except for the source of the PEG [ARC187], and the non-PEGylated C5- binding oligonucleotide portion of avacincaptad pegol with a 5' primary amine [ARC672] or a 5'-hydroxyl terminus [ARC186], in order to evaluate binding of the aptamer to C5 in the absence of PEG.

Avacincaptad pegol is intended to be administered once monthly by intravitreal (IVT) injection however in vivo studies under IV injection were performed in an initial non-clinical development.

3.2.2.1. Primary pharmacodynamic studies

Various in vitro studies (C5-PHARM-001-05, C5-PHARM-002-05, C5-PHARM-003-05, C5-PHARM-004-05 and C5-PHARM-005-05) have been conducted in order to evaluate binding properties and complement activation inhibition.

The aim of Study C5-PHARM-001-05 was to determine the binding affinity and specificity of ARC186 (non-PEGylated C5-binding oligonucleotide) binding to C5 relative to other serum proteins (complement components, coagulation factors); and to demonstrate that conjugation with a high molecular weight PEG moiety (product ARC 1905) has no effect on C5 affinity. It was shown that binding towards C5 human at 25°C was similar with ARC186 binding to C5human equals to 0.14 ± 0.036 nM and ARC1905 binding to C5human to 0.15 ± 0.048 nM respectively. In addition, binding specificity was demonstrated since no recognition towards C1q, C3, C4, C5a des Arg, C6 or the complement regulatory proteins, Factor B and Factor H.

Study C5-PHARM-002-05 was conducted in order to assess the effect(s) of avacincaptad pegol on classical pathway (antibody/antigen-dependent) activation via a sheep erythrocyte hemolysis assay in the presence of human or cynomolgus monkey complement components. It was shown that PEG-conjugation has little effect on human complement activation pathway and ARC190 is less potent in cynomolgus than human (6-fold based on IC50 value: IC50human (ARC1905) ≈ 0.6 nM vs IC50cynomolgus (ARC1905) ≈ 3.65 nM / 17 fold based on IC99 value: IC99human (ARC1905) ≈ 5.09 nM vs IC99cynomolgus (ARC1905) ≈ 87.2 nM). It was addressed by the applicant that pharmacological activity in cynomolgus is 1/10th of the human pharmacological activity.

Study C5-PHARM-003-05 was conducted in order to evaluate the effect(s) of avacincaptad pegol on alternative complement pathway activation utilizing zymosan to activate complement. Inhibition of C5 pathway was measured via C5a levels, complete inhibition of C5 activation via the alternate pathway was achieved and it was confirmed that ARC1905 was less potent in cynomolgus (IC50=536 nM / IC90=1810 nM / IC99=6900 nM) than in humans (IC50=196 nM / IC90=442 nM / IC99=1090 nM). Up to a concentration of Up to 2 μ M no inhibition of C3a generation was noted.

Study C5-PHARM-004-05 describes evaluation of avacincaptad pegol in a simple in vitro Cardiopulmonary bypass (CPB) model. CPB circuits stimulate complement activation through alternate pathway induction at blood/surface and blood/air interfaces. Inhibition of complement cascade was evaluated by measuring levels of C5a and C3a. 1hr of circulation was sufficient to induce complement system activation in CPB model. Whereas generation of C3a fraction was not altered, inhibition of the formation of C5a fraction was noted with $IC_{99} = 1261 \pm 438$ nM in plasma.

Evaluation of anti-complement activity across species (human, cynomolgus and Sprague-Dawley rats) using a sheep erythrocyte hemolysis assay, was performed throughout Study C5-PHARM-005-05. It was highlighted that IC_{50} (human) = 0.35 ± 0.90 nM < IC_{50} (cynomolgus) = 3.69 ± 0.60 nM << IC_{50} (SD-rat) = and 2700 ± 470 nM.

PD related to C5 inhibition was assessed in monkeys during in vivo in the cardiovascular and respiratory safety pharmacology study (Study KSH00039, GLP-status), single-dose toxicity study (Study KSH00033, GLP-status) and repeated dose toxicity (Study KSH00040, GLP-status). In all those studies, blood samples were collected for evaluation of PD parameters [ex vivo inhibition of animal total complement function (ATCF), assessed via inhibition of complement-mediated hemolysis of antibody-coated sheep RBC (sRBC) or zymosan-mediated complement alternative complement pathway activation to yield C5a] ().

In Study KSH00039, all tested doses of avacincaptad pegol have shown to be consistently associated with > 95% inhibition of ATCF at all the time-points. Doses have been selected in order to induce $C_{max} > 130$ µg/mL (10µM) in monkeys (targeted concentration). 0.5 and 2 hrs after dosing, a dose of 10 mg/kg was sufficient to inhibit ATCF (inhibition > 95%) and inhibition of zymosan-mediated generation of C5a of 69% to 78%.

In Study KSH00033, all tested doses (0.1x, 0.3x, 1x, 3x and 10x target concentration) were chosen in order to induce equal or higher concentrations in plasma than the targeted concentration of 130 µg/mL (10 µM) in cynomolgus. It was noted that dose higher than 28.7 mg/kg was suitable to induce an inhibition of ATCF $\geq 98\%$ that can be maintained over a 24-hour infusion. Maximal inhibition of the complement activity was observed in the sheep erythrocyte hemolysis assay at 287 mg/kg (dose-dependent effect) with an effect of 81%.

In Study KSH00040 and as observed in Studies KSH00030 and KSH00033, concentrations higher than 130 µg/mL were associated with > 86% inhibition of ATCF at all the time-points.

3.2.2.2. Secondary pharmacodynamic studies

During the non-clinical development of avacincaptad pegol, affinity for other targets than C5 was investigated against a panel of rat and human proteins was evaluated using radioligand binding assays (Study No. 1059148). In *Study No. 1059148*, the affinity of avacincaptad pegol against a panel of rat and human proteins was evaluated using radioligand binding assays. ARC1905 was able to partially inhibit radioligand binding for 13 proteins (8 human and 5 rat proteins respectively) out of 160 proteins screened, with IC_{50} values for the human proteins ranging from 0.268 to 10.6 µM (3.45 to 136.6 µg/mL).

Oligonucleotides therapeutics have been associated with inhibition of the intrinsic coagulation system, thus the applicant has investigated that potential "off-target" effect (not related to C5 inhibition) of avacincaptad pegol, in vitro (Study C5-PHARM-006-05) and in vivo in cynomolgus monkeys (Study KSH00039, Study KSH00033) and S-D rats (Study KSH00039).

In cynomolgus, ARC1905 intravenous dosing ≥ 30 mg/kg has been shown to induce moderate increase in APTT (76% to 80%) and mild decrease fibrinogen concentrations (-33% to -45%) as reported in *Study KSH00039*. At 100mg/kg, minimal to mild prolongation of PT (11% to 19%) was reported.

In the SDRF (*Study KSH00033*) toxicity study in cynomolgus, ARC1905 was not associated with prolongation of APTT at all the tested doses.

In SD-rats, ARC1905 was associated with mild to moderate prolongation of APTT, but there was no clear correlation with plasma concentration as reported in *Study KSH00038*. Moderate effects on coagulation parameters PT and fibrinogen were also observed.

An in vitro study (*Study C5-PHARM-006-05*) was conducted in order to evaluate potential “off-target” anticoagulant and complement-activating effects of avacincaptad pegol that do not necessarily relate specifically to its C5-blocking function. The anticoagulant properties of avacincaptad pegol were evaluated by clot time analysis, using the activated partial thromboplastin time (APTT) and the prothrombin time (PT) assays. ARC1905 has shown to have a mild anticoagulant activity in human plasma, with prolonging APTT 1.7-fold at 2 mg/mL and with little or no effect on the PT.

3.2.2.3. Safety pharmacology programme

Safety pharmacology was investigated in vivo in monkeys (*Study KSH00039*) and rats (*Study KSH00043*) species and in vitro throughout hERG assay (*Study 050601.BTE*).

Standard hERG assay (*Study 050601.BTE*) was performed with ARC1905 at 10 and 100 µM (1288.2 µg/mL) with cisapride at 90 nM used as positive control. Inhibition of the hERG channel lower than 1% was observed at 10 µM of ARC1905 and around 10 % when challenged with 100 µM. Thus it was not possible to determine the IC₅₀ corresponding value but still considered >> 100 µM.

The objectives of *Study KSH00039* were to identify potential unexpected pharmacologic effects of single IV injections of ascending doses of avacincaptad pegol (0, 10, 30 and 100 mg mg/kg) on the cardiovascular and respiratory systems. No mortality nor effect on cardiovascular and respiratory systems were recorded at all the tested doses.

The objective of the GLP-compliant *Study KSH00043* was to assess the potential for neurotoxic effects in SD-rats after a single bolus IV administration of avacincaptad pegol (0, 26, 100, 260 mg/kg). Whereas avacincaptad pegol is pharmacologically active against C5 in monkeys, it is not in rats. Up to 260 mg/mL no effect on the central nervous system was observed and this dose was set at the NOAEL of the study

3.2.2.4. Pharmacodynamic drug interactions

PD-drug interactions were studied (*Study C5-DI-001-05*) in SD-rats (male) using an equivalent of avacincaptad pegol named ARC187. Difference between avacincaptad pegol and ARC187 relies on the PEG's supplier source. Potential of ARC187 to affect heparin-induced activated clotting time (ACT) values and/or their reversal with protamine, was then investigated. Although, Avacincaptad pegol has shown a weak affinity for protamine in vitro (K_D = 150 ± 27 nM based on data from an identical aptamer, ARC187). The PD- drug interactions study conducted in SD-rats (*Study C5-DI-001-05*) has demonstrated that avacincaptad pegol (ARC187 mean plasma concentration up to 13.60 µM (175 µg/mL) did not interfere with heparin or protamine activity in vivo in rats.

3.2.3. Pharmacokinetics

Avacincaptad pegol concentrations in plasma, vitreous and aqueous fluids, and retinal tissue, were determined by a validated colorimetric hybridization assay (LLOQ of 0.004 µg/mL); a validated electrochemiluminescent hybridization assay (LLOQ of 4 ng/mL); a validated method using high performance liquid chromatography (HPLC) with ultraviolet detection (LLOQ: 0.820 µg/mL); or by non-validated HPLC methods. Avacincaptad pegol radiolabeled concentrations were estimated plasma, blood, faeces and urine of rats by LSC counting method.

Absorption

The systemic PK profile of avacincaptad pegol was characterized following IV administration in CD-1 mice, S-D rats, and cynomolgus monkeys, and IVT administration in NZW rabbits and beagle dogs.

Study C5-PK-001-05 was conducted in female CD-1 mice (3/F/time point). Each animal was administered either ARC187 or avacincaptad pegol by IV bolus injection via the tail vein at 10 mg/kg. Blood samples were obtained by terminal cardiac puncture at pre-dose, and at 0.5, 1, 2, 4, 8, 16, 24, 32, 48, and 72 hours post-dose. Plasma concentrations of test articles were analysed using a validated HPLC assay with UV detection (LLOQ 0.82 µg/mL; calibration curve 0.82 to 410 µg/mL). It was observed the following parameters: a $t_{1/2}$ of 2.23 hours, C_{max} of 259,576 ng/mL and AUC_{0-last} and 912,656 ng·hr/mL. ARC1905 and ARC187 were found to be bioequivalent based on comparisons of mean C_{max} , AUC_{0-last} and AUC_{0-∞} parameter estimates.

The objective of Study C5-PK-002-05 was to determine the pharmacokinetic profile of avacincaptad pegol and 17-[³³P]-avacincaptad pegol after IV bolus injection to male SD- rats (3M/group). Animals were administered avacincaptad pegol or 17-[³³P]-avacincaptad pegol at a nominal dose target of 10 mg/kg (corresponding activity was 54.778 µCi/kg for 17- [³³P]-ARC1905) in a dose volume of ~1.333 mL/kg. Blood was collected at the following time points: pre-dose, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, and 144 hr post dose administration. Plasma concentrations of test articles were analysed using a validated HPLC assay with UV detection (LLOQ 0.82 µg/mL; calibration curve 0.82 to 410 µg/mL). The concentrations of avacincaptad pegol are based on the mass of aptamer, excluding the mass of PEG. The plasma samples obtained from rats dosed with radiolabeled 17-[³³P]-ARC1905 were analyzed by liquid scintillation counting (LSC) for avacincaptad pegol -equivalent concentrations based on specific activity (3.877 µCi/mg). Avacincaptad pegol or avacincaptad pegol -equivalent concentrations in plasma were similar for the first 4 hours post-dose with ARC1905 plasma concentrations declining at a faster rate than the plasma concentration of 17-[³³P]-ARC1905. By 72 hours post-dose, avacincaptad pegol was no longer detectable in plasma by HPLC, while radioactivity associated with 17-[³³P]-ARC1905 was still detected in plasma up to 144 hrs post-dose. The mean C_{max} for ARC1905 or 17-[³³P]-ARC1905 dose groups were similar with values at 239 µg/mL and 204 µg equivalents/ mL, respectively. The AUC values for 17-[³³P]-ARC1905 dose group were approximately 1.5-fold higher than the AUC values for ARC1905 dose group. The $t_{1/2}$, MRT values, for 17-[³³P]-ARC1905 dose group because of the presence of 17-[³³P]-ARC1905 and/or its metabolite that were detected by LSC up to 144 hours-post dose. The CL rate of avacincaptad pegol or 17-[³³P]-ARC1905 were similar, approximately 2.2% and 1.5% of the glomerular filtration rate (GFR, ~314 mL/hr/kg). The V_z and V_{ss} values for the ARC1905 or 17-[³³P]-ARC1905 dose groups were approximately 1- to 2-fold greater, respectively, than the rat blood volume (54 mL/kg). In the blood, the decline of avacincaptad pegol -equivalent concentration was bi-phasic and lower than plasma following a single IV administration of 17-[³³P]-ARC1905 to rats. The blood to plasma ratio was approximately 19 at 144 hours post-dose suggesting association of radiolabeled 17-[³³P]-ARC1905 and/or its metabolites with the cellular fraction of the blood.

TK in cynomolgus has been assessed after IV dosing during the course of the safety pharmacology study (Study KSH00039), single and repeated-dose toxicity studies (Study KSH00033 and Study KSH00040).

Regarding TK profiles estimated in the safety pharmacological study in cynomolgus it was seen that following IV bolus administration of ARC1905, the C_{max} and AUC_{0-last} values increased linearly and proportionally to increasing ARC1905 total doses of 10, 30 and 100 mg/kg. The MRT_{0-last} values were found to be similar across the dose-range tested.

In *Study KSH00033*, it was overall observed no gender differences in TK parameters. In females, C_{max} increased proportionally and linearly to the dose increase up to 287 mg/kg. In males, C_{max} increased proportionally and linearly to the dose increase up to the dose of 86.2 mg/kg but less linearly at 287

mg/kg. Half-life for males ranged between 43.2 to 68.7 hrs and from 41 to 67 hrs for females respectively. After IV administration in cynomolgus, it was observed that avacincaptad pegol was highly distributed and with a low clearance.

In *Study KSH00040*, it was noted that C_{max} and AUC_{0-last} values increased in a linear and proportional manner with increasing avacincaptad pegol total doses of 141, 423, and 1410 mg/kg. No gender differences regarding AUC_{0-last} values. It was observed a high volume of distribution (11-fold greater than monkey blood volume) with a low clearance.

TK in SD-rats has been assessed after IV dosing during the course single and repeated-dose toxicity studies (*Study KSH00038* and *Study 501280*).

In *Study KSH00038*, C_{max} in female rats increased proportionally to the dose increase up to the 54 mg/kg, and less than proportionally to dose increase at 100 to 800 mg/kg. In male rats, C_{max} increased less proportionally to the dose increase at 10 to 800 mg/kg. Regarding AUC_{0-last} values, increased proportionally and linearly to the dose increase in females whereas in male rats it was observed that the increase was less than proportionally to the dose increase. Half-life ranged from 5.7 to 17.2 hrs in male and from 4.5 to 25.7 hrs in female respectively.

In *Study 501280*, C_{max} and AUC_{0-last} values increased in a linear and proportional manner with increasing avacincaptad pegol total doses. CL was found similar across the total dose range tested. TK parameters were also determined in the two definitive EFD studies in pregnant SD rats (*Study 20334075*) and NZW rabbits *Study 20332454* species after IV dosing.

In *Study 20334075*, it was noted that the exposure in rats increased generally in a less than dose proportional manner over the dose range tested on both gestation day (GD) 6 and GD 17.

In *Study 20332454*, it was observed that the exposure in rabbits after IV administration, did generally increase in a more than dose proportional manner over the dose range tested on both GD 7 and GD 19.

Since IVT is the intended route of administration in clinics thus TK profile was investigated in rabbits (*Study XGL0005*) and dogs (*Study XGL0006*) species respectively.

In *Study XGL0005*, it was observed after IVT administration in rabbits that the systemic uptake was low but dose-related with a maximal exposure observed at 24 hours post-injection. No clear differences in mean plasma concentrations was apparent between Study Days 1, 57, and 253/256 and no impact of Lucentis™ co-administration in TK parameters. Half-life was estimated at several days in eye with a slow release from the eye and quantifiable in plasma up to 144 hours post-injection.

In *Study XGL0006*, it was observed after IVT administration in dogs no marked differences in ARC1905 concentrations at Day 1 vs Day 57. ARC1905 concentrations considerably higher on Day 253/255. No impact of Lucentis™ co-administration based on ARC1905 levels.

Distribution

Since avacincaptad pegol is intended to be used in clinics via an IVT route, thus tissue distribution investigations were conducted after single IVT injection in both eyes of D-B rabbits (*Study C5-PK-001-07*).

The objective of *Study C5-PK-001-07* (GLP-status) was to investigate the pharmacokinetics and preliminary toxicological profiles of avacincaptad pegol following a single intravitreal injection (3 mg/each eye) to Dutch-Belted rabbits. Blood samples for Pharmacokinetic evaluation were collected at various time points from selected animals until up to 720 hrs post dose. In addition, aqueous, lens, vitreous, retina and sclera samples were collected from selected animals for analysis. Concentration avacincaptad pegol (ARC1905) of was measured using both HPLC (LLOQ= 0.10 µg/mL) and dual-hybridization ELISA assay (LLOQ= 0.001 µg/mL). Concentration was much lower in aqueous humor than in vitreous humor,

with C_{max} values of approximately 50 and 1000 µg/mL, respectively. The clearance from vitreous humor appeared to be monophasic, with a calculated t_{1/2} in the vitreous of 4 days but ARC1905 still present in the vitreous 30 days (720 hrs) after injection at a level of 11.4 µg/mL (885 nM). Long residence time is related to the PEGylation of the aptamer.ARC1905 with levels of 885 nM in the vitreous humor.

In addition to Study C5-PK-001-07, the applicant has performed an in vitro study (Study KSH00061) in order estimate nonspecific binding of avacincaptad pegol to human plasma proteins (HAS) and alpha1-acid glycoprotein (AGP). The test compound and control compounds, iophenoxate (IOPH) and chlorpromazine (CHPZ), were tested at concentrations ranging from 0-125 µM . Potential binding with HAS and AGP observed at 201 µg/mL.

Metabolism

Metabolism of avacincaptad pegol was exclusively studied in vitro (Study C5-MS-001-05 and Study KSH00057 and Study KSH00065) in various species (rat, monkey, human).

In Study C5-MS-001-05 was to determine the in vitro metabolic stability of avacincaptad pegol in the serum of rat, monkey and human as a function of temperature and aptamer concentration. It was observed that metabolic stability of ARC1905 in human serum > monkey serum > rat serum when incubated up to 72 hours at 4° C, room temperature, or 37° C. Up to 100 µM, the metabolic half- life of ARC1905 was observed to be greater than 72 hrs in rat serum, and significantly greater than 72 hrs in monkey and human sera. The mean percent recovery of ARC1905 at 37°C in rat, monkey, and human serum following 72 hours incubation with 1, 10 or 100 µM of ARC1905 ranged from ~ 41-82% (rat), 62-88% (monkey), and 83-100% (human) respectively. In Study KSH00057, the metabolic stability of the test compound ARC1905 and controls (verapamil and labetalol) in the presence of human liver microsomes was assessed. No loss of avacincaptad pegol was observed at the 30-minute and 90-minute incubation time points, suggesting a human microsomal half-life greater than 90 minutes.

The purpose of the Study KSH00065 was to measure the metabolic stability of the test compound avacincaptad pegol (with galangin as the control compound) in the presence of pooled human, cynomolgus monkey and rat liver S9. It was shown a slow metabolism after incubation with human S9 fraction in comparison with cynomolgus or rat S9 fractions, was observed. In the presence of human S9, the % ARC1905 remaining was 48% at 24 hours, with and without S9 replenishment whereas no signal of ARC1905 parent was detected at the 6 hour and 24 hour time points for both cynomolgus monkey and rat S9, regardless of S9 replenishment.

Excretion

Excretion of 17-[33P]-avacincaptad pegol (radiolabelled avacincaptad pegol product) was investigated after a single IV administration in male SD-rats at 10 mg/kg (Study C5-BD-002-05). The objective of this study was to determine the mass balance of 17-[33P]- avacincaptad pegol (10 mg/kg) in SD- rats and to determine the routes of elimination of ARC1905-derived radioactivity in urine and faeces. It was observed that urinary excretion was the main route of elimination of avacincaptad pegol following a single IV in SD-rats with a mean radioactive recovery in urine of 153%.

PK-drug interactions

See clinical part (section 3.3.1.1).

3.2.4. Toxicology

The applicant has submitted a toxicological program in order to qualify the use of avacincaptad pegol based on the results of various toxicity studies (single and repeated- dose via IV or IVT route, as described in Table 20. Since avacincaptad pegol was originally planned to be used in another disease via

an IV route, findings observed in those studies were submitted by the applicant in order to draw a better picture of the systemic toxicological profile of avacincaptad pegol corresponding to a higher systemic exposure than IVT use.

3.2.4.1. Single dose toxicity

2 GLP-single dose studies were submitted by the applicant using IV as the main route of administration: GLP-single dose IV toxicity studies in SD-rats (Study KSH00038) and in cynomolgus (Study KSH00033) initially selected as the rodent and non-rodent species.

The objectives of Study KSH00038 were to evaluate a range of doses; to determine the potential systemic toxicity, TK, and TD of avacincaptad pegol in Sprague-Dawley rats after a single IV injection (0 saline control, 10, 26, 54, 100, 260, 540, and 800 mg/kg); and to determine the persistence or reversibility of any findings after a 1-, 7-, or 14-day recovery period. Blood samples were collected for evaluation of TD (prolongation of APTT) and for TK evaluations based on plasma avacincaptad pegol concentrations. Mortality (specific cause of deaths not established) and decreased body weight were noted at 540 and 800 mg/kg. Clinical pathological changes were seen at ≥ 260 mg/kg including slight decreases of cholesterol, total protein and albumin levels, minimal decreases of red blood cell parameters and platelet counts, and moderately higher total white blood cell counts. According to the applicant, avacincaptad pegol-related changes to PT, APTT, or fibrinogen values were not clearly identified. Histopathological examinations showed dose-dependent minimal to mild cytoplasmic vacuolation of residente and/or infiltrating mononuclear phagocytic cells in spleen, liver, lymph nodes, bone marrow, choroid plexus of the brain and other tissues at ≥ 54 mg/kg; at 800 mg/kg, minimal basophilic granules in the cytoplasm of renal proximal tubular epithelial cells and minimal bone marrow hypocellularity in females. These findings are related to the PEG uptake and were expected. A NOAEL of 260 mg/kg was proposed by the applicant.

The objectives of Study KSH00033 were to evaluate a range of doses and to determine the potential systemic toxicity, TK, PD, and TD of avacincaptad pegol in cynomolgus after a single IV injection (0, 1, 3, 10, 30, and 100 mg/kg) followed by continuous IV infusion (37.44 mL/kg/day at a rate of 0.026 mL/kg/min) for 24 hours, and to determine the persistence or reversibility of any findings after a 14-day recovery period. Aptamer total tested doses were 0, 2.9, 8.6, 28.7, 86.2, or 287 mg/kg. Regarding TK analysis, blood (~ 0.5 mL) was collected at pre-dose (Day -1), 0.5, 2, 24 (end of infusion) hours after the start of infusion (SOI); and 0.25, 0.5, 1, 4, 8, 12, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hours after the end of infusion (EOI). The plasma samples obtained were analyzed for avacincaptad pegol using a validated HPLC assay with a LLOQ of 0.82 $\mu\text{g/mL}$ and a usable linear concentration range of approximately 0.82 to 410 $\mu\text{g/mL}$. Avacincaptad pegol was associated with dose-dependent changes to several haematological parameters (decreased RBC, haematocrit, and haemoglobin, increased platelets) and clinical chemistry parameters (decreased cholesterol, albumin, globulin, and phosphorus) at ≥ 86.2 mg/kg or at 287 mg/kg. As observed in rat species (*Study KSH00038*), according to the applicant, there were no avacincaptad pegol-related changes to PT, APTT, or fibrinogen values. Also previously observed in rats and related to the PEG moiety, a dose-dependent minimal to moderate cytoplasmic vacuolation of resident and/or infiltrating mononuclear phagocytic cells in liver, spleen, lymph nodes, choroid plexus, thymus and adrenal gland was seen at ≥ 86.2 mg/kg. Vacuoles observed were not associated with degenerative or inflammatory changes and were therefore considered non-adverse. Avacincaptad pegol did not activate complement at the tested doses based on measurement of C3a and Bb in plasma. Inhibition higher than 99% of C5 from cynomolgus (although $1/10^{\text{th}}$ of potency towards human C5) has been observed in the study. The NOAEL of the study was set at 28.7 mg/kg ($C_{\text{max}} = 202\text{--}215$ $\mu\text{g/mL}$ and $\text{AUC}_{0\text{--last}} = 3569\text{--}3869$ $\mu\text{g}\cdot\text{hr/mL}$).

3.2.4.2. Repeat dose toxicity

IV repeated-dose toxicity studies conducted in SD-rats (Study 501280) and in cynomolgus (Study KSH00040) are considered as non-pivotal studies, whereas IVT toxicity studies conducted in NZW rabbits (Study XGL00005) and in beagle dogs (Study XGL00006) are considered pivotal although no pharmacological activity of avacincaptad pegol towards C5 was expected in these two animal species.

Non pivotal studies

The objectives of Study 501280 were to determine the potential systemic toxicity, TK and TD of avacincaptad pegol in SD rats after bolus IV injection (0, 26, 54 or 100 mg/kg) followed by continuous IV infusion (0, 0.034, 0.070, or 0.130 mg/kg/min for cumulative aptamer doses of 0, 367, 760, or 1410 mg/kg) for 7 consecutive days, and to determine the persistence or reversibility of any findings after a 1- or 14-day recovery period. Toxicity was evaluated on the basis of clinical observations, body weights, food consumption, detailed and ophthalmic examinations, and clinical pathology (haematology, plasma chemistry, and urinalysis) and anatomic pathology (organ weights and macroscopic and microscopic findings) parameters. Blood samples were collected via jugular vein for evaluation of TD (prolongation of APTT) and for TK evaluations based on plasma avacincaptad pegol concentrations. IV treatment up to 1410 mg/kg did not induce any mortality. At ≥ 367 mg/kg, decrease in RBC parameters and WBC and platelet counts, and increase PT and APTT values were observed. According to the applicant, avacincaptad pegol was associated with dose-dependent prolongation of APTT at ≥ 760 mg/kg; there were no avacincaptad pegol-related changes to PT and fibrinogen values. Clinical chemistry parameters have underlined a slight increase in glucose and urea levels at the mid dose and high dose, and a dose-dependent decrease in cholesterol, triglyceride, total protein, and albumin levels. Modifications of the weight of organs have been noted such as increased liver, popliteal lymph node, adrenal, and spleen weights and decreased thymus weight were seen at 367, 760, or 1410 mg/kg, which correlated to the histological findings (vacuolation, basophilia and/or hypertrophy/hyperplasia and/or infiltration of macrophages).

Avacincaptad pegol's IV treatment was associated with lymphoid atrophy and/or necrosis in thymus, and myeloid/erythroid hypocellularity in bone marrow from 760 mg/kg.

All the findings were considered reversible except for macrophage hypertrophy/hyperplasia with vacuolation in histological examination.

The NOAEL of the study was not determined. At the lowest dose of 367 mg/kg the exposure to avacincaptad pegol (AUC_{0-last}) was 33355 $\mu\text{g}\cdot\text{hr/mL}$ and the C_{max} was 364 $\mu\text{g/mL}$ respectively.

The objectives of Study KSH00040 were to evaluate a range of doses and to determine the potential systemic toxicity, TK, PD and toxicodynamics TD of ARC1905 in cynomolgus after bolus IV injection (0 saline control, 10, 30, or 100 mg/kg) followed by continuous IV infusion (0, 0.013, 0.039, or 0.13 mg/kg/min and aptamer cumulative doses of 0, 141, 423, or 1410 mg/kg) for 7 consecutive days, and to determine the persistence or reversibility of any findings after a 1- or 14-day recovery period. Toxicity was evaluated on the basis of clinical observations, body weights, food consumption, physical and ophthalmologic examinations, and clinical pathology (haematology, serum chemistry, coagulation profiles and urinalysis) and anatomic pathology (organ weights and macroscopic and microscopic findings) parameters. Blood samples were collected for evaluation of PD parameters (ex vivo inhibition of: animal total complement function (ATCF), assessed via inhibition of complement-mediated hemolysis of antibody-coated sheep red blood cells (sRBC); zymosan-mediated C' activation to yield C5a; or C'-mediated hemolysis of sRBC or chicken red blood cells (cRBC), TD parameters (activation of complement to yield Bb and/or C3a and prolongation of APTT) and for TK evaluations based on plasma ARC1905 concentrations. IV treatment at the highest dose of 1410 mg/kg was associated with high signs of toxicity leading to the death of 6 out of 10 animals due to cardiopulmonary failure, resulting from haemorrhage

and oedema in the heart (myocardium) and lungs. No mortality was observed at a dose ≤ 423 mg/kg and no treatment-related effects on clinical observations, body weights, food consumption, physical and ophthalmologic examinations, or urinalysis parameters.

Other adverse effects reported during the course of the study include: prolongation of coagulation parameters (observed at ≥ 423 mg/kg for APTT and at 1410 mg/kg for PT), anaemia, thrombocytopenia, hypoproteinemia, and increased incidence of rouleaux formation (related to fibrinogen abnormalities). The decrease in haemoglobin and increased incidence of rouleaux formation were observed at all dose levels.

Four animals exhibited decreased total leukocyte counts; however, only two of these were clinically relevant exhibiting severe leukopenia characterized by neutropenia and lymphopenia; these findings were associated with lower thymus weights. This suggests a potential immunosuppression related to avacincaptad pegol-treatment.

Avacincaptad pegol was not associated with activation of Complement, as assessed by plasma C3a and Bb values (first assessed at 0.5 hours after the start of infusion). There were no gender-related differences in avacincaptad pegol-related effects.

Organ weights changes were observed and noted as dose-dependent with at a dose ≥ 141 mg/kg increase for liver, spleen, adrenal, and kidney weights but decrease in thymus weight; at ≥ 424 mg/kg for popliteal lymph nodes and at 1410 mg/kg for lung and heart. Vacuolization of macrophages related to PEG was observed in almost every tissue and incidence and severity was dose-related.

Most findings were reversible or partially reversible, except for vacuolation in macrophages still present in multiple tissues at the end of recovery.

NOAEL was not determined. At the lowest tested dose of 141 mg/kg, C_{max} measured was equivalent to 165 µg/mL and 179 µg/mL for male and female respectively. In terms of AUC_{0-last} it did correspond to 12968 µg.hr/mL in male and 14370 µg.hr/mL in female.

Pivotal studies

The objective of Study XGL00005 was to assess the potential localized and systemic toxicity of avacincaptad pegol when given as a single intravitreal injection or multiple intravitreal injections (doses: 0, 0.15, 0.5, and 1.5 mg/eye) to NZ white rabbits with and without combination treatment with Lucentis™ (0.3 mg/eye). In-life monitoring consisted of the following: mortality checks, body weights, clinical observations, feed observations, physical examinations, ophthalmic examinations, ocular irritation evaluations, intraocular pressure measurements, electroretinography, clinical pathology, macroscopic and microscopic evaluations, as well as organ weight evaluations. Regarding TK, blood samples for evaluation of the plasma concentration of avacincaptad pegol were collected from all animals at 0.5, 3, 8, 24, 72, and 144 hours post-dose (from the first dose for Groups 2 and 6). The plasma samples were analyzed with a colorimetric hybridization-type assay (LOQ 3.4 ng/mL). No test-article related effects on BW, feed consumption, ocular scoring, condition of eyes (assessed by ophthalmic examinations), ERG, ECG, IOP, hematology, or organ weight were observed. Vacuolation, related to the PEG moiety uptake, of the ganglion cell layer of the retina was observed upon microscopic evaluations. This finding was focal and only present at the highest tested dose (avacincaptad pegol 1.5 mg/eye $\pm$ Lucentis 0.3 mg/eye) as early as day 4 after a single IVT injection. The severity of the effect was minimal to moderate and reversible following a 1-month recovery period. After 10 monthly doses, mild retinal vacuolation was observed in the high dose group. The finding did not increase in severity from the beginning till the end of the study and reversible following a 4-week recovery period. The NOEL of the study was 0.5 mg/eye and the NOAEL 1.5 mg/eye. In addition, it was observed in animals receiving Lucentis™, an increase in incidence and in progressive severity of inflammatory changes in eyes (detected by ophthalmic examination).

The objective of Study XGL00006 was to assess the potential local and systemic toxicity of avacincaptad pegol when given as a single intravitreal injection or multiple intravitreal injections to beagle dogs (doses: 0, 0.3, 1 and 3 mg/eye) with and without combination treatment with Lucentis™ (0.5 mg/eye). Avacincaptad pegol and Lucentis™ were given by IVT injection. In-life monitoring consisted of evaluation of the following parameters: mortality checks, body weights, clinical observations, feed observations, physical examinations, ophthalmic examinations, ocular irritation evaluations, intraocular pressure measurements, electrocardiology, electroretinography, clinical pathology, macroscopic and microscopic evaluations, as well as organ weight evaluations. Regarding TK, blood samples (processed to plasma) were collected from all available animals at several time-points on Study Day 1 (following Dose 1), Study Day 57 (following Dose 3), and Study Day 253/255 (males and all recovery animals/females). The plasma samples were analyzed using a validated colorimetric hybridization assay. No test-article related effects on BW, feed consumption, ocular scoring, condition of eyes (assessed by ophthalmic examinations), ERG, ECG, IOP, haematology, or organ weight were noted. As observed in rabbits, vacuolation of the ganglion cell layer of the retina was present. In addition, vacuolation of the optic tract in the brain was also seen. Retinal vacuolation was noted at all dose levels. At Day 4, it was only observed at ≥ 1.0 mg/eye (minimal to moderate and focal). These findings were reversed following a one-month recovery period. After 10 doses, minimal to moderate focal retinal vacuolation was observed at all test article doses. Mild to moderate diffuse retinal vacuolation was observed at the highest tested dose with or without 0.5 mg/eye Lucentis TM. Vacuolation of the optic tract in the brain was also observed at the top dose 3.0 mg/eye and noted as mild. Whereas the retinal vacuolation was reversible in the optic tract, vacuolation in the retinal ganglion cell layer (minimal to mild severity) was still noted at the end of the recovery period. Therefore, a NOEL for avacincaptad pegol could not be determined. The NOAEL was 1 mg/eye.

3.2.4.3. Genotoxicity

The applicant provided data from 3 GLP compliant studies on the assessment of the potential genotoxicity of avacincaptad pegol.

The Bacterial Reverse Mutation Assay evaluated the mutagenic potential of avacincaptad pegol to induce reverse mutations in bacterial DNA at specific loci of several strains of *Salmonella typhimurium* and a single strain of *Escherichia coli*, in the presence and absence of an induced metabolic activation system (the 9000 g supernatant [S9] microsomal fraction of liver homogenate from rats exposed to Aroclor 1254). According to what is reported, the study was adequately conducted and Avacincaptad pegol, with or without S9-activation, was not associated with any precipitates, toxicity, or mutagenicity at concentrations up to 5000 µg per plate and was negative for mutagenic potential using the bacterial reverse mutation assay.

In the In Vitro Mammalian Chromosome Aberration Test, the clastogenic potential of avacincaptad pegol as measured by its ability to induce chromosome aberrations in HPBL in both the absence and presence of an induced metabolic activation system (the 9000 g supernatant [S9] microsomal fraction of liver homogenate from rats exposed to Aroclor 1254) was evaluated. In this study, the results show that avacincaptad pegol, with or without S9 activation, was not associated with any numerical or structural chromosomal aberrations at 1200 µg/mL and did not induce statistically significant increase in numerical or structural chromosomal aberrations above saline control at any concentration evaluated for chromosome aberrations ($p > 0.05$, Fisher's exact test). Thus, avacincaptad pegol was negative for the induction of structural and numerical chromosome aberrations in the in vitro mammalian chromosome aberration test using HPBL.

An In Vivo Micronucleus Assay was also conducted to evaluate the clastogenic potential of avacincaptad pegol as measured by its ability to induce micronucleated polychromatic erythrocytes (MPCEs) in mouse

bone marrow following a single IV administration. The intended clinical route for avacincaptad pegol is IVT injection, but the IV route was used in this study to afford maximal systemic exposure.

Under the conditions of the study, a single intravenous injection of avacincaptad pegol at doses up to and including 2000 mg/kg (total aptamer; 376 mg/kg oligonucleotide) did not cause mortality or life-threatening clinical signs in male and female mice. Avacincaptad pegol at the above-mentioned doses did not induce a significant increase in the incidence of MPCEs in bone marrow of male and female ICR mice. Therefore, avacincaptad pegol was concluded to be negative in the mouse micronucleus assay.

3.2.4.4. Carcinogenicity

No studies were conducted. The applicant submitted a justification to support a waiver request not to conduct the carcinogenicity studies as follow:

“Per ICH’s S1A Guideline entitled, “Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals” (ICH, 1995) and EMA’s recently endorsed S1B(R1) Guideline (ICH, 2022) several factors should be taken into account when assessing the necessity of conducting nonclinical carcinogenicity studies. These factors include: (a) previous demonstration of carcinogenicity potential in the product class; (b) structure-activity relationship suggesting carcinogenic risk; (c) evidence of pre-neoplastic lesions in repeat-dose toxicity studies; and (d) long-term retention of parent compound or metabolites. Of note, the ICH S1A Guideline states that if a drug is administered by ocular route, it may not need carcinogenicity studies unless there is cause for concern or there is significant systemic exposure.

An integrative weight of evidence assessment revealed no indication of carcinogenic activity associated with avacincaptad pegol. This conclusion is supported by multiple elements including the pharmacologic activity of avacincaptad pegol; negative genotoxicity study results; relevant nonclinical and clinical data demonstrating no cause for concern; negligible systemic exposure following the IVT route of administration; an assessment of therapeutics with a similar pharmacology (i.e., eculizumab, ravulizumab, avacopan) or physicochemical properties (i.e., pegatinib, a PEGylated RNA aptamer); feasibility considerations for conducting nonclinical carcinogenicity studies by IVT injection; and adherence to the replacement, reduction, and refinement (3R) principles.”

3.2.4.5. Reproductive and developmental toxicity

Reproductive toxicology evaluation of avacincaptad pegol included preliminary and definitive EFD studies in Sprague-Dawley rats and New Zealand White rabbits. No adverse maternal and developmental effects were observed. These two species were claimed to be appropriate as they are standard species accepted for use in EFD studies and have been demonstrated to be sensitive to developmental toxicants. Additionally, because the activity of avacincaptad pegol in cynomolgus monkeys is one-tenth that of the activity in humans, the use of NHPs as a model for the EFD studies was not appropriate. An EFD study in cynomolgus monkeys would require very high doses in order to demonstrate if exaggerated pharmacology would impact fetal development. This could subsequently result in abortions and confound the study results and thus provide no advantage over the standard rat and rabbit species. The species selection for the EFD studies was also a discussion topic at a Type C meeting held with the FDA in September 2021.

Other developmental and reproductive toxicity (DART, i.e., fertility and early embryonic developmental and pre- and post-natal developmental) studies were not conducted, based on a weight-of-evidence assessment concluding that avacincaptad pegol does not exhibit reproductive or developmental toxicity potential in humans based on its mechanism of action and physiochemical properties, pharmacologic class effects, target elderly patient population, systemic exposure following the IVT route of administration, and the analysis of nonclinical data, including definitive EFD studies, collected to date.

In particular, it was indicated that fertility and pre- and postnatal development toxicity studies were not performed due to the absence of any concern arising after having considered the targeted patient population for this age-related disease, the reported systemic exposure to avacincaptad pegol after intravitreal administration with subsequent unexpected exposure of reproductive tissues and limited potential for induction of systemic adverse effects, as well as the nonclinical data with other approved C5-targeting compounds. Potential effect on embryo-fetal development were also discussed based on the same basis and taking also into account the studies performed in rats and rabbits. A literature review did not identify a significant involvement of the C5 target in development. In addition, an overview of publicly available information with medicinal products targeting C5 did not highlight specific pharmacologically-related concern for reproduction and development. The applicant also summarized the results obtained with a RNA-based aptamer administered intravenously to mice and rabbits, and showing no developmental toxicity- however any potential structure- and off-target-related effects on embryofetal development were addressed in rat and rabbit studies performed with avacincaptad pegol.

Studies with juvenile animals have not been conducted. This is acceptable, based on the intended therapeutic indication.

3.2.4.6. Toxicokinetic data

See PK section.

3.2.4.7. Tolerance

No specific local tolerance studies have been conducted by the applicant. Nevertheless, local tolerance endpoints have been evaluated during single and repeated-dose toxicity wherein ARC1905 was given to animals via an IV (rats and cynomolgus) or IVT route (rabbits and dogs species).

3.2.4.8. Other toxicity studies

No specific local tolerance studies have been conducted by the applicant. Nevertheless, local tolerance endpoints have been evaluated during single and repeated-dose toxicity wherein ARC1905 was given to animals via an IV (rats and cynomolgus) or IVT route (rabbits and dogs species).

Injection site tissues from the single and repeat-dose toxicity studies of ARC1905 administered IV to SD-rats (*Study KSH00038*) and cynomolgus monkeys (*Studies KSH00033* and *KSH00040*) were evaluated by histopathological examination. Macroscopic and microscopic findings at the administration site were noted. These findings were attributable to mechanical trauma associated with the IV catheter placement with no direct relationship to avacincaptad pegol.

The ocular toxicity results of avacincaptad pegol when given as a single IVT injection or multiple IVT injections with and without combination with Lucentis to NZW rabbits or beagle dogs have been presented. In both species, histopathology assessment has revealed vacuolation of the ganglion cell layer of the retina vacuolation observed in rabbits at 1.5 mg/eye (highest tested dose) and in dogs from 0.3 mg/eye (lowest tested dose) up to 3.0 mg/eye. In addition and solely in dog species and at the highest tested dose of 3mg/eye, secondary vacuolation of the optic tract in the brain was noticed. These findings were mostly reversible in both species and there were no effects on ocular function as evident from the ophthalmic evaluations. In both studies, there were no apparent test article-related ocular irritation findings or other ocular changes. Some conjunctival (in both rabbits and dogs) and corneal (only in dogs) findings were attributable to the injection procedures.

3.2.5. Ecotoxicity/environmental risk assessment

In order to assess the ERA the applicant has considered a worst case scenario regarding the posology. Whereas avacincaptad pegol is intended to be administered monthly at a dose level of 2.0 mg oligonucleotide (≈ 8.68 mg of drug substance) per eye (only one eye will be treated), the applicant has chosen to consider the possibility of a bilateral treatment on the same day. This bilateral treatment on the same day would correspond to an intake of 4.0 mg of oligonucleotide (≈ 17.36 mg of drug substance) and therefore would maximize the potential environmental exposure.

Based on current EMA's ERA guideline, the applicant has performed the assessment with a reference dose of 4.0 mg of nucleotide in order to determine the Phase I parameters (logKow, PECSURFACEWATER). Based on the outcomes of the Phase I and according to the action limits described inside the EMA guideline, additional risk assessment (Phase II) would have to be conducted.

As part of the Environmental Risk Assessment and according to the current European guideline (EMA, 2006), the LogKow of the drug substance should be determined to evaluate if Phase II testing is required. If logKow is greater than 4.5, the drug substance should be screened for PBT in Phase II.

The logKow of avacincaptad pegol was determined using the shake-flask method and was reported to be -1.17. As the logKow < 4.5, screening for PBT in Phase II is not required.

The first step in the calculation of PECSURFACEWATER is to use Fpen default value of 0.01. The Fpen may then be refined by providing reasonably justified market penetration data.

As per the current European guideline, for the drug substance, the PECSURFACEWATER has been determined irrespective of its route of administration, pharmaceutical form, metabolism and excretion. The calculation was based on a maximum human dose of 2 mg oligonucleotide (equivalent to 8.68 mg drug substance) per eye, administrated once daily (although the recommended frequency is monthly). Considering a worst-case scenario, a dose of 17.36 mg drug substance was used in the case of two eyes treated concomitantly. Based on the worst-case assumption with once daily dosing and concomitant treatment of both eyes, the PECSURFACEWATER for the drug substance using the Fpen default value (0.01) is 0.0868 $\mu\text{g/L}$ which is above the allowable threshold of 0.01 $\mu\text{g/L}$. However, the recommended dosing frequency of avacincaptad pegol is once monthly, and therefore a refined Fpen was calculated.

Considering published epidemiological data on the prevalence in Europe, the potential market penetration of avacincaptad pegol drug product is refined.

As per Questions in Phase I Decision tree from the EMA draft guideline (EMA, 2018), prevalence data should be as recent as possible as, preferably not older than 5 years. Li JQ et al. performed a systematic review on the prevalence and incidence of AMD, including geography atrophy stage, based on the meta-analysis of observational studies in epidemiology (MOOSE) and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Li's article was selected to be used to support Fpen refinement. The applicant also considered the frequency of administration (once per month) to calculate the refined Fpen. The prevalence value of 0.01 (1%), and the frequency of treatment were considered to refine the Fpen.

The refined Fpen for drug substance calculated based on literature review and actual dosing frequency is 0.00033. Thus refined PECSURFACEWATER can be determined based on the re-evaluation of the Fpen value.

Refined PECSURFACEWATER has been determined based on refined Fpen value but still using the highest possible dose that can be administered at once i.e 17.36 mg. After Fpen refinement, the PECSURFACEWATER value for the drug substance was 0.00285 $\mu\text{g/L}$ which is below the threshold of 0.01

µg/L. According to the current European guideline (EMA, 2006), if a PECSURFACEWATER value is below 0.01 µg/L, a Phase II environmental fate and effect analysis is not required.

Table 1: Summary of main study results

Substance (INN/Invented Name): Avacincaptad pegol			
CAS-number (if available): 1491144-00-3			
PBT screening		Result	Conclusion
Bioaccumulation potential- log <i>K</i> _{ow}	OECD107	-1.17	Potential PBT (Y/N)
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log <i>K</i> _{ow}	-1.17	B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)	0.00285 (refined value)	µg/L	> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)			(Y/N)

3.2.6. Discussion on non-clinical aspects

Pharmacology

Primary pharmacodynamics

a) In vitro studies

Study C5-PHARM-001-05 has revealed that PEG moiety has no impact regarding affinity and specificity towards C5 binding (ARC186 binding to C5human equals to 0.14 ± 0.036 nM and avacincaptad pegol binding to C5human to 0.15 ± 0.048 nM respectively). In addition, binding specificity was demonstrated since no recognition towards C1q, C3, C4, C5a des Arg, C6 or the complement regulatory proteins, Factor B and Factor H was observed.

In study C5-PHARM-002-05, it was shown that PEG-conjugation has little effect on human complement activation pathway and ARC1905 is less potent in cynomolgus than human (6 fold based on IC50 value: IC50human (ARC1905) $\approx$ 0.6 nM vs IC50cynomolgus (ARC1905) $\approx$ 3.65 nM / 17 fold based on IC99 value: IC99human (ARC1905) $\approx$ 5.09 nM vs IC99cynomolgus (ARC1905) $\approx$ 87.2 nM). It was addressed by the applicant that pharmacological activity in cynomolgus is 1/10th of the human pharmacological activity. Therefore cynomolgus can be considered as a relevant species for the non-clinical program bearing in mind lower affinity of avacincaptad pegol for C5 cynomolgus target. Based on human PK data (C_{max} =6.2 nM) and in regards to an IC50human of 0.6 nM, avacincaptad pegol release in the systemic circulation after IVT treatment, will inhibit the classical human complement activation pathway.

Study C5-PHARM-003-05 has confirmed that avacincaptad pegol was less potent in cynomolgus (IC50=536 nM / IC90=1810 nM / IC99=6900 nM) than in humans (IC50=196 nM / IC90=442 nM / IC99=1090 nM). Up to a concentration of Up to 2 μ M no inhibition of C3a generation was noted. Overall, it has been demonstrated that complement activation upstream of C5 action not affected.

In study C5-PHARM-004-05, 1hr of circulation was sufficient to induce complement system activation in CPB model. Whereas generation of C3a fraction was not altered, inhibition of the formation of C5a fraction was noted with IC99= 1261 $\pm$ 438 nM in plasma.

Based on the observed results of study C5-PHARM-005-05 and although affinity of avacincaptad pegol towards cynomolgus C5 is a 1/10th of the human pharmacological activity, cynomolgus species can be considered as a relevant species to assess safety of avacincaptad pegol regarding pharmacological effects and off-target effects whereas rodent species can solely estimate the safety concerns raised by off-target effects.

b) In vivo studies

In Study KSH00039, 0.5 and 2 hrs after dosing, a dose of 10 mg/kg was sufficient to inhibit ATCF (inhibition > 95%) and inhibition of zymosan-mediated generation of C5a of 69% to 78%. Thus it was concluded that avacincaptad pegol prevents activation of classical and alternative complement pathways at all the tested doses.

In Study KSH00033, avacincaptad pegol concentrations higher than 130 μ g/mL, have shown to be consistently associated with > 91% inhibition of ATCF at all the time-points.

In Study KSH00040 and as observed in Studies KSH00030 and KSH00033, concentrations higher than 130 μ g/mL were associated with > 86% inhibition of ATCF at all the time-points. Thus it can be said that avacincaptad pegol is capable of inhibiting activation of classical and alternative complement pathways via ATCF, sRBC hemolysis, cRBC hemolysis and zymosan-mediated generation of C5a in a dose-dependent manner.

Secondary pharmacodynamics

In *Study No. 1059148*, IC50 values for the human proteins are ranging from 0.268 to 10.6 μ M (3.45 to 136.6 μ g/mL). The IC50 values are $\geq$ 10X higher than human plasma concentrations after IVT administration (C_{max} =347 ng/mL). The data support that no significant in vivo interaction is expected with avacincaptad pegol.

Avacincaptad pegol has shown to have a mild anticoagulant activity in human plasma, with prolonging APTT 1.7-fold at 2 mg/mL and with little or no effect on the PT as reported in *Study C5-PHARM-006-05*. Since, the plasma concentration mean C_{max} (= 347 ng/mL) observed during clinical trials is below 2 mg/mL, therefore the risk for anticoagulation effects in humans is low. Similar results were observed for ARC594 (a non-C5 specific aptamer of similar size and PEG content), suggesting that the observed effects on coagulation may be characteristic of aptamers in general and not to C5 inhibition.

In cynomolgus, avacincaptad pegol intravenous dosing ≥ 30 mg/kg has been shown to induce moderate increase in APTT (76% to 80%) and mild decrease fibrinogen concentrations (-33% to -45%) as reported in *Study KSH00039*. At 100mg/kg, minimal to mild prolongation of PT (11% to 19%) was reported.

In the SDRF (*Study KSH00033*) toxicity study in cynomolgus, avacincaptad pegol not associated with prolongation of APTT at all the tested doses.

In SD-rats, ARC1905 was associated with mild to moderate prolongation of APTT, but there was no clear correlation with plasma concentration as reported in *Study KSH00038*. Moderate effects on coagulation parameters PT and fibrinogen were also observed.

Overall secondary pharmacodynamics program conducted by the applicant is sufficient.

Safety pharmacology

Inhibition of the hERG channel (*Study 050601.BTE*) lower than 1% was observed at 10 μ M of avacincaptad pegol and around 10 % when challenged with 100 μ M. Thus it was not possible to determine the IC₅₀ corresponding value but still considered $\gg 100$ μ M. Validity of the test was assessed with 85% of inhibition observed with the positive control. Therefore, avacincaptad pegol up to 100 μ M does not affect the channel indicating no risk of interfering with ventricular repolarization. Since the plasma concentration mean C_{max} (= 347 ng/mL) observed during clinical trials is by far below 1288.2 μ g/mL (IC₁₀) therefore the risk for ventricular repolarization in humans is very low.

Based on the results of *study KSH00039* and at the top dose of 100 mg/kg, avacincaptad pegol plasma concentration is equal to 2072 μ g/mL giving a margin of exposure 6000 fold higher than the mean plasma concentration of 347 ng/mL observed at the clinical dose of 2 mg via IVT administration.

In *Study KSH00043*, up to 260 mg/mL no effect on the central nervous system was observed and this dose was set at the NOAEL of the study.

Safety pharmacology data demonstrate no potential for adverse CNS, respiratory, or cardiovascular effects at clinically relevant exposures.

PD-drug interactions

Study C5-DI-001-05 has demonstrated that avacincaptad pegol (ARC187 mean plasma concentration up to 13.60 μ M (175 μ g/mL) did not interfere with heparin or protamine activity in vivo in rats. This concentration of 175 μ g/mL is ≥ 512 X higher than human plasma concentrations after 2 mg IVT monthly administration (C_{max}=347 ng/mL). Thus, no significant in vivo PD-drug interaction is expected after avacincaptad pegol IVT treatment.

Pharmacokinetics

Absorption

In *Study C5-PK-001-05* it was found that avacincaptad pegol and ARC187 were found to be bioequivalent based on comparisons of mean C_{max}, AUC_{0-last} and AUC_{0- ∞} parameter estimates. The 4% difference in AUC_{0-last} and AUC_{0- ∞} values for ARC1905 relative to ARC187 were well within bioequivalence acceptability criteria of $\pm 20\%$. Demonstration of bioequivalence between avacincaptad pegol and ARC187 has revealed that the PEG supplier has no significant impact on the PK profile.

In rats, following IV administration (*Study C5-PK-002-05*) at 10 mg/kg, avacincaptad pegol was no longer detectable in plasma by HPLC 72 hours post-dose, while radioactivity associated with 17-[³³P]-ARC1905 was still detected in plasma up to 144 hrs post-dose. The mean C_{max} for avacincaptad pegol or 17-[³³P]- avacincaptad pegol dose groups were similar whereas AUC values for 17-[³³P]- avacincaptad pegol dose group were approximately 1.5-fold higher than the AUC values for ARC1905 dose group. The

blood to plasma ratio was approximately 19 at 144 hours post-dose suggesting association of radiolabeled 17-^[33P]- avacincaptad pegol and/or its metabolites with the cellular fraction of the blood.

TK parameters were assessed during the course of GLP-studies in rats, rabbits, dogs and monkeys species. Regarding TK profiles estimated in the safety pharmacological study in cynomolgus it was seen that following IV bolus administration of avacincaptad pegol, the C_{max} and AUC_{0-last} values increased linearly and proportionally to increasing avacincaptad pegol total doses of 10, 30 and 100 mg/kg. The MRT_{0-last} values were found to be similar across the dose-range tested.

In *Study KSH00033*, NOAEL was identified to be 28.7 mg/kg, based on the AUCs at NOAEL (3569 and 3869 µg.hr/mL), margin of exposure based on AUC is > 31.7 fold.

In *Study KSH00040*, NOAEL was not identified, based on the AUCs at the lowest dose of 141 mg/kg, margin of exposure based on AUC is > 112.5 fold.

In *Study KSH00038*, the applicant has set the NOAEL to 260 mg/kg which corresponds to a margin of exposure > 720 fold. Nevertheless, the NOAEL proposed is not validated and the NOAEL of this study is set at 26 mg/kg that leads to a margin of exposure > 17 fold.

In *Study 501280*, once again the NOAEL cannot be determined and margin of exposure of 1390 fold was based on the exposure level at the lowest dose tested of 367 mg/kg.

In *Study 20334075*, it was noted that the exposure in rats increased generally in a less than dose proportional manner over the dose range tested on both gestation day (GD) 6 and GD 17.

In *Study 20332454*, it was observed that the exposure in rabbits after IV administration, did generally increase in a more than dose proportional manner over the dose range tested on both GD 7 and GD 19.

In *Study XGL0005*, the NOAEL was set at 1.5 mg/eye and solely C_{max} levels were measured after a single administration and after 10 injections. AUCs values were not calculated. After a single administration, a C_{max} of 51.3 ng/ml was measured leading to a margin of exposure slightly above 0.75. After 10 injections, a C_{max} of 43.3 ng/ml was measured leading to a margin of exposure slightly above 0.63. Thus no multiple of exposure in comparison with clinical treatment was achieved.

In *Study XGL0006*, the NOAEL was set at 1 mg/eye, it was observed after IVT administration in dogs no marked differences in avacincaptad pegol concentrations at Day 1 vs Day 57. avacincaptad pegol concentrations considerably higher on Day 253/255. No impact of Lucentis™ co-administration based on avacincaptad pegol levels.

Distribution

It was shown in *Study C5-PK-001-07* that low systemic exposure was demonstrated after IVT injection, based on the plasma level (0.1 µg/mL) of avacincaptad pegol. Whereas dual-hybridization ELISA assay method was capable of measuring avacincaptad pegol levels in the plasma, those were below the detection limit for the HPLC assay (LLOQ 0.1 µg/mL). Avacincaptad pegol levels of 885 nM in the vitreous humor were measured, this is 74-fold greater than the maximum expected concentration of C5 in the vitreous humor of healthy or diseased humans (~0.5-12 nM) as reported in the literature. It can therefore be anticipated that all the C5 in the vitreous would be binded to avacincaptad pegol. Ocular distribution has been assessed in animal model for which no binding to the target is known or calculated. Therefore the study can solely demonstrate that ARC1905 plasma levels after IVT injection are low and avacincaptad pegol retention in the vitreous is expected to be shorter in rabbit species in comparison with monkey species due to the highest pharmacological activity of ARC1905 towards monkey C5 vs rabbit C5.

In *Study KSH00061*, it was shown that non-specific plasma protein binding of avacincaptad pegol was minimal and may only occur at concentrations levels higher than exposure observed in clinics after IVT

administration ($C_{max}=347$ ng/mL). Potential binding with HAS and AGP observed at 201 µg/mL would correspond to a safety margin ratio of ≥ 1100 X higher than human plasma concentrations after 2 mg IVT monthly administration.

Metabolism

From *Study C5-MS-001-05*, it was observed that metabolic stability of avacincaptad pegol in human serum > monkey serum > rat serum when incubated up to 72 hours at 4° C, room temperature, or 37° C. Up to 100 µM, the metabolic half-life of avacincaptad pegol was observed to be greater than 72 hrs in rat serum, and significantly greater than 72 hrs in monkey and human sera. The mean percent recovery of ARC1905 at 37°C in rat, monkey, and human serum following 72 hours incubation with 1, 10 or 100 µM of avacincaptad pegol ranged from ~ 41-82% (rat), 62-88% (monkey), and 83-100% (human) respectively.

In the presence of pooled human liver microsomes, no loss of avacincaptad pegol was observed at the 30-minute and 90-minute incubation time points, suggesting a human microsomal half-life greater than 90 minutes, based on the results generated in *Study KSH00057*.

In *Study KSH00065*, it was shown a slow metabolism after incubation with human S9 fraction in comparison with cynomolgus or rat S9 fractions, was observed. In the presence of human S9, the % avacincaptad pegol remaining was 48% at 24 hours, with and without S9 replenishment whereas no signal of ARC1905 parent was detected at the 6 hour and 24 hour time points for both cynomolgus monkey and rat S9, regardless of S9 replenishment.

Excretion

In *Study C5-BD-002-05*, it was observed that urinary excretion was the main route of elimination of avacincaptad pegol following a single IV in SD-rats with a mean radioactive recovery in urine of 153%.

PK-drug interactions

See the discussion on DDI in clinical part (section 3.3.2)

Toxicology

Single dose toxicity studies

In *Study KSH00038*, conducted in rats, histopathological examinations showed dose-dependent minimal to mild cytoplasmic vacuolation in various organs. These findings are related to the PEG uptake and were expected. The NOAEL of 260 mg/kg proposed by the applicant for study KSH00038 may not be validated due to PT and APTT values and therefore a NOAEL of 26 mg/kg could be considered more appropriate. At the NOAEL of 26 mg/kg, exposures in terms of AUC and C_{max} in males and females were: $AUC_{0-last}(\sigma) = 2658$ µg·hr/mL, $AUC_{0-last}(\varphi) = 1933$ µg·hr/mL and $C_{max}(\sigma) = 364$ µg/mL and $C_{max}(\varphi) = 397$ µg/mL. At the NOAEL, the exposure based on AUC value is > 17 times the human exposure at the MRHD (at 2 mg once monthly human $AUC_{0-t} = 113424$ µg·hr/mL).

Since there is lack of pharmacological activity of avacincaptad pegol in rats, outcomes of *Study KSH00038* are only relevant to assess the off-target systemic toxicological profile of avacincaptad pegol in relation to its chemical nature.

In *Study KSH00033*, conducted in cynomolgus monkeys, and as previously observed in rats and related to the PEG moiety, a dose-dependent minimal to moderate cytoplasmic vacuolation of resident and/or infiltrating mononuclear phagocytic cells in liver, spleen, lymph nodes, choroid plexus, thymus and adrenal gland was seen at ≥ 86.2 mg/kg. Vacuoles observed were not associated with degenerative or inflammatory changes and were therefore considered non-adverse. Avacincaptad pegol did not activate complement at the tested doses based on measurement of C3a and Bb in plasma. Inhibition higher than

99% of C5 from cynomolgus (although 1/10th of potency towards human C5) has been observed in the study, therefore the systemic toxicity related to the pharmacological effects has been assessed in addition to the off-target effects, making cynomolgus a relevant species for risk evaluation of avacincaptad pegol.

At the NOAEL of 28.7 mg/kg (C_{max}= 202-215 µg/mL and AUC_{0-last}=3569-3869 µg·hr/mL), the exposure based on AUC value is > 31.7 times the human exposure at the MRHD (at 2 mg once monthly human AUC_{0-t} =113424 µg·hr/mL).

One of the provided justifications for the choice of rats and cynomolgus monkeys for the IV general toxicity studies was based on potential effects on coagulation parameters, which have been reported for antisense oligonucleotide products evaluated in these species. Although avacincaptad pegol has been shown to interact with select coagulation factors in in vitro binding experiments, effects on coagulation in in vivo studies were either not observed or occurred at large margins of exposure or at a low magnitude, not biologically relevant. The coagulation effect commonly seen with oligonucleotide-based therapeutics is specific to base modifications associated with antisense-based therapeutics which are not present in avacincaptad pegol.

Repeated dose toxicity studies

a) Non-pivotal studies

In study 501280, avacincaptad pegol's IV treatment of SD rats, was associated with lymphoid atrophy and/or necrosis in thymus, and myeloid/erythroid hypocellularity in bone marrow from 760 mg/kg. This did suggest a potential immunosuppression after IV repeated administration. Since there is a lack pharmacological activity in rodents, therefore potential immunosuppressive effects observed are not related to any exacerbated pharmacological effects.

All the findings were considered reversible except for macrophage hypertrophy/hyperplasia with vacuolation in histological examination.

The NOAEL of the study was not determined. At the lowest dose of 367 mg/kg the exposure to avacincaptad pegol (AUC_{0-last}) was 33355 µg·hr/mL and the C_{max} was 364 µg/mL. Based on human PK report OPH2000, wherein the human AUC_{0-t} value at 2 mg once monthly was reported to be 23.998 µg·hr/mL and C_{max} equals to 347 ng/mL, it gives a margin to human exposure higher than 276 (based on AUC) and 1000 (C_{max}). Thus effects observed during the course of the study are of a really low concern to be observed in humans.

IV treatment of cynomolgus with avacincaptad pegol during 7 days (Study KSH00040) was also associated with immunosuppressive effects related to treatment as observed in the rat study 501280. The highest dose of 1410 mg/kg was associated with high signs of toxicity leading to the death of 6 out of 10 animals due to cardiopulmonary failure.

Prolongation of coagulation parameters were observed at ≥423 mg/kg for APTT and at 1410 mg/kg for PT. This can be related to the chemical nature of the product.

Avacincaptad pegol was not associated with activation of Complement, as assessed by plasma C3a and Bb values (first assessed at 0.5 hours after the start of infusion), thus it has demonstrated that avacincaptad pegol activity is targeting solely C5.

As expected, vacuolization of macrophages related to PEG was observed in almost every tissue and incidence and severity were dose-related. Most findings were reversible or partially reversible, except for vacuolation in macrophages still present in multiple tissues at the end of recovery.

The NOAEL of the study was not determined, thus at the lowest tested dose of 141 mg/kg, C_{max} measured was equivalent to 165 µg/mL and 179 µg/mL for male and female respectively. In terms of

AUC₀-last it did correspond to 12968 µg.hr/mL in male and 14370 µg.hr/mL in female. Based on human PK report OPH2000, wherein the human AUC₀-t value at 2 mg once monthly was reported to be 113424 µg.hr/mL, which gives a margin to human exposure of 112.5 fold higher.

b) Pivotal studies

Toxicity of avacincaptad pegol via IVT route was investigated throughout repeat-dose IVT toxicity studies conducted in NZ rabbits (Study XGL00005) and in dog species (Study XGL00006). In both studies, avacincaptad pegol did not reveal any test-article related effects on BW, feed consumption, ocular scoring, condition of eyes (assessed by ophthalmic examinations), ERG, ECG, IOP, hematology, or organ weight. Vacuolation, related to the PEG moiety uptake, of the ganglion cell layer of the retina was observed upon microscopic evaluations in both species. In dogs, additional vacuolation of the optic tract in the brain was also observed at the top dose 3.0 mg/eye and noted as mild.

Conducting IVT toxicity studies in rabbits and dogs species have been justified by the applicant throughout his proposal validated by the FDA. The applicant has justified the choice of not conducting the IVT toxicity studies in NHP since rabbits and dogs species are commonly used species for ocular toxicity studies; the non-feasibility of using a murine surrogate, the physical-chemical properties of avacincaptad pegol preventing the use of higher concentrations (viscosity increasing with the increase in concentration); the impossibility to use a dose capable to induce exaggerated pharmacological activity (due to lowest reactivity in comparison with human C5) and that can be properly tolerated. In addition the applicant has reported that the systemic toxicity profile of avacincaptad pegol has been fully investigated via IV injection and with exposures by far higher than those obtained after IVT injection.

Both IVT studies have been conducted in toxicological species wherein avacincaptad pegol does not exhibit a relevant binding towards C5 from rabbit or dog species. While these animal species are not presented as pharmacologically relevant, apparently, no studies have been conducted to test their pharmacological relevance and therefore 5.3 of the SmPC has to better reflect the apparent lack of pharmacological relevance of the animal species, other than cynomolgus monkeys (OI). By using rabbit and dog species, only local tolerance and off target effects have been assessed and that could have been in a way performed solely in one species instead of two.

Justifications raised by the applicant for not conducting IVT toxicity studies in NHP are acknowledged. Indeed, in order to assess any toxicological effect related to the MOA of avacincaptad pegol, high concentrations would be required since activity in NHP is 1/10th of the human activity. Increase in concentration would end-up with an increase in viscosity (delivery problem) and also an increase in IOP is expected at high concentrations. Although in the case of another medicinal product (under MAA process) in the same therapeutic, administered IVT and targeting C3 fraction, IVT toxicity studies were conducted in NHP species. However this has not been underlined and respective affinities towards human and NHP fraction targets. Nevertheless at this stage of the dossier since local tolerance, off target and systemic effects have been investigated, and low multiple or equivalent of the clinical dose has been achieved (based on cross-species vitreous volume comparison) and low systemic exposure has been demonstrated after IVT administration, thus no further studies are required.

Although, pivotal studies in NHP were not conducted, retina vacuolation related to PEG moiety would be expected after IVT dosing and systemic passage would be measured to be low. Since non pivotal studies in NHP after repeated IV dosing were conducted and revealed, at the lowest tested dose of 141 mg/kg, a margin to human exposure of 529 fold higher; therefore systemic effects after IVT administration in humans are expected to be of low concern although IVT toxicity studies were not conducted in the best way.

In terms of margins of local exposure, in the pivotal repeated dose toxicity studies, with intravitreal administration, the NOAEL for rabbits was set at 1.5 mg/eye, the maximum tested dose; the NOAEL for

dogs was set at 1.0 mg/eye, the mid tested dose. Considering the differences in vitreous volume between rabbits and dogs versus humans (3- and 2-fold lower, respectively, according to provided information), in human equivalent doses, the NOAEL for rabbits and dogs are, respectively, slightly higher and identical to the intended human dose. The safety margins between the NOAELs in dogs and rabbits and the intended human dose are low and referred to feasibility issues when administering a product by IVT.

Genotoxicity

Evaluation of the mutagenic potential of avacincaptad pegol was conducted a GLP-compliant Ames test assay (Study AB12SY. 503.BTL) wherein no increase of the number of revertant colonies, was observed in the presence or the absence of metabolic activator up to a dose of 5000 µg/plate of ARC1905. Thus ARC1905 is considered non-mutagenic in the test conditions.

Clastogenic potential of ARC1905 was explored during the course of an in vitro GLP-compliant mammalian chromosome aberration assay (Study AB12SY. 341. BTL). ARC1905, with or without metabolic activator, was not associated with any numerical or structural chromosomal aberrations at 1200 µg/mL (top dose tested since involves 53-56% inhibition of MI) and did not induce statistically significant increase in numerical or structural chromosomal aberrations above saline control at any concentration evaluated for chromosome aberrations. Therefore ARC1905 is considered non-clastogenic.

Regarding the in vivo GLP-compliant micronucleus assay, no TK subsection report has been found inside the full study report therefore in that sense no proper proof of exposure was demonstrated and to validate the negative results observed. In addition, since mice have not been selected as the rodent-species for the original non-clinical program (IV route), no TK data are available for this species. However, the top dose given during the assay corresponds to 2000 mg/kg and usually considered sufficient. In addition, test with positive control has demonstrated a clear positive outcome also in the range of the historical results for the positive control, therefore it can be considered that the animals were properly exposed and also to avacincaptad pegol. Thus the negative result obtained after ARC1905 testing can be endorsed.

Thus, under the test conditions up to 2000 mg/kg, ARC1905 is negative in the in vivo mouse micronucleus assay.

Overall, based on the negative outcomes of the genotoxicity studies (Ames test, in vitro mammalian chromosome aberration test and in vivo micronucleus), in line with the ICH recommended standard battery for genotoxicity testing, avacincaptad pegol is considered non genotoxic.

Carcinogenicity

Rationale for not conducting carcinogenicity studies is based on MOA, the negative outcomes of genotoxicity studies, the intended route of administration (IVT), an analysis of class effects of various C5 inhibitors (e.g avacopan, ravulizumab, eculizumab, pegaptanib) relevant non-clinical and clinical data; and 3Rs rules. During the non-clinical program, no signs of pre-neoplastic lesions have been observed after IVT or IV challenges with avacincaptad pegol.

Additional considerations were presented, related to the fact that long-term carcinogenicity studies with avacincaptad pegol may not be technically feasible or practical as multiple IVT injections in rodents produce cumulative inflammatory changes in the eyes, which would likely obscure the evaluation of neoplastic changes..

Review of clinical trials conducted with avacincaptad pegol, did not reveal any sign of toxicity that could be considered as a signal for any carcinogenic risk. Indeed, no proliferative lesions or immunotoxicity findings in humans were reported up to date during the course of the clinical trials.

Overall the WOE submitted by the applicant for not conducting carcinogenicity studies is accepted.

Reproductive and developmental toxicity

Embryo-foetal development studies were conducted in rats and rabbits by daily intravenous administration of avacincaptad pegol during organogenesis at doses up to 1.2 mg/kg/day. In both species, no adverse maternal and developmental effects were observed at any dose level. In rats, a dose-dependent increase in the incidence of short thoracolumbar supernumerary ribs was observed but interpreted as non-adverse considering the absence of other associated skeletal finding or impact on fetal growth, as well as the nature of the finding which may resolve postnatally (Chernoff and Rogers, 2004; DeSesso and Scialli, 2018).. Since there is no evidence of pharmacological activity of avacincaptad pegol in both rat and rabbits, only adverse findings related to any off-target effect of avacincaptad pegol in these species were covered. The applicant explains that the activity of avacincaptad pegol in cynomolgus monkeys is one-tenth that of the activity in humans, so that very high doses would be required in that species to demonstrate any pharmacology-related effect with subsequent potential for abortions which may confound the study results. Considering those limitations of the monkey model as well as the therapeutic indication, the absence of additional studies in that species is acceptable for the current application. In addition, no fertility and pre/postnatal toxicity studies were conducted based on a weight-of-evidence assessment whose details were not submitted for review. Overall, either no studies were conducted or the studies were conducted in animal species (rat, rabbit) being not pharmacologically relevant.

A detailed weight-of-evidence assessment was provided to complete the assessment for any potential effect on human development and reproduction. Considering the age-related targeted disease, the limited systemic exposure to avacincaptad pegol, the lack of identified conventional pharmacologically-relevant nonclinical species, and the publicly available data not identifying currently any concern for reproduction and development with C5-targeting products, it is agreed that further studies are not necessary to support the MAA of IZELVAY for the treatment of adults with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

The applicant is asked to revise the content of sections 4.6 and 5.3 of the SmPC according to the suggestion in the attached PI document, so that it reflects the lack of demonstrated pharmacological relevance of the animal species used for EFD testing and the limited exposure margins based on a comparison of cumulative exposure (AUC) during organogenesis (**OI**). Indeed, the use of C_{max} values to compare systemic exposure levels in patients and rats/rabbits in EFD studies is not endorsed. As explained by the applicant, comparison of systemic exposure is complex due to different treatment modalities between patients treated once monthly via IVT route and animals receiving daily intravenous administrations during organogenesis. This led to some differences in plasma concentration profiles over time. However, the applicant indicates that the vitreous acts as a reservoir slowly releasing avacincaptad pegol into the circulatory system as the avacincaptad pegol is cleared from the eye. This suggests sustained systemic exposure to avacincaptad pegol between two monthly injections with a C_{max}/C_{trough} ratio of approximately 7. In contrast, systemic exposure was less sustained in EFD studies since drug excretion was not compensated by slowly release from a reservoir; C_{max}/C_{24h} ratios reached 20.6 on GD17 in rats and 532 on GD19 in rabbits at high dose levels. Relying on C_{max}-based comparison would therefore lead to an overestimate exposure ratio value related in part to higher C_{max} (actually C_{0h}) values measured after IV administration in animal studies. Since the AUC reflects the overall actual body exposure to avacincaptad pegol, it is considered the most appropriate parameter for interspecies exposure comparison. As animals in EFD studies were treated daily with AUC data reflecting exposure over 24 hours, whereas patients are treated once every 4 weeks with AUC data reflecting exposure over 28 days, a direct comparison of these AUC values is not relevant. It is therefore suggested that AUC-based safety margins should be established based on cumulative systemic exposure (AUC) during the treatment period in EFD studies (12 and 13 days in rats and rabbits, respectively) versus the

corresponding duration of organogenesis in humans (8 weeks, 2 doses). At the high dose levels in rats and rabbit EFS studies, this would lead to exposure multiples of 6.9 and 4.7, respectively.

The absence of juvenile toxicity studies is acceptable in view of the therapeutic indication.

Local tolerance

Not conducting a dedicated local tolerance study is not an issue since this endpoint has been considered during the course of the studies performed via the IV and IVT routes respectively. No unexpected finding was observed after IV treatment (mechanical trauma related to catheter placement). Regarding IVT administrations, conjunctival and corneal findings were observed in line with injection procedures since the effects were also observed for the animals belonging to the control groups. Avacincaptad pegol treatment-related effects, retinal vacuolation, were observed in both tested species (rabbits and dogs). Vacuoles observed are in line with the uptake of the Pegylated aptamer into ganglion retinal cells. This phenomenon of vacuolation process has been described in the literature in other tissues after the uptake of Pegylated compounds. Therefore, this finding is not considered unexpected and was considered non-adverse in the studies conducted by the applicant since they were not related to any effects in ERG parameters nor and almost fully reversible in both species. Secondary vacuolation of the optic tract in the brain was only noticed in dogs at the top tested dose of 3 mg/eye.

ERA

Avacincaptad pegol PECsurfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as logKow does not exceed 4.5. The applicant should follow the current version of the EMA ERA guideline, as the cited draft (EMA, 2018) is not the final version. An experimental study based on the OCDE 107 method has determined that the log Kow value is -1.17 at a single pH. As per Avacincaptad pegol, the measurement was only performed at one pH level, which is considered appropriate.

~~Since, the study report for the experimental determination of logKow was not found in the dossier, the available data do not allow to conclude definitively on the potential risk of avacincaptad pegol to the environment. Therefore, the applicant is asked to submit the study report regarding the determination of logKow (OC).~~

3.2.7. Conclusion on non-clinical aspects

It was highlighted that avacincaptad pegol binds to human C5 with high affinity and specificity and is an inhibitor of C5 cleavage (as measured by decreased formation of C5a) and inhibits complement activity after activation of the classical and/or alternative complement pathways. Potency of avacincaptad pegol was investigated and it revealed that the highest potency was observed towards human C5, then cynomolgus C5 (1/10th of the human C5 potency), then rat (1/1000th of the human C5 potency). In rabbits and dogs species, specific potency is expected to be higher than 1/100th of the human C5 potency. Based on safety pharmacological studies conducted, QT prolongation or significant effects on CNS, cardiovascular, and respiratory systems are not expected at the clinical dose. Effects considered unrelated to C5 inhibition were limited to mild anticoagulation (prolongation of APTT) effects that were related to the nature of the product: aptamer. Nevertheless, based on human PK data (C_{max}=6.2 nM) and in regards to an IC₅₀human of 0.6 nM, avacincaptad pegol release in the systemic circulation after IVT treatment, will inhibit the classical human complement activation pathway and could lead to an increase of susceptibility to infections.

PK and TK parameters of avacincaptad pegol or its derivative, have been assessed after single and repeated administrations (IV and IVT dosing) in rats, dogs, monkeys and rabbits species. Distribution was assessed throughout IVT administration in rabbits and an in vitro study to estimate nonspecific binding of avacincaptad pegol to human plasma protein. In vivo, low systemic exposure was

demonstrated after IVT injection, based on the plasma level (0.1 µg/mL) of avacincaptad pegol. Long residence time in the vitreous was observed and is related to the PEGylation of the aptamer. In vitro, non-specific plasma protein binding of avacincaptad pegol was minimal and may only occur at concentrations levels higher than exposure observed in clinics after IVT administration (C_{max}=347 ng/mL). Metabolism of avacincaptad pegol was exclusively studied in vitro. Urinary excretion was the main route of elimination of avacincaptad pegol following a single IV in SD-rats. Based on only modest inhibition of CYP1A2 and CYP2D6 at high concentrations, ARC1905 is not likely to cause drug-drug interactions by inhibiting CYP450 enzyme activity considering the low systemic exposure observed following IVT injection (mean C_{max} = 347 ng/mL) in the clinics.

Overall the non-clinical development regarding pharmacokinetics can be considered acceptable.

Non pivotal repeated dose toxicity studies (IV dosing) were conducted in rat and dog species whereas pivotal studies (IVT dosing) were conducted in rabbit and dog species. Single dose toxicity studies, with IV administration, were conducted in rats and cynomolgus monkeys. From these species, only the cynomolgus monkey was pharmacologically relevant.

Vacuolation was observed in various tissues after IV administration and limited to the eye (rabbit and dogs) and brain optical tract (dog species only) after IVT administration. Vacuolation observed were mostly reversible and related to the PEG-uptake.

Immunosuppression was observed after after IV repeated-administration in rats and monkeys. Since there is a lack pharmacological activity in rodents in comparison to humans, therefore potential immunosuppressive effects observed are not considered to be related to any exacerbated pharmacological effects.

Effects on coagulation in in vivo studies were either not observed or occurred at large margins of exposure or at a low magnitude, not biologically relevant. The coagulation effect commonly seen with oligonucleotide-based therapeutics is specific to base modifications associated with antisense-based therapeutics which are not present in avacincaptad pegol.

Both IVT studies have been conducted in toxicological species wherein avacincaptad pegol does not exhibit a relevant binding towards C5 from rabbit or dog species. While these animal species are not presented as pharmacologically relevant, apparently, no studies have been conducted to test their pharmacological relevance. The applicant should clarify this aspect and revise the content of section 5.3 of the SmPC, so that it reflects in a better way the apparent lack of pharmacological relevance of the animal species, other than cynomolgus monkeys (OI). By using rabbit and dog species, only local tolerance and off target effects have been assessed and that could have been in a way performed solely in one species instead of two.

Although, pivotal studies in NHP were not conducted, retina vacuolation related to PEG moiety would be expected after IVT dosing and systemic passage would be measured to be low. Since non pivotal studies in NHP after repeated IV dosing were conducted and revealed, at the lowest tested dose of 141 mg/kg, a margin to human exposure of 112 fold higher; therefore systemic effects after IVT administration in humans are expected to be of low concern although IVT toxicity studies were not conducted in the best way.

In terms of margins of local exposure, in the pivotal repeated dose toxicity studies, with intravitreal administration, the NOAEL for rabbits was set at 1.5 mg/eye, the maximum tested dose; the NOAEL for dogs was set at 1.0 mg/eye, the mid tested dose. Considering the differences in vitreous volume between rabbits and dogs versus humans (3- and 2-fold lower, respectively, according to provided information), in human equivalent doses, the NOAEL for rabbits and dogs are, respectively, slightly higher and identical to the intended human dose. Higher margins of exposure are difficult to obtain due to many factors such as the formulation of the product, the maximum concentration and vitreous volume.

Avacincaptad pegol was negative in the bacterial reverse mutation assay, chromosomal aberration in mammalian cells and in vivo mouse bone marrow micronucleus assays. Thus avacincaptad pegol is considered as non genotoxic.

WOE submitted by the applicant for not conducting carcinogenicity studies was accepted.

Regarding reproductive and developmental toxicity studies, the applicant is asked to revise the content of sections 4.6 and 5.3 of the SmPC according to the suggestion in the attached PI document, so that it reflects the lack of demonstrated pharmacological relevance of the animal species used for EFD testing and the limited exposure margins based on a comparison of cumulative exposures (AUC) during organogenesis.

Not conducting any dedicated local tolerance study is not an issue since this endpoint has been considered during the course of the studies performed via the IV and IVT routes respectively.

ERA conducted by the applicant revealed that avacincaptad pegol PECsurfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as logKow does not exceed 4.5. The applicant should follow the current version of the EMA ERA guideline, as the cited draft (EMA, 2018) is not the final version. An experimental study based on the OCDE 107 method has determined that the log Kow value is -1.17 at a single pH. As per Avacincaptad pegol, the measurement was only performed at one pH level, which is considered appropriate.

~~Since the study report for the experimental determination of logKow was not found in the dossier, the available data do not allow to conclude definitively on the potential risk of avacincaptad pegol to the environment. Therefore, the applicant is asked to submit the study report regarding the determination of logKow (O.C).~~

3.3. Clinical aspects

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Avacincaptad pegol (also known as ARC1095 or ZimuraTM), a pegylated RNA aptamer, is a complement component 5 (C5) inhibitor. It binds specifically and with high affinity to C5 and inhibits cleavage of C5 into C5a, and prevents C5b from joining with C6. The pegylation confer stability to the molecule against biodegradation and delayed clearance in vivo.

In the current submission, the applicant seeks marketing approval for avacincaptad pegol, for the treatment of adults with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

The drug product for registration is a solution for injection, proposed under a single concentration 20 mg/mL. The proposed dose of avacincaptad pegol is 2 mg/eye (0.1 mL of 20 mg/mL solution) administered by intravitreal (IVT) injection once monthly.

The clinical pharmacology program consisted of four studies:

- One first-in-human ascending dose study OPH2000 investigating the safety, tolerability and systemic PK profile of multiple IVT of avacincaptad pegol given in combination with multiple dose of Lucentis® 0.5 mg in patients with neovascular age-related macular degeneration (nAMD)
- Study OPH2001 where avacincaptad pegol was investigated at doses of 0.3 mg and 1 mg once monthly in patients with GA secondary to AMD

- Study OPH2003 where avacincaptad pegol was investigated at doses of 1 mg, 2mg and 4 mg once monthly to evaluate the effect of the product on reduction of GA area growth compared to sham.
- One Phase 3 study ISEE2008 investigating the safety and efficacy of avacincaptad pegol in patients with GA secondary to AMD (pivotal study).

A population PK analysis of avacincaptad pegol was conducted based on available PK plasma samples, as aqueous humor samples were not performed due to the invasive nature of the procedure. No exposure-response (efficacy/safety) analysis was performed.

Methods

Two bioanalytical method was developed to quantify avacincaptad pegol, in human plasma collected in study OPH2000 and study ISEE2008. The methods appears adequate in terms of precision and accuracy, matrix evaluation, selectivity, dilution linearity, short and long term stability. ISR were provided with satisfactory results.

Absorption

As it is not feasible to collect retina, RPE-choroid and other relevant ocular samples from patients, neither the bioavailability nor the distribution in ocular tissues cannot be determined. By definition the bioavailability will be 100% in the vitreous.

In plasma, at steady-state after a 2mg dose /eye, T_{max} was achieved at 2.91 days, with a geometric mean C_{max} of 347 ng/mL and a mean AUC_{0-tau} of 4726 day*ng/mL (Table

Distribution

The distribution in the vitreous humor is assumed to be homogeneous with a volume of 4 mL. The concentrations of avacincaptad pegol in the vitreous humor after dosing with the 2 mg dose are 500,000 ng/mL (2,000 µg /4 mL). Given a C_{max} of 68.4 ng/mL, the systemic exposure is predicted to be 7,000 times lower than exposure in the vitreous humor.

Following IVT administration and after reaching plasma, based on NCA analysis V_z/F was estimated at 4.55 L.

Elimination

No formal investigations on metabolism and excretory pathways of avacincaptad pegol have been conducted. Avacincaptad pegol is expected to be catabolized by endonucleases and exonucleases to oligonucleotides of shorter lengths.

Based on NCA analysis from study ISEE2008, the half-life was estimated at 7.6 days.

Time dependency

Following a once monthly dosing regimen, based on observed C_{min} the accumulation is low (1.39).

Inter-individual variability

In patients with GA secondary to AMD and using NCA approach, the IIV (CV%) in ARC1905 systemic exposure was 59% for C_{max} and 40.6% for AUC_{0-tau}.

Pharmacokinetic in target population

Plasma PK of ARC1905 has been investigated in study OPH2000 in patients (n=60) with nAMD and in patients with GA secondary to AMD as part of the PK substudy ISEE2008 (n=10)

Phase 1 study OPH2000

Study OPH2000 was a Phase 1, trial to establish the safety, tolerability and pharmacokinetic profile of multiple intravitreal injections of ARC1905 (anti-C5 aptamer) given in combination with multiple doses of Lucentis® 0.5 mg/eye in subjects with neovascular age-related macular degeneration. PK data are presented in Table 2.

Table 2: Summary of PK parameter estimates following IVT administration of 0.03, 0.3, 1, 2, 3 mg/eye of ARC1905 in subjects with nAMD

	0.3 mg/eye (N=19)		1 mg/eye (N=16)		2 mg/eye (N=15)		3 mg/eye (N=7)	
Parameter	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV
C _{max} (ng/mL)	21.9	35.9	73.1	34.4	68.4	57.8	97.3	75
T _{max} (day)	5.8	41.7	5.3	38.8	5.7	46.1	6.9	30.8
AUC _{0-t}	233	69.4	1164.1	29	999.9	71.9	1643.4	96.5
AUC _{0-∞}	518.5	26.4	1589	34.2	1948.4	27.9	3349.6	72.6
T _{1/2} (day)	13.7	26.2	13.5	47.7	15.5	43.5	14.5	36.1
* ARC1905 plasma concentrations were not detectable in any subjects receiving 0.03 mg/eye doses.								

Phase 1 study OPH2001

Study OPH2001 was a Phase 1 to study to establish the safety and tolerability of ARC1905 in patients with dry AMD.

Subjects were assigned in an alternating fashion to one of two dose levels of ARC1905: 0.3 or 1 mg/eye. Subjects were treated with 3 initial intravitreal injections of ARC1905 at Day 0, Week 4, Week 8, and a follow-up visit at Week 16. They then received 2 subsequent injections at Week 24 and Week 36, with a final follow-up visit at Week 48. There was a maximum of 5 ARC1905 injections.

No PK plasma samples were performed.

Phase 2/3 study OPH2003

Study OPH2003 was a randomized double masked, sham-controlled study testing avacincaptad pegol vs sham in patients with GA secondary to dry AMD. Two parts were considered:

Part 1, patients were randomized in a 1:1:1 ratio to avacincaptad pegol 1 mg/eye, 2mg/eye, or sham.

Part 2, patients were randomized in a 2:2:1 ratio to avacincaptad pegol 2 mg/eye, 4mg/eye, or sham.

No PK plasma samples were performed.

Phase 3 study ISEE2008 (pivotal study)

Study ISEE2008 was a randomized double masked, sham-controlled study testing avacincaptad pegol 2mg/eye Q4W or Q8W vs sham in patients with GA secondary to dry AMD.

Individual mean plasma concentrations following multiple administrations of avacincaptad pegol are presented in Figure 2 and associated PK parameters in Table 3.

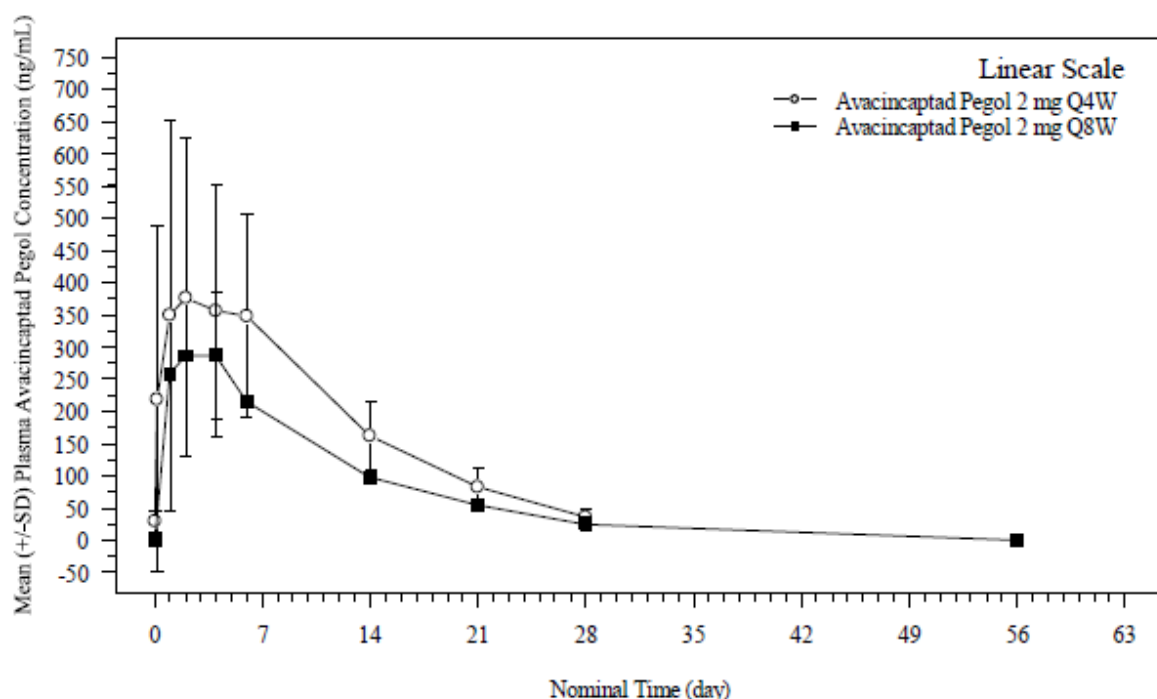


Figure 2: Mean ($\pm$ SD) plasma avacincaptad pegol concentration time profiles following multiple IVT injections

Table 3: Plasma avacincaptad pegol PK parameters following multiple IVT administration of avacincaptad pegol at 2mg Q4W or 2 mg Q8W at steady-state

Plasma PK Parameters	Avacincaptad Pegol 2 mg Q4W	Avacincaptad Pegol 2 mg Q8W ^d
N	8	2
AUC ₀₋₂₈ (day*ng/mL)	4726 (40.6);7 ^a	(2583; 3689); 2
AUC _{0-τ} (day*ng/mL)	4726 (40.6);7 ^a	(2880; 3689); 2
AUC _{last} (day*ng/mL)	4722 (37.5);8 ^a	(2582; 3786); 2
C _{max} (ng/mL)	347 (59.0);8 ^a	(218; 357); 2
t _{max} (day)	2.91 (1.03; 7.00);8 ^c	(3.90; 4.01); 2
C _{min} (ng/mL)	29.6 (53.0);8 ^b	(0.00*; 0.00*); 2
t _{1/2} (day)	7.57 (29.2);5 ^a	(6.17; 7.56); 2
CL/F (L/day)	0.423 (40.6);7 ^a	(0.516; 0.694); 2
V _z /F (L)	4.55 (61.6);5 ^a	(4.59; 7.57); 2

^a Geometric Mean (GeoCV%);n

^b Arithmetic Mean (CV%);n

^c Median (Min, Max);n

^d For Q8W dosing regimen, individual values were reported because there were only 2 observations for this regimen.

* Below Limit of Quantification (BLQ). Set to zero for summary statistics.

Q4W = Every 4 weeks or every month; Q8W = Every 8 weeks or every other month

AUC₀₋₂₈ = Area under the concentration-time curve (AUC) from time zero to 28 days post-dose; AUC_{0- τ} = AUC from time zero to the end of the dosing interval τ , where τ is 28 or 56 days; AUC_{last} = AUC from time zero to the last quantifiable concentration over the dosing interval; C_{max} = Maximum observed concentration; C_{min} = Minimum observed concentration; t_{max} = Time corresponding to occurrence of C_{max}; t_{1/2} = Terminal elimination half-life; CL/F = Apparent clearance and V_z/F = Apparent terminal volume of distribution.

Special Populations

Renal impairment

No formal dedicated PK study was performed in subjects with impaired renal function compared to matched-control healthy subjects to investigate the effect of different degree of renal impairment (RI) on the PK of ARC1905.

As part of the PK substudy of study ISEE2008, avacincaptad pegol was not detected in urine samples.

Dose adjustment is not required in patients with renal impairment.

Hepatic impairment

No formal dedicated PK study was performed in subjects with impaired hepatic function compared to matched-control healthy subjects to investigate the effect of different degree of hepatic impairment (HI) on the PK of ARC1905.

Metabolic clearance of aptamers is largely driven by innate endonuclease and exonuclease catabolism (Geary et al., 2015). As avacincaptad pegol is primarily cleared via nucleases, the liver and CYP450 enzymes do not play a role in its clearance.

Dose adjustment is not required in patients with hepatic impairment.

Gender

The systemic PK of avacincaptad pegol are driven primarily by the distribution of avacincaptad pegol from the eye into the systemic circulation, which is not anticipated to be different between males and females.

No special labeling guidance with respect to dosage and administration of avacincaptad pegol is needed for gender.

Weight

The systemic PK of avacincaptad pegol are primarily driven by the elimination from the eye and eye size does not change with body weight; therefore, there is no scientific rationale for body weight to affect ocular distribution.

No special labeling guidance with respect to dosage and administration of avacincaptad pegol is needed for weight.

Elderly

Avacincaptad pegol is intended to treat AMD patients impacted by GA, a condition of the elderly.

PK sub-study ISEE2008 was conducted in patients with nAMD aged 52 years or older, with a mean age of 74.9 years (range: 52 to 91 years).

No special labelling guidance with respect to dosage and administration of avacincaptad pegol is needed for age.

Children

Pharmacokinetic was not assessed in the paediatric population, since GA secondary to AMD does not occur in this population.

Exposure-response analysis

No ER analysis were performed.

Pharmacokinetic interaction studies

The in vitro effect of avacincaptad pegol on inhibition of human cytochrome P450 enzyme activity was investigated using human recombinant CYP450 isoenzymes, their substrates, and known inhibiting compounds (Table 4).

Table 4: Effect of avacincaptad pegol on inhibition of human cytochrome P450 enzyme activity (study KSH00058)

CYP Isozyme	Substrate	Average IC ₅₀ (μM) of Control Inhibitor	Avacincaptad Pegol Concentration at ~50% Inhibition
CYP1A2	Phenacetin	Fluvoxamine: 0.24 μM	46% at 4 μM
CYP2C9	Diclofenac	Sulfaphenazole: 1.6 μM	>4 μM
CYP2C19	Mephenytoin	Omeprazole: 3.1 μM	>4 μM
CYP2D6	Dextromethorphan	Quinidine: 0.037 μM	47% at 4 μM
CYP3A4	Midazolam	Ketoconazole: 0.53 μM	>4 μM
CYP3A4	Testosterone	Ketoconazole: 0.069 μM	>4 μM

Source: Study Report [KSH00058](#), M.4.2.2.6

CYP = cytochrome P450; IC₅₀ = concentration at approximately 50% inhibition

The concentrations of avacincaptad pegol ranged from 0.203 nM to 4 μM (10 concentrations) and the enzyme reaction was incubated at 37°C for 30 or 60 minutes. Substrate metabolites were monitored by LC-MS/MS bioanalysis (KSH00058, M.4.2.2.6). None of the CYP450 data sets for avacincaptad pegol met the criteria for curve fitting (i.e., yielded a full dose-response curve), but all of the data sets for the control compounds did.

Avacincaptad pegol demonstrated inhibition of CYP2D6 and CYP1A2 (47% and 46%, respectively) at 4 μM. For comparison, the IC₅₀ values of control inhibitor were 0.037 μM and 0.24 μM, respectively. The observed IC₅₀ values for CYP2C9, CYP2C19 and CYP3A4 were >4 μM, where the IC₅₀ values of control inhibitors were 1.6 μM, 3.1 μM, and (for CYP3A4) 0.53 and 0.069 μM, respectively. The IC₅₀ values for the control CYP450 inhibitors were consistent with expected and previous values.

In the case of the CYP3A4 assay using the midazolam substrate, apparent negative inhibition (i.e., stimulation) was observed, particularly at the higher concentrations of test compound.

Pharmacokinetics using human biomaterials

3.3.1.2. Pharmacodynamics

Mechanism of action

Avacincaptad pegol (also known as ARC1905 or Izelvay) is a complement component 5 (C5) inhibitor for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). It functions by specifically binding to human C5 with high affinity, inhibiting cleavage of C5 into C5a, and preventing C5b from joining with C6. The ribonucleic acid (RNA) aptamer is polyethylene glycol (PEG)ylated to confer stability to the molecule against biodegradation and delayed clearance in vivo without diminishing its activity, ultimately contributing to its efficacy in patients with GA.

Primary and Secondary pharmacology

Increased GA area growth, assessed by fundus autofluorescence, is reflective of loss of photoreceptors and irreversible GA disease progression. Reductions in GA growth were observed from baseline through the first year of treatment across all avacincaptad pegol treatment groups in pivotal studies OPH2003 and ISEE2008.

Avacincaptad pegol is administered via IVT injection. With regard to clinical activity, the proposed mechanism of action is not predicated on systemic exposure. To support the adequacy of the clinical dose selection of 2 mg administered once monthly via IVT injection, exposure-response assessments integrated the clinical plasma concentrations following the IVT administration of the 2 mg dose with the in vitro 99% of maximal inhibitory concentration (IC99) for C5, and exposures associated with the no observed effect level (NOEL) and the no observed adverse effect level (NOAEL) doses in toxicological studies. Overall, the projected human eye concentrations of avacincaptad pegol following IVT injection of 2 mg are orders of magnitude above the in vitro IC99 for inhibition of C5, and the measured plasma concentrations in humans are orders of magnitude lower than the NOEL/NOAEL exposures in IV toxicology studies, indicating a wide safety margin.

Avacincaptad pegol has been shown to interact with select coagulation factors during in vitro binding experiments, these studies did not conclusively indicate changes to APTT or PT. In vivo, effects were generally only observed following IV dosing at levels that were greatly exaggerated relative to the intended clinical doses and route of administration. Furthermore, in vivo studies following IVT dosing demonstrated that avacincaptad pegol was not associated with clinically significant anticoagulant effects or risk of prolongation of APTT at relevant human concentrations.

Nucleic acids can activate complement by either classical or alternative pathway mechanisms. Phosphorothioate antisense oligonucleotides, in particular, appear to activate the alternative pathway, possibly via interference with the regulatory activity of Factor H. In study C5-PHARM-006-05 (M.4.2.1.2), the effects of avacincaptad pegol on complement activation upstream of C5 action were evaluated by measuring C3a generation in human serum incubated with up to 2 mg/mL. Zymosan, an activator of the alternative complement pathway, was used as a positive control. Other aptamers were also compared to assess class effects on complement activation. In the absence of aptamer or zymosan, the 15 minutes incubation stimulated an approximately 2-fold increase in C3a levels, from 1.77 ± 0.049 µg/mL in pre-incubation (baseline) samples to 3.86 ± 0.365 µg/mL after incubation. Further increases due to the addition of positive control aptamer or zymosan ranged up to approximately 20 µg/mL. Unlike the positive control aptamer and zymosan, which stimulated approximately 5-fold increases in C3a levels, avacincaptad pegol induced little or no complement activation at concentrations up to 2 mg/mL. Avacincaptad pegol demonstrated no complement activation when evaluated by an in vitro assay to measure the generation of C3a or via in vivo plasma Bb and C3a measurements.

3.3.2. Discussion on clinical pharmacology

The requested results from the PK substudy of ISEE2008 were provided. Ten patients were enrolled in the PK substudy and n=8 received a 2mg/eye Q4W and n=2 received 2 mg/eye Q8W. PK sampling consisted of pre-dose and 4, 24, 48, 96, 144, 336 and 504 post-dose at steady-state followed by pre-dose at subsequent months.

As part of this study a new bioanalytical method was developed to quantify avacincaptad pegol in human K2EDTA plasma and urine using a MSD-ECL platform. Importantly this method have not been cross-validated with the one developed for the quantification of avacincaptad pegol as part of study

OPH2000 (reagent no being longer available and no samples available for the cross-validation). For study OPH2000 the assay validation method was performed in 2008 and 2023 for study ISEE2008.

At steady-state, in the target population (patient with GA secondary to AMD) following a 2mg/eye Q4W, geometric mean C_{max} and AUC₀₋₂₈ days were 347 ng/mL (5-fold greater) and 4726 ng.day/mL (2.4-fold greater). Ancillary PK data from study OPH2000 following an IVT dose of 2mg/eye Q4W, indicated that geometric mean C_{max} and AUC_{0-inf} were 68.4 ng/mL and 1948.4 ng.day/mL.

Thus compared to the ancillary PK data from study OPH2000, C_{max} and AUC_{0tau} are 5-fold and 2.42 fold greater in study ISEE2008 at the same dose. Consequently it appears obvious that both methods does not performed similarly and are not comparable even when using a PopPK analysis to account for this difference.

Consequently all the PK data from study OPH2000 should be completely discarded and the associated results from the PopPK analysis cannot be considered reliable. Performing a PopPK analysis solely based on 10 patients is not sound.

Furthermore given the observed PK data with a geometric mean C_{max} of 347 ng/mL, C_{min} of 29.6 ng/mL and C_{avg} of 168.9 ng/mL (C_{avg}=AUC_{0-28d}/28d), when converting in nM (MM of avacincaptad non pegylated of 12882 Da) and comparing with the IC₉₉ for C5 inhibition in the sheep erythrocyte hemolysis assay of 5.1 nM, there is a high risk to have a systemic C5 inhibition as C_{max}, C_{min} and C_{avg} translate to 26.9, 2.29 and 13.1 nM. The claimed local acting drug is unlikely.

Even when considering the PK data from the two subjects who received IVT administration of avacincaptad pegol at 2mg Q8W, converted to nM, C_{max} and C_{avg} were 17 and 27 nM and 10,2 and 8 nM respectively, both above the IC₉₉ threshold for C5 inhibition.

Population PK analysis

Initially a population pharmacokinetic analysis was developed by using plasma avacincaptad pegol concentration data from study OPH2000. An updated one was submitted at Day 120, incorporating PK data from the PK substudy ISEE2008.

Importantly, as stated above each PK dataset from study OPH2000 and ISEE2008 were generated using two bioanalytical methods which were not cross-validated. To account for this difference a bioanalytical covariate was used on F_{rel} (Relative bioavailability parameter) and was estimated at 172%. To note based on the PopPK analysis, for a typical subject from study ISEE2008 receiving 2mg/eye IVT of avacincaptad (F_{rel}= 1x0.553x2.72), (NCA analysis, Table 3 above), CL/F and V/F are 0.46 L/d (0.42 L/d) and 0.87 L (4.55 L).

Overall this analysis has a low impact and was used to inform the special population sections (Renal impairment, hepatic impairment, and elderly) in the SmPC this analysis cannot be used for any dosing regimen justification or any model-based prediction of efficacy nor safety.

Exposure-response relationship

No exposure-safety or exposure-efficacy analysis has been conducted, which impedes to understand the overall benefit-risk of the current dosing regimens selected. This information should be completed once the Phase 3 trial is finished.

DDI

Regarding the DDI studies, *the potential of avacincaptad pegol to inhibit CYP450 enzymes was evaluated in vitro in Study KSH00058*. The results indicate that at a concentration of 4 µM, avacincaptad pegol exhibited a 49.4% inhibition of CYP2D6 and a 48.9% inhibition of CYP1A2. However, considering that the estimated IC₅₀ values were higher than the worst-case estimate systemic concentration of

avacincaptad pegol ($50 \times C_{max}$, unbound) for CYP inhibition, which was 2.63×10^{-7} M after intravitreal injections, it's improbable that there would be a significant CYP-mediated DDI between avacincaptad pegol and substrates of CYP2D6 and CYP1A2.

The IC₅₀ values for CYP2C9, CYP2C19 and CYP3A4 were greater than 4 μ M, indicating avacincaptad pegol is not an inhibitor of CYP2C9, CYP2C19 and CYP3A4.

However, unexpected results were found for the avacincaptad pegol effect on CYP3A4 substrate (midazolam), showing an induction ranging from 20% to 87.5% at avacincaptad pegol concentrations up from 0.203 nM to 4 μ M.

A potential DDI between avacincaptad pegol and CYP3A4 substrates could not be ruled out. This warrants further investigation, including conducting an in vitro induction study (using midazolam and testosterone as substrates). **(OC)**

Exposure-response relationship

No exposure-safety or exposure-efficacy analysis has been conducted, which impedes to understand the overall benefit-risk of the current dosing regimens selected. This information should be completed once the Phase 3 trial is finished.

3.3.3. Conclusions on clinical pharmacology

The characterization of the PK and PD properties of avacincaptad pegol have been scarcely characterized using data from a Phase 3 PK substudy in subjects with GA secondary to AMD (Study ISEE2008). Although no major objections have been raised, several other concerns remained.

3.3.4. Clinical efficacy

Table 5: Description of clinical efficacy studies with avacincaptad pegol in GA secondary to AMD

Study ID/ Phase/ Status/ Study Report	Number of Study Centers (Locations)	Design Control Type	Study Objective	Primary Endpoint	Key Inclusion Criteria ^a	Study and Control Drugs/Dose/ Route Regimen	Number of Patients Treated – by Arm
OPH2003/ Phase 2/3/ Completed/ CSR OPH2003	63 (North America, Europe, and Israel)	Randomized, double-masked, sham- controlled, 2- Part trial	To assess the safety and efficacy of IVT avacincaptad pegol in patients with GA	GA area measured by FAF at: BL, M6 and M12	Either sex Aged: ≥ 50 years Diagnosis of GA	Study drug: avacincaptad pegol 1, 2, and 4 mg Control: sham IVT once monthly	Avacincaptad pegol ^b 1 mg: 26 2 mg comb. ^c : 67 4 mg: 83 Sham comb. ^c : 110
ISEE2008/ Phase 3/ Ongoing Year 1 CSR ISEE2008	205 (North America, South America, Europe, Australia, and Israel)	Randomized, parallel-group, double-masked, sham-controlled trial	To assess the safety and efficacy of IVT avacincaptad pegol in patients with GA	GA area measured by FAF at: BL, M6, and M12	Either sex Aged: ≥ 50 years Diagnosis of GA	Study drug: avacincaptad pegol 2 mg Control: sham IVT once monthly ^d	Avacincaptad pegol 2 mg: 225 Sham: 222 Total: 447

AMD = age-related macular disease; BL = Baseline; comb. = combined (combination of Part 1 and Part 2 patients); CSR = clinical study report; DA = disc area; FAF = fundus autofluorescence; GA = geographic atrophy; IVT = intravitreal; M# = Month #

^a In Studies OPH2003 and ISEE2008, key ophthalmic inclusion criteria were non-foveal GA, total GA area ≥ 2.5 mm² and ≤ 17.5 mm² (1 and 7 DA respectively), at least one focal lesion should measure ≥ 1.25 mm² (0.5 DA), GA in part within 1500 microns from the foveal center. Foveal disease included the foveal center point; and extrafoveal included disease in the fovea and outside the fovea but did not involve the foveal center point. To ensure a generalizable study population of patients with GA, the patients enrolled in both studies consisted of patients with GA area located inside and/or outside of the 1.5 mm diameter foveal area.

^b In Part 1, a total of 77 patients were randomly assigned in a 1:1:1 ratio to receive avacincaptad pegol 1 mg (N=26), avacincaptad pegol 2 mg (N=25) or sham (N=26). In Part 2, a total of 209 patients were randomly assigned in a 1:2:2 ratio to receive avacincaptad pegol 2 mg (N=42), avacincaptad pegol 4 mg (N=83) or sham (N=84).

^c The avacincaptad pegol 2 mg dose was evaluated by combining both avacincaptad pegol 2 mg arms (Part 1 and Part 2 of Study OPH2003; N=67; also referred to as avacincaptad pegol 2 mg group) and both sham arms (Part 1 and Part 2 of Study OPH2003; N=110; also referred to as sham group). The 4 mg dose was evaluated using the sham arm of Part 2.

^d Patients who were receiving avacincaptad pegol were re-randomized at M12 in a 1:1 ratio to receive avacincaptad pegol 2 mg once monthly from M12 through M23, or sham at M12, M14, M16, M18, M20, and M22, and avacincaptad pegol 2 mg every other month at M13, M15, M17, M19, M21, and M23, with no changes to the Sham arm (SCE Section 2.7.3.1.2.1.2).

3.3.4.1. Dose-response studies

3.3.4.2. Main study(ies)

OPH2003 (GATHER 1)

Methods

OPH2003 was a randomized phase 2b/3, double-masked, Sham-controlled study designed to compare the efficacy and safety of Izelvay 1, 2, and 4 mg vs Sham in patients with GA secondary to dry AMD

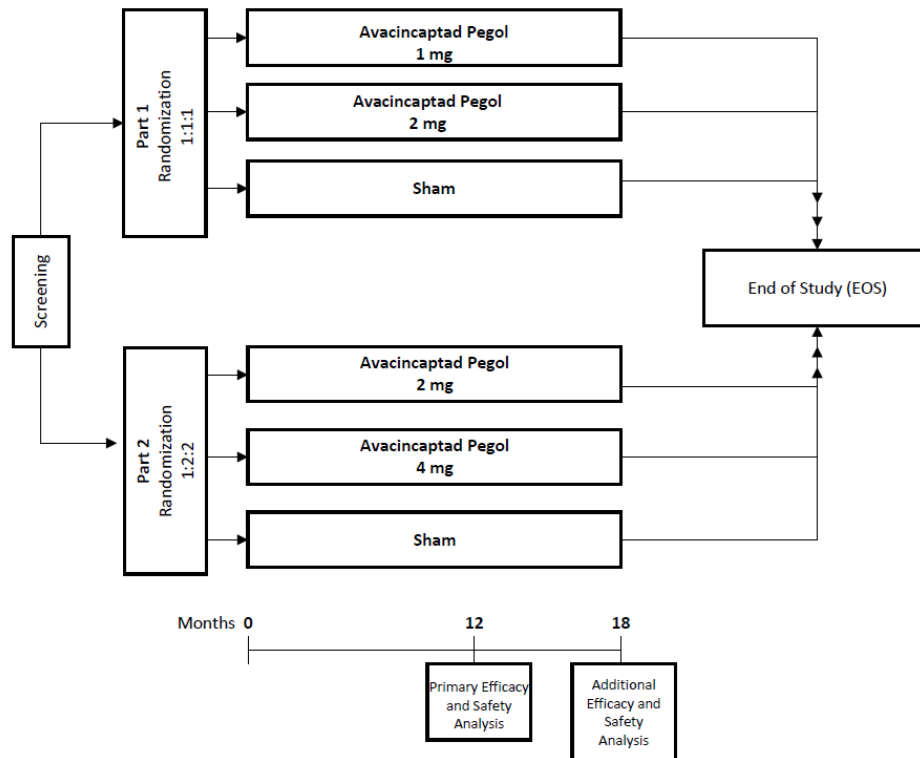


Figure 3: Treatment period

Study Participants

The inclusion criteria included GA patients ≥ 50 years of age diagnosed with disease inside and/or outside of the 1.5 mm diameter foveal area.

Ophthalmic Inclusion Criteria

The following inclusion criteria applied to the Study Eye (SE):

1. Non-foveal GA secondary to dry AMD.
2. Total GA area ≥ 2.5 and ≤ 17.5 mm² (1 and 7 DA respectively), determined by Screening images of FAF.
3. If GA is multifocal, at least one focal lesion should measure ≥ 1.25 mm² (0.5 DA).
4. GA in part within 1500 microns from the foveal centre.
5. The atrophic lesion must be able to be photographed in its entirety.
6. BCVA in the SE between 20/25 to 20/320, inclusive.

7. Clear ocular media and adequate pupillary dilatation in both eyes to allow for all imaging procedures, including good quality stereoscopic fundus photography and FAF.
8. IOP of 21 mmHg or less in the SE.

Ophthalmic Exclusion Criteria

The following exclusion criteria applied to the SE:

1. Evidence of CNV in either eye. If CNV develops in the SE during the course of the study, the patient will be withdrawn from the study.
2. GA secondary to any condition other than AMD in either eye (e.g., drug-induced)
3. Any prior treatment for AMD or any prior IVT treatment for any indication in either eye, except oral supplements of vitamins or minerals
4. Any ocular condition in the SE that would progress during the course of the study that could affect central vision or otherwise be a confounding factor.
5. Concomitant treatment with any ocular or non-ocular medication that is known to be toxic to the lens, retina, or optic nerve.
6. Presence of intraocular inflammation ($\geq$ trace cell or flare), macular hole, pathologic myopia, epiretinal membrane, evidence of significant vitreo-macular traction, vitreous hemorrhage or aphakia (pseudophakia with or without an intact capsule is not an exclusion criteria).
7. Presence or history of idiopathic or autoimmune-associated uveitis in either eye.
8. Significant media opacities, including cataract, which might interfere with VA, assessment of toxicity, fundus photography, or FAF. Patients should not be entered if there is likelihood that they will require cataract surgery in the SE during the study.
9. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis.
10. Any intraocular surgery or thermal laser within 3 months of study entry. Any prior thermal laser in the macular region, regardless of indication
11. Any ocular or periocular infection (including blepharitis), or ocular surface inflammation in the past 12 weeks
12. History of any of the following procedures: Posterior vitrectomy, filtering surgery (e.g., trabeculectomy), glaucoma drainage device, corneal transplant, or retinal detachment.
13. Any sign of diabetic retinopathy in either eye.

Treatments

Active treatment

The study treatment was Izelvay 1 mg, 2 mg, or 4 mg for IVT injection every 4 weeks.

Doses were administered at least 21 days apart.

As a note, the 4 mg dose has been added through the Amendment B.

Control

To maintain masking when study treatments were administered, Sham injections that imitated an IVT injection through the use of an injection syringe without a needle were performed.

Objectives

The objectives of this study were to evaluate the safety and efficacy of Izelvay 1 mg, 2 mg, or 4 mg intravitreal administration when administered in patients with GA secondary to dry AMD.

Outcomes/endpoints

Primary efficacy endpoint

- The primary efficacy endpoint was the mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at 3 time points: Baseline, Month 6, and Month 12.

Secondary efficacy endpoints

Two secondary efficacy endpoints were pre-specified:

- Mean change in best-corrected visual acuity (BCVA) (ETDRS letters) from Baseline to Month 12.
- Mean change in low luminance (LL) BCVA (ETDRS letters) from Baseline to Month 12

Sample size

The sample size determination for this study was based on the Phase 2b screening methodology presented in Fleming and Richardson (2004). The power calculations were based on the released results from a clinical trial of a complement inhibitor, including the estimated precision of the estimated effects on rate of GA growth over 12 months, and including the plausible treatment effect size.

A total of approximately 277 subjects were to be enrolled.

The primary analysis of this trial for each of the two pairwise comparisons of an active dose vs the Sham control was based on a three category decision guideline. To be specific, the decision guideline for this trial was based on whether the estimated reduction in rate of GA growth over 12 months for an active dose versus Sham control was less than 14%, from 14% up to 24.5%, or at least 24.5%.

Note that these categories were not to be interpreted as providing strict decision rules but rather as guidelines that were to be factored into a broader scientific assessment of the benefit to risk profile of the dose regimen. Specifically, the decision guidelines for this trial were:

1. If the estimated reduction in the rate of GA growth over 12 months was less than 14%, then this dose was not plausibly more efficacious than the Sham control; its utility in this indication should be reconsidered.
2. If the estimated reduction in the rate of GA growth over 12 months was from 14% to up to 24.5%, then this dose was plausibly more efficacious than the Sham control and should be evaluated in a subsequent Phase 3 clinical trial.
3. If the estimated reduction in the rate of GA growth over 12 months was at least 24.5%, then this dose would be statistically significantly more effective than the Sham control, with strength of evidence meeting the standard requirement of a 0.0125 one-sided false positive error rate (incorporating an adjustment for multiplicity arising from comparing each dose with the Sham control).

The operating characteristics of these decision rules are described in the study protocol.

There were no interim analyses.

Randomisation and blinding (masking)

In Part 1, 77 patients were randomized in a 1:1:1 ratio to the following dose groups:

- Avacincaptad pegol 1 mg/eye administered via intravitreal (IVT) injection
- Avacincaptad pegol 2 mg/eye administered via IVT injection
- Sham: The Sham procedure included the blunt opening of an empty, needleless syringe barrel placed on the conjunctiva in the inferotemporal quadrant of the eyeball to simulate the pressure of an injection.

In Part 2, 200 patients were randomized in a 1:2:2 ratio to the following dose groups:

- Avacincaptad pegol 2 mg/eye administered via IVT injection + Sham
- Avacincaptad pegol 4 mg/eye (administered as 2 IVT injections of Avacincaptad pegol 2 mg/eye)

Patients were centrally allocated to one of the 3 treatment groups stratified by the following variables:

- Baseline VA < 50 ETDRS letters (20/100 Snellen equivalent) vs > 50 ETDRS letters
- Size of Baseline GA (< 4 DA vs > 4 DA)
- Pattern of FAF at the junctional zone of GA (none/focal vs banded/diffuse)

Randomization was performed using an IRT system based on the stratification information above to randomize each patient and assign a treatment arm.

This was a double-masked study. The patients, investigators, study centre staff (except for the unmasked study centre personnel and unmasked injecting physician), Sponsor personnel (except for those who have been delegated responsibility for working with the study treatment), and data analysts remained masked to the identity of the treatment from the time of randomization until Month 12 and final database lock.

Statistical methods

Analysis populations

Intent-to-treat (ITT) population: The ITT population consisted of all randomized patients who received at least one dose of study drug, irrespective of the dose actually received. Patients were analysed in the treatment group assigned at randomization. Patients were included in a particular analysis, for a particular population, if relevant data was available for analysis (e.g., the primary analysis required both Baseline and at least one post-Baseline GA measurement to calculate a change score).

Per-protocol (PP) population: The PP population consisted of all ITT patients without any significant violation of the protocol.

Multiplicity adjustment

The overall (one-sided) false positive error rate in this study, accounting for the conduct of 2 pairwise comparisons (2 mg and 4 mg) with Sham control, was 0.025 for the analysis of the primary endpoint. The actual test of each dose vs Sham used a Hochberg procedure for significance testing. An analysis of secondary endpoints was carried out with a descriptive intent only, without alpha-adjustment.

Primary endpoint

The primary efficacy endpoint was mean rate of change in GA over 12 months measured by FAF at 3 time points: Baseline, Month 6, and Month 12. To eliminate the dependency of GA growth rates on the Baseline lesion size (Feuer 2013), the square root of the GA area was used in the analysis. Only the Avacincaptad pegol 2 mg and 4 mg groups were evaluated for the primary and secondary efficacy endpoints; the Avacincaptad pegol 1 mg group was for descriptive purposes only and included as a supportive endpoint.

For analyses of the primary endpoint, a Mixed-Effects Repeated Measures (MMRM) model was used to assess the differences between the treatment groups in rate of change of GA area over 12 months. Two separate models were fitted for comparing Avacincaptad pegol 4 mg vs Sham control and Avacincaptad pegol 2 mg vs Sham control. Both models were fitted by using restricted maximum likelihood (REML) and included Baseline VA (< 50 letters vs ≥ 50 letters), size of the Baseline GA (< 4 DA vs ≥ 4 DA), and pattern of FAF at the junctional zone of GA (none/focal vs banded/diffuse) as used in the randomization as covariates. For Avacincaptad pegol 2 mg vs Sham control model, fixed effects included treatment, visit, part (Part 1 vs Part 2), the Baseline VA (< 50 letters vs ≥ 50 letters), size of the Baseline GA (< 4 DA vs ≥ 4 DA), pattern of FAF at the junction zone of GA (none/focal vs banded/diffuse), treatment by visit interaction, and the stratification factors by visit interactions. For Avacincaptad pegol 4 mg vs Sham control model, the same fixed effects were used excluding part (Part 1 vs Part 2). An unstructured (co)variance structure was used to model the within-patient errors. If this analysis failed to converge, alternative structures (e.g., heterogeneous autoregressive or heterogeneous compound symmetry, in this order) were considered.

Secondary endpoints

The same MMRM analysis model was used as described above for the primary endpoint.

Sensitivity analyses

Similar sensitivity analyses were performed in GATHER 1 and GATHER 2 studies to assess the impact of alternative handling of missing data. Please refer to the statistical method section for GATHER 2 study.

Subgroup analyses

Subgroups were investigated as follows:

- Size of Baseline GA (< 4 DA vs ≥ 4 DA)
- Baseline VA < 50 ETDRS letters (20/100 Snellen equivalent) vs ≥ 50 ETDRS letters
- Pattern of FAF at the junctional zone of GA (none/focal vs banded/diffuse)
- Patients from Part 1 vs Part 2

Changes in planned analyses

There were several protocol amendments with major modifications to study design and planned analyses.

Table 6: Changes to study design and planned analyses

Protocol version	Study design	Planned analyses / endpoints
Original (6 November 2015)	Only 1 randomisation procedure (what will become part 1 in subsequent versions) Planned interim analysis after 300 patients have reached month 18 Overall sample size between 300 and 600 patients depending on IA.	Primary endpoint is change in BCVA at Month 24 Secondary endpoints are rate of change in GA over 24 months, and change in low luminance best corrected visual acuity (ETDRS letters) at Month 24 The methodology for controlling type I error (including the handling of IA) is said to be included in a SAP (<i>not available for this protocol version</i>).
Amendment B (16 October 2017)	The study has now 2 study parts with separate randomisation procedures, i.e. Part 2 has been added. The interim analysis has been removed. Overall sample size is now 200 patients (approximately 66 from part 1 and 135 from part 2).	Primary endpoint has been modified, it is now mean rate of change in GA over 12 months Secondary endpoints have also been changed. They are change in BCVA at Month 12 and change in low luminance BCVA at Month 12
Amendment C (28 March 2018)	The sample size for both study parts has been increased, from 66 to 77 in part 1 and from 135 to 200 in part 2) for a total of 277 randomised.	The primary and secondary endpoints remain as per Amendment B.

Results

Participant flow

A total of 816 patients were screened and 530 patients were screen failures. The most common (>70%) reasons for screen failure were related to the patient's not meeting specific Ophthalmic Inclusion Criteria. A total of 286 patients were randomized and treated in the study.

Table 7: Patient Disposition – Month 12 (ITT Population)

Number of patients (%)	Part 1			Part 2			Combined*	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
Patients completing through Month 12	24 (92.3%)	20 (80.0%)	21 (80.8%)	35 (83.3%)	58 (69.9%)	75 (89.3%)	55 (82.1%)	96 (87.3%)
Number of patients who discontinued early in Month 12	2 (7.7%)	5 (20.0%)	5 (19.2%)	7 (16.7%)	25 (30.1%)	9 (10.7%)	12 (17.9%)	14 (12.7%)
Adverse event	0	0	1 (3.8%)	0	1 (1.2%)	0	0	1 (0.9%)
Protocol violation	0	0	0	0	0	0	0	0
Investigator decision	0	0	0	1 (2.4%)	2 (2.4%)	1 (1.2%)	1 (1.5%)	1 (0.9%)
Sponsor decision	1 (3.8%)	2 (8.0%)	0	3 (7.1%)	8 (9.6%)	2 (2.4%)	5 (7.5%)	2 (1.8%)
Withdrawal by patient	1 (3.8%)	3 (12.0%)	3 (11.5%)	3 (7.1%)	13 (15.7%)	5 (6.0%)	6 (9.0%)	8 (7.3%)
Lost to follow-up	0	0	1 (3.8%)	0	0	0	0	1 (0.9%)
Patient non-compliance	0	0	0	0	0	0	0	0
Death	0	0	0	0	1 (1.2%)	1 (1.2%)	0	1 (0.9%)
Other	0	0	0	0	0	0	0	0
Number of patients who completed through								
Month 3 visit	25 (96.2%)	23 (92.0%)	23 (88.5%)	40 (95.2%)	76 (91.6%)	81 (96.4%)	63 (94.0%)	104 (94.5%)
Month 6 visit	25 (96.2%)	21 (84.0%)	21 (80.8%)	36 (85.7%)	68 (81.9%)	78 (92.9%)	57 (85.1%)	99 (90.0%)
Month 9 visit	24 (92.3%)	20 (80.0%)	21 (80.8%)	35 (83.3%)	62 (74.7%)	74 (88.1%)	55 (82.1%)	95 (86.4%)
Month 12 visit	23 (88.5%)	18 (72.0%)	17 (65.4%)	34 (81.0%)	56 (67.5%)	72 (85.7%)	52 (77.6%)	89 (80.9%)

Source: Post-text Table 14.1.2

ITT = intent-to-treat population

Note: Discrepancy between 'Number of patients completing through Month 12' and 'Number of patients who completed through Month 12 visit' are due to ongoing patients who missed Month 12 visit.

*Combination of Part 1 and Part 2 patients.

Recruitment

OPH2003 was conducted between 15 Dec 2015 and 23 Apr 2020 at 63 sites in seven countries, including Croatia, Czech Republic, Estonia, Hungary, Israel, Latvia, and the United States.

First patient first visit was on 26 Jan 2016.

Conduct of the study

There were 3 global Amendments:

- Amendment A on 7 March 2016. Changes, among others, include:

- Introduced a new inclusion criteria:

Total GA area ≥ 2.5 and ≤ 17.5 mm² (1 and 7 disk areas [DA] respectively), determined by screening images of FAF.

If GA is multifocal, at least one focal lesion should measure ≥ 1.25 mm² (0.5 DA).

GA must be in part within 1500 microns from the foveal center.

- Introduced a new exclusion criteria:

Evidence of CNV in either eye. If CNV develops in the SE during the course of the study, the patient will be withdrawn from the study.

Presence of other causes of choroidal neovascularization, including pathologic myopia (spherical equivalent of -8 diopters or more, or axial length of 25mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis.

- Amendment B on 16 October 2017. Changes, among others, include:

- Change of the categorization of the study from Phase 2/3 to Phase 2b
- Stop of the enrolment in the Part 1:

It was initially planned to enrol approximately 300 subjects will be randomized in a 1:1:1 ratio to the following dose groups: Izelvay 1mg/eye, Izelvay 2mg/eye, and Sham. This was then limited to approximately 66 subjects.

- Addition of a Part 2, initially not planned:

It was planned to enrol approximately 135 subjects randomized in a 1:2:2 ratio to the following dose groups: Izelvay 2mg/eye mg/eye + Sham, Izelvay 4mg/eye (administered as two injections of Izelvay 2 mg), and Sham+ Sham.

- Change of the primary and the secondary endpoints (see related section).
- The duration of the study is shortened from 24 months to 18 months.

- Amendment C on 28 March 2018. Changes, among others, include:

- Increase of the sample size from 66 to 77 for the part 1, and from 135 to 200 for the Part 2.

Baseline data

Demographic and other baseline characteristics of the randomized subjects are presented in below tables.

Table 8: Demographics and baseline characteristics (ITT population)

Number of patients (%)	Part 1			Part 2			Combined*	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
Sex, n (%)								
Male	11 (42.3%)	7 (28.0%)	8 (30.8%)	15 (35.7%)	25 (30.1%)	23 (27.4%)	22 (32.8%)	31 (28.2%)
Female	15 (57.7%)	18 (72.0%)	18 (69.2%)	27 (64.3%)	58 (69.9%)	61 (72.6%)	45 (67.2%)	79 (71.8%)
Ethnicity, n (%)								
Not Hispanic or Latino	25 (96.2%)	24 (96.0%)	25 (96.2%)	42 (100%)	82 (98.8%)	83 (98.8%)	66 (98.5%)	108 (98.2%)
Hispanic or Latino	1 (3.8%)	1 (4.0%)	1 (3.8%)	0	1 (1.2%)	1 (1.2%)	1 (1.5%)	2 (1.8%)
Race, n (%)								
American Indian/Alaska Native	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)
Asian	1 (3.8%)	0	0	0	0	0	0	0
Native Hawaiian/Pacific Islander	0	0	0	0	0	0	0	0
White	25 (96.2%)	25 (100%)	25 (96.2%)	42 (100%)	82 (98.8%)	82 (97.6%)	67 (100%)	107 (97.3%)
Other	0	0	1 (3.8%)	0	1 (1.2%)	1 (1.2%)	0	2 (1.8%)

	Part 1			Part 2			Combined*	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
Number of patients (%)								
Age (years)								
Mean	73.8	77.7	78.1	79.4	79.2	78.2	78.8	78.2
Standard Deviation	7.97	9.57	8.43	10.65	8.31	8.98	10.22	8.82
Median	75.5	80.0	79.0	83.0	80.0	78.0	82.0	79.0
Q1;Q3	67.0; 79.0	73.0; 86.0	74.0; 85.0	71.0; 87.0	74.0; 86.0	71.0; 83.0	72.0; 87.0	73.0; 83.0
Range	56; 91	58; 94	57; 90	52; 94	57; 95	54; 97	52; 94	54; 97
Age Group (years), n (%)								
<65	3 (11.5%)	4 (16.0%)	2 (7.7%)	6 (14.3%)	5 (6.0%)	4 (4.8%)	10 (14.9%)	6 (5.5%)
65 to 74	8 (30.8%)	5 (20.0%)	5 (19.2%)	8 (19.0%)	19 (22.9%)	22 (26.2%)	13 (19.4%)	27 (24.5%)
75 to 84	14 (53.8%)	9 (36.0%)	12 (46.2%)	12 (28.6%)	38 (45.8%)	38 (45.2%)	21 (31.3%)	50 (45.5%)
≥85	1 (3.8%)	7 (28.0%)	7 (26.9%)	16 (38.1%)	21 (25.3%)	20 (23.8%)	23 (34.3%)	27 (24.5%)
Current Smoking Status, n (%)								
Non-active	20 (76.9%)	15 (60.0%)	19 (73.1%)	27 (64.3%)	57 (68.7%)	55 (65.5%)	42 (62.7%)	74 (67.3%)
Active	6 (23.1%)	10 (40.0%)	7 (26.9%)	15 (35.7%)	26 (31.3%)	29 (34.5%)	25 (37.3%)	36 (32.7%)
Lens status, n (%)								
Aphakic	0	0	0	0	0	0	0	0
Pseudophakic	17 (65.4%)	15 (60.0%)	16 (61.5%)	29 (69.0%)	56 (67.5%)	62 (73.8%)	44 (65.7%)	78 (70.9%)
Phakic	9 (34.6%)	10 (40.0%)	10 (38.5%)	13 (31.0%)	27 (32.5%)	22 (26.2%)	23 (34.3%)	32 (29.1%)
Not Done	0	0	0	0	0	0	0	0
If Phakic, Grade:								
Nuclear								
0	4 (15.4%)	3 (12.0%)	4 (15.4%)	1 (2.4%)	3 (3.6%)	1 (1.2%)	4 (6.0%)	5 (4.5%)
1	2 (7.7%)	6 (24.0%)	5 (19.2%)	10 (23.8%)	14 (16.9%)	17 (20.2%)	16 (23.9%)	22 (20.0%)

Number of patients (%)	Part 1			Part 2			Combined*	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
2	3 (11.5%)	1 (4.0%)	1 (3.8%)	1 (2.4%)	10 (12.0%)	4 (4.8%)	2 (3.0%)	5 (4.5%)
3	0	0	0	1 (2.4%)	0	0	1 (1.5%)	0
4	0	0	0	0	0	0	0	0
Posterior subcapsular cataract								
0	7 (26.9%)	9 (36.0%)	9 (34.6%)	12 (28.6%)	22 (26.5%)	19 (22.6%)	21 (31.3%)	28 (25.5%)
1	1 (3.8%)	1 (4.0%)	0	1 (2.4%)	5 (6.0%)	3 (3.6%)	2 (3.0%)	3 (2.7%)
2	1 (3.8%)	0	1 (3.8%)	0	0	0	0	1 (0.9%)
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
Cortical								
0	6 (23.1%)	8 (32.0%)	6 (23.1%)	10 (23.8%)	17 (20.5%)	14 (16.7%)	18 (26.9%)	20 (18.2%)
1	2 (7.7%)	2 (8.0%)	3 (11.5%)	2 (4.8%)	9 (10.8%)	5 (6.0%)	4 (6.0%)	8 (7.3%)
2	1 (3.8%)	0	1 (3.8%)	1 (2.4%)	1 (1.2%)	3 (3.6%)	1 (1.5%)	4 (3.6%)
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0

Source: [Post-text Table 14.1.4.1](#) and [Post-text Table 14.1.11.1](#)

ITT = intent-to-treat

*Combination of Part 1 and Part 2 patients.

Table 9: Baseline visual acuity score - study eye (ITT population)

	Part 1			Part 2			Combined ^a	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
BCVA (ETDRS Letters)								
Mean	70.5	71.6	71.3	69.4	69.5	68.3	70.2	69.0
SD	8.04	7.48	7.48	11.25	9.81	11.03	10.01	10.35
Median	71.0	74.0	72.5	72.5	71.0	70.5	73.0	71.0
Q1;Q3	66.0; 77.0	67.0; 77.0	67.0; 78.0	60.0; 76.0	64.0; 77.0	64.5; 77.0	66.0; 77.0	65.0; 77.0
Range	52; 82	50; 81	57; 82	27; 83	29; 83	28; 80	27; 83	28; 82
n	26	25	26	42	83	84	67	110
≥ 50 letters	26 (100%)	25 (100%)	26 (100%)	41 (97.6%)	82 (98.8%)	79 (94.0%)	66 (98.5%)	105 (95.5%)
< 50 letters	0	0	0	1 (2.4%)	1 (1.2%)	5 (6.0%)	1 (1.5%)	5 (4.5%)
Low Luminance BCVA (ETDRS Letters)								
Mean	38.1	43.0	36.7	33.1	36.8	33.9	36.7	34.5
SD	22.71	19.74	21.24	21.25	20.87	18.77	21.10	19.32
Median	45.0	44.5	36.0	28.0	40.0	31.0	37.5	32.0
Q1;Q3	15.0; 58.0	28.0; 58.5	19.0; 54.0	18.0; 50.0	18.0; 57.0	18.0; 51.0	19.0; 55.0	18.0; 53.0
Range	0; 68	4; 77	3; 72	1; 77	1; 74	0; 69	1; 77	0; 72
n	26	24	26	42	83	84	66	110
	Part 1			Part 2			Combined ^a	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
≥ 50 letters	11 (42.3%)	11 (44.0%)	10 (38.5%)	11 (26.2%)	33 (39.8%)	25 (29.8%)	22 (32.8%)	35 (31.8%)
< 50 letters	15 (57.7%)	13 (52.0%)	16 (61.5%)	31 (73.8%)	50 (60.2%)	59 (70.2%)	44 (65.7%)	75 (68.2%)
NA	0	1 (4.0%)	0	0	0	0	1 (1.5%)	0

Source: [Post-text Table 14.1.6.1](#)

BCVA = best-corrected visual acuity; ETDRS = early treatment diabetic retinopathy study; ITT = intent-to-treat population; NA = not applicable; SD = standard deviation; VA = visual acuity

Note: The mean value of the Screening and Day 1 VA Score is used as the Baseline value for BCVA. The Screening VA Score is used as the Baseline value for Low Luminance BCVA.

^aCombination of Part 1 and Part 2 patients.

Table 10: Baseline fundus autofluorescence – study eye (ITT population)

Number of patients (%)	Part 1			Part 2			Combined*	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
Localization of Hypo FAF								
Foveal ^b	2 (7.7%)	5 (20.0%)	4 (15.4%)	0	2 (2.4%)	2 (2.4%)	5 (7.5%)	6 (5.5%)
Extrafoveal ^b	23 (88.5%)	20 (80.0%)	22 (84.6%)	42 (100%)	81 (97.6%)	82 (97.6%)	62 (92.5%)	104 (94.5%)
Ungradable	1 (3.8%)	0	0	0	0	0	0	0
Temporal Peripapillary Atrophy								
Yes	24 (92.3%)	24 (96.0%)	26 (100%)	38 (90.5%)	79 (95.2%)	80 (95.2%)	62 (92.5%)	106 (96.4%)
No	1 (3.8%)	1 (4.0%)	0	3 (7.1%)	4 (4.8%)	4 (4.8%)	4 (6.0%)	4 (3.6%)
Ungradable	1 (3.8%)	0	0	1 (2.4%)	0	0	1 (1.5%)	0
If Yes, Peripapillary Confluent with Macular GA								
Yes	2 (8.3%)	2 (8.3%)	1 (3.8%)	4 (10.5%)	7 (8.9%)	7 (8.8%)	6 (9.7%)	8 (7.5%)
No	21 (87.5%)	22 (91.7%)	25 (96.2%)	34 (89.5%)	72 (91.1%)	73 (91.3%)	56 (90.3%)	98 (92.5%)
Ungradable	1 (4.2%)	0	0	0	0	0	0	0
If Yes, Localization of Peripapillary Atrophy								
Temporal only	6 (25.0%)	7 (29.2%)	7 (26.9%)	7 (18.4%)	13 (16.5%)	20 (25.0%)	14 (22.6%)	27 (25.5%)
Nasal and temporal	17 (70.8%)	17 (70.8%)	19 (73.1%)	30 (78.9%)	62 (78.5%)	58 (72.5%)	47 (75.8%)	77 (72.6%)
Ungradable	1 (4.2%)	0	0	1 (2.6%)	4 (5.1%)	2 (2.5%)	1 (1.6%)	2 (1.9%)
Macular Atrophy Gradable								
Yes	25 (96.2%)	25 (100%)	26 (100%)	42 (100%)	82 (98.8%)	84 (100%)	67 (100%)	110 (100%)
No	1 (3.8%)	0	0	0	1 (1.2%)	0	0	0
Number of patients (%)	Part 1			Part 2			Combined*	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
If No, Reason								
No observable GA	0	0	0	0	0	0	0	0
Lesion exceeds image	0	0	0	0	0	0	0	0
Poor image quality	1 (100%)	0	0	0	1 (100%)	0	0	0
Ill-defined lesion borders	0	0	0	0	0	0	0	0
Ungradable	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
If Yes, Area of GA (mm ²)								
Mean	7.37	6.60	7.33	7.77	7.90	7.45	7.33	7.42
Standard Deviation	4.321	3.346	3.728	4.010	4.179	3.893	3.793	3.838
Median	7.38	6.48	6.51	6.30	6.91	6.67	6.47	6.67
Q1;Q3	3.83; 8.37	4.16; 9.05	3.99; 10.81	4.71; 9.42	4.55; 11.55	4.24; 10.30	4.46; 9.33	4.15; 10.47
Range	0.3; 16.6	0.6; 12.9	3.1; 14.3	2.8; 17.3	2.5; 17.2	2.2; 17.2	0.6; 17.3	2.2; 17.2
n	25	25	26	42	82	84	67	110
Hyper FAF								
Yes	25 (96.2%)	25 (100%)	26 (100%)	41 (97.6%)	82 (98.8%)	83 (98.8%)	66 (98.5%)	109 (99.1%)
No	0	0	0	0	0	0	0	0
Ungradable	1 (3.8%)	0	0	1 (2.4%)	1 (1.2%)	1 (1.2%)	1 (1.5%)	1 (0.9%)

Number of patients (%)	Part 1			Part 2			Combined ^a	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
If Yes, Hyper FAF pattern								
Fine granular-punctate spots	7 (28.0%)	6 (24.0%)	8 (30.8%)	1 (2.4%)	9 (11.0%)	17 (20.5%)	7 (10.6%)	25 (22.9%)
Branching	1 (4.0%)	4 (16.0%)	3 (11.5%)	3 (7.3%)	4 (4.9%)	1 (1.2%)	7 (10.6%)	4 (3.7%)
Fine granular-dusty	10 (40.0%)	9 (36.0%)	8 (30.8%)	17 (41.5%)	26 (31.7%)	28 (33.7%)	26 (39.4%)	36 (33.0%)
Trickling	3 (12.0%)	2 (8.0%)	3 (11.5%)	10 (24.4%)	13 (15.9%)	17 (20.5%)	12 (18.2%)	20 (18.3%)
Reticular	2 (8.0%)	1 (4.0%)	1 (3.8%)	6 (14.6%)	15 (18.3%)	8 (9.6%)	7 (10.6%)	9 (8.3%)
Patchy	0	1 (4.0%)	0	0	1 (1.2%)	0	1 (1.5%)	0
Banded	2 (8.0%)	1 (4.0%)	3 (11.5%)	0	0	1 (1.2%)	1 (1.5%)	4 (3.7%)
Focal	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)
Not determinable	0	1 (4.0%)	0	4 (9.8%)	14 (17.1%)	10 (12.0%)	5 (7.6%)	10 (9.2%)

Source: Post-text Table 14.1.5

FAF = fundus autofluorescence; GA = geographic atrophy; ITT = intent-to-treat population

Note: The baseline values are taken as the last non-missing value prior to the first dose of study drug.

^aCombination of Part 1 and Part 2 patients.

^bFoveal disease includes the foveal center point; extrafoveal includes disease in the fovea and outside the fovea but does not involve the foveal center point.

The injection compliance was 87% (avacincaptad pegol 2 mg) and 89% (sham) at Month 12 and 82% and 86% respectively at Month 18.

Numbers analysed

A summary of the number of subjects in each analysis set is presented in Table 11.

Table 11: Patient populations

Number of patients	Part 1			Part 2			Combined ^a	
	Zimura 1 mg	Zimura 2 mg	Sham	Zimura 2 mg	Zimura 4 mg	Sham	Zimura 2 mg	Sham
Randomization population	26	25	26	42	83	84	67	110
Number of patients randomized but not treated	0	0	0	0	0	0	0	0
ITT population ^b	26	25	26	42	83	84	67	110
Per-protocol population ^c	17	18	18	29	52	69	47	87
Safety population ^d	26	25	26	42	83	84	67	110

Source: Post-text Table 14.1.1.1

ITT = intent-to-treat population

^aCombination of Part 1 and Part 2 patients.

^bThe ITT population consisted of all randomized patients who received at least one dose of study drug, irrespective of the dose actually received. Patients were analyzed in the dose group assigned at randomization.

^cThe PP population consisted of all ITT patients without significant violation of the protocol.

^dThe Safety population included all patients who received at least one injection of the study drug. Patients who ever received an injection of Zimura were analyzed in the appropriate Zimura group according to the actual injections received.

Outcomes and estimation

Primary endpoint

Mean Rate of Change in GA from Baseline at Month 12

Table 12: Mean rate of change in GA from baseline to month 12 (MRM analysis; square root transformation) - study eye (ITT population)

	Zimura 2 mg ^a N=67	Sham ^a N=110	Zimura 4 mg N=83	Sham N=84
Square root area of GA (mm) at Baseline				
Mean	2.618	2.633	2.715	2.636
Standard Deviation	0.7001	0.7009	0.7320	0.7091
Median	2.544	2.583	2.629	2.583
Q1;Q3	2.111; 3.054	2.038; 3.235	2.133; 3.399	2.059; 3.209
Range	0.75; 4.16	1.49; 4.15	1.57; 4.15	1.49; 4.15
n	67	110	82	84
Square root area of GA (mm) at Month 12				
Mean	3.032	3.119	3.083	3.143
Standard Deviation	0.6643	0.7182	0.7713	0.7201
	Zimura 2 mg ^a N=67	Sham ^a N=110	Zimura 4 mg N=83	Sham N=84
Median	2.948	3.025	3.015	3.044
Q1;Q3	2.558; 3.471	2.618; 3.681	2.491; 3.699	2.636; 3.694
Range	1.91; 4.52	1.67; 4.81	1.66; 4.54	1.67; 4.81
n	49	90	55	72
MRM Analysis ^b - Rate of change from Baseline to Month 12				
Least Squares Mean	0.292	0.402	0.321	0.444
Standard Error	0.077	0.075	0.074	0.072
Difference ^c	-	0.110	-	0.124
% Difference ^d	-	27.38	-	27.81
95% CI	-	0.030; 0.190	-	0.038; 0.209
P-value	-	0.0072	-	0.0051

Source: Post-text Table 14.2.1.1

CI = confidence interval; GA = geographic atrophy; ITT = intent-to-treat population; MRM = model for repeated measures; SAP = statistical analysis plan; VA = visual acuity

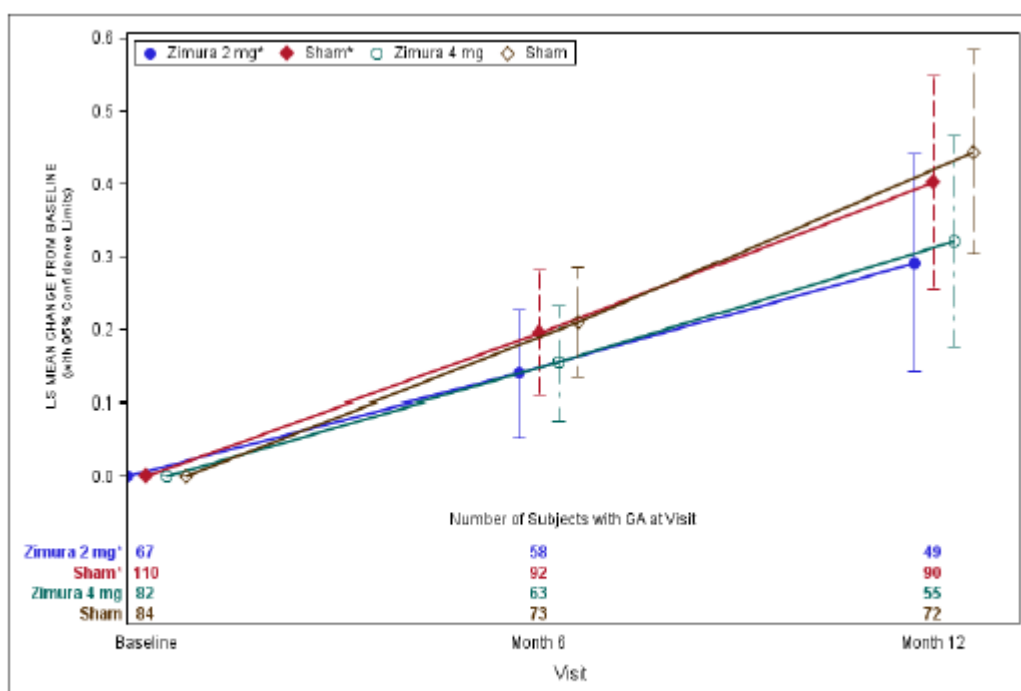
Notes: Baseline SAP is calculated per the SAP. For Part 1 patients, VA stratification factors at randomization are not available. Clinical values are used instead.

^aCombination of Part 1 and Part 2 patients.

^bMRM is specified in the SAP, Appendix 16.1.9.

^cDifference in least squares means between groups calculated as (Sham) minus (Zimura).

^d% Difference is calculated by 100*(Difference)/(Least Squares Mean from Sham).



Source: Post-text Figure 14.2.1

GA = geographic atrophy; MRM = model for repeated measures

*Combination of Part 1 and Part 2 patients.

Figure 4: Mean rate of change in geographic atrophy area over time (MRM analysis; square root transformation) – study eye – month 12

Secondary endpoints

Mean change in best-corrected visual acuity (BCVA) (ETDRS letters) from Baseline to Month 12

Table 13: Mean change in BCVA (ETDRS letters) from baseline to month 12 (MRM analysis) - study eye (ITT population)

	Zimura 2 mg ^a N=67	Sham ^a N=110	Zimura 4 mg N=83	Sham N=84
BCVA at Baseline (ETDRS Letters)				
Mean	70.2	69.0	69.5	68.3
Standard Deviation	10.01	10.35	9.81	11.03
Median	73.0	71.0	71.0	70.5
Q1;Q3	66.0; 77.0	65.0; 77.0	64.0; 77.0	64.5; 77.0
Range	27; 83	28; 82	29; 83	28; 80
n	67	110	83	84
BCVA at Month 12 (ETDRS Letters)				
Mean	67.8	66.5	67.9	66.1
Standard Deviation	15.23	12.95	14.83	13.51
Median	71.5	69.0	72.0	67.5
Q1;Q3	63.0; 78.0	60.0; 75.0	62.0; 78.0	60.0; 76.0
Range	15; 93	8; 89	15; 88	8; 89
n	54	92	58	74
MRM Analysis ^b - Change from Baseline to Month 12				
Least Squares Mean	-7.90	-9.29	-3.79	-3.51
Standard Error	2.66	2.59	3.11	2.99
Difference ^c	1.39	-	-0.28	-
95% CI	-1.52; 4.30	-	-4.01; 3.46	-
P-value	0.3464	-	0.8830	-

Source: [Post-text Table 14.2.4.1](#)

BCVA = best-corrected visual acuity; CI = confidence interval; ETDRS = early treatment diabetic retinopathy study; ITT = intent-to-treat population; MRM = model for repeated measures; SAP = statistical analysis plan; VA = visual acuity

Notes: Baseline VA is calculated per the SAP. For Part 1 patients, VA stratification factors at randomization are not available. Clinical values are used instead.

^aCombination of Part 1 and Part 2 patients.

^bMRM is specified in the SAP, [Appendix 16.1.9](#).

^cDifference in least squares means between groups calculated as (Zimura) minus (Sham).

Mean change in low luminance (LL) BCVA (ETDRS letters) from Baseline to Month 12

Table 14: Mean change in low luminance visual acuity scores (ETDRS letters) from baseline to month 12 (MRM analysis) – study eye (ITT population)

	Zimura 2 mg ^a N=67	Sham ^a N=110	Zimura 4 mg N=83	Sham N=84
Low Luminance Visual Acuity at Baseline (ETDRS Letters)				
Mean	36.7	34.5	36.8	33.9
Standard Deviation	21.10	19.32	20.87	18.77
Median	37.5	32.0	40.0	31.0
Q1;Q3	19.0; 55.0	18.0; 53.0	18.0; 57.0	18.0; 51.0
Range	1; 77	0; 72	1; 74	0; 69
n	66	110	83	84
Low Luminance Visual Acuity at Month 12 (ETDRS Letters)				
Mean	35.0	32.4	36.9	31.7
Standard Deviation	20.10	19.35	17.84	19.29
Median	31.5	31.0	34.5	30.5
Q1;Q3	19.0; 51.0	18.5; 50.5	22.0; 52.0	17.0; 50.0
Range	0; 70	0; 71	1; 73	0; 71
n	54	92	58	74
MRM Analysis ^b - Change from Baseline to Month 12				
Least Squares Mean	-1.03	-1.41	1.53	2.97
Standard Error	3.40	3.30	3.53	3.39
	Zimura 2 mg ^a N=67	Sham ^a N=110	Zimura 4 mg N=83	Sham N=84
Difference ^c	0.38	-	-1.44	-
95% CI	-3.34; 4.10	-	-5.66; 2.78	-
P-value	0.8405	-	0.5017	-

Source: [Post-text Table 14.2.4.3](#)

CI = confidence interval; ETDRS = early treatment diabetic retinopathy study; ITT = intent-to-treat population;

MRM = model for repeated measures; SAP = statistical analysis plan; VA = visual acuity

Notes: Baseline VA is calculated per the SAP. For Part 1 patients, VA stratification factors at randomization are not available. Clinical values are used instead.

^aCombination of Part 1 and Part 2 patients.

^bMRM is specified in the SAP, [Appendix 16.1.9](#).

^cDifference in least squares means between groups calculated as (Zimura) minus (Sham).

Ancillary analyses

Mean Rate of Change in GA from Baseline at Month 18

Table 15: Mean rate of change in GA from baseline to month 18 (MRM analysis; square root transformation) - study eye (ITT population)

	Zimura 2 mg ^a N=67	Sham ^a N=110	Zimura 4 mg N=83	Sham N=84
Square root area of GA (mm) at Baseline				
Mean	2.618	2.633	2.715	2.636
Standard Deviation	0.7001	0.7009	0.7320	0.7091
Median	2.544	2.583	2.629	2.583
Q1;Q3	2.111; 3.054	2.038; 3.235	2.133; 3.399	2.059; 3.209
Range	0.75; 4.16	1.49; 4.15	1.57; 4.15	1.49; 4.15
n	67	110	82	84
Square root area of GA (mm) at Month 18				
Mean	3.063	3.282	3.108	3.294
Standard Deviation	0.5821	0.7563	0.8158	0.7641
Median	3.006	3.251	2.874	3.281
Q1;Q3	2.645; 3.366	2.780; 3.862	2.546; 3.524	2.797; 3.868
Range	2.03; 4.49	1.78; 4.96	1.61; 4.74	1.78; 4.96
n	41	78	45	64
MRM Analysis ^b - Rate of change from Baseline to Month 18				
Least Squares Mean	0.430	0.599	0.391	0.559
Standard Error	0.092	0.089	0.087	0.083
Difference ^c	-	0.168	-	0.167
% Difference ^d	-	28.11	-	29.97
95% CI	-	0.066; 0.271	-	0.062; 0.273

Source: Post-text Table 14.2.1.1.A

CI = confidence interval; GA = geographic atrophy; ITT = intent-to-treat population; MRM = model for repeated measures; SAP = statistical analysis plan; VA = visual acuity

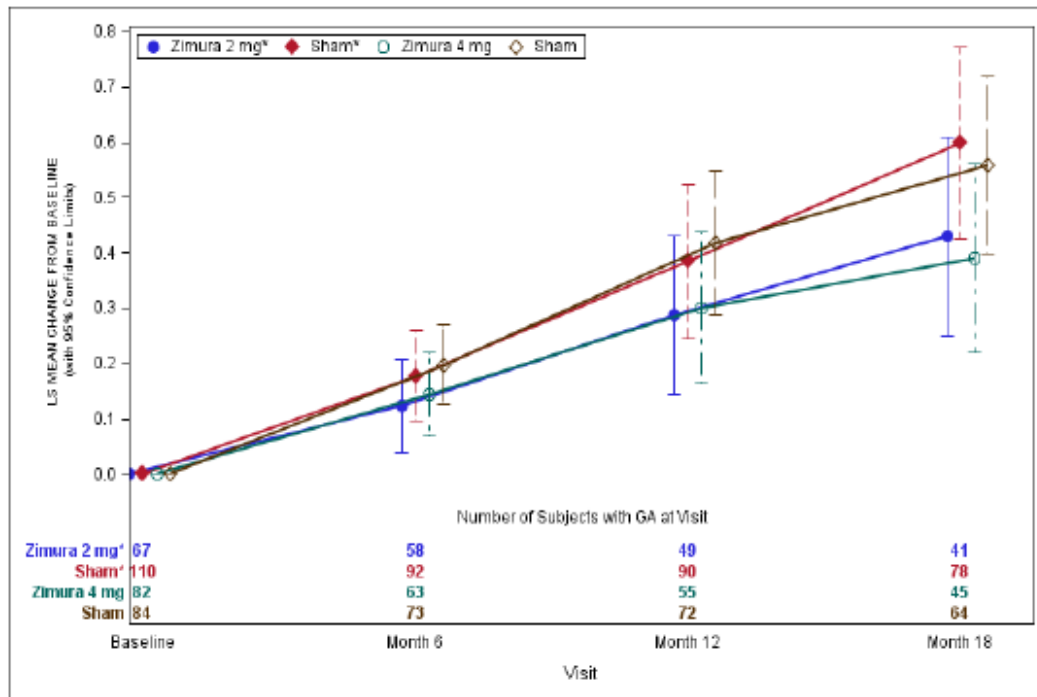
Notes: Baseline GA is calculated per the SAP. For Part 1 patients, VA stratification factors at randomization are not available. Clinical values are used instead.

^aCombination of Part 1 and Part 2 patients.

^bMRM is specified in the SAP, Appendix 16.1.9.

^cDifference in least squares means between groups calculated as (Sham) minus (Zimura).

^d% Difference is calculated by 100*(Difference)/(Least Squares Mean from Sham).



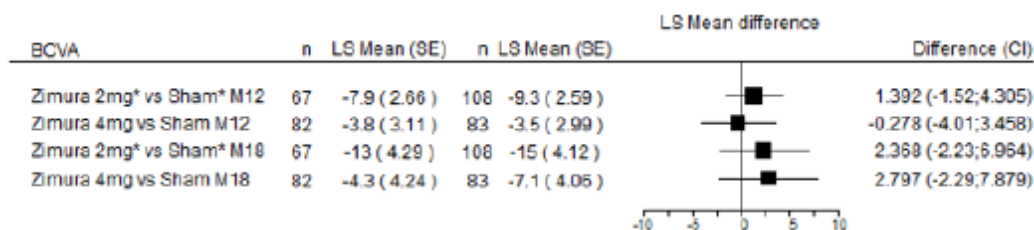
Source: Post-text Figure 14.2.1.A

GA = geographic atrophy; MRM = model for repeated measures

*Combination of Part 1 and Part 2 patients.

Figure 5: Mean rate of change in geographic atrophy area over time (MRM analysis; square root transformation) – study eye – month 18

Mean Change in BCVA from Baseline at Month 18



Source: Post-text Figure 14.2.4.1

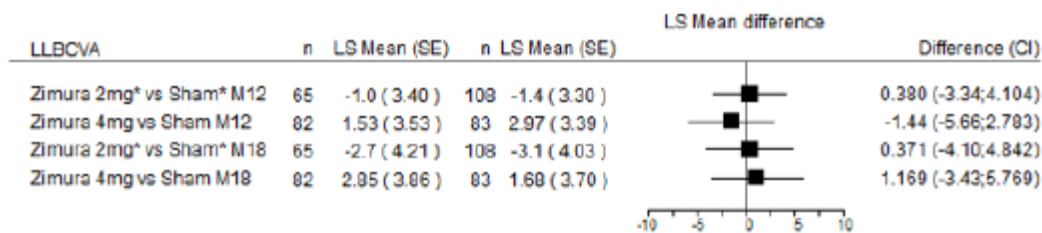
BCVA = best-corrected visual acuity; CI = confidence interval; ETDRS = early treatment diabetic retinopathy study; LS = least squares; MMRM = mixed-effects for repeated measures; SAP = statistical analysis plan; SE = study eye

Notes: MMRM is specified in the SAP, Appendix 16.1.9. Difference in least squares means between groups calculated as (Zimura) minus (Sham).

*Combination of Part 1 and Part 2 patients.

Figure 6: Mean change in BCVA scores (ETDRS letters) from baseline to month 12 and month 18 (MMRM analysis) – study eye

Mean change in low luminance BCVA from Baseline to Month 18



Source: Post-text Figure 14.2.4.2

BCVA = best-corrected visual acuity; CI = confidence interval; ETDRS = early treatment diabetic retinopathy study; LL = low luminance; LS = least squares; MMRM = mixed-effects for repeated measures; SAP = statistical analysis plan; SE = study eye; VA = visual acuity

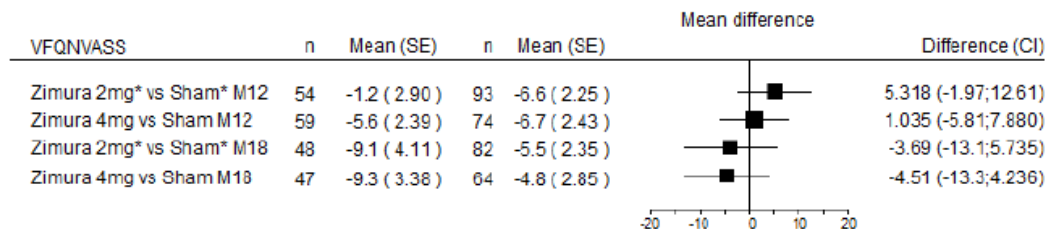
Notes: MMRM is specified in the SAP, Appendix 16.1.9. Difference in least squares means between groups calculated as (Zimura) minus (Sham).

*Combination of Part 1 and Part 2 patients.

Figure 7: Mean change in LL VA scores (ETDRS letters) from baseline to month 12 and month 18 (MMRM analysis) – study eye

VFQ-25 at Month 12 and Month 18

Near Vision Activities Sub-Scale



Source: Post-text Figure 14.3.2.3

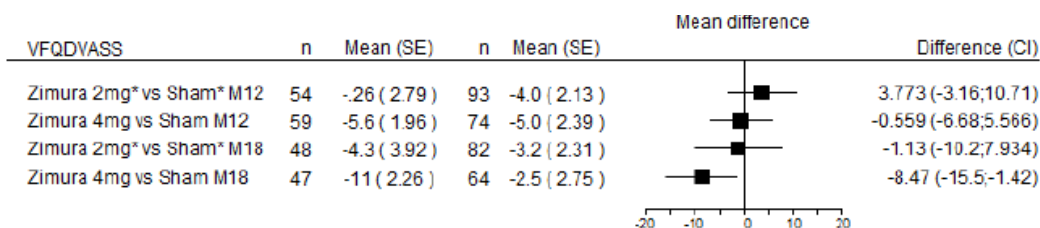
CI = confidence interval; NVASS = near vision activities sub-scale; SE = study eye; VFQ = Visual Function Questionnaire

Notes: A 2 Sample T-test was used to obtain the difference in means. Difference in means between groups calculated as (Zimura) minus (Sham).

*Combination of Part 1 and Part 2 patients.

Figure 8: Forest plot: mean change in VFQ-25 values (near vision activities sub-scale) from baseline to month 12 and month 18 – study eye

Distance Vision Activities Sub-Scale



Source: Post-text Figure 14.3.2.2

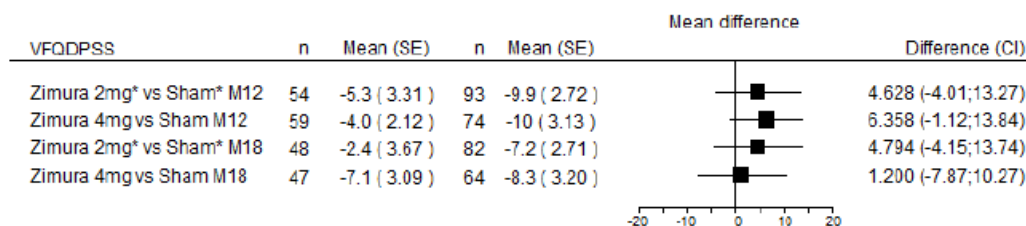
CI = confidence interval; DVASS = distance vision activities sub-scale; SE = study eye; VFQ = Visual Function Questionnaire

Notes: A 2 Sample T-test was used to obtain the difference in means. Difference in means between groups calculated as (Zimura) minus (Sham).

*Combination of Part 1 and Part 2 patients.

Figure 9: Forest plot: mean change in VFQ-25 values (distance vision activities sub-scale) from baseline to month 12 and month 18 – study eye

Dependency Sub-Scale



Source: Post-text Figure 14.3.2.1

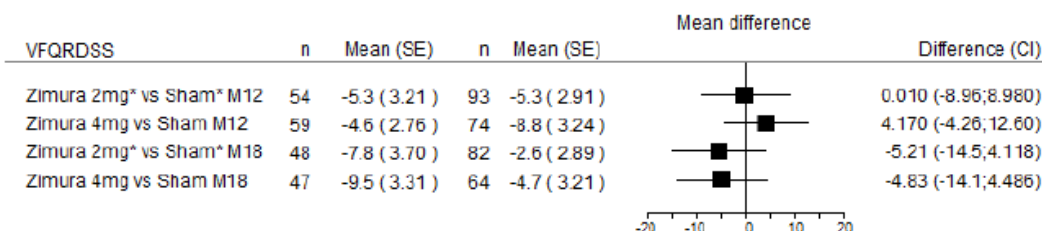
CI = confidence interval; DPSS = dependency sub-scale; SE = study eye; VFQ = Visual Function Questionnaire

Notes: A 2 Sample T-test was used to obtain the difference in means. Difference in means between groups calculated as (Zimura) minus (Sham).

*Combination of Part 1 and Part 2 patients.

Figure 10: Forest plot: mean change in VFQ-25 values (dependency sub-scale) from baseline to month 12 and month 18 – study eye

Role Difficulties Sub-Scale



Source: Post-text Figure 14.3.2.4

CI = confidence interval; RDSS = role difficulties sub-scale; SE = study eye; VFQ = Visual Function Questionnaire

Notes: A 2 Sample T-test was used to obtain the difference in means. Difference in means between groups calculated as (Zimura) minus (Sham).

*Combination of Part 1 and Part 2 patients.

Figure 11: Forest plot: mean change in VFQ-25 values (role difficulties sub-scale) from baseline to month 12 and month 18 – study eye

ISEE2008 (GATHER 2)

Methods

This is Phase 3 multicentre, randomized, double masked, sham-controlled clinical trial to assess the safety and efficacy of intravitreal administration of Izelvay (complement C5 inhibitor) in patients with Geographic Atrophy secondary to dry age-Related macular degeneration.

Patients were randomized in a 1:1 ratio to the following monthly treatment groups:

- Izelvay 2 mg
- Sham

Patients receiving monthly Izelvay 2 mg were re-randomized at Month 12 in a 1:1 ratio to the following treatment groups:

- Izelvay 2 mg administered monthly from Month 12 through Month 23
- Sham administered at Months 12, 14, 16, 18, 20, and 22, and
- Izelvay 2 mg administered every other month at Months 13, 15, 17, 19, 21, and 23

All patients will have a final follow up visit at Month 24.

Study Participants

The inclusion criteria included GA patients ≥ 50 years of age diagnosed with disease inside and/or outside of the 1.5 mm diameter foveal area.

Inclusion criteria

Ophthalmic Inclusion Criteria

The following inclusion criteria applied to the Study Eye (SE):

1. Non-foveal GA secondary to dry AMD.
2. Total GA area ≥ 2.5 and ≤ 17.5 mm² (1 and 7 DA respectively), determined by Screening images of FAF.
3. If GA is multifocal, at least one focal lesion should measure ≥ 1.25 mm² (0.5 DA).
4. GA in part within 1500 microns from the foveal centre.
5. The atrophic lesion must be able to be photographed in its entirety.
6. BCVA in the SE between 20/25 to 20/320, inclusive.
7. Clear ocular media and adequate pupillary dilatation in both eyes to allow for all imaging procedures, including good quality stereoscopic fundus photography and FAF.
8. IOP of 21 mmHg or less in the SE.

Ophthalmic Exclusion Criteria

The following exclusion criteria applied to the SE:

1. Evidence of choroidal neovascularization (CNV) in either eye. If CNV developed in either eye during the course of the study, the investigator was to follow Section 10.3 'Development of Wet AMD During the Trial' in the protocol.
2. GA secondary to any condition other than AMD in either eye (e.g., drug-induced).
3. Any prior treatment for AMD or any prior IVT treatment for any indication in either eye, except oral supplements of vitamins or minerals.
4. Any ocular condition in the SE that would progress during the course of the study that could affect central vision or otherwise be a confounding factor.
5. Concomitant treatment with any ocular or non-ocular medication that is known to be toxic to the lens, retina, or optic nerve.
6. Presence of intraocular inflammation ($\geq$ trace cell or flare), macular hole, pathologic myopia, epiretinal membrane, evidence of significant vitreo-macular traction, vitreous hemorrhage or aphakia (pseudophakia with or without an intact capsule was not an exclusion criteria).
7. Presence or history of idiopathic or autoimmune-associated uveitis in either eye.
8. Significant media opacities, including cataract, which might interfere with VA, assessment of toxicity, fundus photography, or FAF. Patients should not have entered if there is likelihood that they would have required cataract surgery in the SE during the study.
9. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis.

10. Any intraocular surgery or thermal laser within 3 months of study entry. Any prior thermal laser in the macular region, regardless of indication.
11. Any ocular or periocular infection (including blepharitis), or ocular surface inflammation in the 12 weeks prior to study entry.
12. History of any of the following procedures: Posterior vitrectomy, filtering surgery (e.g., trabeculectomy), glaucoma drainage device, corneal transplant, or retinal detachment.
13. Any sign of diabetic retinopathy in either eye.

Treatments

Active treatment

The study treatment was Izelvay 2 mg (100 µL of 20 mg/mL solution for injection), administered via monthly IVT injection

Doses were administered at least 21 days apart.

Control

To maintain masking when study treatments were administered, Sham injections that imitated an IVT injection through the use of an injection syringe without a needle were performed.

Objectives

The objectives of this study are to evaluate the safety and efficacy of Izelvay intravitreal administration in patients with geographic atrophy secondary to age-related macular degeneration (AMD).

Outcomes/endpoints

Primary efficacy endpoints

- The mean rate of growth (slope) estimated based on GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12 (square root transformation)

Secondary efficacy endpoints

There are no secondary efficacy endpoints.

As a note, the primary endpoint before Amendment C was:

- The mean rate of change in GA over 12 months measured by FAF at three time points: Baseline, month 6 and Month 12 (square root transformation)

Sample size

The sample size for this study was based on the 12-month results of Study OPH2003 (GATHER1). The pre-specified primary endpoint, mean change in GA growth over 12 months, equivalent to the mean rate of GA growth used in this study, was measured by FAF based on readings at time points (Baseline, Month 6, and Month 12) and was calculated using the square root transformation of the GA area. The FAF images were assessed by an independent masked RC. The reduction in the mean rate of GA growth over 12 months was 0.11 mm ($p = 0.0072$) for the Avacincaptad pegol 2 mg group compared to the Sham control group.

A total of approximately 400 patients were planned to be randomized in the ISEE2008 (GATHER2) trial. The effect of treatment was planned to be assessed on the square root transformation of the

mean rate of GA growth (slope) estimated based on GA area measured in at least 3 time points over 12 months, where the analysis of variance included the stratification factors. If the SD for the primary endpoint in GATHER2 was as assumed in the design of the GATHER1 trial, (which was 7% higher than was actually observed in that trial) and if the 2 mg dose of Avacincaptad pegol truly provided a 0.11 mm reduction in the mean rate of GA growth over 12 months, then the trial would have 97% power to detect that effect when using a test statistic having (one-sided) 2.5% false positive error rate. Note that the power of the trial would be slightly lower when using an alpha-level that would be adjusted by (two-sided) 0.001 for each independent Data Safety Monitoring Board (DSMB) meeting at which any data were reviewed.

The DSMB met approximately every 6 months through the primary endpoint at Month 12; there were 4 regularly scheduled meetings with review of new data and one ad-hoc meeting with in-depth review of previous data. The scope of the DSMB review was to review aggregate and individual patient data related to safety, data integrity, and overall conduct of the study, and to provide recommendations to continue, modify, or terminate the study depending upon the review of the safety data. The safety data provided to the committee was prepared by an independent statistician. The DSMB was not intended to conduct an interim analysis or stop the study early in the event of persuasive efficacy.

There were no interim analyses.

Randomisation and blinding (masking)

At Day 1, patients were centrally allocated to one of the 2 treatment groups stratified by a dynamic minimization procedure using clinical site in a 1:1 ratio stratified by factors known to be of prognostic importance in AMD:

- Baseline VA < 50 ETDRS letters (20/100 Snellen equivalent) vs > 50 ETDRS letters
- Size of Baseline GA (< 4 DA vs > 4 DA)
- Pattern of FAF at the junctional zone of GA (none/focal vs banded/diffuse).

Patients initially randomized to Avacincaptad pegol 2 mg at Day 1 were re-randomized at Month 12 in a 1:1 ratio to Avacincaptad pegol 2 mg monthly versus every other month (alternating with Sham) using the same minimization procedure as used for the initial randomization (i.e., using the same factors at Baseline).

Randomization was performed using an IRT system based on the stratification information above to randomly assign each patient to a treatment arm.

This was a double-masked study. The patients, investigators, study centre staff (except for the unmasked study centre personnel and unmasked injecting physician), Sponsor personnel (except for those who have been delegated responsibility for working with the study treatment), and data analysts remained masked to the identity of the treatment from the time of randomization until Month 12 database lock, when select Sponsor roles were unmasked to treatment assignments.

As Study ISEE2008 remains ongoing at time of this Year 1 CSR and to preserve the integrity of the study data through final database lock (at Month 24), a separate masked team from the Sponsor and external service providers was established to engage in and manage study activities.

Statistical methods

Analysis populations

Main SAP

Intent-to-treat (ITT) population: The ITT population consisted of all randomized subjects who received at least one dose of study drug. Subjects were analysed in the treatment group assigned at randomization.

Per-protocol (PP) population: The PP population consisted of all ITT patients that did not meet criteria excluding them from the PP analyses. Such criteria were defined prior to database lock in a masked fashion.

Year 2 SAP

Addition of the re-randomised analysis set.

Re-randomized analysis set (Re-Rand): The subset of the ITT analysis set who were re-randomized at Month 12 and who were on sham and completed the Month 12 visit.

Multiplicity adjustment

Main SAP

An alpha-level adjustment was made in the assessment of statistical significance at the time of the final analysis, equal to (two-sided) 0.001 for each DSMB meeting for any look at the data. There were no formal interim analyses for early termination for benefit and, in turn, the DSMB did not make recommendations for early termination even if emerging data provided strongly favourable evidence for benefit. Rather, the principal justification for the DSMB to have had access to emerging data on efficacy as well as safety data during DSMB meetings was to enable the DSMB to more effectively safeguard interests of study participants through a properly informed assessment of benefit-risk.

Analyses of outcomes other than the primary endpoint were carried out with a descriptive intent only.

Year 2 SAP

The following hypotheses were conducted sequentially:

1. Hypothesis testing in avacincaptad pegol 2 mg EM versus sham for mean GA growth rate (slope) from Baseline over 24 months
2. Hypothesis testing in avacincaptad pegol 2 mg versus sham for time to persistent vision loss using the Kaplan-Meier method with a log-rank test from Baseline over 24 months
3. Hypothesis testing in avacincaptad pegol 2 mg EOM versus sham for mean GA growth rate (slope): similarly as in (1)
4. Hypothesis testing in avacincaptad pegol 2 mg versus sham for mean change in BCVA (in ETDRS letters) from Baseline to Month 24
5. Hypothesis testing in avacincaptad pegol 2 mg versus sham for mean change in LL BCVA (in ETDRS letters) from Baseline to Month 24
6. Hypothesis testing in avacincaptad pegol 2 mg versus sham for mean change in VFQ-25 overall composite score from Baseline to Month 24

The hypothesis testing was evaluated according to a hierarchical testing procedure with type-1 error at a 5% 2-sided significance level. If the primary analysis testing GA growth rate (avacincaptad pegol 2 mg versus sham) based on Year 1 data was statistically significant, the hypotheses tests were to be analysed in a sequential way. A test was performed only if all the preceding tests were statistically significant.

Primary endpoint

Main SAP

The primary efficacy endpoint is the mean rate of growth (slope) estimated based on GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12 (square root transformation). The observed GA area measurements were also analysed.

In alignment with the primary objective of the study, the main estimand used for the evaluation of the primary outcome was described as:

The difference in the mean rate of growth (slope) estimated based on GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12 (square root transformation) between treatment conditions (Avacincaptad pegol versus Sham) in the target patient population, regardless of any non-adherence to or interruption of study treatment, and regardless of initiation of alternative treatment.

The following 5 attributes defined the main estimand for primary endpoint evaluation:

A. Population:

Population defined through inclusion/exclusion criteria to reflect the targeted patient population. Analysis was performed on all randomized patients who received at least one dose of study drug.

B. Treatment (monthly):

Avacincaptad pegol 2 mg versus Sham.

C. Primary variable:

Mean rate of growth (slope) of the square root of GA area over 12 months.

D. Intercurrent events (ICE's) and strategies:

1. Treatment changes (i.e., interruptions, non-adherence, dose changes, and discontinuation): "treatment policy" – i.e., treatment changes were ignored and all data collected contributed to the analysis regardless of whether or not these followed such ICE's.

Coronavirus Disease 2019 (COVID-19): "treatment policy" – i.e., impact of COVID-19 pandemic was ignored and all data collected contributed to the analysis regardless of whether or not these followed such ICE's.

E. Population-level summary:

Difference between groups in mean rate of growth (slope) of the square root of GA area over 12 months.

The primary estimator was described as follows.

A MMRM was applied to all available data, using as response variable the square root of GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12. The MMRM was used to assess the difference between the treatment groups in terms of the rate of growth (slope) of the square root of GA area over 12 months. A model was fitted by using restricted maximum likelihood (REML) and included Baseline VA (< 50 letters vs. ≥ 50 letters), and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) as used in the randomization as covariates. For the model, fixed effects included time, treatment, Baseline VA (< 50 letters vs. ≥ 50 letters), pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse), treatment by time interaction, Baseline VA (< 50 letters vs. ≥ 50 letters) by time interaction, and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) by time interaction. The model included an unstructured modelling of within-subject correlations. If this analysis failed to converge, alternative structures (e.g.,

heterogeneous autoregressive, heterogeneous compound symmetry, autoregressive, or compound symmetry, in this order) were considered.

In addition to the analyses described above, a similar analysis was conducted using the observed GA area measurement.

The analyses described above were also repeated in a supportive manner for the PP population.

Year 2 SAP

A mixed model for repeated measures (MMRM) was applied to all available data, using response variable of the GA growth area over time from Baseline up to Month 24 in 5 time points: Baseline, Month 6, Month 12, Month 18, and Month 24. The MMRM was used to assess the difference between the treatment groups in terms of the rate of growth (slope [mm²/year]) of the GA area over time through 24 months. Time was defined as a continuous variable in number of study days since the baseline assessment. Treatment groups included avacincaptad pegol EM, avacincaptad pegol EOM, and sham (Re-Rand analysis set). A model was fitted by using restricted maximum likelihood and included time, treatment, and treatment-by-time interaction as fixed effects with patient as random effect. A treatment policy strategy was used to handle intercurrent events.

Unlike the primary analysis at Year 1 which used square-root transformation of GA growth area, in the Year 2 analysis, the untransformed GA growth using observed GA area of measurement was used as the endpoint.

Supportive endpoints

Main SAP

The following supportive outcomes were conducted for both ITT and PP populations.

- Mean change in BCVA (ETDRS letters) from Baseline to Month 12
- Mean change in LL BCVA (ETDRS letters) from Baseline to Month 12

Descriptive tables were provided for these supportive outcomes based on the observed data. Any hypothesis testing performed as part of analysing these supportive outcomes was considered exploratory.

For analyses of BCVA and LL BCVA, a MMRM was used to assess the differences between the treatment groups at Month 12. The model was fitted by using REML. The model included Baseline VA (< 50 letters vs. ≥ 50 letters), size of the Baseline GA (< 4 DA vs. ≥ 4 DA), and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) as used in the randomization as covariates. Fixed effects included treatment, visit, the Baseline VA (< 50 letters vs. ≥ 50 letters), size of the Baseline GA (< 4 DA vs. ≥ 4 DA), pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse), treatment by visit interaction, and the stratification factors by visit interactions for Avacincaptad pegol 2 mg vs. Sham control model. An unstructured (co)variance structure was used to model the within-subject errors. If this analysis failed to converge, alternative structures (e.g., heterogeneous autoregressive or heterogeneous compound symmetry, in this order) were considered. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Significance tests were based on appropriate treatment contrasts at Month 12.

For analyses of observed (non-square root transformed) area of GA over 12 months, the same analysis model was used as specified above.

Year 2 SAP

Time to persistent vision loss was defined as the time to the first occurrence of at least 15 ETDRS letters loss in 2 or more consecutive visits from Baseline up to Month 24 for the ITT analysis set. Patients without a persistent vision loss event were censored at the last assessment of BCVA prior to the end of the study or at the randomization if no post-baseline BCVA assessment was available.

The time-to-event analysis was conducted using the Kaplan-Meier method with a log-rank test and a Cox proportional hazards regression model with the hazard ratio and associated 2-sided 95% confidence interval (CI). Statistical significance of testing with the p-value from the logrank test was used in the hierarchical testing procedure.

The mean change in BCVA from Baseline to Month 24 in the avacincaptad pegol 2 mg treatment group was compared to sham using an MMRM model with change from Baseline as the response; visit, treatment, and treatment-by-visit interaction as fixed effects; and patient as random effect on the ITT analysis set.

Mean Change in LL BCVA (in ETDRS Letters) Analysis The mean change in LL BCVA from Baseline to Month 24 was analysed similarly as in the BCVA analysis described above with change from Baseline of LL BCVA as the response variable.

Sensitivity analyses

Sensitivity Analyses for Missing Data

Four analyses described by Miller et al. 2001 were performed for further insight into the potential impact of missing data on the results:

1. the observed means from the active arm and the Sham arm was imputed to patients with missing data in the arm they were allocated to;
2. the average of observed means from the active arm and the Sham arm were imputed to all patients with missing data;
3. the observed mean from the Sham arm was imputed to all patients with missing data;
4. the observed means from the active arm and the Sham arm were imputed to patients with missing data in the opposite arm they were allocated to (a "cross-over" scheme);

MI based on models compatible with Missing Not At Random (MNAR) missingness mechanisms were used. Two approaches were considered:

1. The "shift imputation" approach: for missing values at a particular visit, it was assumed that their expected value was smaller (shifted) by a specified amount (i.e., a specified shift in the size of GA), than for the observed responses (implying that the missing values were more likely corresponding to smaller changes vs. Baseline than the observed ones). Increasing values of the shift were explored to investigate the sensitivity of the results. This approach was applied to data with arbitrary missing data patterns. The "tipping point" was the value of the shift that causes statistical significance to be lost. For a robust treatment effect, the tipping point was considered an implausible value of the shift used in the missing data imputation.
2. The "pattern-mixture-model imputation" approach: missing values at Month 12 were imputed by using the pattern-mixture-model restrictions. In particular, Complete-Case Missing Value and Neighboring-Case Missing Value restrictions were applied.

Similar sensitivity analyses investigating the impact of missing data were performed for the year 2 data.

Sensitivity Analysis for Stratification Error

On 16 Nov 2020, the Duke RC notified the Sponsor that an error occurred at the RC in the reporting of FAF results used as stratification factors for randomization of eligible patients into the GATHER2 (Study ISEE2008) clinical trial.

As a result, 38 patients randomized with Baseline GA size between 4 mm² and 10 mm² were placed in a stratum that included participants with size ≥ 10 mm² rather than being placed in stratum that included participants with size < 10 mm².

To assess the impact of this stratification error, 2 sensitivity analyses were done by performing analyses that stratify by 3-level covariates for the Baseline GA size. The first analysis was stratified by: < 4 mm² vs. ≥ 4 mm² to < 10 mm² vs. ≥ 10 mm², and the second analysis was stratified by: patients randomized prior to 16 Nov 2020 vs. < 4 mm² vs. ≥ 4 mm².

Sensitivity Analysis for Observed GA Measurement

The sensitivity of the results from the analyses of observed (non-square root transformed) area of GA over 12 months was conducted using the same analysis model.

Subgroup analyses

In a descriptive manner, treatment effect was presented for subsets created by multiple covariates. Among these covariates were the stratification factors: Baseline VA (< 50 vs. ≥ 50 ETDRS letters), Baseline GA (< 4 vs. ≥ 4 DA), Pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) as well as age (< 65 vs. $65\sim 74$ vs. $75\sim 84$ vs. ≥ 85), gender (male vs. female), race (American Indian/Alaska Native vs. Black or African American vs. Asian vs. Native Hawaiian/Pacific Islander vs. White vs. Other), and ethnicity (Hispanic or Latino vs. Not Hispanic or Latino).

Changes in planned analyses

With protocol global amendment C (24 May 2021), the primary endpoint was modified from the change from baseline in GA area at month 12 to the rate of growth in GA (i.e. the slope) from baseline to month 12.

The imaging data analyses for 12 supportive endpoints were not assessed at the time of primary database lock for this Year 1 CSR as imaging data were not available. In addition, analysis of the PP population for the supportive endpoints and patient disposition was not performed as per the SAP.

The original SAP (SAP version 4.0) was approved prior to the database lock for the primary analyses and covers all analyses performed on Year 1 (Screening through Month 12) data (Appendix 16.1.9). A separate SAP was developed to specify all analyses performed on cumulative Year 2 data (from Baseline through Month 24).

A brief SAP addendum (version 1.0) to the original SAP version 4.0 for cumulative analysis of Year 2 data was approved on 03 August 2022, before the unmasking of Year 1 data for the primary analysis. The addendum specified a sequential testing procedure for the Year 2 analysis.

The testing of persistent vision loss, which was not included in the initial Year 2 SAP (version 1.0), was introduced with the Year 2 SAP version 2.0 (22 June 2023), after the performance of the primary month 12 analysis. The final SAP Year 2 provided details for the Year 2 and final analysis of Study ISEE2008 and was approved on 05 September 2023, before the unmasking of Year 2 data.

Results

Participant flow

A total of 1583 patients were screened, and 1135 patients were screen failures. The most common (>95%) reasons for screen failure were related to the patient not meeting specific ophthalmic inclusion criteria or ophthalmic exclusion criteria.

Table 16: Patient disposition – month 12 (ITT population)

Number of patients (%)	Zimura 2 mg N=225	Sham N=222	Total N=447
Patients completing through Month 12	200 (88.9%)	205 (92.3%)	405 (90.6%)
Number of patients who discontinued early in Year 1	25 (11.1%)	17 (7.7%)	42 (9.4%)
Adverse event	3 (1.3%)	2 (0.9%)	5 (1.1%)
Protocol violation	0	0	0
Investigator decision	0	0	0
Sponsor decision	0	0	0
Withdrawal by patient	17 (7.6%)	13 (5.9%)	30 (6.7%)
Lost to follow-up	2 (0.9%)	1 (0.5%)	3 (0.7%)
Patient non-compliance	1 (0.4%)	0	1 (0.2%)
Death	2 (0.9%) ^a	1 (0.5%)	3 (0.7%)
Other	0	0	0
Number of patients who completed through			
Month 3 visit	216 (96.0%)	220 (99.1%)	436 (97.5%)
Month 6 visit	209 (92.9%)	215 (96.8%)	424 (94.9%)
Number of patients (%)	Zimura 2 mg N=225	Sham N=222	Total N=447
Month 9 visit	204 (90.7%)	206 (92.8%)	410 (91.7%)
Month 12 visit	194 (86.2%)	199 (89.6%)	393 (87.9%)

Source: Post-text Table 14.1.2

AE = adverse event; ITT = intent-to-treat.

Note: Discrepancy between 'Number of patients completing through Month 12' and 'Number of patients who completed through Month 12 visit' are due to ongoing patients who missed the Month 12 visit.

^a Patient ██████████ (Zimura) died due to the AE of bilateral pneumonia 3 months after last study visit date (Month 9 visit) shortly after Month 12 visit would have occurred. The patient had not completed any additional study visits since Month 9 visit due to AE's of atrial fibrillation, bronchitis, and pneumonia. The AE of bilateral pneumonia was reported before the Year 1 cutoff date, but the patient died soon after. For completeness, this event is included in the AE leading to death (Post-text Table 14.3.10.1) and Listing 16.2.9.1. However, as the death occurred after the Year 1 cutoff date, it is not reflected in the disposition table.

Recruitment

GAHER 2 was conducted between 22 June 2020 and 25 July 2022 at 205 sites in 20 countries, including France, Germany, Italy, Spain, and the United States.

First patient first visit was 22 June 2020.

Conduct of the study

There were 3 global Amendments:

- Amendment A on 30 September 2020. Changes, among others, include:

- Precision regarding inclusion criteria (underlined):

The following inclusion criteria apply to the study eye (SE), one study eye per patient. If both eyes qualify the inclusion criteria, it is in the investigator's discretion to determine the SE.

- Amendment B on 18 December 2020.
- Amendment C on 24 May 2021. Changes, among others, include:
 - Primary endpoint use the mean rate of growth (slope) estimated based on GA area instead of the mean rate of change in GA.

Baseline data

Demographic and other baseline characteristics of the randomized subjects are presented in below tables.

Table 17: Demographics and baseline characteristics (ITT population)

Number of patients (%)	Zimura 2 mg N=225	Sham N=222	Total N=447
Sex, n (%)			
Male	71 (31.6%)	66 (29.7%)	137 (30.6%)
Female	154 (68.4%)	156 (70.3%)	310 (69.4%)
Ethnicity, n (%)			
Not Hispanic or Latino	168 (74.7%)	178 (80.2%)	346 (77.4%)
Hispanic or Latino	27 (12.0%)	23 (10.4%)	50 (11.2%)
Not reported	30 (13.3%)	21 (9.5%)	51 (11.4%)
Race, n (%)			
American Indian/Alaska Native	1 (0.4%)	0	1 (0.2%)
Black or African American	0	1 (0.5%)	1 (0.2%)
Asian	1 (0.4%)	1 (0.5%)	2 (0.4%)
Native Hawaiian/Pacific Islander	0	0	0
White	182 (80.9%)	186 (83.8%)	368 (82.3%)
Other	10 (4.4%)	13 (5.9%)	23 (5.1%)
Not reported	31 (13.8%)	21 (9.5%)	52 (11.6%)
Age (years)			
Mean	76.3	76.7	76.5
Standard deviation	8.61	8.82	8.71
Median	77.0	77.0	77.0
Q1; Q3	71.0; 83.0	71.0; 83.0	71.0; 83.0
Range	51; 93	51; 96	51; 96

Number of patients (%)	Zimura 2 mg N=225	Sham N=222	Total N=447
Age group (years), n (%)			
<65	19 (8.4%)	20 (9.0%)	39 (8.7%)
65 to 74	72 (32.0%)	65 (29.3%)	137 (30.6%)
75 to 84	91 (40.4%)	91 (41.0%)	182 (40.7%)
≥85	43 (19.1%)	46 (20.7%)	89 (19.9%)
Current smoking status, n (%)			
Non-active	119 (52.9%)	115 (51.8%)	234 (52.3%)
Active	106 (47.1%)	107 (48.2%)	213 (47.7%)
Lens status, n (%)			
Aphakic	0	0	0
Pseudophakic	123 (54.7%)	128 (57.7%)	251 (56.2%)
Phakic	102 (45.3%)	94 (42.3%)	196 (43.8%)
Not done	0	0	0
If Phakic, Grade:			
Nuclear			
0	12 (5.3%)	8 (3.6%)	20 (4.5%)
1	62 (27.6%)	61 (27.5%)	123 (27.5%)
2	25 (11.1%)	24 (10.8%)	49 (11.0%)
3	3 (1.3%)	1 (0.5%)	4 (0.9%)
4	0	0	0
Posterior subcapsular cataract			
0	87 (38.7%)	82 (36.9%)	169 (37.8%)
1	12 (5.3%)	9 (4.1%)	21 (4.7%)
2	3 (1.3%)	3 (1.4%)	6 (1.3%)
3	0	0	0
4	0	0	0
Cortical			
0	57 (25.3%)	49 (22.1%)	106 (23.7%)
1	38 (16.9%)	40 (18.0%)	78 (17.4%)
2	7 (3.1%)	5 (2.3%)	12 (2.7%)
Number of patients (%)			
	Zimura 2 mg N=225	Sham N=222	Total N=447
3	0	0	0
4	0	0	0

Source: [Post-text Table 14.1.4.1](#) and [Post-text Table 14.1.11.1](#)

ITT = intent-to-treat.

Note: Baseline was the last available measurement prior to the first administration of study drug.

Table 18: Baseline visual acuity score - study eye (ITT population)

	Zimura 2 mg N=225	Sham N=222	Total N=447
BCVA (ETDRS Letters)			
Mean	70.9	71.6	71.2
Standard deviation	8.93	9.35	9.14
	Zimura 2 mg N=225	Sham N=222	Total N=447
Median	73.0	74.0	73.0
Q1; Q3	66.0; 77.0	68.0; 78.0	67.0; 78.0
Range	34; 83	8; 88	8; 88
n	225	222	447
≥ 50 letters	221 (98.2%)	217 (97.7%)	438 (98.0%)
< 50 letters	4 (1.8%)	5 (2.3%)	9 (2.0%)
Low luminance BCVA (ETDRS letters)			
Mean	41.0	39.6	40.3
Standard deviation	19.70	19.58	19.63
Median	42.0	41.5	42.0
Q1; Q3	25.5; 58.0	25.5; 55.0	25.5; 56.0
Range	0; 76	0; 79	0; 79
n	224	220	444
≥ 50 letters	95 (42.2%)	93 (41.9%)	188 (42.1%)
< 50 letters	129 (57.3%)	127 (57.2%)	256 (57.3%)
Missing	1 (0.4%)	2 (0.9%)	3 (0.7%)

Source: [Post-text Table 14.1.6.1](#)

BCVA = best corrected visual acuity; ETDRS = early treatment diabetic retinopathy study; ITT = intent-to-treat; VA = visual acuity.

Notes: The Baseline ETDRS VA score is the mean value of the Screening and Day 1 VA scores rounded up to the nearest integer if not already an integer. If either the Screening or Day 1 VA score was missing (including an invalid VA), the Baseline VA is equal to the other, non-missing value. Day 1 visit VA score was used as the Baseline value for the low luminance BCVA.

Table 19: Baseline fundus autofluorescence – study eye (ITT population)

Number of patients (%)	Zimura 2 mg N=225	Sham N=222	Total N=447
Localization of hypo-FAF ^a			
Foveal	0	0	0
Extrafoveal	225 (100%)	222 (100%)	447 (100%)
Ungradable	0	0	0
Missing	0	0	0
Multifocal GA			
Yes	178 (79.1%)	178 (80.2%)	356 (79.6%)
No	47 (20.9%)	44 (19.8%)	91 (20.4%)
Temporal peripapillary atrophy			
Yes	192 (85.3%)	185 (83.3%)	377 (84.3%)
No	32 (14.2%)	37 (16.7%)	69 (15.4%)
Ungradable	1 (0.4%)	0	1 (0.2%)
If yes, peripapillary confluent with macular GA			
Number of patients (%)	Zimura 2 mg N=225	Sham N=222	Total N=447
Yes	12 (6.3%)	17 (9.2%)	29 (7.7%)
No	180 (93.8%)	168 (90.8%)	348 (92.3%)
Ungradable	0	0	0
Macular atrophy gradable			
Yes	225 (100%)	222 (100%)	447 (100%)
No	0	0	0
If yes, area of GA (mm ²)			
Mean	7.48	7.81	7.65
Standard deviation	4.005	3.885	3.945
Median	6.36	7.04	6.67
Q1; Q3	4.11; 9.72	4.59; 10.32	4.27; 10.16
Range	2.3; 17.6	2.4; 17.2	2.3; 17.6
n	225	222	447
Size of baseline GA ^b			
≥4 disc areas	54 (24.0%)	64 (28.8%)	118 (26.4%)
< 4 disc areas	171 (76.0%)	158 (71.2%)	329 (73.6%)
Hyper-FAF ^a			
None/Focal	8 (3.6%)	4 (1.8%)	12 (2.7%)
Banded/Diffuse	217 (96.4%)	218 (98.2%)	435 (97.3%)
Ungradable	0	0	0
If banded/diffuse, is there diffuse trickling?			
Yes	77 (35.5%)	90 (41.3%)	167 (38.4%)
No	140 (64.5%)	128 (58.7%)	268 (61.6%)
Ungradable	0	0	0

Source: [Post-text Table 14.1.5](#)

FAF = fundus autofluorescence; GA = geographic atrophy; ITT = intent-to-treat population; IWRS = interactive web response system

Note: The baseline values are taken as the last non-missing value prior to the first dose of study drug.

^a Foveal disease includes the foveal center point; extrafoveal includes disease in the fovea and outside the fovea but does not involve the foveal center point.^b The category is derived from imaging data. It is not based on randomization stratification from IWRS.

Only one patient discontinued due to non-compliance. The injection compliance was 91% (avacincaptad pegol 2 mg) and 94% (sham).

Numbers analysed

A summary of the number (percentage) of subjects in each analysis set is presented in Table 20.

Table 20: Patient populations

Number of patients	Zimura 2 mg	Sham	Total
Randomization population	225	223	448
Number of patients randomized but not treated	0	1	1
ITT population ^a	225	222	447
Per-protocol population ^b	220	217	437
Safety population ^c	225	222	447

Source: Post-text Table 14.1.1.1

ITT = intent-to-treat population; PP = per-protocol.

^a The ITT population consisted of all randomized patients who received at least one dose of study drug, irrespective of the dose actually received. Patients were analyzed in the dose group assigned at randomization.

^b The PP population consisted of all ITT patients who did not meet criteria for analysis restrictions.

^c The safety population included all patients who received at least one injection of the study drug. Patients who ever received an injection of Zimura were analyzed in the appropriate Zimura group according to the actual injections received.

Outcomes and estimation

Primary endpoint

Mean Rate of Change in GA from Baseline at Month 12

Table 21: Mean rate of growth (slope) in GA area from baseline to month 12 (MMRM analysis; square root transformation) - study eye (ITT population)

	Zimura 2 mg N=225	Sham N=222
MMRM Analysis ^a — Rate of growth (slope) change from Baseline to Month 12		
Growth rate	0.336	0.392
Standard error	0.032	0.033
Difference ^b	-	0.056
Standard error of the difference	-	0.020
95% CI	-	0.016; 0.096
% Difference ^c	-	14.25
SP-value	-	0.0064

Source: Post-text Table 14.2.1.1

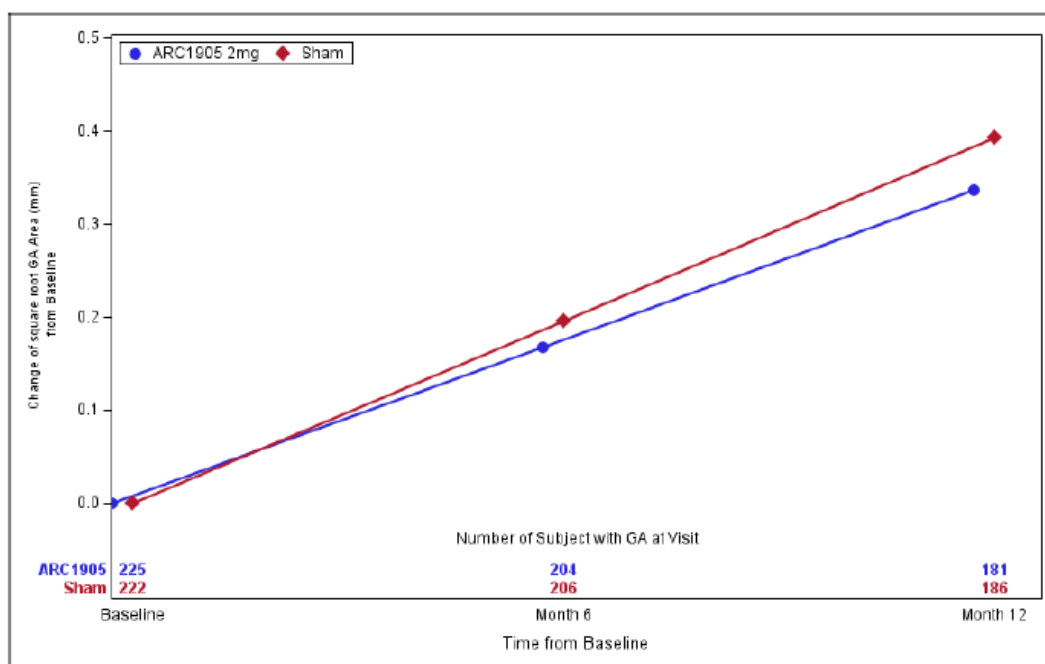
CI = confidence interval; GA = geographic atrophy; ITT = intent-to-treat population; MMRM = mixed model for repeated measures; SAP = statistical analysis plan.

Note: Baseline GA is the measurement at the Screening visit.

^a MMRM is specified in the SAP, Appendix 16.1.9.

^b Difference in growth rate between groups calculated as (Sham) minus (Zimura 2 mg).

^c % Difference is calculated by 100*(Difference)/(Growth rate from Sham).



Source: Post-text Figure 14.2.1.1

GA = geographic atrophy; ITT = intent-to-treat; MMRM = mixed model for repeated measures.

Figure 12: Mean rate of growth (slope) in GA area over time (MMRM analysis; square root transformation) – study eye – month 12 (ITT population)

Secondary endpoint

There are no secondary endpoints.

Ancillary analyses

Mean Change in BCVA at Month 12

Table 22: Mean change in BCVA (ETDRS letters) from baseline to month 12 (MMRM analysis) – study eye (ITT population)

	Zimura 2 mg N=225	Sham N=222
MMRM Analysis ^a – Change from Baseline to Month 12		
Least Squares Mean	1.34	0.96
Standard Error	1.483	1.513
Difference ^b	0.38	-
Standard error of the difference	0.920	-
95% CI	-1.43; 2.19	-
P-value	0.6781	-

Source: Post-text Table 14.2.4.1

BCVA = best corrected visual acuity; CI = confidence interval; ETDRS = early treatment diabetic retinopathy study; ITT = intent-to-treat; MMRM = mixed model for repeated measures; SAP = statistical analysis plan; VA = visual acuity.

Notes: The Baseline ETDRS VA score is the mean value of the Screening and Day 1 VA Scores rounded up to the nearest integer if not already an integer. If either the Screening or Day 1 VA score is missing (including an invalid VA), the Baseline VA is equal to the other, non-missing value.

^aMMRM is specified in the SAP, Appendix 16.1.9.

^bDifference in least squares means between groups calculated as (Zimura 2 mg) minus (Sham).

Mean Change in Low Luminance Visual Acuity at Month 12

Table 23: Mean change in LL BCVA scores (ETDRS letters) from baseline to month 12 (MMRM Analysis) – study eye (ITT population)

	Zimura 2 mg N=225	Sham N=222
MMRM Analysis ^a – Change from Baseline to Month 12		
Least squares mean	-4.35	-2.29
Standard error	2.301	2.356
Difference ^b	-2.06	-
Standard error of the difference	1.428	-
95% CI	-4.86; 0.75	-
P-value	0.1503	-

Source: Post-text Table 14.2.4.3

BCVA = best corrected visual acuity; CI = confidence interval; ETDRS = early treatment diabetic retinopathy study; ITT = intent-to-treat population; MMRM = mixed model for repeated measures; SAP = statistical analysis plan.

Note: Day 1 visit is used as the Baseline.

^a MMRM is specified in the SAP, Appendix 16.1.9.

^b Difference in least squares means between groups calculated as (Zimura 2 mg) minus (Sham).

VFQ-25 at Month 12 and Month 18

Descriptive results in changes in Quality of Life using VFQ-25 at Month 12 are presented below.

Table 24: Summary of mean change (SD) from baseline in VFQ-25 values (general health, general vision, ocular pain, social functioning, mental health, driving, color vision, and peripheral vision sub-scales) at month 12 – study eye (ITT population)

Sub-Scale	Zimura 2 mg N=225	Sham N=222
Mean Change (SD)		
General Health	-2.4 (18.28)	-3.1 (19.93)
General Vision	0.6 (15.36)	-1.0 (15.80)
Ocular Pain	1.9 (16.79)	0.2 (16.38)
Social Functioning	-5.9 (19.83)	-6.1 (19.63)
Mental Health	-1.0 (20.26)	-0.2 (20.87)
Driving	-5.6 (17.52)	-4.5 (21.91)
Color Vision	-2.7 (19.59)	-2.7 (21.63)
Peripheral Vision	-3.6 (22.67)	-3.0 (24.10)

Source: Post-text Table 14.2.11.05, Post-text Table 14.2.11.06, Post-text Table 14.2.11.07,

Post-text Table 14.2.11.08, Post-text Table 14.2.11.09, Post-text Table 14.2.11.10, Post-text Table 14.2.11.11,

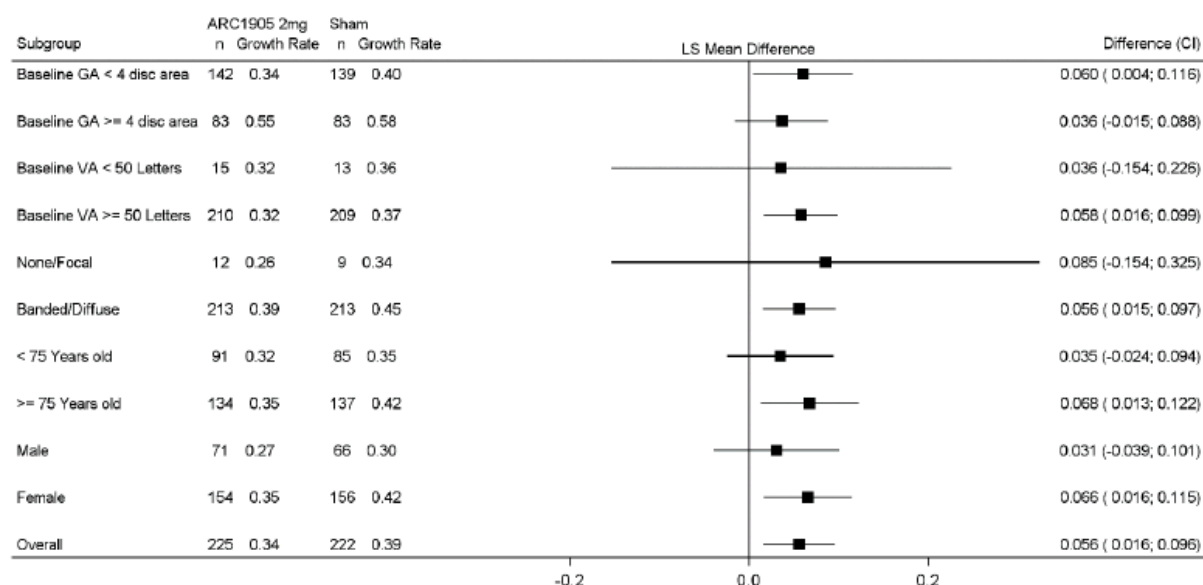
Post-text Table 14.2.11.12

ITT = intent-to-treat population; SD = standard deviation; VFQ = Visual Function Questionnaire

Notes: Baseline is the last non-missing measurement prior to the first dose of study drug. Change from baseline value rounded up to the next integer (e.g. -14.5=-15, +14.5=+15).

Subgroup analysis

The pre-specified demographic subgroup analyses are summarized in the below figure.



Source: [Post-text Figure 14.2.2](#)

CI = confidence interval; GA = geographic atrophy; ITT = intent-to-treat; LS = least squares; MMRM = mixed-effects repeated measures; SE = study eye; VA = visual acuity

Notes: MMRM is specified in the statistical analysis plan, [Appendix 16.1.9](#). Difference in LS means between group: calculated as (Sham) minus (Zimura).

Figure 13: Subgroup analysis: mean rate of growth (slope) in GA area from baseline to month 12 (MMRM analysis; square root transformation) – study eye (Izelvay 2 mg vs Sham) in ITT population

3.3.4.3. 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 25: Summary of efficacy for trial ISEE2008

Title: A Phase 3 Multicenter, Randomized, Double-Masked, Sham Controlled Clinical Trial to Assess the Safety and Efficacy of Intravitreal Administration of Izelvay™ (Complement C5 Inhibitor) in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration		
Study identifier	ISEE2008 (GATHER2) EudraCT number: 2020-000676-38	
Design	ISEE2008 was a randomized, double-masked, Sham-controlled study testing Izelvay versus Sham in patients with GA secondary to AMD. On Day 1, patients were centrally allocated to 1 of the 2 treatment groups by a dynamic minimization procedure using clinical site in a 1:1 ratio stratified by factors known to be of prognostic importance in AMD	
	Duration of main phase:	12 months
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	12 months
Hypothesis	Superiority	
Treatments groups	Izelvay 2 mg/eye administered monthly via IVT injection	Izelvay. 12 months, 225 subjects randomized
	Sham	Sham procedure. 12 months, 223 subjects randomized

Title: A Phase 3 Multicenter, Randomized, Double-Masked, Sham Controlled Clinical Trial to Assess the Safety and Efficacy of Intravitreal Administration of Izelvay™ (Complement C5 Inhibitor) in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration				
Study identifier	ISEE2008 (GATHER2) EudraCT number: 2020-000676-38			
Endpoints and definitions	Primary endpoint	Mean rate of growth (slope) estimated based on GA area	Mean rate of growth (slope) estimated based on GA area measured by fundus autofluorescence (FAF) in at least 3 time points: Baseline, Month 6, and Month 12 (square root transformation).	
Database lock	?			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Intent to treat 12 Months			
Descriptive statistics and estimate variability	Treatment group	Izelvay 2 mg/eye administered monthly via IVT injection	Sham	
	Number of subject	225	222	
	Growth rate (mean rate)	0.336	0.392	
	Standard error	0.032	0.033	
Effect estimate per comparison	Primary endpoint	Comparison groups		Izelvay 2mg/eye vs. sham
		Difference between groups		0.056
		95% CI		0.016; 0.096
		P-value		0.0064
Notes	There are no secondary endpoints (only exploratory).			

3.3.4.4. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials			
Non Controlled trials			

3.3.4.5. In vitro biomarker test for patient selection for efficacy

Not applicable

3.3.4.6. Analysis performed across trials (pooled analyses and meta-analysis)

The pooled analysis on the mean rate of GA area growth (slope) (using square root transformation) from Baseline to Month 12 when compared with sham are presented below.

Table 26: Mean rate of growth (slope) in geographic atrophy area from baseline to month 12 (MRM analysis) (square root transformation) - study eye ITT analysis set - pooled OPH2003 and ISEE2008

	ARC1905 2mg (N=292)	Sham (N=332)	ARC1905 1mg (N=26)	Sham OPH2003 (Part 1) (N=26)	ARC1905 4mg (N=83)	Sham OPH2003 (Part 2) (N=84)
MRM Analysis - Rate of growth (slope) from Baseline to Month 12						
Growth Rate	0.333	0.406	0.206	0.267	0.307	0.416
Standard Error	0.028	0.028	0.082	0.090	0.069	0.066
Difference *		0.073		0.061		0.109
Standard Error of the Difference		0.018		0.051		0.042
% Difference **		18.04		22.79		26.31
95% C.I.		0.038, 0.109		-0.042, 0.164		0.027, 0.192
p-value		<.0001		0.2391		0.0100

The pooled analysis on the mean change in BCVA from Baseline to Month 12 when compared with sham are presented below.

Table 27: Mean change in best corrected visual acuity score (ETDRS letters) from baseline to month 12 (MRM analysis) - study eye ITT analysis set - pooled OPH2003 and ISEE2008

	ARC1905 2mg (N=292)	Sham (N=332)
MRM Analysis - Rate of change from Baseline to Month 12		
Least Squares Mean	-0.26	-1.02
Standard Error	1.276	1.269
Difference *	0.76	
Standard Error of the Difference	0.778	
95% C.I.	-0.77, 2.29	
p-value	0.3279	

The pooled analysis on the mean change in LLBCVA from Baseline to Month 12 when compared with sham are presented below.

Table 28: Mean change in low luminance visual acuity score (ETDRS letters) from baseline to month 12 (MRM analysis) - study eye ITT analysis set - pooled OPH2003 and ISEE2008

	ARC1905 2mg (N=292)	Sham (N=332)
MRM Analysis - Rate of change from Baseline to Month 12		
Least Squares Mean	-3.88	-2.35
Standard Error	1.901	1.882
Difference *	-1.53	
Standard Error of the Difference	1.156	
95% C.I.	-3.80, 0.74	
p-value	0.1869	

3.3.4.7. Supportive study(ies)

ISEE2009 Study is an Open-label Extension (OLE) Phase 3 Trial to Assess the Safety of Intravitreal Administration of avacincaptad pegol (Complement C5 Inhibitor) in Patients with Geographic Atrophy Who Previously Completed Phase 3 Study ISEE2008 (GATHER 2)

Approximately 400 patients who completed Study ISEE2008 (GATHER 2) through the Month 24 visit on study treatment (either avacincaptad pegol or Sham) and consent to participate will be administered monthly avacincaptad pegol 2 mg from Month 1 through Month 17 (maximum 17 total doses); or until avacincaptad pegol is commercially available.

All patients will have a final follow up visit at Month 18 or if the study is terminated early, Month 18 final follow up procedures will be followed. Premature termination of this clinical trial may occur because of a regulatory authority decision, market authorization of study drug and commercial availability, change in opinion of the Institutional Review Board (IRB)/ Ethics Committee (EC), or at the discretion of IVERIC bio.

3.3.5. Discussion on clinical efficacy

Design and conduct of clinical studies

OPH2003 (GATHER 1)

Study OPH2003 (GATHER 1) was randomised, double-masked and controlled phase 2b/3 trial that tested 1 mg, 2 mg and 4 mg doses. The 4 mg dose required to 2 IVT injections.

Based on its sample size considerations and the modifications made to its design while the study was already ongoing, it is clear that the study was not initially planned as a confirmatory trial but rather as an investigation of the most adequate dose regimen(s) to be included in a subsequent phase 3 trial.

Indeed, major modifications were made to the study design while the study was ongoing, which raise concerns about the study integrity. Indeed, the second part of the study was introduced with protocol amendment B, an interim analysis was removed and the sample size was changed on two occasions (amendments B and C). Moreover, the primary endpoint (and therefore, also the secondary endpoints) was changed with protocol amendment C. It is noted that under the original protocol with change in BCVA as primary endpoint, the study would have failed to reach statistical significance.

As highlighted in the CHMP reflection paper on methodological issues in confirmatory clinical trials (CHMP/EWP/2459/02), "adaptations to confirmatory trials introduced without proper planning will render the trial to be considered exploratory." It is further noted that "the need to modify a number of design aspects, e.g. re-assess sample size, (...) change dosing, treatment duration (...) may change the emphasis from a confirmatory trial to an hypothesis generating, or exploratory, trial".

As a consequence, GATHER 1 is not considered a pivotal trial of this MAA. It is nevertheless considered of supportive nature.

The two parts of the study had separate randomisation procedures, with different randomisation ratios. For the avacincaptad pegol 2 mg treatment group, the randomisation ratio was 1:1 vs Sham in study part 1, whereas it was 1:2 in part 2. As data from both study parts are pooled when comparing avacincaptad pegol 2 mg to sham, the difference in randomisation ratios can potentially result in biased estimates of treatment effect. In this situation, the consistency of results by study part is key to assessing the reliability of the pooled data.

Of note, the wording of the primary endpoint in GATHER 1 study report ("rate of GA growth over 12 months") could be misleading. It is clear from the statistical model that the study primary endpoint could be simply expressed as the change from baseline in GA area at month 12, using square root transformation. Additional (post-hoc) analyses investigating the slope over 12 months have been performed in the SCE, which is a different approach from the study primary endpoint.

The handling of missing data raises several issues. First, the exclusion of patients without either a baseline or at least one post-baseline measurement is of concern. As it is unlikely that data from patients without baseline or post-baseline measurements were missing completely at random (MCAR), this is likely to result in biased estimates. Moreover, other missing measurements are not imputed, and therefore implicitly assumed to be missing at random (MAR). There is a number of sensitivity analyses (making use of multiple imputations) which are performed by the applicant to assess the

potential impact of missing data. This is acknowledged but it is unclear whether patients excluded from the primary analysis (due to not providing baseline and at least one post-baseline measurement) are included in these sensitivity analyses. Therefore, the applicant is requested to provide (OC):

- The number of patients who are completely excluded from the primary analysis due to either baseline or post-baseline missing measurements.
- A sensitivity analysis of the primary endpoint where all randomised patients are included, using a MAR multiple imputation approach to missing data (including for patients with no baseline or no post-baseline measurements)
- If this is not already the case, repeat the set of sensitivity analyses (shift imputation approach, pattern-mixture-model approach, and all four Miller methods previously performed) where all randomised patients are included, i.e. including patients with no baseline or no post-baseline measurements

ISEE2008 (GATHER 2)

Study ISEE2008 (GATHER 2) was a randomised, double-masked and controlled phase 3 trial. Given the exploratory nature of GATHER 1 (see above), the GATHER 2 study is considered the sole pivotal trial of this MAA.

In this study patients received avacincaptad pegol 2 mg IVT monthly during the first year of treatment; during the second year of treatment they received avacincaptad pegol 2 mg IVT monthly or every other month. In answer to D120, 24-month data which have become available since 06 Dec 2023 have been provided.

The approach to explore the monthly vs. the every other month treatment schedules can be followed in order to establish the preferable dosing recommendation. However, splitting the active 2 mg group in two different arms reduces the number of patients treated with the finally selected schedule

Only one eye (study eye) was treated in both studies. Patients with foveal involvement or those with CNV in either eye were not allowed to enter. The selection of extrafoveal GA may be acceptable from a practical point of view in order to reduce the variability. However, a reduced effect in terms of growth reduction has been reported in patients with foveal lesions treated with complement inhibition factors (such as pegcetacoplan or lampanizumab) compared to extrafoveal GA. Since GA is a bilateral condition the need of treating both eyes is likely. The two eyes may be asymmetrically affected, or the foveal-sparing GA may progress involving the fovea during the GA treatment.

One error occurred in the reporting of FAF outcomes and consequently 38 patients randomized with baseline GA size between 4 to 10 mm² were placed in a stratum that included participants with size ≥ 10 mm² rather than being placed in stratum that included participants with size < 10 mm². The impact of this stratification error was performed with two sensitivity analyses that stratified by 3-level covariates for the Baseline geographic atrophy size. Although the motivations for using the minimization algorithm are understood, the Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013) states that in case that dynamic allocation algorithms are used, re-randomisation methods in the analysis should be considered to properly control type I error. The applicant should discuss the considerations taken into account in relation of the control of type I error (OC).

A team from the applicant are said to be unblinded at Month 12 database lock, and a separate masked team from the applicant and external service providers to be established to manage study activities until the Month 24 final database lock. Although it is not possible to exclude the dissemination of information beyond unmasked personnel following the month 12 database lock and unmasking, the measures taken appear generally appropriate.

The primary endpoint was modified from the change from baseline in GA area at month 12 to the rate of growth in GA (i.e. the slope) from baseline to month 12 at the time of protocol global amendment C (24 May 2021). Any change regarding the primary endpoint or its statistical analysis is generally viewed critically as it has the potential to impact study integrity. Nevertheless, it is acknowledged that the change was not initiated by the applicant, but rather requested by the FDA as part of the Special Protocol Assessment. Moreover, the analysis results under the initial primary endpoint definition (change from baseline at Month 12) have also been provided in Table 14.2.3.6, which allows for some consistency assessment.

The overall (one-sided) type I error rate in this trial was 0.025, and the only hypothesis test is for the primary endpoint (all other analyses are descriptive). The applicant states that an alpha-level adjustment was made in the assessment of statistical significance at the time of the final analysis, equal to (two-sided) 0.001 for each DSMB meeting for any look at the data. However, the number of DSMB data looks as well as the final adjustment of the alpha-level for the primary analysis (derived from the number of DSMB looks) could not be found. This information is necessary to interpret the statistical significance of the primary analysis results, and should be provided by the applicant (OC).

The ITT population used for the primary analysis included all randomized patients who received at least one dose of study drug. Although the definition is not fully in line with the ITT principle, only one patient was randomised but not treated, which is not thought to affect study conclusions.

The primary statistical analysis can be acceptable provided that the linearity assumption of the "slope" model is verified. It is acknowledged that both the piecewise linear analysis and the plots of the mean change provided by the applicant show trajectories that are approximately linear. In addition, the residual plots do not seem to question the linear assumption. Regarding the need for square-root transformation, it is noted that the residual distribution is asymmetric when the analysis is performed based on observed data. This is likely related to the positively skewed distribution of GA lesions. On the other hand, residuals do not appear to deviate from the normality assumption for the analysis based on square root transformed measurements. Therefore, the square root transformation seems preferable than no transformation.

Year 2 analyses

The year 2 analyses are described in a separate SAP, for which three versions have been made available. The last two versions (v2.0 and v3.0) have been finalized before the year 2 database lock (8 September 2023), but later than the year 1 database lock (24 August 2022). The original version of the year 2 SAP of Study ISEE2008 was finalized prior to the year 1 database lock, but is only a brief (one page) addendum to the first SAP.

A testing procedure has been introduced in the year 2 SAP, which is meant to be followed in a sequential manner, only if the primary hypothesis test from the month 12 SAP has reached statistical significance. This additional hierarchical testing procedure has not been described in the study protocol. Moreover, the testing sequence has been modified with version 2.0 of the year 2 SAP, notably with the inclusion of time to persistent vision loss in the procedure. The late introduction of the hierarchical testing procedure for year 2 analyses, and its modification after the month 12 database lock in the second version of the SAP, both raise concerns regarding the adequacy of the testing procedure. Moreover, all other analysis details, including the analysis population (e.g. the definition of the re-randomised set) and the statistical models, were also defined in the year 2 SAP versions 2.0 and 3.0, i.e. after the month 12 database lock.

Although some measures were taken to limit the extent of personnel being unmasked after the month 12 primary analysis, it is not possible to exclude a dissemination of information beyond unmasked personnel following the month 12 database lock. Therefore, it is difficult to rule out data driven

decisions leading to an updated plan of analyses after the initial unmasking of the year 1 database lock. A logical consequence is that type I error control cannot be ensured, so that year 2 analyses are deemed exploratory in nature.

The year 2 analyses of GA area are performed on the re-randomized (Re-Rand) analysis set, which includes patients who were re-randomized at Month 12 or who were on sham and completed the Month 12 visit. The definition of this analysis set is problematic as it does not constitute a randomised set of patients. Indeed, only the patients who completed the Month 12 visit in the avacincaptad pegol arm were re-randomised, i.e. not the patients on sham. Patients completing the Month 12 visit in the avacincaptad pegol arm may not be entirely comparable to the patients completing Month 12 on sham. Considering that all comparisons in the Year 2 SAP testing procedure are performed vs sham, they are susceptible to some degree of bias.

Other analyses (e.g. time to persistent vision loss) are performed based on the ITT population, and compare avacincaptad pegol 2mg overall versus sham. The underlying assumption of such analyses is the poolability of the avacincaptad pegol EM and EOM treatment arms. The pattern of missing data resulting from drop-out patterns before and after month 12 is also of importance, given that all relevant analyses rely on the questionable assumption of data missing at random. These uncertainties further highlight the exploratory nature of the year 2 analyses.

Unlike the primary analysis of GA area growth at Year 1, which used square-root transformation of GA growth area, the Year 2 analysis uses the untransformed GA growth as the endpoint. Although the consistency of Year 1 GA growth area results regardless of transformation is acknowledged, the review of the residual plots indicated that the square-root transformation was preferable.

Moreover, the MMRM is not adjusted for the initial randomisation stratification factor. The applicant justifies the absence of adjustment for randomisation strata by the fact that patients have been re-randomised at Month 12. This argument is not understood, as the initial randomisation stratification factors remain of prognostic importance, regardless of the re-randomisation. This is also particularly important in the context of the Re-Rand analysis set, which does not reflect the initial randomisation, and might therefore benefit from some adjustment.

Therefore, the applicant is requested to provide the 2-year GA growth area analysis with an updated MMRM based on the square-root transformation of GA growth area, and additionally adjusted for Baseline VA (< 50 letters vs. ≥ 50 letters), and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) as used in the primary Month 12 analysis. The MMRM analysis based on untransformed GA growth area should also be repeated with an adjustment for Baseline VA (< 50 letters vs. ≥ 50 letters) and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) (**OC**).

Efficacy data and additional analyses

OPH2003 (GATHER 1)

A total of 286 patients were randomized and treated in the study, 77 patients in Part 1 and 209 in Part 2. Among them, 26 patients were treated in the 1 mg group, 67 patients in the combined 2 mg group, 83 patients in the 4 mg group, and 110 patients in the combined Sham group.

The study population is considered to reflect the population for the intended indication. Baseline demographics appear balanced across treatment groups.

The primary endpoint (mean Rate of Change in GA from Baseline at Month 12) was statistically met for both arms (2 and 4 mg) versus sham with similar size effect.

- The 2 mg arm showed a statistically significant reduction of 27.38% compared to Sham ($p = 0.0072$).
- The 4 mg arm showed a statistically significant reduction of 27.81% compared to Sham ($p = 0.0051$) :

Avacincaptad pegol 1 mg dose resulted not better than placebo (sham) on the affected area of atrophy. This dose was discarded as a therapeutic dose. Only 2 mg dose progressed to Phase 3.

However, the formal demonstration of superiority remains questionable notably due to the change of primary endpoint during the course of the study.

Regarding the first key secondary outcome, the difference in least square means in BCVA from Baseline to Month 12 (first key secondary endpoint) between the 2 mg arm and the corresponding sham arm is quite small (1.39). Regarding the 4 mg arm, the difference even smaller (-0.28) and seems to favour the sham group. It is not clear why the effect is more pronounced in the 2 mg group compared to the 4 mg group. The applicant justifies in the answer to D120 the inconsistency by the fact that as GA progresses, patients temporarily compensate for their deteriorating vision by utilizing the remaining islands of viable retinal tissue, and then experience natural fluctuations in BCVA measurements. While this could be understood, no literature was provided to support the assumption.

Regarding the second key secondary outcome, the differences in least square means in LLVA from Baseline to Month 12 (second key secondary endpoint) between the 2 mg arm and its corresponding sham arm is also small (1.39). Regarding the 4 mg arm the difference is also smaller (-0.28) and seems to favour the sham group. It is not clear why the effect is more pronounced in the 2 mg group compared to the 4 mg group. Similar justification than for BCVA has been provided in the answer to D120. This questions again the impact of the treatment on the visual parameters.

Even if the 2 key secondary endpoint show a trend of less deterioration in the 2 mg group versus Sham group, the difference is small and is even less pronounced in the high dose arm. The clinical relevance of the observed difference of the change in BCVA and LLVA do not allow at this stage to ensure that the change in GA rate translates into clinical benefit for patients (MO).

The applicant also provided supportive data for the primary endpoint and the 2 key secondary endpoints at M18.

Regarding rate of Change in GA from baseline to Month 18 (28.11% in the 2 mg group and 29.7% in the 4 mg group) the reduction is slightly more pronounced than in month 12 (27.35% in the 2 mg group and 27.81% in the 4 mg group) but the relevance of this gain is not clear and should be discussed by the applicant (OC).

The effect on BCVA and LLVA are also slightly larger (difference in least squares means versus sham of 2.37 in the 2 mg arm and 2.80 in the 4 mg arm for BCVA and 0.38 in the 2 mg arm and -1.44 in the 4 mg arm for LLVA). However the differences remain low and their clinical relevance questionable.

The applicant also provided descriptive quality of life assessed in the ITT population by VFQ-25, of which 4 pre-specified sub-scales were considered of interest (near vision activities, distance vision activities dependency, and role difficulties). The changes from Baseline in pre-specified the sub-scales showed trends of improvement in some sub-scale but the results are not clinically relevant and some even favouring the Sham group.

At Month 12 no effect on visual function was shown in avacincaptad pegol treated group with respect to sham group. It could be due to the fact that longer treatment would be required to reveal a clinical benefit. The results measured in GATHER 1 Study at Month 18 did not show further relevant effect, being of note that only 67 patients were treated with avacincaptad pegol (versus 110 patients on

sham). Since no efficacy results are available beyond this time point it cannot be determined at present how long the treatment will be required to detect an effect and if this effect will be of sufficient magnitude.

ISSE2008 (GATHER 2)

A total of 448 patients were randomized in the study (225 patients in the Avacincaptad pegol group and 223 patients in the Sham group). Overall both groups were well balanced at baseline.

The included patient population as defined by inclusion and exclusion criteria reflects the target population and appears adequate. Baseline ocular characteristics in the study eye reflect a population with a conserved visual acuity and at risk for faster GA progression (extrafoveal lesion, lesion size, predominant diffuse FAF pattern). Some other risk factors such as number/size of drusen and the uni or multifocality nature of the lesions were not systematically considered.

The overall geographic distribution of the patients (ISE Table 14.1.1.2) shows that the majority of the patients were from North America (53.1%). Only 10.4% of patients were from Eastern Europe and 36.5% from the Rest of the World. European population is clearly underrepresented, with some centres recruiting patients from HR, CZ, ES, HU, LT, FR, DE, IT. It can be assumed that the diagnosis and treatment of the condition and the management of the majority of patients can be considered equivalent to that performed in the EU.

At Month 12, the primary efficacy objective was met. A statistically significant difference of 0.056 mm per year (95% confidence interval [CI] = 0.016; 0.096) in the mean rate of GA growth, in favor of Avacincaptad pegol, compared to Sham ($p = 0.0064$) was demonstrated. This represents a 14.25% reduction in mean rate of GA area growth at Months 12.

The face to face comparison of the 2 studies shows that the size of the effect (reduction in lesion size compared with placebo) was almost halved in this study compared with the phase II study (OPH 2003). This is of concern given that this is a confirmatory study (OC)

There were no predefined secondary endpoints in this study, visual acuity and quality of life data are only exploratory endpoints. The absence of secondary endpoints, and moreover with controlled of the alpha risk to assess the visual function is an important issue. This hampered the study's ability to translate the size of the effect observed with the surrogate endpoint into a clinical benefit for the patient (MO).

Exploratory efficacy endpoints are only descriptive included (BCCVA, LLVA and QoL):

The difference in last square means in BCVA from baseline to month 12 was 0.38 (1.34 ETDRS letters in the avacincaptad pegol group versus 0.96 in the Sham group). The difference in last square means in LLVA from baseline to month 12 was -2.06 (-4.35 ETDRS letters in the Avacincaptad pegol group versus -2.26 in the Sham group) favoring the Sham group. The clinical relevance of the observed difference of the change in BCVA and LLVA is not clear and in any case, the descriptive nature of these data precludes any conclusion on the effect of avacincaptad pegol on visual acuity.

Regarding QoL assessed by VFQ-25, of which 4 pre-specified sub-scales were considered of interest (near vision activities, distance vision activities, dependency, and role difficulties), the mean change from Baseline (SD) in the 4 pre-specified sub-scale at Month 12 did not allow to conclude that there was a relevant difference in terms of quality of life.

In answer to D120, 24-month data of GATHER2 Study which have become available since 06 Dec 2023 have been provided. Of 225 patients who were initially assigned to receive avacincaptad pegol 2 mg monthly, at Month 12, 96 of them were re-randomized to receive avacincaptad pegol 2 mg EM and 93 patients to receive avacincaptad pegol 2 mg EOM in Year 2. Of 223 patients who were

initially assigned to the sham group, 203 remained in the study at the end of Year 1 and continued to receive sham in Year 2.

As commented above in the AR, year 2 analyses are deemed exploratory in nature considering the methodological issues, including that is difficult to rule out data driven decisions leading to an updated plan of analyses after the initial unmasking of the year 1 database lock, and randomization issues. Additionally, for the secondary and exploratory endpoint, the applicant has pooled the data of the the EM (every month: 2 mg/eye administered via IVT injection monthly) arm and the EOM (every other month: mg/eye administered via IVT every other month) arm. The applicant explained that is for powering reason. However, given that it is not demonstrated that EM and EOM have a similar efficacy, there is no scientific rational to conduct such a pooling. Indeed, between Month 12 and Month 24, one arm have received overall half a dosing than the other one. This makes the results difficult to interpret. Therefore, the applicant should provide all secondary and exploratory analysis at Month 24 for the EM and the EOM arms separately (OC).

Regarding demographics and baseline characteristics, quite imbalance can be observed in the EOM group versus the EM and/or sham groups, in particular for gender, age groups, and dry age-related macular degeneration. The applicant should discuss the impact of these imbalance on the interpretation of the results (OC).

At Month 24, difference in mean growth (Slope) from baseline was statistically significant for the Izelvay arms compared to sham: 0.362 mm² per year (95% CI: 0.066, 0.657) for avacincaptad pegol EM, and 0.488 mm² per year (95% CI: 0.189, 0.788) for avacincaptad pegol EOM. However, the fact that the magnitude of the effect is numerically larger in the EOM group while patient have received half of the dosing during the second year is questioning; this is inconsistent with the frequency of injection. This is need to be further discussed by the applicant (OC). Additionally, at Month 12 the difference in mean growth from baseline compared to sham was 0.376 mm² per year (95% CI: 0.122; 0.631). This appears close to the effect at Month 24. The applicant should discuss on whether the maximum anatomical effect is almost reached at Month 12 (OC).

As commented above, secondary and exploratory endpoints are difficult to interpret given the pooling of the EM and EOM data. However, mean change in BCVA scores from baseline to Month 24 and mean change in LL-BCVA scores from baseline to Month 24 were not met. Difference with sham were not statistically significant. But, more worrisome, although the difference was numerically limited -0.83 letter (95% IC: -3.79, 2.12) for BCVA, and -1.49 (95% IC: -4.79, 1.81). But, more worrisome, these differences were in disfavor of Izelvay. Additionally, contrary to Month 12, there was a larger room to show an effect considering that the loss in BCVA in the sham group compared to baseline was -6.48 letters, and the loss in LL-BCVA -9.1.

Regarding the comments on the time to event analysis (i.e. time to persistent vision loss), using the 15 letters cut-off which is usually recommended for responder analysis and considered as clinically relevant, the risk probability at Month 24 for experiencing persistent vision loss of ≥ 15 ETDRS letters was 18.2% in the avacincaptad pegol and 19.3% in the sham group. The difference appears extremely limited, and not convincing (MO).

Finally, quality of life analyses are also of concern. Indeed, regarding the VQF-25 composite score, the difference was not statistically significant but slightly in disfavor of Izelvay versus sham: -0.712 (95% CI: -3.326, 1.903). Regarding subscales, mean change from baseline in the near vision activities sub-scale, in the distance vision activities sub-scale, in the dependency sub-scale, in the role difficulties sub-scale, in the general vision sub-scale, in the ocular pain sub-scale, the social functioning sub-scale, in the mental health sub-scale, in the driving sub-scale, in the color vision sub-scale, and in the peripheral vision sub-scale, the change from baseline was worst for Izelvay than for sham. This further questioning the interest to treat patients with GA with Izelvay (MO).

In conclusion, the surrogacy value for clinical benefit of GA lesion growth has not been yet established. It is crucial that the magnitude of the GA growth slowing effect observed can be translated in a clinically relevant impact on clinical function. This demonstration needs to be based on evidence from visual function parameters, which is not the case at this stage. Additionally, these concerns on the efficacy of Iselvay in the treatment of the patient with GA secondary to AMD are strengthened by the methodological issues results of the OPH2003 Study and Month 24 results of the ISEE2008 Study as supportive only. Moreover, beyond the need to demonstrate the surrogacy, there are uncertainties on the estimation of the anatomical effect for which estimation is almost halved from a study to another one (MO).

Additional expert consultation

Not at this stage

Assessment of paediatric data on clinical efficacy

Not applicable

Additional efficacy data needed in the context of a <conditional> MA <under exceptional circumstances

Not applicable

3.3.6. Conclusions on clinical efficacy

The efficacy of avacincaptad pegol for the treatment of adults with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) is not considered established at this stage. Although the effect versus sham was demonstrated based on measurement of GA area at month 12, it needs to be demonstrated that it represents a valid surrogate measure for visual function and that change in GA lesion size can translate into a clinical benefit for the patient. This might be because a longer treatment duration is needed to demonstrate a clinical benefit; in this context, efficacy results at 24 months appear to be crucial in establishing the benefit-risk ratio of the treatment. Furthermore, the lack of evidence of effect of avacincaptad pegol in patients with foveal involved GA does not support the proposed wide therapeutic indication.

3.3.7. Clinical safety

The safety profile of Avacincaptad pegol, also known as ARC1905 or Zimura, in geographic atrophy (GA) is mainly based on the pooled unmasked safety data up to month 12 from the Cohort 1 studies (n=780 patients) consisting of one pivotal randomized study ISEE2008/GATHER 2 (ongoing 24-months phase 3 study, n=447) and two supportive studies OPH2001 (completed phase I open label study, n=47) and OPH2003/GATHER 1 (randomized completed 18-months phase 2/3 study, n=286).

The proposed dosing regimen by the applicant in the current application is 2 mg administered by IVT injection every 4 weeks studied in OPH2003 and ISEE2008. In ISEE2008, patients were treated by 12 monthly injection of avacincaptad pegol 2mg or sham followed by either monthly or alternated monthly injection with sham up to year 2. At year 2, patients were re-randomized to receive avacincaptad pegol 2 mg monthly or every other month. In OPH2003, patients were treated with sham or monthly injection of avacincaptad pegol (1mg, 2mg or 4 mg).

GA is typically a progressive condition and usually bilateral, with about half of patients developing GA in both eyes within 7 years of initial diagnosis [Boyer et al, 2017; Lindblad et al, 2009]. However bilateral treatment was not evaluated in clinical trials in patients with GA secondary to AMD which is

acknowledged. In OPH2003, 83 patients were treated by twice the recommended dose (4 mg), thus limited data are available and results are not considered as fully applicable to bilateral treatment but supportive of the expected safety profile. Indeed, the clinical safety of a dose of 4 mg avacincaptad pegol (two IVT injections [2 mg each] per eye per day), evaluated in study OPH2003, shows that the safety profile of the 4 mg dose is worse than that of the 2 mg dose: the overall frequency of AEs (85.5% vs. 79.5%) and the frequency of ocular AEs in the study eye (71.1% vs 51.0%), ocular AEs in the study eye related to injection procedure (51.8% vs. 28.8%) and ocular AEs in the study eye leading to study drug discontinuation (1.2% vs. 0.7%) was higher in the 4 mg group compared to the 2 mg. The frequency of non-ocular AEs was slightly lower in the 4 mg dose group (54.2% vs. 56.2%) but serious non-ocular AEs were more frequently reported in patients treated with the 4 mg dose than the 2 mg dose (20.5% vs. 12.3%). Overall, these data show that even though bilateral treatment has not been specifically studied, an increased risk in adverse events with bilateral treatment seems likely. In section 4.4 of the SmPc, the applicant mentions that "the safety and efficacy of avacincaptad pegol administered in both eyes concurrently have not been studied" which is endorsed. The applicant should further discuss on how bilateral treatment is expected to be conducted in clinical trials (concomitant or alternate injections) with its impact on the safety profile of bilateral avacincaptad pegol including risk of systemic infections as PK findings showed an inhibition of C5 complement. Depending on the provided discussion, the applicant should propose adequate modifications to the SmPC as available in other IVT products (OC).

Furthermore, unmasked long-term safety data up to 18 months (OPH2003/GATHER 1) were provided in this submission with unmasked 6 month data from ISEE2009 (ISEE2008/GATHER 2 extension study) and as requested the applicant provided non-masked Year 2 safety data for ISEE2008 (Months 13 to 24). The safety analyses were conducted according to the treatment that the patients actually received (avacincaptad pegol 2 mg EM or avacincaptad pegol 2 mg EOM/sham). However, all patients who had ever received an injection of avacincaptad pegol in the 24-month study period were also analyzed in the avacincaptad pegol overall group. Missing values of safety data were not imputed, and safety summaries were based on the observed data.

Supportive data in other ocular indications (nAMD, Stargardt and IPCV) were also provided with safety data from Cohort 2 (OPH2000, OPH2007, OPH2004, OPH2005 and OPH2002). However, as these studies are not in the range of the targeted indication and posology, the use of these data is considered limited.

Table 29: Integrated summary of safety (safety pooling)

Clinical Trial	Status (Region)	Objective(s) of the Clinical Trial	Clinical Trial Phase, Design and Type of Control	Indication Studied	Number of Patients Treated	Duration	IVT Dose/ Treatment Regimen
Clinical Trials in the Target Indication (Cohort 1)							
OPH2001	Completed (USA, EU)	Safety and tolerability in GA AMD patients	Phase 1: OL, MD	Dry AMD	47	12 months	Monthly IVT injections at Day 0, Week 4, Week 8 plus subsequent IVT injections at Week 24 and Week 36 of: Avacincaptad pegol 0.3 mg (N=24) or Avacincaptad pegol 1 mg (N=23)
OPH2003	Completed (USA, EU, Israel)	Efficacy and safety in GA AMD patients	Phase 2/3: R, MC, DM, SC, MD	GA secondary to dry AMD	286	18 months	Monthly IVT injections of: Avacincaptad pegol 1 mg (N=26) or Avacincaptad pegol 2 mg (N=25) or Sham (N=26) or Avacincaptad pegol 2 mg + sham (N=42) or Avacincaptad pegol 4 mg (2 mg + 2 mg) (N=83) or Sham + sham (N=84)
ISSE2008 (Month 12)	Ongoing (USA, EU, South America, Canada, Israel, Australia)	Efficacy and safety in GA AMD patients PK-Sub Study	Phase 3: R, MC, DM, SC, MD PK	GA secondary to AMD	447	24 months; unmasked 12-month data are pooled in Cohort 1, masked data > 12 months are presented separately	12 monthly IVT injections of: Avacincaptad pegol 2 mg (N=225) or Sham (N=222) At Month 12 patients treated with avacincaptad pegol 2 mg monthly were re-randomized 1:1 to monthly or every other month avacincaptad pegol 2 mg (alternating with sham). Sham continues in Year 2.
Clinical Trials in Other Indications (Cohort 2)							
OPH2000	Completed (USA, EU, Israel, Australia)	Safety, tolerability, and PK in nAMD patients	Phase 1: OL, PG, MD, CWA	nAMD	60	3 - 6 months	Up to 6 monthly IVT doses of: Lucentis 0.5 mg + avacincaptad pegol 0.03 mg (N= 3) or Lucentis 0.5 mg + avacincaptad pegol 0.3 mg (N=19) or
							Lucentis 0.5 mg + avacincaptad pegol 1 mg (N=16) or Lucentis 0.5 mg + avacincaptad pegol 2 mg (N=15) or Lucentis 0.5 mg + avacincaptad pegol 3/1 mg ^a (N=7)
OPH2007	Completed (USA, EU)	Safety and tolerability in nAMD patients	Phase 2a: OL, MC, MD, CWA	nAMD	64	6 months	<u>Cohort 1 (N=10):</u> Monthly IVT injections of Lucentis 0.5 mg and 2 days later avacincaptad pegol 4 mg (2 mg + 2 mg); <u>Cohort 2 (N=10):</u> Monthly IVT injections of Lucentis 0.5 mg + avacincaptad pegol 2 mg on the same day <u>Cohort 3 (n=22):</u> Induction Phase (3 months): 2 IVT injections/month 14 days apart of 1. Lucentis 0.5 mg + avacincaptad pegol 2 mg on the same day; 2. avacincaptad pegol 2 mg Maintenance Phase (3 months): Monthly IVT injections of Lucentis 0.5 mg + avacincaptad pegol 2 mg on the same day <u>Cohort 4 (n=22):</u> Induction Phase (3 months): 2 IVT injections/month 14 days apart of 1. Lucentis 0.5 mg + avacincaptad pegol 2 mg on the same day; 2. avacincaptad pegol 2 mg Maintenance Phase (3 months): Monthly IVT injections of avacincaptad pegol 2 mg and 2 days later Lucentis 0.5 mg + avacincaptad pegol 2 mg on the same day

OPH2002	Completed (USA)	Safety and tolerability in IPCV patients	Phase 2a: OL, MD, CWA	IPCV	4	3 months	3 monthly IVT injections of: Lucentis 0.5 mg + avacincaptad pegol 1 mg (N=2) or Avastin 1.25 mg + avacincaptad pegol 1 mg (N=1) or Eylea 2 mg + avacincaptad pegol 1 mg (N=1)
OPH2004	Completed (USA)	Safety and tolerability in nAMD patients	Phase 2a: OL, MD, CWA	nAMD	1	18 months	3 monthly IVT injections followed by IVT injections every 3 months of: Avastin 1.25 mg + avacincaptad pegol 2 mg (N=1) or Lucentis 0.5 mg + avacincaptad pegol 2 mg (N=0) or Eylea 2 mg + avacincaptad pegol 2 mg (N=0) Retreatment during the intervening visits based on prespecified criteria
Clinical Trials In Other Indications (Ongoing; Masked; Not Pooled)							
OPH2005	Ongoing (USA, EU, Canada)	Efficacy and safety in patients with Stargardt Disease	Phase 2b: R, MC, DM, SC, MD	Autosomal recessive Stargardt disease	Planned ~120	18 months	<u>Avacincaptad pegol (N=60)</u> Induction Phase (3 months): 2 IVT injections/month 14 days apart of avacincaptad pegol 2 mg Maintenance Phase (15 months): Monthly IVT injections of avacincaptad pegol 4 mg (2 mg + 2 mg) <u>Sham (N=60)</u> Induction Phase: 2 sham injections/month 14 days apart Maintenance Phase: 2 sham injections directly after each other once a month

AMD = age-related macular degeneration; Avacincaptad pegol = avacincaptad pegol (investigational name); CWA = combined with anti-VEGF therapy; DM = double-masked; EU = European Union; GA = geographic atrophy; IPCV = idiopathic polypoidal choroidal vasculopathy; IVT = intravitreal; MC = multicenter; MD = multidose; N = number of patients; NA = not applicable; nAMD = neovascular age-related macular degeneration; OL = open-label; PG = parallel group; PK = pharmacokinetic; R = randomized; SC = sham-controlled; SD = single-dose; USA = United States of America; VEGF = vascular endothelial growth factor a Due to a drug stability issue with the 3 mg dose, patients originally assigned to 3 mg have been transitioned to the 1 mg dose under Amendment D.

3.3.7.1. Patient exposure

Up to the initial data cut-off on 24 August 2022 a total of 626 patients have received avacincaptad pegol, of which 292 patients have received the dose intended for marketing (2 mg) in the target indication. In total, 242 patients (82.4%) on the 2 mg dose completed the Month 12 visit without discontinuation from the study. Additionally, 41 patients (71.6%) in the 2 mg treatment group have completed the Month 18 visit in the OPH2003 study. Only seven patients have been treated for at least 24 months up to the data cut-off date. Based on the requirements for drug exposure as specified in ICH E1, the safety database as of 24 August 2022 is sufficient, although it is rather limited with regard both to size and to time of exposure, considering that GA is a common and chronic disease that affects approximately 5 million people globally (Fleckenstein, 2018).

A total of 82,4% of the patient in the 2 mg group, 67,5% in the 4 mg group and 86,7% in the sham group completed month 12 visit. In the 4 mg group (OPH2003 studies, patient received 2 IVT of 2 mg), the incidence of patient discontinuation was the highest (30,1%) compared to other groups (13,0% in the 2 mg vs 9,6% in the sham). Patient discontinuation was mainly due to "patient request" (7,9% in the 2 mg vs 15,7% in the 4 mg and 6,3% in the sham) or "sponsor decision" (2,1% in the 2 mg vs 9,6% in the 4 mg vs 0,9% in the sham). Discontinuation due to adverse event was low ($\leq 1\%$) and similar between groups. Furthermore, death was reported in similar proportions between sham (0,6%) and 2 mg (0,7%) while slightly higher in the 4 mg group (1,2%). Up to 18 months (OPH2003) similar tendencies can be observed, 71,6% in 2 mg group, 55,4% in the 4 mg group and 77,3% in the sham group completed month 18 visit.

Up to month 12, the majority of the patient received 10-12 injections 88,9% in the sham group, 86% in the 2 mg group and 72,3% in the 4 mg group. The mean number of injections was similar between the sham (n=11,1) and the 2 mg (n=10,8) and slightly lower in the 4 mg group (n=9,8). The injection

fidelity rate was of 90% in the 2 mg, 92,7% in the sham and 81,8% in the 4 mg group. Mean treatment duration were similar between 2 mg (336,5 days) and sham group (344,8 days). Up to month 18 (OPH2003), on the 67 patients in the 2 mg group, 67.2% received 16-18 IVT injections and 11,9% received 13-15 IVT injections.

In Year 2, for the study ISEE2008 patient were re-randomized and could receive avacincaptad pegol 2 mg EM (every month) or avacincaptad pegol 2 mg EOM (every other month)/sham. All safety analyses were performed on the Safety and the Re-Rand analysis sets. Up to month 24, patients were administered with a mean of 22.52 (SD:2.95) injections for avacincaptad pegol EM (n=96 patients) and 16.98 injections (SD:1.86) for avacincaptad pegol EOM (n=93 patients). The fidelity rate was similar in both groups irrespective of the differing dosing regimen in Year 2 (EM: 0.938 versus EOM: 0.943).

Description of patient's demographics and baseline characteristics as well as prior and concomitant treatment are available in the clinical efficacy section.

3.3.7.2. Adverse events

Common TEAEs

Table 30: TEAEs in studies OPH2003 and ISEE2008 at month 12 (safety population)

Number of Patients (%)	OPH2003		ISEE2008	
	Avacincaptad Pegol 2 mg (combined) N=67	Sham (combined) N=110	Avacincaptad Pegol 2 mg N=225	Sham N=222
TEAEs	50 (74.6%)	77 (70.0%)	178 (79.1%)	157 (70.7%)
Ocular, study eye	35 (52.2%)	38 (34.5%)	110 (48.9%)	83 (37.4%)
Non-ocular	39 (58.2%)	60 (54.5%)	125 (55.6%)	127 (57.2%)
Serious TEAEs	7 (10.4%)	20 (18.2%)	30 (13.3%)	37 (16.7%)
Ocular, study eye	0	0	2 (0.9%)	2 (0.9%)
Non-ocular	7 (10.4%)	20 (18.2%)	29 (12.9%)	35 (15.8%)
TEAE leading to study drug discontinuation	0	1 (0.9%)	6 (2.7%)	2 (0.9%)
Ocular, study eye	0	0	2 (0.9%)	0
Non-ocular	0	1 (0.9%)	4 (1.8%)	2 (0.9%)

Source: OPH2003 CSR Table 33, Table 34, ISEE2008 CSR Table 19, and Table 20, M.5.3.5.1
CSR = clinical study report; TEAE = treatment-emergent adverse event

In Cohort 1, more patient presented TEAEs with avacincaptad pegol (79,5% in the 2 mg) compared to sham (69,5%). While non-ocular TEAE were reported in similar proportions between 2 mg avacincaptad pegol and sham (56,2% vs 55,7%), ocular TEAE in the study eye were more reported in the avacincaptad pegol 2 mg group (51,0% vs 36,4%) while ocular TEAE in the fellow eye were reported in comparable proportions between arms (18,7% in sham, 20,5% in 2 mg and 19,3% in 4 mg).

Ocular TEAE in the 2 mg were assessed as related to injection procedure in 28,8% (20,8 % in the sham group) and to study drug in 1,4% (0,6% in sham). In Avacincaptad pegol 2 mg, 2,1% of the patients discontinued study drug, of those ocular TEAEs was assessed as related to study drug in 2 patients (0,7%). In Avacincaptad pegol 4 mg, ocular TEAE were reported in 71,1% of the patients and 51,8% were assessed as related to injection procedure.

TEAEs were mild to moderate in severity and severe non-ocular TEAE were reported in similar proportions between arms (11,0% in 2 mg, 10,5% in sham and 4 mg) while ocular TEAE in the study eye were slightly more reported in avacincaptad pegol (2,4% in 2 mg, 1,8% in 4 mg and 0,6% in sham). Serious TEAEs were reported with a higher incidence in the sham group and were for the majority non-ocular

TEAE (12,3% in the 2 mg vs 16,6% in the sham). Serious ocular TEAEs in the study eye were reported with comparable incidence between group and were low ($\leq 1\%$). One patient in the 2 mg arm (0,3%) reported a serious ocular TEAE related to study drug. TEAE lead to patient's death in 4 patients (3 patient in 2 mg and 1 patient in the 4 mg arm) and no death were assessed as related to avacincaptad pegol treatment or the injection procedure.

Up to 18 month (OPH2003), similar tendencies were observed. Two additional deaths occurred between month 12 and month 18 however none were assessed as related to study drug.

Up to month 24 (study ISEE2008), 92.4% in the avacincaptad pegol group and 82.9% in the sham group experienced at least one TEAE with comparable proportions between avacincaptad pegol EM (92.7%) and the avacincaptad pegol EOM group (95.7%). Ocular TEAE in the study eye occurred in higher proportions with 69.8% of the patients in the avacincaptad pegol 2 mg EM group and 64.5% in the avacincaptad pegol 2 mg EOM group compared to 48.8% in the sham group. Non-ocular TEAEs occurred in 74.0% of the patients in the avacincaptad pegol 2 mg EM group and 84.9% in the avacincaptad pegol 2 mg EOM group compared to 71.4% in the sham group. Ocular TEAEs in the study eye related to study drug injection procedure were reported in 38.5% in the avacincaptad pegol 2 mg EM group, 33.3% in the avacincaptad pegol 2 mg EOM group and 20.2% in sham group. Ocular TEAE in the study eye related to study drug occurred in low proportions 5.2% in avacincaptad 2 mg EM group, 2.2% in avacincaptad pegol 2 mg EOM group and 1.0% in sham. Regarding TEAEs severity, 7.3% (n=7), 3.2% (n=3), and 1.0% (n=2) of patients experienced severe ocular AEs in the study eye in the avacincaptad pegol EM, avacincaptad pegol EOM, and sham treatment groups, respectively. Serious ocular TEAEs occurred in slightly higher proportions in avacincaptad pegol arm (26.7%) compared to sham arm (23%) and was comparable between dosing regimens for avacincaptad pegol groups (26.0% in EM arm and 26.9 in EOM arm). Serious TEAEs causing permanently discontinued study drug were reported in low proportions and with comparable incidences in avacincaptad pegol 2 mg EM arm (3.1%) and in sham arm (3.0%) while being lower in avacincaptad pegol 2 mg EOM arm (1.1%). Serious non-ocular TEAEs were reported in slightly higher incidence in the avacincaptad pegol 2 EOM arm (26.9%) while comparable between avacincaptad pegol 2 mg EM arm (20.8%) and sham arm (20.7%). A lower incidence of serious non-ocular TEAEs leading to permanently discontinued study drug were observed in avacincaptad pegol arm (2.1% in EM arm and 1.1% in EOM arm) compared to sham arm (3.0). Similar trends were seen for TEAEs leading to permanently discontinued study drug (4.9% in avacincaptad pegol 2 mg group and 4.1% in sham arm). TEAEs leading to death occurred in low proportions 1.8% in avacincaptad pegol group vs 2.3% in sham group.

Table 31: Summary of TEAEs – Month 24

	Re-Rand Analysis Set			Safety Analysis Set	
	Avacincaptad Pegol 2 mg EM N=96	Avacincaptad Pegol 2 mg EOM N=93	Sham N=203	Avacincaptad Pegol 2 mg N=225	Sham N=222
Number of patients (%) with at least 1:					
TEAE	89 (92.7)	89 (95.7)	167 (82.3)	208 (92.4)	184 (82.9)
TEAE related to injection procedure	37 (38.5)	31 (33.3)	41 (20.2)	84 (37.3)	47 (21.2)
TEAE related to avacincaptad pegol/sham	5 (5.2)	2 (2.2)	2 (1.0)	7 (3.1)	2 (0.9)
Ocular TEAE (SE)	67 (69.8)	60 (64.5)	99 (48.8)	144 (64.0)	107 (48.2)
Ocular TEAE related to injection procedure (SE)	37 (38.5)	31 (33.3)	41 (20.2)	83 (36.9)	47 (21.2)
Ocular TEAE related to avacincaptad pegol/sham (SE)	5 (5.2)	2 (2.2)	2 (1.0)	7 (3.1)	2 (0.9)
Serious TEAE	25 (26.0)	25 (26.9)	44 (21.7)	60 (26.7)	51 (23.0)
Serious ocular TEAE (SE)	3 (3.1)	1 (1.1)	2 (1.0)	4 (1.8)	2 (0.9)
Severe TEAE	21 (21.9)	24 (25.8)	35 (17.2)	54 (24.0)	41 (18.5)
Severe ocular TEAE (SE)	7 (7.3)	3 (3.2)	2 (1.0)	11 (4.9)	2 (0.9)
TEAE leading to study drug discontinuation*	3 (3.1)	2 (2.2)	7 (3.4)	11 (4.9)	9 (4.1)
Ocular TEAE leading to study drug discontinuation (SE)	1 (1.0)	0	0	4 (1.8)	0
TEAE leading to death	1 (1.0)	1 (1.1)	5 (2.5)	4 (1.8)	5 (2.3)

Source: [Post-text Table 14.3.2.1a](#) and [Table 14.3.2.1b](#)

AE = adverse event; CNV = choroidal neovascularization; CRF = case report form; EM = every month; EOM = every other month; Re-Rand = re-randomized; SE = study eye; TEAE = treatment-emergent adverse event.

Note: TEAEs are AEs occurring after the first injection on Day 1 up to 30 days after the last dose of study drug. However, all occurrences of CNV are collected as TEAEs, even if the last study visit occurred more than 30 days after the last dose of the study drug. See [Section 9.5.1.2.1.1](#) for specific details on collection and reporting methods and timing for Year 2 AEs.

* TEAEs leading to study drug discontinuation = TEAEs leading to study discontinuation per CRF completion guidance.

Ocular TEAEs

Table 32: Ocular TEAEs ≥ 1% of patients, at month 12 (safety population)

Number of Patients (%)	Pooled Pivotal Registration Studies (OPH2003 and ISEE2008)	
	Avacincaptad Pegol 2 mg N=292	Sham N=332
Conjunctival haemorrhage	37 (12.7%)	30 (9.0%)
Intraocular pressure increased	25 (8.6%)	3 (0.9%)
Choroidal neovascularisation	21 (7.2%)	12 (3.6%)
Conjunctival hyperaemia	15 (5.1%)	17 (5.1%)
Punctate keratitis	15 (5.1%)	22 (6.6%)
Eye pain	11 (3.8%)	9 (2.7%)
Vitreous detachment	9 (3.1%)	11 (3.3%)
Dry eye	8 (2.7%)	10 (3.0%)
Visual impairment	7 (2.4%)	4 (1.2%)
Vision blurred	7 (2.4%)	4 (1.2%)
Vitreous floaters	7 (2.4%)	2 (0.6%)
Cataract	6 (2.1%)	8 (2.4%)
Visual acuity reduced transiently	6 (2.1%)	2 (0.6%)
Blepharitis	6 (2.1%)	1 (0.3%)
Eye irritation	5 (1.7%)	9 (2.7%)
Conjunctival oedema	5 (1.7%)	5 (1.5%)
Ocular hypertension	5 (1.7%)	0
Retinal haemorrhage	4 (1.4%)	7 (2.1%)
Visual acuity reduced	4 (1.4%)	7 (2.1%)
Corneal abrasion	4 (1.4%)	3 (0.9%)
Keratitis	4 (1.4%)	1 (0.3%)
Eye pruritus	3 (1.0%)	2 (0.6%)
Blindness transient	3 (1.0%)	0
Lacrimation increased	3 (1.0%)	6 (1.8%)
Ocular hyperaemia	1 (0.3%)	4 (1.2%)

Source: ISS Table 14.3.3.1.1.1.C1, M.5.3.5.3

ISS = Integrated Summary of Safety; TEAE = treatment-emergent adverse event

The most reported SOC for ocular TEAE in the study eye consisted of "Eye disorders" which was in higher incidence in the avacincaptad pegol groups (47,9% in the 2 mg and 62,7% in the 4 mg) compared to sham (35,2%). The most reported PT with higher incidence in the avacincaptad pegol group were Intraocular pressure increased (19.3% in 4 mg, 8.6% in 2 mg and 0.9% in sham), Conjunctival haemorrhage (12,7% in 2 mg vs 9% in sham), Choroidal neovascularisation (7,2% in 2 mg and 3,6% in sham), Eye pain (higher in 4 mg 7,2 % vs 3,8 % in 2 mg and 2,7% in sham), Vision blurred (2,4% in avacincaptad pegol arms vs 1,2% in sham), Blepharitis (2,1% in 2 mg, 3,6% in 4 mg and 0,3% in sham), Vitreous floaters (2,4% on 2 mg vs 0,6% in sham) and visual impairment (2,4% in 2 mg vs 3,6% in 4 mg vs 1,2% in sham). Eye pain, conjunctival haemorrhage, vitreous floaters and IOP increase are AEs associated to IVT injection procedure and commonly reported in this type of CT. IOP increased was reported in much higher incidence in the avacincaptad pegol 2 mg (8,6%) and 4 mg (19,3%) than sham (0,3%). The higher incidence of IOP increase in the 4 mg can be explained due to the difference in volume of IVT injection (100 µL for 2 mg and 200 µL total for 4 mg). Up to Month 18 (OPH2003), similar tendencies could be observed.

Ocular TEAEs in the study eye were assessed as study drug related in 4 cases of CNV (1,4%) in the 2 mg group vs 2 cases in the sham group. Ocular TEAE in the study eye assessed as related to avacincaptad pegol were for the majority IVT injection procedure-related (20,2% in sham vs 22,4% in 2 mg vs 51,8% in 4 mg) and consisted mainly of IOP (7,2% in 2 mg vs 0,3% in sham), Conjunctival haemorrhage (12% in 2 mg vs 8,7% in sham) and Eye pain (3,1% in 2 mg vs 2,4% in sham). Other TEAE were reported in similar proportions between 2 mg and sham arms or in higher proportion in sham. Higher incidence were seen in the avacincaptad pegol 4 mg arm for all ocular TEAEs related to injection procedure.

Ocular TEAE were mainly moderate (11% in 2 mg vs 10,2% in sham) or mild (36,7% in 2 mg vs 25,6% in sham) in severity and severe ocular TEAEs were slightly more reported in 2 mg arm (2,4% vs 0,6% in sham). In the avacincaptad pegol 2 mg arm, Choroidal neovascularisation, VA reduced transiently, and IOP increased were each reported as severe ocular TEAEs for two patients (0.7%) each. Severe ocular TEAEs of retinal artery occlusion (transient) were reported for study OPH2003 in two patients (one in 2 mg arm and one in 4 mg arm). Up to month 18, 2 additional severe events in the avacincaptad pegol arm were reported at month 18, one case of optic ischemic neuropathy and one case of nAMD. None were assessed as related to avacincaptad pegol.

Up to month 24, ocular TEAE in the study eye occurred in 69.8% of the patients in the avacincaptad pegol 2 mg EM group and 64.5% in the avacincaptad pegol 2 mg EOM group compared to 48.8% in the sham group. The most reported PT in the study eye were consistent with data up to month 12 and consisted of Intraocular pressure increased (14.6% in avacincaptad pegol EM arm, 11.8% in EOM and 1.0% in sham), Conjunctival haemorrhage (17.7% in EM; 17.2% in EOM and 7.4% in sham), Choroidal neovascularisation (16.7% in EM arm, 9.7% in EOM and 9.9% in sham), Punctate keratitis (9.4% in EM arm, 11.8% in EOM and 5.9% in sham), Cataract (9.4% in EM arm, 5.4% in EOM and 6.9% in sham), Conjunctival hyperaemia (8.3% in EM arm, 4.3% in EOM and 5.9% in sham), vitreous detachment (6.3% in EM arm, 4.3% in EOM and 3.9% in sham), retinal haemorrhage (3.1% in EM arm, 6.5% in EOM and 3.4% in sham) and visual acuity reduced (1.0% in EM arm, 5.4% in EOM and 3.0% in sham). Over the entire study, the majority of ocular AEs were mild or moderate in severity in all treatment groups. Severe ocular TEAEs in the study eye occurred in eleven patients (4.9%) in the avacincaptad pegol group (7.3% in EM, 3.2% in EOM) and 2 patients (1.0%) in the sham group. Furthermore, 6 of these patients who received avacincaptad pegol had 16 events that were considered related to injection procedure: IOP increased (8 events); blindness transient (3 events); VA reduced transiently (2 events); eye pain, culture-positive endophthalmitis, and vitreous detachment (1 event each). In Year 2, 5 (5.2%) patients in the avacincaptad pegol EM, 1 (1.1%) patient in the avacincaptad pegol EOM, and 1 (0.5%) patient in the sham group experienced severe ocular TEAEs in the study eye. Except for one patient in the avacincaptad pegol EM and one patient in the sham group, all of these events were judged by the investigator as related to the injection procedure.

A higher proportions of ocular TEAEs in the study eye assessed as related to study administration injection procedure were reported in the avacincaptad pegol 2 mg group 36.9% (38.5% in EM and 33.3% in EOM) compared to sham (21.2%). The most commonly reported ($\geq 2\%$ of patients in any treatment group) ocular TEAEs in the study eye through Month 24 that were judged related to the injection procedure were conjunctival haemorrhage (17.7% EM, 12.9% EOM, 6.9% sham), IOP increased (12.5% EM, 10.8% EOM, 0% sham), conjunctival hyperaemia (7.3% EM, 4.3% EOM, 5.4% sham), punctate keratitis (4.2% EM, 7.5% EOM, 3.9% sham), eye pain (4.2% EM, 5.4% EOM, 3.0% sham) and eye irritation (2.1% EM, 1.1% EOM, 3.4% sham). These events are expected secondary to IVT injection procedures. Conjunctival haemorrhage and IOP increased were more frequent in the avacincaptad pegol group compared to the sham group which is expected due to the insertion of the IVT needle in the avacincaptad pegol group. In Year 2, the most commonly reported ocular TEAEs in the study eye ($\geq 2\%$ of patients in any treatment group) were conjunctival haemorrhage (5.9%), IOP increased (3.3%), and punctate keratitis (2.6%). Conjunctival haemorrhage and IOP increased were more frequently reported

in the avacincaptad pegol EM group (12.5% and 8.3%, respectively) compared to avacincaptad pegol EOM (6.5% and 5.4%, respectively).

Ocular TEAEs in the study eye assessed as related to study drug occurred in low proportions. There were 9 (2.0%) patients across treatment groups with ocular TEAEs related to the study drug through Month 24: 7 patients (3.1%) in the avacincaptad pegol group (overall) and 2 patients (0.9%) in the sham group, all of whom experienced TEAEs of CNV. One of these 2 patients in the sham group also experienced a TEAE of retinal haemorrhage that was considered related to the study drug. Of the 7 patients experiencing CNV in the avacincaptad pegol treatment group during the entire study, 5 (5.2%) patients received avacincaptad pegol EM and 2 (2.2%) patients received avacincaptad pegol EOM in Year 2. In Year 2, there were 3 (0.8%) patients in total with ocular TEAEs related to the study drug (CNV): 2 patients (2.1%) in the avacincaptad pegol EM and 1 patient (1.1%) in the avacincaptad pegol EOM group.

Table 33: Ocular TEAEs occurring in $\geq 2\%$ of patients by SOC and PT (All causalities) – study eye – month 24

Number of Patients (%) System Organ Class Preferred Term	Re-Rand Analysis Set			Safety Analysis Set	
	Avacincaptad Pegol 2 mg EM N=96	Avacincaptad Pegol 2 mg EOM N=93	Sham N=203	Avacincaptad Pegol 2 mg N=225	Sham N=222
Patients (%) with at least 1 TEAE	67 (69.8)	60 (64.5)	99 (48.8)	144 (64.0)	107 (48.2)
Eye disorders	62 (64.6)	58 (62.4)	95 (46.8)	135 (60.0)	103 (46.4)
Conjunctival hemorrhage	17 (17.7)	16 (17.2)	15 (7.4)	38 (16.9)	20 (9.0)
CNV ^a	16 (16.7)	9 (9.7)	20 (9.9)	26 (11.6)	20 (9.0)
Punctate keratitis	9 (9.4)	11 (11.8)	12 (5.9)	20 (8.9)	16 (7.2)
Conjunctival hyperemia	8 (8.3)	4 (4.3)	12 (5.9)	14 (6.2)	15 (6.8)
Cataract	9 (9.4)	5 (5.4)	14 (6.9)	14 (6.2)	14 (6.3)
Dry eye	6 (6.3)	5 (5.4)	13 (6.4)	11 (4.9)	14 (6.3)
Eye pain	6 (6.3)	5 (5.4)	7 (3.4)	15 (6.7)	8 (3.6)
Vitreous detachment	6 (6.3)	4 (4.3)	8 (3.9)	12 (5.3)	8 (3.6)
Retinal hemorrhage	3 (3.1)	6 (6.5)	7 (3.4)	9 (4.0)	7 (3.2)
Eye irritation	4 (4.2)	1 (1.1)	9 (4.4)	6 (2.7)	9 (4.1)
Visual acuity reduced	1 (1.0)	5 (5.4)	6 (3.0)	6 (2.7)	7 (3.2)
Visual impairment	3 (3.1)	4 (4.3)	3 (1.5)	9 (4.0)	3 (1.4)
Vision blurred	5 (5.2)	3 (3.2)	2 (1.0)	8 (3.6)	2 (0.9)
Vitreous floaters	5 (5.2)	1 (1.1)	1 (0.5)	8 (3.6)	1 (0.5)
Blepharitis	4 (4.2)	3 (3.2)	1 (0.5)	7 (3.1)	1 (0.5)
Lacrimation increased	1 (1.0)	0	5 (2.5)	2 (0.9)	6 (2.7)
Ocular hypertension	4 (4.2)	3 (3.2)	0	8 (3.6)	0
Posterior capsule opacification	1 (1.0)	2 (2.2)	5 (2.5)	3 (1.3)	5 (2.3)
Dry age-related macular degeneration	1 (1.0)	2 (2.2)	4 (2.0)	4 (1.8)	4 (1.8)
Visual acuity reduced transiently	5 (5.2)	1 (1.1)	1 (0.5)	6 (2.7)	1 (0.5)
Keratitis	2 (2.1)	1 (1.1)	2 (1.0)	3 (1.3)	2 (0.9)

Blindness transient	2 (2.1)	2 (2.2)	0	5 (2.2)	0
Meibomian gland dysfunction	2 (2.1)	0	2 (1.0)	2 (0.9)	2 (0.9)
Retinal degeneration	2 (2.1)	1 (1.1)	1 (0.5)	3 (1.3)	1 (0.5)
Eye pruritis	0	2 (2.2)	1 (0.5)	3 (1.3)	1 (0.5)
Retinal cyst	2 (2.1)	0	1 (0.5)	2 (0.9)	1 (0.5)
Foreign body sensation in eyes	2 (2.1)	0	0	2 (0.9)	0
Conjunctivitis allergic	0	2 (2.2)	0	2 (0.9)	0
Infections and Infestations	5 (5.2)	2 (2.2)	7 (3.4)	7 (3.1)	7 (3.2)
Conjunctivitis	2 (2.1)	1 (1.1)	3 (1.5)	3 (1.3)	3 (1.4)
Conjunctivitis viral	2 (2.1)	1 (1.1)	1 (0.5)	3 (1.3)	1 (0.5)
Hordeolum	0	0	4 (2.0)	0	4 (1.8)
Injury, poisoning and procedural complications	5 (5.2)	1 (1.1)	0	8 (3.6)	1 (0.5)
Corneal abrasion	3 (3.1)	1 (1.1)	0	4 (1.8)	1 (0.5)
Investigations	14 (14.6)	11 (11.8)	2 (1.0)	30 (13.3)	2 (0.9)
IOP increased	14 (14.6)	11 (11.8)	2 (1.0)	30 (13.3)	2 (0.9)

Non-Ocular TEAEs

Incidences of non-ocular TEAEs were comparable between arms (56,2% in 2 mg vs 55,7% in sham and 54,2% in 4 mg) with the most reported SOC being Infections and infestations (25,7% in 2 mg vs 21,4% in sham and 28,9% in 4 mg), Musculoskeletal and connective tissue disorders (9,9% in 2 mg vs 10,8% in sham and 9,6% in 4 mg) and Injury, poisoning and procedural complications (14,7% in 2 mg vs 13,6% in sham and 13,3% in 4 mg). Most reported PT in 2 mg were urinary tract infection, fall, nasopharyngitis with comparable incidences between 2 mg arm and sham and which are consistent with the study population. Up to Month 18, similar tendencies could be observed.

No non-ocular TEAEs were assessed as related to study drug or sham. Non-ocular TEAEs assessed as related to IVT injection-procedure were low (1% in 2 mg vs 0,3% in sham) and consisted of application site irritation (sham group), drug hypersensitivity, contusion, and headache (2 mg group). Non-ocular TEAEs were mainly mild (25,7%) to moderate (19,5%) in the 2 mg arm and comparable proportions of severe non-ocular TEAEs were reported between arms (10,5% in sham vs 11% in 2 mg arm). Severe non-ocular TEAEs were reported in single patients for the majority except for fall, upper GI haemorrhage, pneumonia and pulmonary embolism. None were assessed as related to avacincaptad pegol.

Table 34: Non-ocular TEAEs ≥ 1% of patients, at month 12 (safety population)

Number of Patients (%)	Pooled Pivotal Registration Studies (OPH2003 and ISEE2008)	
	Avacincaptad Pegol 2 mg N=292	Sham N=332
Fall	20 (6.8%)	24 (7.2%)
Urinary tract infection	18 (6.2%)	21 (6.3%)
Hypertension	11 (3.8%)	10 (3.0%)
Nasopharyngitis	10 (3.4%)	10 (3.0%)
COVID-19	9 (3.1%)	9 (2.7%)
Atrial fibrillation	8 (2.7%)	6 (1.8%)
Back pain	7 (2.4%)	9 (2.7%)
Pneumonia	7 (2.4%)	3 (0.9%)
Headache	6 (2.1%)	10 (3.0%)
Basal cell carcinoma	6 (2.1%)	6 (1.8%)
Influenza	6 (2.1%)	3 (0.9%)
Oedema peripheral	6 (2.1%)	0
Contusion	5 (1.7%)	7 (2.1%)
Sinusitis	5 (1.7%)	6 (1.8%)
Skin laceration	5 (1.7%)	5 (1.5%)
Tooth infection	5 (1.7%)	3 (0.9%)
Arthralgia	5 (1.7%)	1 (0.3%)
Osteoarthritis	5 (1.7%)	2 (0.6%)
Cystitis	4 (1.4%)	5 (1.5%)
Osteoporosis	4 (1.4%)	4 (1.2%)
Upper respiratory tract infection	4 (1.4%)	3 (0.9%)
Diarrhoea	4 (1.4%)	3 (0.9%)
Bronchitis	3 (1.0%)	7 (2.1%)
Dizziness	3 (1.0%)	5 (1.5%)
Rhinitis	3 (1.0%)	3 (0.9%)
Syncope	3 (1.0%)	3 (0.9%)
Cholelithiasis	3 (1.0%)	2 (0.6%)
Ligament sprain	3 (1.0%)	2 (0.6%)
Skin abrasion	3 (1.0%)	2 (0.6%)
Sciatica	3 (1.0%)	2 (0.6%)
Cardiac failure congestive	3 (1.0%)	1 (0.3%)
Cellulitis	3 (1.0%)	1 (0.3%)
Ear infection	3 (1.0%)	1 (0.3%)
Gastroenteritis	3 (1.0%)	1 (0.3%)
Pulmonary embolism	3 (1.0%)	1 (0.3%)
Atrial flutter	3 (1.0%)	0
Coronary artery disease	2 (0.7%)	4 (1.2%)
Herpes zoster	1 (0.3%)	6 (1.8%)
Chronic obstructive pulmonary disease	1 (0.3%)	6 (1.8%)
Mitral valve incompetence	0	4 (1.2%)
Squamous cell carcinoma	0	4 (1.2%)
Transient ischaemic attack	0	4 (1.2%)

Source: ISS Table 14.3.3.2.1.C1, M.5.3.5.3

ISS = Integrated Summary of Safety; TEAE = treatment-emergent adverse event

Up to month 24, non-ocular TEAEs occurred in 74.0% of the patients in the avacincaptad pegol 2 mg EM group and 84.9% in the avacincaptad pegol 2 mg EOM group compared to 71.4% in the sham group. The most reported SOC were Infections and infestations (42.7% EM, 45.2% EOM and 41.9% sham), Injury, poisoning and procedural complications (21.9% in EM, 19.0% in EOM and 21.7% in sham), Cardiac disorders (19.4% EOM vs 13.5% EM vs 14.3% sham) and Musculoskeletal and connective tissue disorders (21.9% EOM vs 11.8% EM vs 17.2% sham). Some discrepancies could be observed for reported non-ocular TEAEs on a SOC level but they were consistent with the reported incidences of non-ocular medical history between the two different dosing regimens (EM and EOM) and compared to sham.

Up to Year 2, non-ocular AEs related to the injection procedure were few. Two patients across all treatment groups had a non-ocular event related to the injection procedure with none related to avacincaptad pegol/sham. Furthermore, no non-ocular TEAEs were reported to be related to the injection procedure, avacincaptad pegol, or sham at Month 24.

During the entire study, a total of 43 patients (19.1%) in the avacincaptad pegol group (overall) and 39 patients (17.6%) in the sham group experienced at least 1 severe non-ocular TEAE overall. The frequency of severe non-ocular TEAEs was higher in the avacincaptad pegol EOM (22.6%) than in the EM group (14.6%). No severe non-ocular TEAE was reported to be related to the injection procedure, avacincaptad pegol, or sham.

Table 35: Non-ocular TEAE by SOC AND PT (all causalities) occurring in ≥2% patients at month 24

Number of Patients (%) System Organ Class Preferred Term	Re-Rand Analysis Set			Safety Analysis Set	
	Avacincaptad Pegol 2 mg EM N=96	Avacincaptad Pegol 2 mg EOM N=93	Sham N=203	Avacincaptad Pegol 2 mg N=225	Sham N=222
Number of patients (%) with at least 1 non-ocular TEAE	71 (74.0)	79 (84.9)	145 (71.4)	172 (76.4)	160 (72.1)
Cardiac disorders	13 (13.5)	18 (19.4)	29 (14.3)	36 (16.0)	32 (14.4)
Atrial fibrillation	3 (3.1)	3 (3.2)	8 (3.9)	9 (4.0)	9 (4.1)
Ventricular extrasystoles	3 (3.1)	2 (2.2)	1 (0.5)	5 (2.2)	1 (0.5)
Coronary artery disease	1 (1.0)	2 (2.2)	3 (1.5)	3 (1.3)	3 (1.4)
Atrioventricular block first degree	1 (1.0)	2 (2.2)	2 (1.0)	4 (1.8)	2 (0.9)
Atrial flutter	1 (1.0)	2 (2.2)	1 (0.5)	3 (1.3)	1 (0.5)
Bundle branch block right	1 (1.0)	2 (2.2)	1 (0.5)	3 (1.3)	1 (0.5)
Cardiac failure congestive	1 (1.0)	2 (2.2)	0	4 (1.8)	1 (0.5)
Sinus bradycardia	0	2 (2.2)	0	2 (0.9)	0
Ear and labyrinth disorders	2 (2.1)	2 (2.2)	6 (3.0)	4 (1.8)	7 (3.2)
Vertigo	1 (1.0)	2 (2.2)	3 (1.5)	3 (1.3)	4 (1.8)
Gastrointestinal disorders	15 (15.6)	11 (11.8)	21 (10.3)	27 (12.0)	22 (9.9)
Diarrhoea	3 (3.1)	3 (3.2)	1 (0.5)	6 (2.7)	1 (0.5)
Constipation	1 (1.0)	0	4 (2.0)	1 (0.4)	4 (1.8)
Abdominal pain	0	2 (2.2)	1 (0.5)	2 (0.9)	1 (0.5)
Inguinal hernia	2 (2.1)	1 (1.1)	0	3 (1.3)	0
Toothache	2 (2.1)	0	1 (0.5)	2 (0.9)	1 (0.5)
Diverticulum intestinal	2 (2.1)	0	2 (1.1)	2 (0.9)	0
General disorders and administration site conditions	4 (4.2)	10 (10.8)	15 (7.4)	14 (6.2)	16 (7.2)
Oedema peripheral	0	7 (7.5)	1 (0.5)	7 (3.1)	1 (0.5)
Fatigue	2 (2.1)	0	2 (1.0)	2 (0.9)	2 (0.9)
Chest pain	0	2 (2.2)	1 (0.5)	2 (0.9)	1 (0.5)
Infections and infestations	41 (42.7)	42 (45.2)	85 (41.9)	92 (40.9)	89 (40.1)
COVID-19	15 (15.6)	14 (15.1)	36 (17.7)	32 (14.2)	36 (16.2)
Urinary tract infection	10 (10.4)	6 (6.5)	25 (12.3)	19 (8.4)	27 (12.2)
Nasopharyngitis	5 (5.2)	7 (7.5)	9 (4.4)	13 (5.8)	9 (4.1)

Cystitis	4 (4.2)	2 (2.2)	6 (3.0)	6 (2.7)	6 (2.7)
Pneumonia	3 (3.1)	4 (4.3)	2 (1.0)	8 (3.6)	3 (1.4)
Sinusitis	2 (2.1)	5 (5.4)	4 (2.0)	7 (3.1)	4 (1.8)
Herpes zoster	1 (1.0)	1 (1.1)	7 (3.4)	2 (0.9)	7 (3.2)
Influenza	1 (1.0)	1 (1.1)	6 (3.0)	3 (1.3)	6 (2.7)
Bronchitis	2 (2.1)	3 (3.2)	3 (1.5)	5 (2.2)	3 (1.4)
Tooth infection	4 (4.2)	1 (1.1)	3 (1.5)	5 (2.2)	3 (1.4)
Diverticulitis	3 (3.1)	1 (1.1)	3 (1.5)	4 (1.8)	4 (1.8)
Upper respiratory tract infection	2 (2.1)	2 (2.2)	3 (1.5)	4 (1.8)	3 (1.4)
Gastroenteritis	2 (2.1)	1 (1.1)	1 (0.5)	4 (1.8)	1 (0.5)
Asymptomatic COVID-19	0	2 (2.2)	0	2 (0.9)	0
Clostridium difficile	0	2 (2.2)	0	0	2 (0.9)
Injury, poisoning and procedural complications	21 (21.9)	27 (19.0)	44 (21.7)	55 (24.4)	46 (20.7)
Fall	12 (12.5)	13 (14.0)	24 (11.8)	30 (13.3)	26 (11.7)
Contusion	2 (2.1)	6 (6.5)	5 (2.5)	8 (3.6)	6 (2.7)
Skin laceration	0	4 (4.3)	7 (3.4)	4 (1.8)	7 (3.2)
Skin abrasion	2 (2.1)	3 (3.2)	2 (1.0)	5 (2.2)	2 (0.9)
Ligament sprain	0	3 (3.2)	2 (1.0)	3 (1.3)	2 (0.9)
Animal bite	2 (2.1)	0	2 (1.0)	2 (0.9)	2 (0.9)
Facial bones fracture	0	2 (2.2)	1 (0.5)	2 (0.9)	1 (0.5)
Head injury	2 (2.1)	0	1 (0.5)	2 (0.9)	1 (0.5)
Wrist fracture	0	2 (2.2)	1 (0.5)	2 (0.9)	1 (0.5)
Investigations	12 (12.5)	10 (10.8)	17 (8.4)	23 (10.2)	17 (7.7)
Blood pressure increased	0	3 (3.2)	2 (1.0)	3 (1.3)	2 (0.9)
SARS-CoV-2 test positive	1 (1.0)	2 (2.2)	2 (1.0)	3 (1.3)	2 (0.9)
Blood urea increased	1 (1.0)	2 (2.2)	1 (0.5)	3 (1.3)	1 (0.5)
Gamma-glutamyltransferase increased	2 (2.1)	0	2 (1.0)	2 (0.9)	2 (0.9)
Blood creatinine increased	0	2 (2.2)	1 (0.5)	2 (0.9)	1 (0.5)
Blood potassium increased	2 (2.1)	0	1 (0.5)	2 (0.9)	1 (0.5)
Metabolism and nutrition disorders	9 (9.4)	10 (10.8)	13 (6.4)	19 (8.4)	14 (6.3)
Diabetes mellitus	2 (2.1)	1 (1.1)	3 (1.5)	3 (1.3)	3 (1.4)
Gout	1 (1.0)	2 (2.2)	1 (0.5)	3 (1.3)	1 (0.5)
Hypercholesterolaemia	0	2 (2.2)	2 (1.0)	2 (0.9)	3 (1.4)
Hyponatraemia	1 (1.0)	2 (2.2)	0	3 (1.3)	0
Vitamin D deficiency	2 (2.1)	0	1 (0.5)	2 (0.9)	1 (0.5)
Musculoskeletal and connective tissue disorders	21 (21.9)	11 (11.8)	35 (17.2)	35 (15.6)	35 (15.8)

Back pain	4 (4.2)	4 (4.3)	10 (4.9)	8 (3.6)	14 (4.5)
Osteoarthritis	4 (4.2)	2 (2.2)	6 (3.0)	7 (3.1)	6 (2.7)
Osteoporosis	4 (4.2)	2 (2.2)	3 (1.5)	7 (3.1)	3 (1.4)
Arthralgia	2 (2.1)	1 (1.1)	2 (1.0)	4 (1.8)	2 (0.9)
Spinal stenosis	2 (2.1)	1 (1.1)	2 (1.0)	3 (1.3)	2 (0.9)
Muscle spasms	2 (2.1)	0	1 (0.5)	2 (0.9)	1 (0.5)
Rotator cuff syndrome	3 (3.1)	0	0	3 (1.3)	0
Osteopenia	2 (2.1)	0	0	2 (0.9)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	9 (9.4)	6 (6.5)	19 (9.4)	16 (7.1)	23 (10.4)
Basal cell carcinoma	3 (3.1)	4 (4.3)	4 (2.0)	7 (3.1)	5 (2.3)
Squamous cell carcinoma	1 (1.0)	1 (1.1)	5 (2.5)	2 (0.9)	5 (2.3)
Breast cancer	2 (2.1)	0	0	2 (0.9)	0
Nervous system disorders	7 (7.3)	15 (16.1)	41 (20.2)	25 (11.1)	46 (20.7)
Headache	2 (2.1)	2 (2.2)	10 (4.9)	6 (2.7)	12 (5.4)
Sciatica	3 (3.1)	2 (2.2)	7 (3.4)	5 (2.2)	7 (3.2)
Dizziness	0	3 (3.2)	4 (2.0)	4 (1.8)	5 (2.3)
Syncope	0	3 (3.2)	4 (2.0)	3 (1.3)	4 (1.8)
Cerebrovascular accident	0	2 (2.2)	4 (2.0)	2 (0.9)	4 (1.8)
Restless legs syndrome	0	2 (2.2)	1 (0.5)	2 (0.9)	1 (0.5)
Psychiatric disorders	3 (3.1)	4 (4.3)	3 (1.5)	9 (4.0)	4 (1.8)
Depression	0	2 (2.2)	0	2 (0.9)	0
Renal and urinary disorders	7 (7.3)	7 (7.5)	8 (3.9)	15 (6.7)	10 (4.5)
Chronic kidney disease	0	2 (2.2)	2 (1.0)	2 (0.9)	3 (1.4)
Nephrolithiasis	0	2 (2.2)	1 (0.5)	2 (0.9)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	8 (8.3)	12 (12.9)	17 (8.4)	22 (9.8)	19 (8.6)
Chronic obstructive pulmonary disease	2 (2.1)	3 (3.2)	4 (2.0)	5 (2.2)	4 (1.8)
Cough	1 (1.0)	3 (3.2)	2 (1.0)	4 (1.8)	2 (0.9)
Skin and subcutaneous tissue disorders	7 (7.3)	5 (5.4)	14 (6.9)	12 (5.3)	14 (6.3)
Actinic keratosis	2 (2.1)	0	2 (1.0)	2 (0.9)	2 (0.9)
Vascular disorders	11 (11.5)	14 (15.1)	20 (9.9)	28 (12.4)	24 (10.8)
Hypertension	7 (7.3)	8 (8.6)	12 (5.9)	17 (7.6)	15 (6.8)
Haematoma	2 (2.1)	1 (1.1)	1 (0.5)	3 (1.3)	1 (0.5)

Source: Post-text Table 14.3.6.6a and 14.3.6.6b

3.3.7.3. Serious adverse events, deaths, and other significant events

Table 36: Serious ocular TEAEs, study eye, in studies OPH2003 and ISEE2008 at month 12 (safety population)

Number of Patients (%)	OPH2003		ISEE2008	
	Avacincaptad Pegol 2 mg (combined) N=67	Sham (combined) N=110	Avacincaptad Pegol 2 mg N=225	Sham N=222
Serious ocular TEAEs, study eye	0	0	2 (0.9%)	2 (0.9%)
Choroidal neovascularisation	0	0	2 (0.9%)	1 (0.5%)
Visual acuity reduced	0	0	0	1 (0.5%)
Visual acuity reduced transiently	0	0	0	1 (0.5%)

Sources: OPH2003 CSR Section 12.3.3.3.1.2, ISEE2008 CSR Section 12.3.3.2.2, both M.5.3.5.1
CSR = clinical study report; TEAE = treatment-emergent adverse event

Twelve deaths have been reported across the eight clinical studies performed with avacincaptad pegol. Six of these deaths were not considered treatment-emergent as the events occurred beyond 30 days after the last dose of study drug. Of these, two deaths occurred in patients receiving sham, two in

patients receiving avacincaptad pegol (0.3 mg: bacteraemia; 1 mg: oesophageal varices rupture and haemorrhage) and two occurred in studies that are still masked. None of the deaths that occurred in patients receiving avacincaptad pegol were considered related to the study drug or procedure by the investigator.

Regarding the six deaths that were considered treatment-emergent, four occurred in cohort 1, one in study OPH2003 between month 12 and 18 and one in study OPH2005. Four of the six TEAEs leading to death occurred in patients that had received avacincaptad pegol 2 mg and one in a patient that had received avacincaptad pegol 4 mg; the remaining death occurred in study OPH2005. The causes of death were pneumonia (2 patients), road traffic accident (2 patients), cerebral infarction and neurogenic shock (one patient each).

Sixteen deaths occurred during the study up to Month 24 of which nine of the deaths were due to TEAEs. Two additional deaths were reported after the Month 24 visit via the safety follow-up of the SAEs. Four deaths occurred in the avacincaptad pegol group due to TEAE: one due to chronic cardiac failure, one due to biliary obstruction, one due to pneumonia, and one other due to neurogenic shock. Five deaths occurred in the sham group due to TEAE: 1 due to cardio-respiratory arrest, one due to COVID-19 and cardiac failure, one due to cerebral infarction and cardiac failure, one due to aortic aneurysm, and the other due to circulatory collapse. None of the deaths were considered related to study drug or injection/sham procedure. Proportions of serious Ocular TEAEs were low and comparable between arms (0,7% in avacincaptad pegol 2 mg and 0,6% in sham) up to month 12. None were reported in the fellow eye. In avacincaptad pegol 2 mg, serious ocular TEAEs consisted of CNV (n=2, one assessed as related to study drug). None were assessed as related to IVT injection-procedure. Up to Month 18 (OPH2003), two serious ocular TEAEs were reported; one case of retinal detachment (4 mg) and one case of optic ischemic neuropathy (2 mg). None were assessed as related to avacincaptad pegol. Ocular SAEs in the study eye at Month 24 were reported in 6 (1.3%) patients in total; 4 [1.8%] patients in avacincaptad pegol 2 mg group (CNV in one patients, endophthalmitis in one patient and device dislocation (posterior displacement of the intraocular lens) in one patient in EM group and CNV in one patient in EOM group) and 2 patients [0.9%] in sham group (Visual acuity reduced in two patients). Of these, 2 patients experienced serious ocular TEAEs in Year 2. Both patients were treated with avacincaptad pegol EM. Two ocular SAEs (one event of retinal haemorrhage and one event of neuromyelitis optica spectrum disorder) were reported in the fellow eye at Year 2.

Proportions of serious non-ocular TEAEs were slightly higher in the sham group (16,6% vs 12,3% in the 2 mg group) up to month 12. The most reported SOC for the 2 mg was Injury, poisoning and procedural complications. Most of the non-ocular serious TEAEs by PT were reported for only one patient each in the 2 mg arm expect Atrial fibrillation, Upper GI haemorrhage, Pneumonia, Fall, Pulmonary embolism and Cellulitis which is generally consistent with the study population. No serious non-ocular TEAEs were assessed as related to avacincaptad pegol. No non-ocular SAEs by PT occurred with a frequency of $\geq 3\%$ in any treatment group at Month 18. Up to Year 2, non-ocular SAEs occurred in 24.4% of patients in the avacincaptad pegol group (overall) and in 22.1% of patients in the sham group. The proportion of patients with at least 1 non-ocular SAE was numerically higher in the avacincaptad pegol EOM group (26.9%) compared to EM (20.8%). Serious non-ocular TEAEs occurred in $\geq 2\%$ in the avacincaptad pegol 2 mg EOM arm and consisted of Chest pain (2.2% n=2 vs 0% in avacincaptad pegol 2 mg EM arm and sham arm; Clostridium difficile infection 2.2% n=2 vs 0 I in avacincaptad pegol 2 mg EM arm and sham arm, Cerebrovascular accident 2.2% n=2 vs 0 in avacincaptad pegol 2 mg EM arm and 2.0% n=4 in sham arm). During the entire study, there were no non-ocular SAEs related to the injection procedure, avacincaptad pegol, or sham.

3.3.7.4. Special Safety Topics and Treatment-Emergent Adverse Events of Special Interest

Overall, between 0% and 10.8 % of the patients in Cohort 1 experienced a TEAEI and less than 1% were assessed as related to study drug. Up to month 12, for Avacincaptad pegol 2 mg group, a total 20.5% of the patient experienced a TEAEI vs 7.5% in the sham group. IOP increased ≥ 30 mmHg and CNV were the most reported with respectively 11.3% (vs 1.2% in sham group) and 7.2% (vs 3.6% in sham group) of the patients being concerned in the avacincaptad pegol 2 mg arm. Up to 18 months, similar tendencies were observed with 32.2% of the patients in Avacincaptad pegol 2 mg arm and 18.1% on the sham group presenting at least 1 TEAEI event. The most reported TEAEIs were IOP increased ≥ 30 mmHg (14.7% vs 1.2% in sham group), CNV (11.6% vs 6.9% in sham group) and BVCA decrease (8.9% vs 11.4% in sham).

Endophthalmitis

No events of endophthalmitis were reported in Cohort 1 (up to Month 12). In study OPH2002 (clinical trial conducted in IPCV), one mild case of endophthalmitis was reported which was assessed as related to IVT injection-procedure. In study ISEE2008, one patient was administered monthly injection of avacincaptad pegol 2 mg in the right eye. Four days after the latest dose of study drug administration on the Month 22 visit, the subject was diagnosed with endophthalmitis in the study eye which was severe. The event was assessed as related to injection procedure. The dose of treatment was not changed and patient was treated for endophthalmitis positive to staphylococcus epidermidis.

Intraocular inflammation

One resolved mild case of vitritis assessed as not related to IVT injection or study drug was reported in Cohort 1 in the avacincaptad pegol 2 mg arm. No cases of retinal vasculitis or retinal occlusive vasculitis were reported. Up to month 18, one mild case of cystoid macular oedema assessed as not related to avacincaptad pegol occurred.

In Cohort 2, six event of mild vitreous haze (n=3 patients) and one mild case of anterior chamber cells trace were assessed as related to IVT injection procedure. None of the TEAEIs were SAE and all events were resolved.

Up to month 24, in study ISEE2008, one event of intraocular inflammation (IOI) was reported in a patient who received avacincaptad pegol 2 mg EM. This was a non-serious event of trace vitreal cells (lasting 13 days), which was moderate in severity and not related to the study drug or the injection procedure. The event resolved, and the patient fully recovered and continued in the study with study drug injections after resolution.

Cataract

In study ISEE2008, up to month 24, similar proportion of phakic patients in the avacincaptad pegol and sham groups overall exhibited a TEAE of the high-level term of "cataract conditions" in the study eye (9.8% and 12.8%, respectively) and between dosing regimen a higher proportion was observed in avacincaptad pegol EM treatment group (13.6%) versus EOM (8.5%). Similar tendencies were observed for the fellow eye. There were no reported events of traumatic cataract.

Increase of IOP ≥ 30 mmHg

Table 37: IOP $\geq$ 30 mmHg – study eye (cohort 1)

	Cohort 1			
	Sham ^a N=332	Avacincaptad pegol 1 mg ^b N=49	Avacincaptad pegol 2 mg ^a N=292	Avacincaptad pegol 4 mg ^c N=83
Number of patients (%)				
Patients with IOP $\geq$ 30 mmHg at any time				
Yes	4 (1.2%)	3 (6.1%)	33 (11.3%)	25 (30.1%)
No	328 (98.8%)	46 (93.9%)	259 (88.7%)	58 (69.9%)
Overall prevalence per 1000 injections ^d	1.09	7.58	11.06	37.59
Incidence over time ^e				
0 – 3 months	3 (0.9%)	1 (2.0%)	12 (4.1%)	10 (12.0%)
>3 – 6 months	0	0	6 (2.2%)	8 (12.1%)
>6 – 9 months	1 (0.3%)	2 (4.3%)	11 (4.4%)	3 (5.8%)
>9 – 12 months	0	0	4 (1.7%)	4 (9.1%)

Source: ISS Table 14.3.3.7.1.C1 (M.5.3.5.3); data for the avacincaptad pegol 0.3 mg group are included in the ISS table

IOP = intraocular pressure

^a Data from Studies OPH2003 and ISEE2008

^b Data from Studies OPH2001 and OPH2003

^c Data from Study OPH2003

^d Prevalence per 1000 injections is defined as the number of patients with the first occurrence of the event multiplied by 1000 and divided by the total number of injections administered up to the first occurrence of the event that is specific to each patient.

^e Incidence is defined as the number of patients with the first occurrence of the event divided by the number of patients at risk of the event in the given time period. A patient is at risk if the patient had an injection in previous and/or current time periods who has not experienced an event in the earlier time periods and has not discontinued from the clinical trial in the previous time period.

Up to month 12, the proportion of patient presenting a transient IOP $\geq$ 30 mmHg was much higher in the avacincaptad pegol 30,1% in 4 mg arm, 11,3% in 2 mg arm and 1,2% in sham. However, it is to be taken into account that in the sham group the sham procedure included the blunt opening of an empty, needleless syringe barrel placed on the conjunctiva in the inferotemporal quadrant of the eyeball to simulate the pressure of an injection. The overall prevalence per 1000 injections were of 37,59 for 4 mg arm 11,06 for 2 mg arm and 1,09 for sham group. Incidences over time were highest at 0 - 3 months and >6 - 9 months for avacincaptad pegol 2 mg arm and at 0-6 month for avacincaptad pegol 4 mg arm. The incidence being three times higher in the avacincaptad pegol can be explained by the 2 IVT injections being administered in the 4 mg arm vs 1 IVT injection in the 2 mg arm.

Patients in the 2 mg and 4 mg arm both had a mean value IOP of 18,2 mmHg after the first injection. Up to month 12, the majority of patient in avacincaptad pegol groups had an IOP $\leq$ 21 mmHg and a change from baseline $\leq$ 5 mmHg after the first injection and $\leq$ 10 mmHg after second injection (4 mg arm). The Mean IOP value change (mmHg) in the study eye were stable up to month 12 and 18 months.

The majority of the events of IOP increased were transient, mild or moderate, assessed as related to IVT injection procedure and resolved on the same day. Paracentesis was required in 3,1 % (2,90 per 1000 injections) of the patient in the 2 mg group and 2,4% (2,50 per 1000 injections) in the 4 mg group.

Table 38: Elevation of IOP requiring surgical intervention – study eye (cohort 1)

	Cohort 1			
	Sham ^a N=332	Avacincaptad pegol 1 mg ^b N=49	Avacincaptad pegol 2 mg ^a N=292	Avacincaptad pegol 4 mg ^c N=83
Number of patients (%)				
Patients with IOP requiring surgical intervention at any time				
Yes	0	1 (2.0%)	9 (3.1%)	2 (2.4%)
No	332 (100%)	48 (98.0%)	283 (96.9%)	81 (97.6%)
Overall prevalence per 1000 injections ^d	0.00	2.49	2.90	2.50
Incidence over time ^e				
0 – 3 months	0	0	4 (1.4%)	1 (1.2%)
>3 – 6 months	0	1 (2.1%)	4 (1.5%)	1 (1.3%)
>6 – 9 months	0	0	1 (0.4%)	0
>9 – 12 months	0	0	0	0

Source: ISS Table 14.3.3.7.3.C1 (M.5.3.5.3); data for the avacincaptad pegol 0.3 mg group are included in the ISS table

IOP = intraocular pressure

^a Data from Studies OPH2003 and ISEE2008

^b Data from Studies OPH2001 and OPH2003

^c Data from Study OPH2003

^d Prevalence per 1000 injections is defined as the number of patients with the first occurrence of the event multiplied by 1000 and divided by the total number of injections administered up to the first occurrence of the event that is specific to each patient.

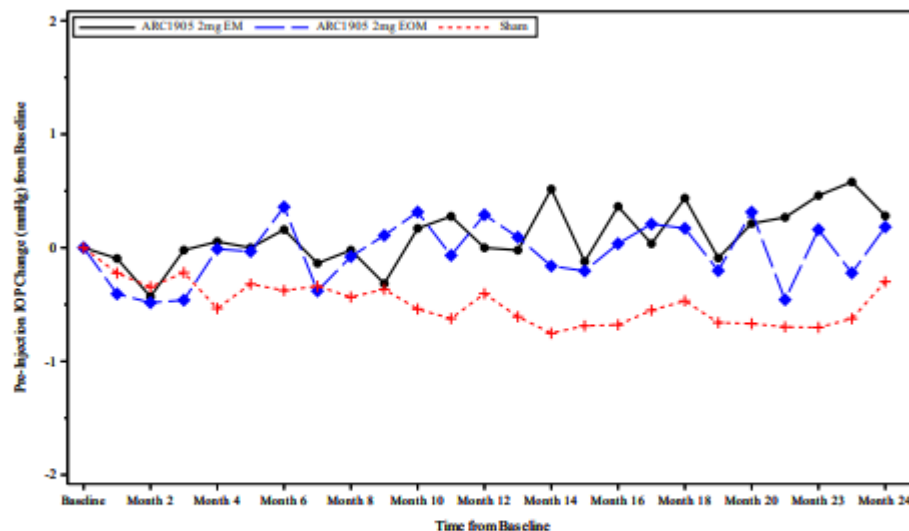
^e Incidence is defined as the number of patients with the first occurrence of the event divided by the number of patients at risk of the event in the given time period. A patient is at risk if the patient had an injection in previous and/or current time periods who has not experienced an event in the earlier time periods and has not discontinued from the clinical trial in the previous time period.

Up to 18 months (OPH2003), 30 patients presented IOP $\geq$ 35 mmHg at any time including 6 patients in the 2 mg arm. Five patients in the 2 mg arm and 3 patients in the 4 mg were treated by paracentesis for IOP increase.

In Cohort 2, a much higher prevalence of IOP increased was reported in the avacincaptad pegol 4 mg arm (57,69 per 1000 injections) compared to 2 mg arm (20,07 per 1000 injections) over the 6-month treatment period. Furthermore, 2,9% of the patient were treated by paracentesis for a total prevalence of 3,36 per 1000 injections.

Up to month 24, 32 (7.2%) patients across treatment groups reported to have experienced a TEAE of increased IOP: 30 (13.3%) patients in the avacincaptad pegol group (overall) and 2 (0.9%) patients in the sham group. There were 28 subjects in the avacincaptad pegol 2 mg group (overall) and 4 subjects in the sham group who had reported a TEAEI of IOP $\geq$ 30 mmHg in the study eye during the study. The majority of these events occurred post-injection (27 of 32 [84.4%] were transient, and resolved the same day. There were no events of increased IOP reported as related to the study drug. Moreover, 7.6% of the patients who received avacincaptad pegol (overall) had a transient IOP $\geq$ 35 mmHg post-injection (0.647% of all injections). Ten patients (4.4%) in avacincaptad pegol underwent at least 1 post-injection paracentesis over the 24-month treatment period, there were a total of 44 cases of post-injection paracentesis (0.982% per number of total injections).

The proportion of patients in the avacincaptad pegol 2 mg EM and the avacincaptad pegol 2 mg EOM group that experienced increased IOP was similar (14 [14.6%] and 11 [11.8%]). Of these, 8.3% of patients in the avacincaptad pegol EM treatment group experienced a transient IOP $\geq$ 35 mmHg 30 minutes post-injection (0.693% of all injections) and 6.5% of patients in the avacincaptad pegol EOM treatment group (0.432% of all injections). There were 8 (3.6%) patients in the avacincaptad pegol 2 mg group who experienced ocular hypertension.

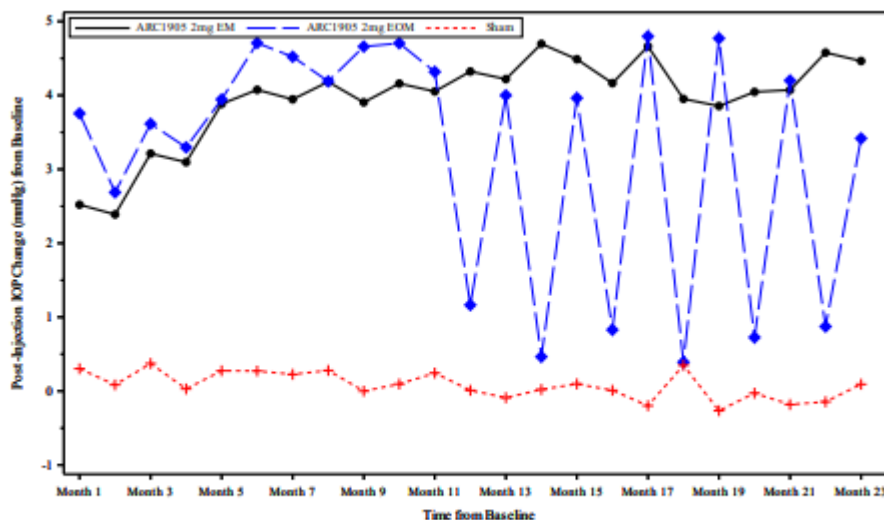


Source: Post-text Figure 14.3.1.2b

EM = every month; EOM = every other month; IOP = intraocular pressure.

Notes: This figure presents mean values of IOP per visit for each treatment group. Within each visit, the mean IOP change from Baseline at pre-injection (for applicable treatment groups) are presented.

Figure 14: Pre-injection mean IOP change from baseline (mmHg) up to month 24 by visit in the study eye (re-randomised analysis set)



Source: Post-text Figure 14.3.1.4b

EM = every month; EOM = every other month; IOP = intraocular pressure

Figure 15: Post-injection mean IOP (mmHg) change from baseline up to month 24 by visit in the study eye (re-randomised analysis set)

Table 39: Summary of patient who experienced IOP $\geq$ 35 mmHg, who had a paracentesis, or who received IOP-lowering medication up to month 24 – study 24

Number of Patients (%)	Re-Rand Analysis Set			Safety Analysis Set	
	Avacincaptad Pegol 2 mg EM N=96	Avacincaptad Pegol 2 mg EOM N=93	Sham N=203	Avacincaptad Pegol 2 mg N=225	Sham N=222
Patients who experienced IOP $\geq$ 35 mmHg:					
Pre-injection (or not on an injection day)	0	1 (1.1)	1 (0.5)	1 (0.4)	1 (0.5)
30 minutes after the injection	8 (8.3)	6 (6.5)	2 (1.0)	17 (7.6)	2 (0.9)
At any time	11 (11.5)	9 (9.7)	2 (1.0)	25 (11.1)	2 (0.9)
Patients with paracentesis:					
Paracentesis on an injection day	5 (5.2)	3 (3.2)	0	10 (4.4)	0
Patients who received IOP-lowering medication:					
IOP-lowering medication before randomization	5 (5.2)	6 (6.5)	11 (5.4)	15 (6.7)	13 (5.9)
Chronic IOP-lowering medication during the study ^a	6 (6.3)	6 (6.5)	3 (1.5)	13 (5.8)	3 (1.4)
Post-injection IOP-lowering medication on injection day ^b	7 (7.3)	8 (8.6)	3 (1.5)	18 (8.0)	3 (1.4)

Source: [Post-text Table 14.3.15.6a](#) and [Table 14.3.15.6b](#)

EM = every month; EOM = every other month; IOP = intraocular pressure; Re-Rand = re-randomized.

^a New onset of IOP-lowering medication used for 45 days or more and administration continuing at the end of the first year of the study or at the time of discontinuation for patients who discontinued before Month 24.

^b New onset of IOP-lowering medication post-injection on an injection day.

Table 40: Summary of paracentesis and IOP $\geq$ 35 mmHg per total number of injections up to month 24 – study eye

	Re-Rand Analysis Set			Safety Analysis Set	
	Avacincaptad Pegol 2 mg EM N=96	Avacincaptad Pegol 2 mg EOM N=93	Sham N=203	Avacincaptad Pegol 2 mg N=225	Sham N=222
Total number of injections	2163	2081	NA	4482	NA
Number (%) of paracenteses per total number of injections	27 (1.248)	12 (0.577)	0	44 (0.982)	0
Number (%) of IOP $\geq$ 35 mmHg per Total Number of Injections					
Pre-injection	0	2 (0.096)	1 (0.022)	2 (0.045)	1 (0.021)
30 minutes after the injection	15 (0.693)	9 (0.432)	2 (0.043)	29 (0.647)	2 (0.042)

Source: [Post-text Table 14.3.15.7a](#) and [Table 14.3.15.7b](#)

EM = every month; EOM = every other month; IOP = intraocular pressure; NA = not applicable; Re-Rand = re-randomized.

Notes: Percentages are based on the total number of injections in the respective treatment group.

Transient vision loss

Table 41: Transient vision loss – study eye (cohort 1)

Number of patients (%)	Cohort 1			
	Sham ^a N=332	Avacincaptad pegol 1 mg ^b N=49	Avacincaptad pegol 2 mg ^a N=292	Avacincaptad pegol 4 mg ^c N=83
Patients with transient vision loss at any time				
Yes	0	0	4 (1.4%)	1 (1.2%)
No	332 (100%)	49 (100%)	288 (98.6%)	82 (98.8%)
Overall prevalence per 1000 injections ^d	0.00	0.00	1.28	1.24
Incidence over time ^e				
0 – 3 months	0	0	2 (0.7%)	1 (1.2%)
>3 – 6 months	0	0	1 (0.4%)	0
>6 – 9 months	0	0	1 (0.4%)	0
>9 – 12 months	0	0	0	0

Source: ISS Table 14.3.3.7.2.C1 (M.5.3.5.3); data for the avacincaptad pegol 0.3 mg group are included in the ISS table

^a Data from Studies OPH2003 and ISEE2008

^b Data from Studies OPH2001 and OPH2003

^c Data from Study OPH2003

^d Prevalence per 1000 injections is defined as the number of patients with the first occurrence of the event multiplied by 1000 and divided by the total number of injections administered up to the first occurrence of the event that is specific to each patient.

^e Incidence is defined as the number of patients with the first occurrence of the event divided by the number of patients at risk of the event in the given time period. A patient is at risk if the patient had an injection in previous and/or current time periods who has not experienced an event in the earlier time periods and has not discontinued from the clinical trial in the previous time period.

In Cohort 1, the majority of the patients did not present transient vision loss in the study eye. Incidence of transient vision loss was of 1,4% in avacincaptad pegol 2 mg arm (prevalence of 1,28 per 1000 injections) and of 1,2% in 4 mg arm (prevalence of 1,24 per 1000 injections). None were reported as an SAE nor lead to study discontinuation. All events started after the injection on the day of the injection, resolved on the same day and were considered as related to injection procedure.

Severe ocular TEAEs of retinal artery occlusion (transient) were reported for study OPH2003 in two patients (3 events at day 1, month 10 and 17 in one patient in 2 mg arm and 5 events at day 1, Months 3, 4, 7 and 8 in one patient in the 4 mg arm) which resolved on the same day for both and were not associated to an inflammation and with a stable VA for both patients. The events of transient retinal artery occlusion lead to study discontinuation for the patient in the 4 mg arm due to the Investigator decision. All events were assessed as related to IVT injection procedure. Up to month 18 (OPH2003), two additional patients presented transient events of retinal artery occlusion in the 4 mg arm; four mild events at Month 13, 14, 16 and 17 for one patient and one moderate event at Month 15 for the other patient).

Similar tendencies were observed in Cohort 2, two patients reported transient vision loss (one in 2 mg and one in 0,3 mg groups) assessed as related to IVT injection procedure and resolved on the same day. None lead to study discontinuation nor were an SAE.

Up to month 24, there were 7 (1.6%) patients total who experienced VA reduced transiently and 5 (1.1%) patients who experienced blindness transient; all except 1 patient who experienced VA reduced transiently were in the avacincaptad pegol group. The percentage of patients who experienced VA reduced transiently (5.2% versus 1.1%, respectively) was slightly higher in the avacincaptad pegol EM treatment group than in the EOM treatment group. The percentage of patients who experienced blindness transient (2.2% [EM] versus 2.1% [EOM]) was comparable between both avacincaptad pegol treatment groups. There were 6 severe AEs of transient vision loss: 3 events of blindness transient in 2

avacincaptad pegol patients (all lasting 1 day), which were resolved/recovered and related to injection procedure, and 3 events of VA reduced transiently in 2 avacincaptad pegol patients (2 events lasting 1 day and 1 event lasting 16 days), which were resolved/recovered, and 2 of the 3 events were related to injection procedure. There was 1 SAE of VA reduced transiently in a sham patient (lasting 19 days) that occurred in Year 1 that was resolved/recovered and not related to the injection procedure or avacincaptad pegol/sham. In addition, there was one SAE of VA reduced in the same patient that was not resolved/recovered and not related to the injection procedure or avacincaptad pegol/sham.

BCVA Decrease $\geq$ 30 Letters

Table 42: BCVA decrease $\geq$ 30 letters – study eye (cohort 1)

	Cohort 1			
	Sham ^a N=332	Avacincaptad pegol 1 mg ^b N=49	Avacincaptad pegol 2 mg ^a N=292	Avacincaptad pegol 4 mg ^c N=83
Number of patients (%)				
Patients with BCVA decrease ≥ 30 letters at any time				
Yes	11 (3.3%)	3 (6.1%)	9 (3.1%)	6 (7.2%)
No	321 (96.7%)	46 (93.9%)	283 (96.9%)	77 (92.8%)
Risk difference (%) between Avacincaptad pegol 2 mg and sham			-0.2%	
Time to first onset	n=11	n=3	n=9	n=6
0 – 3 months	1 (9.1%)	0	1 (11.1%)	0
>3 – 6 months	5 (45.5%)	2 (66.7%)	2 (22.2%)	2 (33.3%)
>6 – 9 months	2 (18.2%)	0	5 (55.6%)	3 (50.0%)
>9 – 12 months	3 (27.3%)	1 (33.3%)	1 (11.1%)	1 (16.7%)

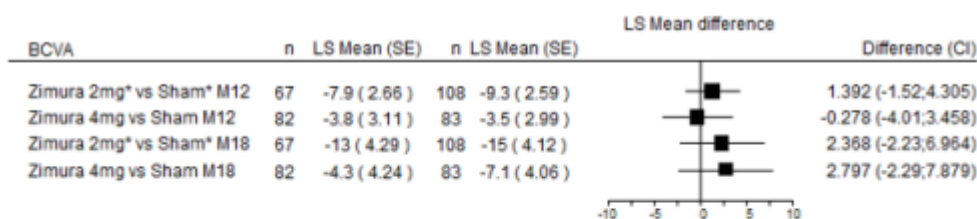
Source: ISS Table 14.3.3.7.4.C1 (M.5.3.5.3); data for the avacincaptad pegol 0.3 mg group are included in the ISS table

BCVA = best-corrected visual acuity

^a Data from Studies OPH2003 and ISEE2008

^b Data from Studies OPH2001 and OPH2003

^c Data from Study OPH2003



Source: OPH2003 CSR Figure 4 (M.5.3.5.1)

BCVA = best-corrected visual acuity; CI = confidence interval; CSR = clinical study report; ETDRS = Early Treatment Diabetic Retinopathy Study; ITT = intent-to-treat; LS = least squares; MMRM = mixed-effects model for repeated measures; SAP = Statistical Analysis Plan; SE = standard error

Notes: MMRM is specified in the OPH2003 SAP Section 7.3, M.5.3.5.1. Difference in least squares means between treatment groups calculated as (avacincaptad pegol) minus (sham).

*Combination of Part 1 and Part 2 patients.

Figure 16: Mean change in BCVA scores (ETDRS letters) from baseline to month 12 and month 18 (MMRM analysis) – study eye, study OPH2003 (ITT analysis set)

In Cohort 1, 4% of the patients treated by avacincaptad pegol (nine in 2mg, six in 4 mg and three in 1 mg) presented a BVCA decrease $\geq$ 30 Letters in the study eye which is similar to sham (3.3%). The majority of the patients in the avacincaptad pegol 2 mg and 4 mg groups had a decrease between 6-9 months after treatment initiation. Up to 18 months (OPH2003), seventeen patients had a BCVA decrease $\geq$ 30 letters between Month 12 and Month 18 including four patients in avacincaptad pegol, 2 arm and three patients in 4 mg arm.

Up to month 24, the incidence of BCVA decrease of ≥ 30 letters from Baseline occurring in the SE was comparable across all treatment groups in the Re-Rand analysis set (13.5%, 8.6%, and 11.8% patients in the avacincaptad pegol EM, avacincaptad pegol EOM, and sham groups, respectively). Overall, 22 patients in the avacincaptad pegol treatment group experienced one or more visits with BCVA decrease ≥ 30 letters from Baseline compared to 26 patients in the sham group experiencing one or more visits with ≥ 30 letters BCVA loss from Baseline.

Choroidal neovascularisation (CNV)

Table 43: CNV – study eye (cohort 1)

	Cohort 1			
	Sham ^a N=332	Avacincaptad pegol 1 mg ^b N=49	Avacincaptad pegol 2 mg ^a N=292	Avacincaptad pegol 4 mg ^c N=83
Number of patients (%)				
Patients with CNV at any time				
Yes	12 (3.6%)	1 (2.0%)	21 (7.2%)	8 (9.6%)
No	320 (96.4%)	48 (98.0%)	271 (92.8%)	75 (90.4%)
Time to first onset	n=12	n=1	n=21	n=8
0 – 3 months	2 (16.7%)	1 (100%)	4 (19.0%)	0
>3 – 6 months	5 (41.7%)	0	4 (19.0%)	4 (50.0%)
>6 – 9 months	1 (8.3%)	0	7 (33.3%)	1 (12.5%)
>9 – 12 months	4 (33.3%)	0	6 (28.6%)	3 (37.5%)

Source: ISS Table 14.3.3.7.5.C1 (M.5.3.5.3); data for the avacincaptad pegol 0.3 mg group are included in the ISS table
CNV = choroidal neovascularization; RC = reading center

^a Data from Studies OPH2003 and ISEE2008

^b Data from Studies OPH2001 and OPH2003

^c Data from Study OPH2003

NOTE: Events of CNV (in the study eye) that were reported based on findings at the Month 12 visit and confirmed by the RC were included regardless of AE cut-off date.

Table 44: Ocular TEAEs in the study eye of patients with CNV in study ISEE2008 up to month 12

Treatment arm	CNV without other ocular TEAE	CNV with other ocular TEAEs	CNV with BCVA ≥ 30 letters loss from Baseline	CNV with IOP ≥ 30 mmHg post IVT injection
Avacincaptad pegol 2 mg N=15	9	6	3*	2
Sham N=9	5	4	2*	0

Source: Listings 16.1.1.1 and 16.1.1.2, ISS Listings 14.3.5.4.C1 and 14.3.5.6.C1 (M.5.3.5.3)

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; IOP = intraocular pressure; TEAE = treatment-emergent adverse event

* One patient in the avacincaptad pegol arm had transient BCVA loss ≥ 30 letters from Baseline at Month 9 associated with intravitreal injection. All other patients (two patients in the avacincaptad pegol arm and two patients in the sham arm) had BCVA loss ≥ 30 letters from Baseline that did not recover up to Month 12.

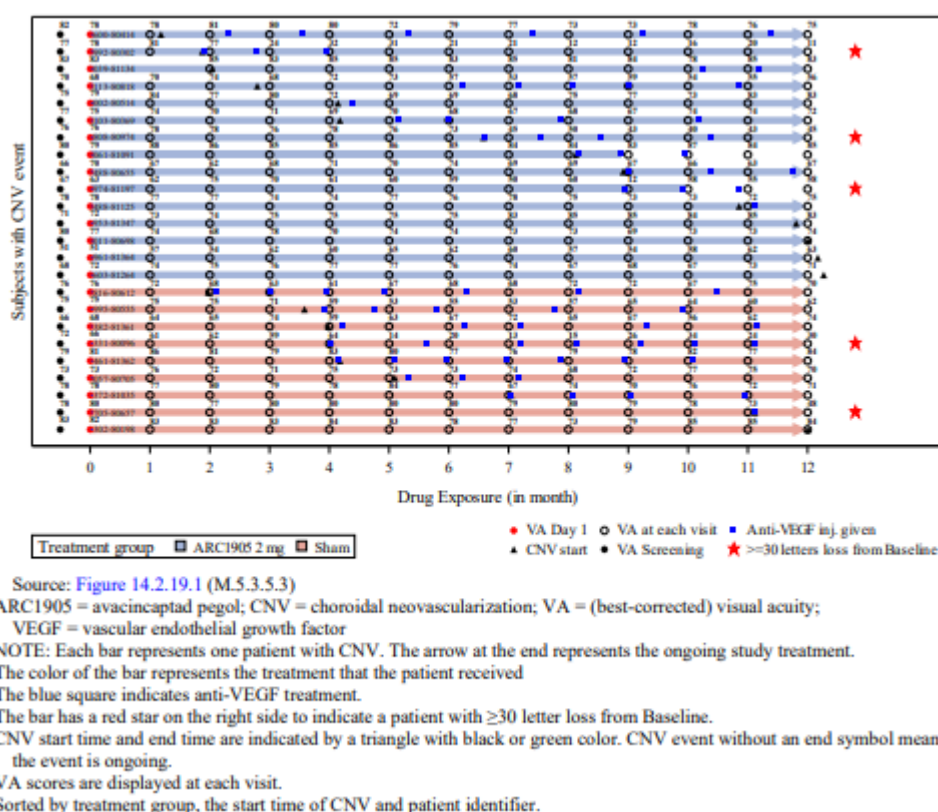


Figure 17:Swimmer plot for patients with CNV events (ISEE2008)

In ISEE2008, in case of CNV diagnosis patients could remain in the trial while receiving concomitant anti-VEGF therapy (aflibercept or ranibizumab) while in study OPH2003, patients were withdrawn from study per protocol. In Cohort 1, CNV was reported in the avacincaptad pegol 2 mg group (7.2%) compared to the sham group (3.6%) in patients with GA secondary to AMD. In ISEE2008, 15 patients developed CNV of which two were an SAE (one severe and related to study drug and one mild and not related), four were assessed as related to study drug and cases occurred with a time to onset between 36 and 373 days. All patients were not recovered/not resolved and required no dose change with medication. In OPH2003, one patient in the avacincaptad pegol 1 mg group had CNV which was moderate, non-SAE, not related and not recovered/not resolved. In the 2 mg arm, six patients developed CNV of which none were an SAE, none were assessed as related to avacincaptad pegol, all were mild or moderate, and all were not recovered/ not resolved. In the 4 mg arm, eight patients developed CNV of which none were an SAE, none were assessed as related to avacincaptad pegol, all were mild to moderate, all were not recovered/not resolved. Cases occurred for the majority of the time more than 3 months after treatment initiation in the 2 mg and 4 mg groups.

In the 2 mg arm, concomitant ocular TEAE were: BCVA loss ≥ 30 letters associated to RPE tear or subretinal fibrosis (n=2), epiretinal membrane (n=1), conjunctivitis (n=1), transient IOP elevation ≥ 30 mmHg post-injection (n=1) with BVCA loss ≥ 30 letters (n=1). Up to 18 months (OPH2003), eight patients in 2 mg arm (including six which had the onset up to month 12) and thirteen patients in the 4 mg arm (including eight which had the onset up to month 12) experienced CNV in the study eye. The annual rate of CNV for the combined 2 mg group decreased over time with 10.1 per 100 patient-years (vs 3.0 in sham) for the first year and 4.0 (vs 0) per 100 patient-years for year 2 (up to 18 months) in study OPH2003. As expected a higher rate could be observed for the avacincaptad pegol 4 mg 11.5 (vs 2.5 in sham) per 100 patient-years for the first year and 9.9 (vs 0 in sham) per patient-years for the second year (up to month 18) in study OPH2003.

In study ISEE2008, the incidence of CNV remained constant between the first year with 6.7% (vs 4.1% in sham) and 7.3% in the second year for the avacincaptad pegol 2 mg EM while being lower for the avacincaptad pegol 2 mg EOM with an incidence of 4.3% (lower compared to the sham 5.4%).

There is a potential for patients with non-exudative (dry) AMD to develop neovascularization and progress to (wet) exudative AMD. Currently, CNV is an identified important risk for avacincaptad pegol and special warning and precaution are proposed by the applicant in the SmPC with additional warning regarding anti-VEGF treatment. GA associated to AMD and nAMD are driven by two different pathophysiology however some commonalities may affect the progression of the disease such as increased complement pathway activity/levels (Heesterbeek et al, 2020). Indeed, increased activation of the complement pathway (C3, C5, and interleukin-6) is thought to be involved in development and progression of AMD which associated to an increase in VEGF production may increase the risk of developing CNV (Ehlken et al, 2019). Both complement and VEGF demonstrated a role in late-stage AMD pathobiology however at this stage it is unknown if any correlation can be made regarding the development of CNV in patient treated by avacincaptad pegol.

Up to month 24, in the avacincaptad pegol 2 mg arm, 22.2% (4/14) of the patients who had CNV in the study eye had CNV in the fellow eye vs 10.6% (22/185) who did not. Additionally, 33.3% (5/15) of the patients in the sham arm who had CNV in the study eye had CNV in the fellow eye vs 7.2% (15/192) who did not. Thus, the occurrence of CNV in 1 eye seems to be associated with a higher likelihood of occurrence of CNV in the contralateral eye regardless of the study treatment.

A comparative analysis of the changes in visual acuity observed between the avacincaptad pegol 2 mg and sham groups for patients who received anti-VEGF treatment after an event of choroidal neovascularisation was provided. This analysis was performed only with data from study ISEE2008, because only in this study patients who developed CNV in the study eye continued in the study and received concurrent avacincaptad pegol 2 mg or sham with anti-VEGF treatment - either Lucentis (ranibizumab) or Eylea (aflibercept). During the 24 months of the study, 24 patients in the avacincaptad pegol 2 mg arm and 18 patients in the sham arm received concurrent anti-VEGF treatment. The mean change in BCVA before the CNV onset compared with after the last anti-VEGF treatment (BCVA after anti-VEGF minus BCVA before CNV) decreased by 10.5 and 8.8 letters in the avacincaptad pegol 2 mg and sham arms, respectively. In addition, the mean change in BCVA before anti-VEGF treatment compared with after the last anti-VEGF treatment (BCVA after anti-VEGF minus BCVA before anti-VEGF) decreased by 9.6 and 6.7 letters in the avacincaptad pegol 2 mg and sham arms, respectively. The difference in BCVA decrease between the 2 treatment arms is within 3 letters in both cases, which is considered not clinically significant. In both groups, the same proportion of patients (16.7%; 4/24 patients in the avacincaptad pegol 2 mg arm and 3/18 patients in the sham arm) experienced severe vision loss (BCVA decrease $\geq$ 30 letters from baseline) in the study eye. The reason for this was mainly due to either other retinal comorbidities or GA disease progression. Taken together, these data suggest that patients treated with intravitreal avacincaptad pegol are not at risk of developing an untreatable (or less-treatable) CNV.

In study ISEE2008, 6,7% of the patient in 2 mg arm and 4,1% in sham arm developed CNV and received as protocol concomitant anti-VEGF injections (0-7) during the study. A total of 24 patients in the avacincaptad pegol (ACP) arm and 18 patients in the sham arm who developed CNV in the study eye received anti-VEGF treatment during the 24-month Study ISEE2008. Approximately 70% and 55.6% of the patient presented a TEAE after receiving anti-VEGF for avacincaptad pegol 2 mg and for sham respectively. Regarding non-ocular TEAEs, comparable proportions were reported between avacincaptad pegol with anti VEGF arm and avacincaptad pegol alone arm apart for the SOC cardiac disorders (29.2% ACP with anti-VEGF arm vs 14.4% ACP alone arm), General disorders and administration site conditions (12.5% ACP with anti-VEGF arm vs 5.5% ACP alone arm) and Investigations (37.5% ACP with anti-VEGF arm vs 21.4% ACP alone arm) however no PT were reported more than n>2 except for COVID-19. For

ocular TEAEs, comparable incidence in the study eye were observed in patients who received avacincaptad pegol 2 mg with anti-VEGF compared with avacincaptad pegol 2 mg alone, sham alone, or sham with anti-VEGF treatment. For IOP increased, the incidence was higher in the avacincaptad pegol with anti-VEGF arm compared with avacincaptad pegol alone arm (16.7% vs. 12.9%) however the incidence of IOP increased was 12.5% in the avacincaptad pegol before anti VEGF arm compared with 4.2% in avacincaptad pegol after anti-VEGF arm. No new safety issue is raised regarding patient treated with avacincaptad pegol who presented CNV and received anti-VEGF therapy.

Rhegmatogenous Retinal Detachment/ Retinal Tear

In Cohort 1, no cases of rhegmatogenous retinal detachment were reported. Two events of retinal tear were reported in the study eye for avacincaptad pegol arm (vs one in fellow eye), none were an SAE nor were considered related to the IVT injection procedure or the study drug.

Up to month 18, one event of temporal rhegmatogenous retinal detachment with a temporal retinal tear in the study eye which was mild, recovered and assessed as related to IVT injection procedure occurred prior to Month 13 pre-injection visit. The event lead to patient discontinuation due to investigator's decision.

In Cohort 2, three events of rhegmatogenous retinal detachment occurred (mild or moderate, one related to IVT, one SAE). In OPH2005, one patient experienced a TEAE of retinal tear (non-serious, resolved).

Vitreous haemorrhage

Two patients presented event of vitreous haemorrhage in the study eye in Cohort 1. None were an SAE, nor related to study drug nor lead to patient discontinuation. One of the cases of vitreous haemorrhage (in the avacincaptad pegol 2 mg group) was considered related to the injection procedure.

No events were reported up to month 18 and in Cohort 2.

Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

One serious event of NAION in a patient receiving avacincaptad pegol 2 mg was reported in Study OPH2003 at Month 18 and was considered unrelated to study drug and injection procedure. There were no events of NAION reported in Study ISEE2008 up to month 24.

Systemic infection

Based on human PK data ($C_{max}=6.2$ nM) and in regards to an IC_{50} human of 0.6 nM, avacincaptad pegol release in the systemic circulation after IVT treatment, will inhibit the classical human complement activation pathway and could lead to an increase of susceptibility to infections (see *OC raised in PK section*).

In Cohort 1, comparable incidences were reported for the SOC of "infections and infestations" with 25.7% for the avacincaptad pegol 2 mg group and 24.1% for the sham group. Serious systemic events occurred in 3.1% of patients in the avacincaptad pegol 2 mg group and 3% of patients in the sham group. The incidence of upper respiratory tract infection was similar across groups (2.1% in the avacincaptad pegol 2 mg arm compared with 1.5% in the sham arm). The incidence of sepsis was slightly higher in the avacincaptad pegol 2 group (0.7% (2 patients) in the avacincaptad pegol 2 mg arm vs. 0 in the sham arm) and the incidence of nasopharyngitis and pneumonia was higher in the avacincaptad pegol 2 mg arm compared to the sham group (6.8% vs. 4.2% and 3.4% vs. 1.8%, respectively), but none of the TEAEs of nasopharyngitis, pneumonia and sepsis were deemed to be related to the study drug or injection procedure. No additional significant imbalances were noted. Up to month 18, similar tendencies were observed.

Although infections and infestations were only slightly more frequent up to month 12 in avacincaptad pegol 2 mg treated patients compared to the sham group, the frequency was markedly higher in the 4 mg group (sham: 24.1%, avacincaptad pegol 2 mg: 25.7%, avacincaptad pegol 4 mg: 28.9%), with relevant imbalances in upper respiratory tract infections (sham: 0.9%, avacincaptad pegol 2 mg: 1.4%, avacincaptad pegol 4 mg: 4.8%) and sepsis (sham: 0, avacincaptad pegol 2 mg: 0.3%, avacincaptad pegol 4 mg: 3.6%). In addition, serious infections and infestations were significantly higher in the 4 mg group (sham: 3.0%, 2 mg: 3.1%, 4 mg: 8.4%). In study OPH2003, no non-ocular TEAEs linked to systemic infection were reported to be related to Zimura/Sham or to administration injection procedure up to Month 18.

Up to month 24 in ISEE2008, non-ocular infections and infestations were similar in both the avacincaptad pegol 2 mg group (overall) (40.9%) and the sham group (40.1%). The number of patients who experienced non-ocular infections and infestations (42.7% versus 45.2%, respectively) was comparable between avacincaptad pegol EM and EOM groups. The most commonly reported PT were "COVID-19" (32 patients (14.2%) in avacincaptad pegol group vs 36 patients (16.2%) in sham group), "Urinary tract infection" (27 patients [12.2%] in sham vs 19 patients [8.4%] in avacincaptad pegol). One (0.4%) case of COVID-19 pneumonia was reported in the avacincaptad pegol treatment group. There were numerically more cases of pneumonia in the avacincaptad pegol group (8 patients; 3.6%) compared to the sham group (3 patients; 1.4%). There were 7 (3.2%) cases of herpes zoster reported in the sham group and 2 (0.9%) cases in the avacincaptad pegol 2 mg group.

Up to month 24 in ISEE2008, ocular infections and infestations occurred with similar frequency in the avacincaptad pegol group (7 patients; 3.1%) and the sham group (7 patients; 3.2%). These events included conjunctivitis, conjunctivitis viral, hordeolum, and one event of culture-positive endophthalmitis.

Drug Hypersensitivity and Eye Irritation

No events of ocular and non-ocular hypersensitivity were assessed as related to avacincaptad pegol or sham. The reported events were for the majority post-injection events and related to the injection procedure such as conjunctival oedema, corneal oedema or eyelid oedema or events related to the injection preparation process, such as conjunctivitis due to betadine sensitivity. "Rash," "pruritus," "urticaria," as well as PTs of "drug hypersensitivity" and "eye irritation" were comparable between patients receiving avacincaptad pegol and patients receiving sham.

3.3.7.5. Laboratory findings

In Cohort 1, incidence of notable laboratory values was comparable between avacincaptad pegol and sham. Moreover, notable laboratory results were infrequent; none were reported as related to the study drugs, and none led to discontinuation from the study drug.

Proportions of subject with clinically notable elevated pulse (increase from baseline of ≥ 15 bpm) were comparable between arm while slightly more patient in avacincaptad pegol 2 mg had a decrease from baseline of ≥ 15 bpm (1.7% in 2 mg vs 0.3% in sham) with no clinical observation associated. Proportions of subject with clinically notable values for systolic and diastolic blood pressure were observed. Overall, no clinically meaningful differences between the treatment groups for the pulse, systolic and diastolic blood pressure parameters were observed.

The majority of the ECGs showed no change from Baseline throughout month 12 and 18. At month 12 (OPH2003), two patients in 2 mg arm presented clinically significant change from either normal or not clinically significantly abnormal at baseline, one patient reported left axis deviation and one patient reported old septal infarct compared to two patient in the sham group which consisted of one patient with sinus bradycardia and one patient with second degree atrioventricular block. At month 18, in the 2

mg arm, one patient reported elevated heart rate and one patient reported nonspecific ECG changes. Overall, there were no clinically relevant differences in the nature of changes between treatment groups and changes were consistent with those expected in the study population.

Shift in ophthalmic examination from baseline to month 12 were comparable between treatment groups with no change compared to baseline and ophthalmic examinations were for the majority normal except for the macula which is consistent with the studied population.

As anticipated, due to the IVT injection volume effect in the avacincaptad pegol 2 mg (100 µL injection volume) and 4 mg (100 µL + 100 µL injection volume) groups, the mean post-first injection IOP values were higher compared to the mean pre-injection IOP values at each study visit. Additionally, as a result of the second injection in the avacincaptad pegol 4 mg group (200 µL in total per injection day), there was an additional increase in the post-second injection IOP values compared to the mean post-first injection values in this group. However, both of these increases were transient and at the next scheduled monthly visit, the mean IOP values generally returned to or near to the previous pre-injection levels. In the avacincaptad pegol 4 mg group, which received two sequential injections of avacincaptad pegol 2 mg per injection day, there was a small increase in mean pre-injection IOP over the 12-month period.

3.3.7.6. *In vitro* biomarker test for patient selection for safety

Not applicable.

3.3.7.7. *Safety in special populations*

Subgroup analyses were performed by age and sex in Cohort 1. Interpretation of these individual analyses is limited given the small number of subjects within certain subgroups.

The majority of patients were ≥ 65 years of age and of female sex. Treatment exposure was comparable between age and sex categories with a majority of patients who received 10-12 injections. TEAE were reported in comparable proportion arm between age categories and in higher incidence in the avacincaptad pegol 2 mg except for patients aged ≥ 85 years for which TEAE were reported in similar proportions between sham and avacincaptad pegol. Less patients presented TEAE in the sham arm for patient aged < 65 years old compared to other age categories. Ocular TEAEs were reported in similar proportions between age categories for the avacincaptad pegol arm and the safety profile was consistent across the four age categories to the overall safety profile of avacincaptad pegol 2 mg. Serious TEAE were more reported in the sham group except for patient < 65 years old. Severe TEAEs were reported with comparable proportions between age categories and in higher proportion in avacincaptad pegol arm except for patients 65-74 years old. Ocular TEAE leading to study discontinuation occurred in 2 patients in the avacincaptad 2 mg arm in the 65-74 years old age category. Non-ocular TEAE were reported in similar proportions between avacincaptad pegol and sham across age categories except for patients < 65 years old (62.1% in 2 mg vs 42.3% in sham) however as number size in this age category was below 30 patients in each arm, interpretation of these results is very limited.

Table 45: Overall summary of TEAEs - by age group

	< 65 years		65 – 74 years		75 – 84 years		≥ 85 years	
	Sham N=26	Avacin- captad pegol 2 mg N=29	Sham N=92	Avacin- captad pegol 2 mg N=85	Sham N=141	Avacin- captad pegol 2 mg N=112	Sham N=73	Avacin- captad pegol 2 mg N=66
Number of patients (%)								
TEAE – All causalities	15 (57.7%)	24 (82.8%)	62 (67.4%)	67 (78.8%)	99 (70.2%)	92 (82.1%)	55 (75.3%)	49 (74.2%)
TEAE related to injection procedure	2 (7.7%)	5 (17.2%)	18 (19.6%)	22 (25.9%)	33 (23.4%)	39 (34.8%)	16 (21.9%)	19 (28.8%)
TEAE related to study drug	0	0	0	1 (1.2%)	0	1 (0.9%)	2 (2.7%)	2 (3.0%)
Ocular TEAE – All causalities – Study eye	6 (23.1%)	15 (51.7%)	32 (34.8%)	44 (51.8%)	55 (39.0%)	58 (51.8%)	28 (38.4%)	32 (48.5%)
Ocular TEAE related to injection procedure – Study eye	2 (7.7%)	5 (17.2%)	18 (19.6%)	22 (25.9%)	33 (23.4%)	38 (33.9%)	16 (21.9%)	19 (28.8%)
Ocular TEAE related to study drug – Study eye	0	0	0	1 (1.2%)	0	0	2 (2.7%)	2 (3.0%)
Serious TEAE – All causalities	2 (7.7%)	4 (13.8%)	12 (13.0%)	6 (7.1%)	29 (20.6%)	18 (16.1%)	14 (19.2%)	9 (13.6%)
Serious ocular TEAE – All causalities – Study eye	0	0	1 (1.1%)	1 (1.2%)	0	0	1 (1.4%)	1 (1.5%)
Serious ocular TEAE related to injection	0	0	0	0	0	0	0	0

procedure – Study eye								
Serious ocular TEAE related to study drug – Study eye	0	0	0	1 (1.2%)	0	0	0	0
Severe TEAE – All causalities ^a	2 (7.7%)	3 (10.3%)	12 (13.0%)	10 (11.8%)	17 (12.1%)	16 (14.3%)	6 (8.2%)	9 (13.6%)
Severe ocular TEAE – All causalities – Study eye ^a	0	0	1 (1.1%)	5 (5.9%)	1 (0.7%)	2 (1.8%)	0	0
Severe ocular TEAE related to injection procedure – Study eye ^a	0	0	0	2 (2.4%)	0	2 (1.8%)	0	0
Severe ocular TEAE related to study drug – Study eye ^a	0	0	0	1 (1.2%)	0	0	0	0
TEAE leading to study drug discontinuation – All causalities	0	1 (3.4%)	0	2 (2.4%)	2 (1.4%)	2 (1.8%)	1 (1.4%)	1 (1.5%)
Ocular TEAE leading to study drug discontinuation – All causalities – Study eye	0	0	0	2 (2.4%)	0	0	0	0
AE leading to death	0	1 (3.4%)	0	0	0	1 (0.9%)	0	1 (1.5%)

Source: ISS Tables 14.3.2.2.1 – 14.3.2.2.4 (M.5.3.5.3)

AE = adverse event; CNV = choroidal neovascularization; RC = reading center; TEAE = treatment-emergent adverse event
^a Severe AE = Incapacitating with inability to work or do usual activity

NOTE 1: Data from Studies OPH2003 and ISEE2008

NOTE 2: TEAEs are AEs occurring after the first injection on Day 1 up to 30 days after the last dose of study drug. Events of CNV (in the study eye) that were reported based on findings at the Month 12 visit and confirmed by the RC were included regardless of AE cut-off date.

TEAE were reported in higher incidence in the male population in both arm (59,8% in sham vs 69,9% in 2 mg arm) however SOC were reported in comparable proportions between arms except for Nervous system disorders reported in higher proportion in sham. Serious TEAEs were reported in similar proportion in the male population and in higher proportion in the sham arm for the female population. The most frequently reported PTs in both female and male patients were consistent with the common TEAEs reported for the overall population.

Table 46: Overall summary of TEAEs - by sex group

	Male		Female	
	Sham N=97	Avacincaptad pegol 2 mg N=93	Sham N=235	Avacincaptad pegol 2 mg N=199
Number of patients (%)				
TEAE – All causalities	73 (75.3%)	81 (87.1%)	158 (67.2%)	151 (75.9%)
TEAE related to injection procedure	19 (19.6%)	26 (28.0%)	50 (21.3%)	59 (29.6%)
TEAE related to study drug	1 (1.0%)	2 (2.2%)	1 (0.4%)	2 (1.0%)
Ocular TEAE – All causalities – Study eye	42 (43.3%)	50 (53.8%)	79 (33.6%)	99 (49.7%)
Ocular TEAE related to injection procedure – Study eye	19 (19.6%)	26 (28.0%)	50 (21.3%)	58 (29.1%)
Ocular TEAE related to study drug – Study eye	1 (1.0%)	2 (2.2%)	1 (0.4%)	2 (1.0%)
Serious TEAE – All causalities	18 (18.6%)	19 (20.4%)	39 (16.6%)	18 (9.0%)
Serious ocular TEAE – All causalities – Study eye	0	2 (2.2%)	2 (0.9%)	0
Serious ocular TEAE related to injection procedure – Study eye	0	0	0	0
Serious ocular TEAE related to study drug – Study eye	0	1 (1.1%)	0	0
Severe TEAE – All causalities ^a	15 (15.5%)	18 (19.4%)	22 (9.4%)	20 (10.1%)
Severe ocular TEAE – All causalities – Study eye ^c	0	3 (3.2%)	2 (0.9%)	4 (2.0%)
Severe ocular TEAE related to injection procedure – Study eye ^c	0	1 (1.1%)	0	3 (1.5%)
Severe ocular TEAE related to study drug – Study eye ^c	0	1 (1.1%)	0	0
TEAE leading to study drug discontinuation – All causalities	3 (3.1%)	5 (5.4%)	0	1 (0.5%)
Ocular TEAE leading to study drug discontinuation – All causalities – Study eye	0	1 (1.1%)	0	1 (0.5%)
TEAE leading to death	0	3 (3.2%)	0	0

Source: ISS Table 14.3.2.2.5 (male) and 14.3.2.2.6 (female) (M.5.3.5.3)

AE = adverse event; CNV = choroidal neovascularization; RC = reading center; TEAE = treatment-emergent adverse event

^a Severe AE = Incapacitating with inability to work or do usual activity

NOTE 1: Data from Studies OPH2003 and ISEE2008

NOTE 2: TEAEs are AEs occurring after the first injection on Day 1 up to 30 days after the last dose of study drug. Events of CNV (in the study eye) that were reported based on findings at the Month 12 visit and confirmed by the RC were included regardless of AE cut-off date.

Overall, no significant differences in the safety profile of avacincaptad pegol were seen regarding patient age nor sex.

No subgroup analyses by extrinsic factors were performed.

3.3.7.8. Immunological events

No immunogenicity data issued from immunogenicity assays are available at this stage. In the ongoing study ISEE2009 (open extension study including patient who completed ISE2008), assessments of anti-drug antibodies (ADA) will be performed at pre-dose at Month 1, Month 2, Month 4, Month 7, Month 13, and Month 18. Up to the data cut-off date, 25,4% (n=16) of the 63 enrolled patient completed month 3 visit. The applicant will submit an interim report on day 180 as the analysis of the sample is ongoing and a full data report after completion of study ISEE2009 which is endorsed. **The applicant refers to document ICDIM 722 Validation Report for the detailed methodology of a validated enzyme-linked immunosorbent assay which was designed to detect anti-avacincaptad pegol antibodies in human serum however the document ICDIM 722 Validation Report could not be found in the submitted file (OC).**

3.3.7.9. Safety related to drug-drug interactions and other interactions

No dedicated clinical studies evaluating the drug-drug interaction potential of avacincaptad pegol have been conducted.

In study ISEE2008, patient who developed CNV remained in the study with continued study treatment and received concomitant IVT anti-VEGF therapy. According the applicant, no new safety concerns have been identified when patients who developed CNV continued with avacincaptad pegol 2 mg treatment and received concurrent IVT anti-VEGF therapy. However, the applicant was requested to further discuss on this topic.

Moreover, non-clinical data showed unexpected results for avacincaptad pegol effect on CYP3A4 substrate (midazolam) as discussed in the non-clinical AR (section pharmacokinetic drug interaction). A potential DDI between avacincaptad pegol and CYP3A4 substrates could not be ruled out and further investigation were requested including conducting an in vitro induction study (using midazolam and testosterone as substrates).

3.3.7.10. Discontinuation due to adverse events

In Cohort 1, up to month 12, discontinuation due to adverse event were slightly higher in avacincaptad pegol groups 2 mg (2,1%) and 4 mg (2,4%) than with sham (0,9%). No ocular and non-ocular TEAE leading to study discontinuation were related to study drug. Two patients in avacincaptad pegol 2 mg presented vitreous detachment and IOP increase assessed as IVT injection procedure related which lead to study discontinuation. More patient discontinued study due to non-ocular TEAE (1,4%) than ocular TEAE (0,7%) in the avacincaptad pegol 2 mg arm. Up to Month 18, four additional TEAEs lead to patient study discontinuation (one fatal case of cerebral infarction, one serious case of optic ischemic neuropathy, one serious case of retinal detachment and one serious cerebral haemorrhage). None were assessed as related to the injection procedure or to avacincaptad pegol/sham.

Table 47: TEAEs leading to study treatment discontinuation (cohort 1)

System Organ Class Preferred Term Number of patients (%)	Cohort 1			
	Sham ^a N=332	Avacincaptad pegol 1 mg ^b N=49	Avacincaptad pegol 2 mg ^a N=292	Avacincaptad pegol 4 mg ^c N=83
Number of patients with at least one ocular TEAE – all causalities – Study eye	0	0	2 (0.7%)	1 (1.2%)
Eye disorders	0	0	1 (0.3%)	1 (1.2%)
Macular degeneration	0	0	0	1 (1.2%)
Vitreous detachment	0	0	1 (0.3%)	0
Investigations	0	0	1 (0.3%)	0
Intraocular pressure increased	0	0	1 (0.3%)	0
Number of patients with at least one non-ocular TEAE – all causalities	3 (0.9%)	0	4 (1.4%)	1 (1.2%)
Infections and infestations	0	0	2 (0.7%)	0
Pneumonia	0	0	2 (0.7%)	0
Injury, poisoning and procedural complications	0	0	0	1 (1.2%)
Road traffic accident	0	0	0	1 (1.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.3%)	0
Acute leukaemia	0	0	1 (0.3%)	0
Nervous system disorders	3 (0.9%)	0	0	0
Cerebrovascular accident	1 (0.3%)	0	0	0
Dementia	1 (0.3%)	0	0	0
Transient ischaemic attack	1 (0.3%)	0	0	0
Vascular disorders	0	0	1 (0.3%)	0
Neurogenic shock	0	0	1 (0.3%)	0

Source: ISS Tables 14.3.3.3.1.1.C1 (ocular, study eye) 14.3.3.3.1.2.C1 (ocular, fellow eye), and 14.3.3.4.1.C1 (non-ocular) (M.5.3.5.3); data for the avacincaptad pegol 0.3 mg group are included in the ISS tables

AE = adverse event; CNV = choroidal neovascularization; RC = reading center; TEAE = treatment-emergent adverse event

^a Data from Studies OPH2003 and ISEE2008

^b Data from Studies OPH2001 and OPH2003

^c Data from Study OPH2003

NOTE 1: TEAEs are AEs occurring after the first injection on Day 1 up to 30 days after the last dose of study drug. Events of CNV (in the study eye) that were reported based on findings at the Month 12 visit and confirmed by the RC were included regardless of AE cut-off date.

NOTE 2: No ocular TEAEs were present for the fellow eye (all causalities) leading to study treatment discontinuation

Up to month 24, twenty (4.5%) patients in total discontinued the study due to a TEAE: 11 (4.9%) patients in the avacincaptad pegol group (overall) and 9 patients (4.1%) in the sham group. The proportion of patients with TEAEs leading to study discontinuation was comparable between avacincaptad pegol EM (3.1%) and EOM (2.2%) groups. Non-ocular TEAEs leading to study drug discontinuation occurring in the avacincaptad pegol group were pneumonia, acute leukaemia, chronic cardiac failure, biliary obstruction, vascular dementia, chronic obstructive pulmonary disease, and neurogenic shock in one patient each (0.4%). Four patients in the avacincaptad pegol group had ocular TEAEs leading to study drug discontinuation: CNV, vitreous detachment, IOP increased, and device dislocation, and 2 of them (vitreous detachment; IOP increased) were also related to the injection procedure. There were no TEAEs leading to study drug discontinuation related to avacincaptad pegol/sham.

Table 48: TEAEs leading to study drug discontinuation by SOC and PT (All Causalities) – month 24

Number of Patients (%) System Organ Class Preferred Term	Re-Rand Analysis Set			Safety Analysis Set	
	Avacincaptad Pegol 2 mg EM N=96	Avacincaptad Pegol 2 mg EOM N=93	Sham N=203	Avacincaptad Pegol 2 mg N=225	Sham N=222
Patients (%) with at least 1 TEAE	3 (3.1)	2 (2.2)	7 (3.4)	11 (4.9)	9 (4.1)
Cardiac disorders	1 (1.0)	0	3 (1.5)	1 (0.4)	3 (1.4)
Cardiac failure	0	0	2 (1.0)	0	2 (0.9)
Cardiac failure chronic	1 (1.0)	0	0	1 (0.4)	0
Cardio-respiratory arrest	0	0	1 (0.5)	0	1 (0.5)
Eye disorders	0	0	0	2 (0.9)	0
Choroidal neovascularisation	0	0	0	1 (0.4)	0
Vitreous detachment	0	0	0	1 (0.4)	0
Hepatobiliary disorders	0	1 (1.1)	0	1 (0.4)	0
Biliary obstruction	0	1 (1.1)	0	1 (0.4)	0
Infections and infestations	0	0	1 (0.5)	1 (0.4)	1 (0.5)
COVID-19	0	0	1 (0.5)	0	1 (0.5)
Pneumonia	0	0	0	1 (0.4)	0
Investigations	0	0	0	1 (0.4)	0
IOP increased	0	0	0	1 (0.4)	0
Musculoskeletal and connective tissue disorders	0	0	1 (0.5)	0	1 (0.5)
Rheumatoid arthritis	0	0	1 (0.5)	0	1 (0.5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1 (0.5)	1 (0.4)	1 (0.5)
Acute leukaemia	0	0	0	1 (0.4)	0
Meningioma	0	0	1 (0.5)	0	1 (0.5)
Nervous system disorders	0	1 (1.1)	1 (0.5)	1 (0.4)	3 (1.4)
Cerebral infarction	0	0	1 (0.5)	0	1 (0.5)
Dementia	0	0	0	0	1 (0.5)
Transient ischemic attack	0	0	0	0	1 (0.5)
Vascular dementia	0	1 (1.1)	1 (0.5)	1 (0.4)	0
Product issues	1 (1.0)	0	0	1 (0.4)	0
Device dislocation	1 (1.0)	0	0	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	1 (1.0)	0	0	1 (0.4)	0
Chronic obstructive pulmonary disease	1 (1.0)	0	0	1 (0.4)	0
Vascular disorders	0	0	2 (1.0)	1 (0.4)	2 (0.9)
Aortic aneurysm	0	0	1 (0.5)	0	1 (0.5)
Circulatory collapse	0	0	1 (0.5)	0	1 (0.5)
Neurogenic shock	0	0	0	1 (0.4)	0

Source: [Post-text Table 14.3.8.1a](#) and [Table 14.3.8.1b](#)

AE = adverse event; COVID-19 = coronavirus disease 2019; EM = every month; EOM = every other month; IOP = intraocular pressure; PT = Preferred Term; Re-Rand = re-randomized; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Note: TEAEs are AEs occurring after the first injection on Day 1 up to 30 days after the last dose of study drug. However, all occurrences of CNV are collected as TEAEs, even if the last study visit occurred more than 30 days after the last dose of the study drug. See Section 9.5.1.2.1.1 for specific details on collection and reporting methods and timing for Year 2 AEs.

3.3.7.11. Use in Pregnancy and Lactation

There are no available data on avacincaptad pegol use in pregnant women to evaluate the drug-associated risks. Pregnant women were excluded from studies. Avacincaptad pegol has negligible systemic exposure following the intravitreal route of administration. Animal studies in rats and rabbits did not indicate harmful effects with respect to reproductive toxicity however, concerns exist as to the pharmacological relevance of these species (rat and rabbit).

From all avacincaptad pegol clinical trials, there were three reports of pregnancy in partners of male patients, which resulted in birth of three normal newborns, one of whom had a premature delivery. However, avacincaptad pegol is administered directly into the vitreous to exert local effects in the eye, avacincaptad pegol plasma concentrations are predicted to be approximately 7,000 fold lower than vitreal concentrations, and passage into the semen has not been studied, no consequences are anticipated for the foetus exposed via the father.

No information is available on the clinical use of avacincaptad pegol during breastfeeding, on the presence of avacincaptad pegol in human milk, on the effect on the breastfed infant, or effects on milk production. Because avacincaptad pegol is administered directly into the vitreous to exert local effects in the eye and avacincaptad pegol plasma concentrations are predicted to be approximately 7,000 fold lower than vitreal concentrations, the amount in milk is likely to be low. The elimination half-life is 12 days and is indicative of potential accumulation in infant.

3.3.7.12. Overdose, Drug Abuse, Withdrawal and Rebound

There is no known potential for abuse of Avacincaptad pegol and no abuse studies have been performed. Overdose and drug potential are unlikely as the drug is administered IVT by a physician in a clinic. All patients should be monitored for post-injection IOP increase and treatment initiated with paracentesis if necessary. There is unlikely to be a misuse problem with avacincaptad pegol as it does not affect the central nervous system. There is a low probability of any potential withdrawal syndrome since the elimination half-life of avacincaptad pegol is slow (12 days).

3.3.7.13. Effect on ability to drive or operate machine

Avacincaptad pegol can be associated to temporal visual disturbances that may affect a person's vision dependent ability to drive or operate machine.

3.3.7.14. Post marketing experience

Izelvay has been recently approved by the FDA in August 2023. The applicant provided post-marketing safety data (US) for the reporting period of 04 Aug 2023 to 03 Feb 2024 which provides 1070 patient-years or 12,841 patient-months of exposure to avacincaptad pegol. Overall, 32 events (including 13 serious event) were reported of which 8 were serious and unexpected. One event of retinal vasculitis as off-label use in a patient treated for Stargardt disease with pegcetacoplan (left eye) and avacincaptad pegol (right eye). The patient presented retinal vasculitis in both eyes. The outcome is unknown. One patient presented non-arteritic anterior ischemic optic neuropathy, vitritis, visual impairment geographic atrophy secondary to AMD progression after two injections of avacincaptad pegol (right eye). The outcome is unknown. Overall, based on the submitted post-marketing data, the safety profile of avacincaptad pegol seems similar to the profile seen in clinical trials. No new safety signal was identified.

3.3.8. Discussion on clinical safety

The safety profile of Avacincaptad pegol in geographic atrophy (GA or dry AMD) is based on the pooled unmasked safety data up to month 12 from the Cohort 1 studies (n=780 patients) consisting of one pivotal randomized study ISEE2008/GATHER 2 (ongoing 24-months phase 3 study, n=447) and two supportive studies OPH2001 (completed phase I open label study, n=47) and OPH2003/GATHER 1 (randomized completed 18-months phase 2/3 study, n=286). At year 2, patients were re-randomized to receive avacincaptad pegol 2 mg monthly (EM) or every other month by alternating avacincaptad pegol 2 mg/sham (EOM). Safety data up to Year 2 were provided for the Re-randomized analysis set (n=96 patients in EM, n=98 patients in EOM and n=203 patients for sham) and for the overall avacincaptad pegol (n=225 patients) and sham (n=222 patients) arms (all patients who had ever received an injection of avacincaptad pegol in the 24-month study period).

The proposed dosing regimen by the applicant in the current application is 2 mg administered by IVT injection every 4 weeks for the first 12 months followed by an administration as studied in OPH2003 and ISEE2008. GA is typically a progressive condition and usually bilateral, with about half of patients developing GA in both eyes within 7 years of initial diagnosis [Boyer et al, 2017; Lindblad et al, 2009]. However bilateral treatment was not evaluated in clinical trials in patients with GA secondary to AMD which is acknowledged. In OPH2003, 83 patients were treated by twice the recommended dose (4 mg), thus limited data are available and results are not considered as fully applicable to bilateral treatment but supportive of the expected safety profile. However, the clinical safety of a dose of 4 mg avacincaptad pegol (two IVT injections [2 mg each] per eye per day), evaluated in study OPH2003, shows that the safety profile of the 4 mg dose is worse than that of the 2 mg dose: the overall frequency of AEs (85.5% vs. 79.5%) and the frequency of ocular AEs in the study eye (71.1% vs 51.0%), ocular AEs in the study eye related to injection procedure (51.8% vs. 28.8%) and ocular AEs in the study eye leading to study drug discontinuation (1.2% vs. 0.7%) was higher in the 4 mg group compared to the 2 mg. The frequency of non-ocular AEs was slightly lower in the 4 mg dose group (54.2% vs. 56.2%) but serious non-ocular AEs were more frequently reported in patients treated with the 4 mg dose than the 2 mg dose (20.5% vs. 12.3%). Overall, these data show that even though bilateral treatment has not been specifically studied, an increased risk in adverse events with bilateral treatment seems likely, including the risk of increased systemic infection. In section 4.4 of the SmPc, the applicant mentions that "the safety and efficacy of avacincaptad pegol administered in both eyes concurrently have not been studied" which is endorsed. **The applicant should further discuss on how bilateral treatment is expected to be conducted in clinical trials (concomitant or alternate injections) with its impact on the safety profile of bilateral avacincaptad pegol including risk of systemic infections as PK findings showed an inhibition of C5 complement. Depending on the provided discussion, the applicant should propose adequate modifications to the SmPC as available in other IVT products (OC).**

Additionally, unmasked long-term safety data up to 18 months (OPH2003/GATHER 1) were provided in this submission with unmasked 6 month data from ISEE2009 (ISEE2008/GATHER 2 extension study) and 24-month unmasked data from ISEE2008.

Supportive data in other ocular indications (nAMD, Stargardt and IPCV) were also provided with safety data from Cohort 2 (OPH2000, OPH2007, OPH2004, OPH2005 and OPH2002). However, as these studies are not in the range of the targeted indication and posology, the use of these data is considered limited.

Patient disposition and exposure

In Cohort 1, 82,4% of the patient in the 2 mg group, 67,5% in the 4 mg group and 86,7% in the sham group completed month 12 visit. In the 4 mg arm (OPH2003), the incidence of patient discontinuation was the highest (30,1%) at month 12 compared to other groups (13,0% in the 2 mg vs 9,6% in the

sham). Patient discontinuation was mainly due to "patient request" (7,9% in the 2 mg vs 15,7% in the 4 mg and 6;3% in the sham) or "sponsor decision" (2,1% in the 2 mg vs 9,6% in the 4 mg vs 0,9% in the sham). Discontinuation due to adverse event was similar between groups 2 mg (1,0%) and 4 mg (1,2%) and with sham (0,9%). Furthermore, death was reported in similar proportions between sham (0,6%) and 2 mg (0,7%) while slightly higher in the 4 mg group (1,2%). Up to 18 months (OPH2003) similar tendencies can be observed, 71,6% in 2 mg group, 55,4% in the 4 mg group and 77,3% in the sham group completed month 18 visit. Up to month 24, the proportion of patients in the Re-Rand analysis set who completed the study through Month 24 was comparable in the avacincaptad pegol EM, avacincaptad pegol EOM, and sham treatment groups (92.7%, 89.2%, and 90.6%, respectively). The most reported reason for study discontinuation being withdrawal by patient (4.2% EM, 3.2% EOM and 3.4% in sham) AE (2.1% EM, 1.1% EOM and 3.0% in sham). The proportion of patients in the ITT analysis set who completed the study through Month 24 was similar in the avacincaptad pegol 2 mg and the sham treatment groups (77.8% and 82.9%) with the most common reason for discontinuation being withdrawal by patients (12.4% in avacincaptad pegol 2 mg arm and 9.9% in sham).

In Cohort 1, up to month 12, the majority of the patient received 10-12 injections 88,9% in the sham group, 86% in the 2 mg group and 72,3% in the 4 mg group. The mean number of injections was similar between the sham (n=11,1) and the 2 mg (n=10,8) and slightly lower in the 4 mg group (n=9,8). The injection fidelity rate was of 90% in the 2 mg, 92,7% in the sham and 81,8% in the 4 mg group. Mean treatment duration were similar between 2 mg (336,5 days) and sham group (344,8 days). Up to month 18 (OPH2003), on the 67 patients in the 2 mg group, 67.2% received 16-18 IVT injections and 11,9% received 13-15 IVT injections.

Up to month 24, patients were administered with a mean of 22.52 (SD:2.95) injections for avacincaptad pegol EM (n=96 patients) and 16.98 injections (SD:1.86) for avacincaptad pegol EOM (n=93 patients). The fidelity rate was similar in both groups irrespective of the differing dosing regimen in Year 2 (EM: 0.938 versus EOM: 0.943).

Demographic characteristics

In Cohort 1, the population consisted for the majority of female white non-Hispanic/Latino patient aged ≥ 75 years old non- active smokers (2/3) with light or medium iris color, pseudophakic or phakic for the majority. Mean baseline BVCA score in the study eye was comparable between groups (70,8 letters for 2 mg vs 70,7 in sham) and lower in the fellow eye (60,9 letters for 2 mg vs 60,2 in sham). Mean baseline IOP was similar between groups and between study eye and the fellow eye. Additionally, evidence of choroidal neovascularisation in either eye and any prior treatment for AMD or any prior IVT treatment for any indication in either eye except oral supplements of vitamins or minerals were exclusion criteria

Overall, comparable proportions were reported for baseline demographics and disease characteristics between groups in particular between sham and 2 mg. Regarding reported prior ocular medical history, all patients had medical history of nAMD in the study eye which is consistent with the studies population and with the most reported PTs being cataract (more than 70%), vitreous detachment (more than 40%) and dry eye (more than 14%) with comparable proportions between sham, 2 mg and 4 mg groups. Concerning medical history, the most reported SOC in all groups were cardiac disorders (38,3% in sham vs 39% in 2 mg), gastrointestinal disorders (43,7% in sham vs 38,7% in 2 mg), metabolism and nutrition disorders (52,1% in sham vs 60,6% in 2 mg), Musculoskeletal and connective tissue disorders (54,5% in sham vs 49,7% in 2 mg) and vascular disorders (74,4% in sham vs 70,9% in 2 mg) with overall comparable proportions between sham, 2 mg and 4 mg.

Prior ocular and non-ocular medical history were consistent with the studies population and well-balanced between arms. Prior and concomitant medication and surgeries and procedure were consistent with the studied population. Prior surgeries were reported in comparable proportions across treatment arms with the most reported type being cataract operations (50,7% in 2 mg and 49,7% in sham) which is consistent

with the reported ocular history. Concomitant surgeries and procedures were reported in 1/3 of the patients across treatment arms with the most reported being paracentesis eye and cataract operation. Similar tendencies were observed for prior and concomitant surgeries and procedures in the study eye.

Subgroup analyses were performed by age and sex in Cohort 1. Interpretation of these individual analyses is limited given the small number of subjects within certain subgroups. Treatment exposure was comparable between age and sex categories with a majority of patient who received 10-12 injections. No significant differences in the safety profile of avacincaptad pegol were seen regarding patient age nor sex.

For Year 2, demographic characteristics and medical history for the patients who were re-randomized in EM and EOM group for avacincaptad pegol 2 mg group are discussed in *Efficacy section*.

Overview of adverse events

Ocular TEAEs

In Cohort 1, up to month 12 more patient presented TEAEs with avacincaptad pegol (79,5% in the 2 mg) compared to sham (69,6%) and similarly up to month 24 92.4% in the avacincaptad pegol group and 82.9% in the sham group experienced at least one TEAE with comparable proportions between avacincaptad pegol EM (92.7%) and the avacincaptad pegol EOM group (95.7%). This imbalance was mainly driven by the ocular TEAE in the study eye which were more reported in the avacincaptad pegol 2 mg group (51,0% vs 36,4%) while ocular TEAE in the fellow eye were reported in comparable proportions between arms (18,7% in sham, 20,5% in 2 mg and 19,3% in 4 mg) up to Year 1. Up to Year 2, in study ISEE2008, similar tendencies were observed with ocular TEAE in the study eye occurring in higher proportions with 69.8% of the patients in the avacincaptad pegol 2 mg EM group and 64.5% in the avacincaptad pegol 2 mg EOM group compared to 48.8% in the sham group.

Up to Year 1, the most reported SOC for ocular TEAEs in the study eye consisted of "Eye disorders" which was in higher incidence in the avacincaptad pegol groups (47,9% in the 2 mg and 62,7% in the 4 mg) compared to sham (35,2%). The most reported PT with higher incidence in the avacincaptad pegol group were Intraocular pressure increased, Conjunctival haemorrhage, Choroidal neovascularisation, Eye pain, Vision blurred, Vitreous floaters and visual impairment. Up to Month 18 (OPH2003), similar tendencies could be observed. Up to Year 2, the most reported PT in the study eye were consistent with data up to month 12 and consisted of Intraocular pressure increased (14.6% in avacincaptad pegol EM arm, 11.8% in EOM and 1.0% in sham due to the sham procedure simulating the pressure of an IVT injection), Conjunctival haemorrhage (17.7% in EM; 17.2% in EOM and 7.4% in sham), Choroidal neovascularisation (16.7% in EM arm, 9.7% in EOM and 9.9% in sham), Punctuate keratitis (9.4% in EM arm, 11.8% in EOM and 5.9% in sham), Cataract (9.4% in EM arm, 5.4% in EOM and 6.9% in sham), Conjunctival hyperaemia (8.3% in EM arm, 4.3% in EOM and 5.9% in sham), vitreous detachment (6.3% in EM arm, 4.3% in EOM and 3.9% in sham), retinal haemorrhage (3.1% in EM arm, 6.5% in EOM and 3.4% in sham) and visual acuity reduced (1.0% in EM arm, 5.4% in EOM and 3.0% in sham). Severe ocular TEAEs in the study eye occurred in eleven patients (4.9%) in the avacincaptad pegol group (7.3% in EM, 3.2% in EOM) and 2 patients (1.0%) in the sham group. Furthermore, 6 of these patients who received avacincaptad pegol had 16 events that were considered related to injection procedure.

Up to Year 1, ocular TEAE in the study eye in the 2 mg were assessed as related to injection procedure in 28,8% (20,8 % in the sham group) and to study drug in 1,4% (0,6% in sham). In Avacincaptad pegol 2 mg, 2,1% of the patients discontinued study drug, of those ocular TEAEs was assessed as related to study drug in 2 patients (0,7%). In Avacincaptad pegol 4 mg, ocular TEAE were reported in 71,1% of the patients and 51,8% were assessed as related to injection procedure. Ocular TEAEs in the study eye were assessed as study drug related in 4 cases of CNV (1,4%) in the 2 mg group vs 2 cases (0,6%) in the sham group. Ocular TEAE in the study eye assessed as related to avacincaptad pegol were for the

majority IVT injection procedure-related (20,2% in sham vs 28,8% in 2 mg vs 51,8% in 4 mg) and consisted mainly of IOP (7,2% in 2 mg vs 0,3% in sham), Conjunctival haemorrhage (12% in 2 mg vs 8,7% in sham) and Eye pain (3,1% in 2 mg vs 2,4% in sham). Up to Year 2, ocular TEAEs in the study eye related to study drug injection procedure were reported in 38.5% in the avacincaptad pegol 2 mg EM group, 33.3% in the avacincaptad pegol 2 mg EOM group and 20.2% in sham group. The most commonly reported ($\geq 2\%$ of patients in any treatment group) ocular TEAEs in the study eye through Month 24 that were judged related to the injection procedure were conjunctival haemorrhage (17.7% EM, 12.9% EOM, 6.9% sham), IOP increased (12.5% EM, 10.8% EOM, 0% sham), conjunctival hyperaemia (7.3% EM, 4.3% EOM, 5.4% sham), punctate keratitis (4.2% EM, 7.5% EOM, 3.9% sham), eye pain (4.2% EM, 5.4% EOM, 3.0% sham) and eye irritation (2.1% EM, 1.1% EOM, 3.4% sham). These events are expected secondary to IVT injection procedures. Ocular TEAE in the study eye related to study drug occurred in low proportions 5.2% in avacincaptad 2 mg EM group, 2.2% in avacincaptad pegol 2 mg EOM group and 1.0% in sham. Ocular TEAEs in the study eye assessed as related to study drug occurred in low proportions 2.2% in avacincaptad 2 mg EM group, 2.2% in avacincaptad pegol 2 mg EOM group and 1.0% in sham.

TEAEs were mild to moderate in severity and severe ocular TEAE were slightly more reported in avacincaptad pegol (Year 1: 2,4% in 2 mg, 1,8% in 4 mg and 0,6% in sham; Year 2: 7.3% EM, 3.2% EOM and 1.0% sham). Ocular TEAE were mainly moderate (11% in 2 mg vs 10,2% in sham) or mild (36,7% in 2 mg vs 25,6% in sham) in severity and severe ocular TEAEs were slightly more reported in 2 mg arm and higher in the every month dosing regimen compared to every other month dosing regimen (77.3% vs 3.2%). In the avacincaptad pegol 2 mg arm, Choroidal neovascularisation, VA reduced transiently, and IOP increased were each reported as severe ocular TEAEs for two patients (0.7%) each up to Year 1. Severe ocular TEAEs of retinal artery occlusion (transient) were reported for study OPH 2003 in two patients (one in 2 mg arm and one in 4 mg arm). Up to month 18, 2 additional severe events in the avacincaptad pegol arm were reported at month 18, one case of optic ischemic neuropathy and one case of nvAMD. None were assessed as related to avacincaptad pegol. Up to year 2 in ISEE2008, 5 (5.2%) patients in the avacincaptad pegol EM, 1 (1.1%) patient in the avacincaptad pegol EOM, and 1 (0.5%) patient in the sham group experienced severe ocular TEAEs in the study eye which were for the majority assessed as injection procedure related.

The safety profile of EOM administration appears more favorable, with lower incidence than EM treatment of adverse events related to the injection procedure (38.5% EM; 33.3% EOM and 20.2% sham), ocular adverse events (69.8% EM, 64.5% EOM, 48.8% sham) and serious ocular adverse events (26% EM, 26.9% EOM and 21.7% sham). These data cast doubts on the proposed EM posology and the related safety risks after the first year of treatment. The applicant should discuss whether EOM injections would be preferable, taking into account available safety data and patient burden associated with intravitreal injections. (OC)

Non-ocular TEAE Up to Year 1, incidences of non-ocular TEAEs were comparable between arms (56,2% in 2 mg vs 55,7% in sham and 54,2% in 4 mg) with the most reported SOC being Infections and infestations (25,7% in 2 mg vs 21,4% in sham and 28,9% in 4 mg), Musculoskeletal and connective tissue disorders (9,9% in 2 mg vs 10,8% in sham and 9,6% in 4 mg) and Injury, poisoning and procedural complications (14,7% in 2 mg vs 13,6% in sham and 13,3% in 4 mg). Most reported PT in 2 mg were urinary tract infection, fall, nasopharyngitis with comparable incidences between 2 mg arm and sham and which are consistent with the study population. Up to Month 18, similar tendencies could be observed. Up to Year 2, non-ocular TEAEs occurred in 74.0% of the patients in the avacincaptad pegol 2 mg EM group and 84.9% in the avacincaptad pegol 2 mg EOM group compared to 71.4% in the sham group. The most reported SOC were Infections and infestations (comparable incidence between treatment arms), Injury, poisoning and procedural complications (21.9% in EM, 19.0% in EOM and 21.7% in sham), Cardiac disorders (19.4% EOM vs 13.5% EM vs 14.3% sham) and Musculoskeletal and

connective tissue disorders (21.9% EOM vs 11.8% EM vs 17.2% sham). Some discrepancies could be observed for reported non-ocular TEAEs on a SOC level but they were consistent with the reported incidences of non-ocular medical history between the two different dosing regimens (EM and EOM) and compared to sham.

During study ISEE2008, non-ocular AEs related to the injection procedure were few. Two patients across all treatment groups had a non-ocular event (headache and contusion) related to the injection procedure with none related to avacincaptad pegol/sham. Furthermore, no non-ocular TEAEs were reported to be related to the injection procedure, avacincaptad pegol, or sham at Month 24.

Up to Year 1, non-ocular TEAEs were mainly mild (25,7%) to moderate (19,5%) in the 2 mg arm and comparable proportions of severe non-ocular TEAEs were reported between arms (10,5% in sham and 4 mg vs 11% in 2 mg arm). Severe non-ocular TEAEs were reported in single patients for the majority except for fall, upper GI haemorrhage, pneumonia and pulmonary embolism. None were assessed as related to avacincaptad pegol. Up to Year 2, a total of 43 patients (19.1%) in the avacincaptad pegol group (overall) and 39 patients (17.6%) in the sham group experienced at least 1 severe non-ocular TEAE overall. The frequency of severe non-ocular TEAEs was higher in the avacincaptad pegol EOM (22.6%) than in the EM group (14.6%). No severe non-ocular TEAE was reported to be related to the injection procedure, avacincaptad pegol, or sham.

Serious TEAEs, death and study discontinuation due to adverse events

Up to Year 1, serious TEAEs were reported with a higher incidence in the sham group and were for the majority non-ocular TEAE (12,3% in the 2 mg vs 16,6% in the sham). Serious ocular TEAEs in the study eye were reported with comparable incidence between group and were low ($\leq 1\%$). One patient in the 2 mg arm (0,3%) reported a serious ocular TEAE related to study drug. TEAE lead to patient's death in 4 patients (3 patient in 2 mg and 1 patient in the 4 mg arm) and no death were assessed as related to avacincaptad pegol treatment or the injection procedure. Up to 18 month (OPH2003), similar tendencies were observed.

Up to year 1, proportions of serious ocular TEAEs were low and comparable between arms (0,7% in avacincaptad pegol 2 mg and 0,6% in sham). None were reported in the fellow eye. In avacincaptad pegol 2 mg, serious ocular TEAEs consisted of CNV (n=2, one assessed as related to study drug). None were assessed as related to IVT injection-procedure. Up to Month 18 (OPH2003), two serious ocular TEAEs were reported; one case of retinal detachment (4 mg) and one case of optic ischemic neuropathy (2 mg). None were assessed as related to avacincaptad pegol. Up to Year 2, serious ocular TEAEs occurred in slightly higher proportions in avacincaptad pegol arm (26.7%) compared to sham arm (23%) and was comparable between dosing regimens for avacincaptad pegol groups (26.0% in EM arm and 26.9 in EOM arm). Ocular SAEs in the study eye at Month 24 were reported in 6 (1.3%) patients in total; 4 [1.8%] patients in avacincaptad pegol 2 mg group (CNV in one patients, endophthalmitis in one patient and device dislocation (posterior displacement of the intraocular lens) in one patient in EM group and CNV in one patient in EOM group) and 2 patients [0.9%] in sham group (Visual acuity reduced in two patients). Of these, 2 patients experienced serious ocular TEAEs in Year 2. Both patients were treated with avacincaptad pegol EM. Two ocular SAEs (one event of retinal haemorrhage and one event of neuromyelitis optica spectrum disorder) were reported in the fellow eye at Year 2.

Up to Year 1, proportions of non-ocular serious TEAEs were slightly higher in the sham group (16,6% vs 12,3% in the 2 mg group). The most reported SOCs for the 2 mg were Infections and Infestations and Injury, poisoning and procedural complications. Most of the non-ocular serious TEAEs by PT were reported for only one patient each in the 2 mg arm except Atrial fibrillation, Upper GI haemorrhage, Pneumonia, Fall, Pulmonary embolism and Cellulitis which is generally consistent with the study population. No serious non-ocular TEAEs were assessed as related to avacincaptad pegol. No non-ocular SAEs by PT occurred with a frequency of $\geq 3\%$ in any treatment group at Month 18.

Up to Year 2, serious non-ocular TEAEs were reported in slightly higher incidence in the avacincaptad pegol 2 EOM arm (26.9%) while comparable between avacincaptad pegol 2 mg EM arm (20.8%) and sham arm (20.7%). Serious non-ocular TEAEs occurred in $\geq 2\%$ in the avacincaptad pegol 2 mg EOM arm and consisted of Chest pain (2.2% n=2 vs 0% in avacincaptad pegol 2 mg EM arm and sham arm; Clostridium difficile infection 2.2% n=2 vs 0 in avacincaptad pegol 2 mg EM arm and sham arm, Cerebrovascular accident 2.2% n=2 vs 0 in avacincaptad pegol 2 mg EM arm and 2.0% n=4 in sham arm). During the entire study, there were no non-ocular SAEs related to the injection procedure, avacincaptad pegol, or sham.

Up to Year 1, a total of 12 deaths occurred of which 6 were reported in Cohort 1 including 4 TEAEs: one TEAE of road traffic accident in OPH2003, one TEAE of neurogenic shock, two TEAE of pneumonia. One case of chronic obstructive pulmonary disease and chronic respiratory failure (OPH2003) and one case of metastatic ovarian cancer (ISEE2008) were also reported for two deaths, all were not considered as TEAEs since they occurred ≥ 30 days after last dose. Up to Month 18 (OPH2003), two additional deaths occurred, one case of oesophageal varices rupture and haemorrhage and one case of cerebral infarction. None were assessed as related to avacincaptad pegol. One patient died of bacteraemia in Cohort 2. One road traffic accident was reported in OPH2005.

Up to Year 2, TEAEs leading to death occurred in low proportions 1.8% in avacincaptad pegol group vs 2.3% in sham group. Sixteen deaths occurred during the study up to Month 24 of which nine of the deaths were due to TEAEs and none were assessed as related to the study drug or injection procedure. In Cohort 1, up to Year 1, discontinuation due to adverse event were slightly higher in avacincaptad pegol groups 2 mg (2,1%) and 4 mg (2,4%) than with sham (0,9%). No ocular and non-ocular TEAE leading to study discontinuation were related to study drug. Two patients in avacincaptad pegol 2 mg presented vitreous detachment and IOP increase assessed as IVT injection procedure related which lead to study discontinuation (one patient each). More patient discontinued study due to non-ocular TEAE (1,4%) than ocular TEAE (0,7%) in the avacincaptad pegol 2 mg arm. Up to Month 18, four additional TEAEs lead to patient study discontinuation (one fatal case of cerebral infarction, one serious case of optic ischemic neuropathy, one serious case of retinal detachment and one serious cerebral haemorrhage). None were assessed as related to the injection procedure or to avacincaptad pegol/sham. Up to Year 2, a lower incidence of serious non-ocular TEAEs leading to permanently discontinued study drug were observed in avacincaptad pegol arm (2.1% in EM arm and 1.1% in EOM arm) compared to sham arm (3.0). Similar trends were seen for TEAEs leading to permanently discontinued study drug (4.9% in avacincaptad pegol 2 mg group and 4.1% in sham arm). Non-ocular TEAEs leading to study drug discontinuation occurring in the avacincaptad pegol group were pneumonia, acute leukaemia, chronic cardiac failure, biliary obstruction, vascular dementia, chronic obstructive pulmonary disease, and neurogenic shock in one patient each (0.4%). Four patients in the avacincaptad pegol group had ocular TEAEs leading to study drug discontinuation: CNV, vitreous detachment, IOP increased, and device dislocation, and 2 of them (vitreous detachment; IOP increased) were also related to the injection procedure. There were no TEAEs leading to study drug discontinuation related to avacincaptad pegol/sham.

Treatment-Emergent Adverse Events of Interest (TEAEI)

Up to month 12, for Avacincaptad pegol 2 mg group, a total 20.5% of the patient experienced a TEAEI vs 7.5% in the sham group. IOP increased ≥ 30 mmHg and CNV were the most reported with respectively 11.3% (vs 1.2% in sham group) and 7.2% (vs 3.6% in sham group) of the patients being concerned in the avacincaptad pegol 2 mg arm. Up to 18 months, similar tendencies were observed with 32.2% of the patients in Avacincaptad pegol 2 mg arm and 18.1% on the sham group presenting at least 1 TEAEI event. The most reported TEAEIs were IOP increased ≥ 30 mmHg (14.7% vs 1.2% in sham group), CNV (11.6% vs 6.9% in sham group) and BVCA decrease (8.9% vs 11.4% in sham).

Endophthalmitis

No events of endophthalmitis were reported in Cohort 1 (up to Month 12). In study OPH2002 (clinical trial conducted in IPCV), one mild case of endophthalmitis was reported which was assessed as related to IVT injection-procedure. In study ISEE2008, one patient was administered monthly injection of avacincaptad pegol 2 mg in the right eye. Four days after the latest dose of study drug administration on the Month 22 visit, the subject was diagnosed with endophthalmitis in the study eye which was severe. The event was assessed as related to injection procedure. The dose of treatment was not changed and patient was treated for endophthalmitis positive to staphylococcus epidermidis.

Intraocular inflammation

Regarding IOI, one resolved mild case of vitritis assessed as not related to IVT injection or study drug was reported in Cohort 1 in the avacincaptad pegol 2 mg arm. No cases of retinal vasculitis or retinal occlusive vasculitis were reported. Up to month 18, one mild case of cystoid macular oedema assessed as not related to avacincaptad pegol occurred. In Cohort 2, six event of mild vitreous haze (n=3 patients) and one mild case of anterior chamber cells trace were assessed as related to IVT injection procedure. None of the TEAEs were SAE and all events were resolved.

Up to month 24, in study ISEE2008, one non serious, moderate and resolved event of Vitreal cells was reported in a patient who received avacincaptad pegol 2 mg EM.

Cataract

In study ISEE2008, up to month 24, similar proportion of phakic patients in the avacincaptad pegol and sham groups overall exhibited a TEAE of the high-level term of "cataract conditions" in the study eye (9.8% and 12.8%, respectively) and between dosing regimen a higher proportion was observed in avacincaptad pegol EM treatment group (13.6%) versus EOM (8.5%). Similar tendencies were observed for the fellow eye. There were no reported events of traumatic cataract.

IOP increased

Up to month 12, the proportion of patient presenting a transient IOP ≥ 30 mmHg was much higher in the avacincaptad pegol 30,1% in 4 mg arm, 11,3% in 2 mg arm and 1,2% in sham. However, it is to be taken into account that in the sham group, the sham procedure simulated the pressure of an injection. The overall prevalence per 1000 injections were of 37,59 for 4 mg arm 11,06 for 2 mg arm and 1,09 for sham group. Incidences over time were highest at 0 - 3 months and >6 - 9 months for avacincaptad pegol 2 mg arm and at 0-6 month for avacincaptad pegol 4 mg arm. Patients in the 2 mg and 4 mg arm both had a mean value IOP of 18,2 mmHg after the first injection. Up to month 12, the majority of patient in avacincaptad pegol groups had an IOP ≤ 21 mmHg and a change from baseline ≤ 5 mmHg after the first injection and ≤ 10 mmHg after second injection (4 mg arm). The Mean IOP value change (mmHg) in the study eye were stable up to month 12 and 18 months.

Up to Year 2, 32 (7.2%) patients across treatment groups reported to have experienced a TEAE of increased IOP: 30 (13.3%) patients in the avacincaptad pegol group (overall) and 2 (0.9%) patients in the sham group. There were 28 subjects in the avacincaptad pegol 2 mg group (overall) and 4 subjects in the sham group who had reported a TEAEI of IOP ≥ 30 mmHg in the study eye during the study. The proportion of patients in the avacincaptad pegol 2 mg EM and the avacincaptad pegol 2 mg EOM group that experienced increased IOP was similar (14 [14.6%] and 11 [11.8%]). Of these, 8.3% of patients in the avacincaptad pegol EM treatment group experienced a transient IOP ≥ 35 mmHg 30 minutes post-injection (0.693% of all injections) and 6.5% of patients in the avacincaptad pegol EOM treatment group (0.432% of all injections). The majority of the events of IOP increased were transient, mild or moderate, assessed as related to IVT injection procedure and resolved on the same day.

Up to Year 1, paracentesis was required in 3,1 % (2,90 per 1000 injections) of the patient in the 2 mg group and 2,4% (2,50 per 1000 injections) in the 4 mg group. Up to 18 months (OPH2003), 30 patients presented IOP $\geq$ 35 mmHg at any time including 6 patients in the 2 mg arm. Five patients in the 2 mg arm and 3 patients in the 4 mg were treated by paracentesis for IOP increase. Similar tendencies could be observed in Cohort 2. Up to Year 2, ten patients (4.4%) in avacincaptad pegol underwent at least 1 post-injection paracentesis over the 24-month treatment period, there were a total of 44 cases of post-injection paracentesis (0.982% per number of total injections).

Transient vision loss

In Cohort 1, the majority of the patients did not present transient vision loss in the study eye. Incidence of transient vision loss was of 1,4% in avacincaptad pegol 2 mg arm (prevalence of 1,28 per 1000 injections), 1,2% in 4 mg arm (prevalence of 1,24 per 1000 injections) and none in sham arm. None were reported as an SAE nor lead to study discontinuation. All events started after the injection on the day of the injection, resolved on the same day and were considered as related to injection procedure. Severe ocular TEAEs of retinal artery occlusion (transient) were reported for study OPH2003 in two patient (3 events at day 1, month 10 and 17 in one patient in 2 mg arm and 5 events at day 1, Months 3, 4, 7 and 8 in one patient in the 4 mg arm) which resolved on the same day for both and were not associated to an inflammation and with a stable VA for both patient. The events of transient retinal artery occlusion lead to study discontinuation for the patient in the 4 mg arm due to the Investigator decision. All events were assessed as related to IVT injection procedure. Up to month 18 (OPH2003), two additional patients presented transient events of retinal artery occlusion in the 4 mg arm; four mild events at Month 13, 14, 16 and 17 for one patient and one moderate event at Month 15 for the other patient). Up to month 24, there were 7 (1.6%) patients total who experienced VA reduced transiently and 5 (1.1%) patients who experienced blindness transient; all except 1 patient who experienced VA reduced transiently were in the avacincaptad pegol group. The percentage of patients who experienced VA reduced transiently (5.2% versus 1.1%, respectively) was slightly higher in the avacincaptad pegol EM treatment group than in the EOM treatment group. The percentage of patients who experienced blindness transient (2.2% [EM] versus 2.1% [EOM]) was comparable between both avacincaptad pegol treatment groups. There were 6 severe AEs of transient vision loss: 3 events of blindness transient in 2 avacincaptad pegol patients (all lasting 1 day), which were resolved/recovered and related to injection procedure, and 3 events of VA reduced transiently in 2 avacincaptad pegol patients (2 events lasting 1 day and 1 event lasting 16 days), which were resolved/recovered, and 2 of the 3 events were related to injection procedure.

BCVA decrease ($\geq$ 30 Letters)

Up to month 24, the incidence of BCVA decrease of $\geq$ 30 letters from Baseline occurring in the SE was comparable across all treatment groups in the Re-Rand analysis set (13.5%, 8.6%, and 11.8% patients in the avacincaptad pegol EM, avacincaptad pegol EOM, and sham groups, respectively. Overall, 22 patients in the avacincaptad pegol treatment group experienced one or more visits with BCVA decrease $\geq$ 30 letters from Baseline compared to 26 patients in the sham group experiencing one or more visits with $\geq$ 30 letters BCVA loss from Baseline.

In Cohort 1, 4% of the patient treated by avacincaptad pegol (nine in 2mg, six in 4 mg and three in 1 mg) presented a BVCA decrease $\geq$ 30 Letters in the study eye which is similar to sham (3.3%). The majority of the patient in the avacincaptad pegol 2 mg and 4 mg groups had a decrease between 6-9 months after treatment initiation. Up to 18 months (OPH2003), seventeen patients had a BCVA decrease $\geq$ 30 letters between Month 12 and Month 18 including four patients in avacincaptad pegol, 2 arm and three patients in 4 mg arm.

Choroidal Neovascularization (CNV)

In ISEE2008, in case of CNV diagnosis patients could remain in the trial while receiving concomitant anti-VEGF therapy (aflibercept or ranibizumab) while in study OPH2003, patients were withdrawn from study per protocol. In Cohort 1, up to Year 1, CNV was reported in the avacincaptad pegol 2 mg group (7.2%) compared to the sham group (3.6%) in patients with GA secondary to AMD. In ISEE2008, 15 patients developed CNV of which two were an SAE (one severe and related to study drug and one mild and not related), four were assessed as related to study drug and cases occurred with a time to onset between 36 and 373 days. All patients were not recovered/not resolved and required no dose change with medication. In OPH2003, one patient in the avacincaptad pegol 1 mg group had CNV which was moderate, non-SAE, not related and not recovered/not resolved. In the 2 mg arm, six patients developed CNV of which none were an SAE, none were assessed as related to avacincaptad pegol, all were mild or moderate, and all were not recovered/ not resolved. In the 4 mg arm, eight patients developed CNV of which none were an SAE, none were assessed as related to avacincaptad pegol, all were mild to moderate, all were not recovered/not resolved. Cases occurred for the majority of the time more than 3 months after treatment initiation in the 2 mg and 4 mg groups. In study ISEE2008, up to Year 2, the incidence of CNV remained constant between the first year with 6.7% (vs 4.1% in sham) and 7.3% in the second year for the avacincaptad pegol 2 mg EM while being lower for the avacincaptad pegol 2 mg EOM with an incidence of 4.3% (lower compared to the sham 5.4%).

The annual rate of CNV for the combined 2 mg group decreased over time with 10.1 per 100 patient-years (vs 3.0 in sham) for the first year and 4.0 (vs 0) per 100 patient-years for year 2 (up to 18 months) in study OPH2003. As expected a higher rate could be observed for the avacincaptad pegol 4 mg 11.5 (vs 2.5 in sham) per 100 patient-years for the first year and 9.9 (vs 0 in sham) per patient-years for the second year (up to month 18) in study OPH2003.

In the 2 mg arm, concomitant ocular TEAE were: BCVA loss $\geq$ 30 letters associated to RPE tear or subretinal fibrosis (n=2), epiretinal membrane (n=1), conjunctivitis (n=1), transient IOP elevation $\geq$ 30 mmHg post-injection (n=1) with BVCA loss $\geq$ 30 letters (n=1). Up to 18 months (OPH2003), eight patients in 2 mg arm (including six which had the onset up to month 12) and thirteen patients in the 4 mg arm (including eight which had the onset up to month 12) experienced CNV in the study eye.

There is a potential for patients with non-exudative (dry) AMD to develop neovascularization and progress to (wet) exudative AMD. Currently, CNV is an identified important risk for avacincaptad pegol and special warning and precaution are proposed by the applicant in the SmPC with additional warning regarding anti-VEGF treatment. According to the applicant, the biological mechanism behind why development of CNV appears to increase with treatment of GA via complement inhibition is unclear. Indeed, both complement and VEGF demonstrated a role in late-stage AMD pathobiology however at this stage it is unknown if any correlation can be made regarding the development of CNV in patient treated by avacincaptad pegol.

The occurrence of CNV in 1 eye seems to be associated with a higher likelihood of occurrence of CNV in the contralateral eye regardless of the study treatment. Indeed, up to month 24, in the avacincaptad pegol 2 mg arm, 22.2% (4/14) of the patients who had CNV in the study eye had CNV in the fellow eye vs 10.6% (22/185) who did not. Additionally, 33.3% (5/15) of the patients in the sham arm who had CNV in the study eye had CNV in the fellow eye vs 7.2% (15/192) who did not.

With regard to the impact on visual acuity in patients who developed CNV, a comparative analysis of the changes in visual acuity observed between the avacincaptad pegol 2 mg and sham groups for patients who received anti-VEGF treatment after an event of choroidal neovascularisation was provided. This analysis was performed only with data from study ISEE2008, because only in this study patients who developed CNV in the study eye continued in the study and received concurrent avacincaptad pegol 2 mg or sham with anti-VEGF treatment - either Lucentis (ranibizumab) or Eylea (aflibercept). During the

24 months of the study, 24 patients in the avacincaptad pegol 2 mg arm and 18 patients in the sham arm received concurrent anti-VEGF treatment. The mean change in BCVA before the CNV onset compared with after the last anti-VEGF treatment (BCVA after anti-VEGF minus BCVA before CNV) decreased by 10.5 and 8.8 letters in the avacincaptad pegol 2 mg and sham arms, respectively. In addition, the mean change in BCVA before anti-VEGF treatment compared with after the last anti-VEGF treatment (BCVA after anti-VEGF minus BCVA before anti-VEGF) decreased by 9.6 and 6.7 letters in the avacincaptad pegol 2 mg and sham arms, respectively. The difference in BCVA decrease between the 2 treatment arms is within 3 letters in both cases, which is considered not clinically significant. In both groups, the same proportion of patients (16.7%; 4/24 patients in the avacincaptad pegol 2 mg arm and 3/18 patients in the sham arm) experienced severe vision loss (BCVA decrease $\geq$ 30 letters from baseline) in the study eye. The reason for this was mainly due to either other retinal comorbidities or GA disease progression. Taken together, these data suggest that patients treated with intravitreal avacincaptad pegol are not at risk of developing an untreatable (or less-treatable) CNV.

In study ISEE2008, 6.7% of the patient in 2 mg arm and 4.1% in sham arm developed CNV and received as protocol concomitant anti-VEGF injections (0-7) during the study. A total of 24 patients in the avacincaptad pegol (ACP) arm and 18 patients in the sham arm who developed CNV in the study eye received anti-VEGF treatment during the 24-month Study ISEE2008. Approximately 70% and 55.6% of the patient presented a TEAE after receiving anti-VEGF for avacincaptad pegol 2 mg and for sham respectively. Regarding non-ocular TEAEs, comparable proportions were reported between avacincaptad pegol with anti VEGF arm and avacincaptad pegol alone arm apart for the SOC cardiac disorders (29.2% ACP with anti-VEGF arm vs 14.4% ACP alone arm), General disorders and administration site conditions (12.5% ACP with anti-VEGF arm vs 5.5% ACP alone arm) and Investigations (37.5% ACP with anti-VEGF arm vs 21.4% ACP alone arm) however no PT were reported more than n>2 except for COVID-19. For ocular TEAEs, comparable incidence in the study eye were observed in patients who received avacincaptad pegol 2 mg with anti-VEGF compared with avacincaptad pegol 2 mg alone, sham alone, or sham with anti-VEGF treatment. For IOP increased, the incidence was higher in the avacincaptad pegol with anti-VEGF arm compared with avacincaptad pegol alone arm (16.7% vs. 12.9%) however the incidence of IOP increased was 12.5% in the avacincaptad pegol before anti VEGF arm compared with 4.2% in avacincaptad pegol after anti-VEGF arm. No new safety issue is raised regarding patient treated with avacincaptad pegol who presented CNV and received anti-VEGF therapy.

Retinal tear/Rhegmatogenous Retinal Detachment and vitreous

In Cohort 1, no cases of rhegmatogenous retinal detachment were reported. Two events of retinal tear were reported in the study eye for avacincaptad pegol arm (vs one in fellow eye), none were an SAE nor were considered related to the IVT injection procedure or the study drug.

Up to month 18, one event of temporal rhegmatogenous retinal detachment with a temporal retinal tear in the study eye which was mild, recovered and assessed as related to IVT injection procedure occurred prior to Month 13 pre-injection visit. The event lead to patient discontinuation due to investigator's decision.

Two patients presented event of vitreous haemorrhage in the study eye in Cohort 1. None were an SAE, nor related to study drug nor lead to patient discontinuation. One of the cases of vitreous haemorrhage (in the avacincaptad pegol 2 mg group) was considered related to the injection procedure. No events were reported up to month 18.

Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

One serious event of NAION in a patient receiving avacincaptad pegol 2 mg was reported in Study OPH2003 at Month 18 and was considered unrelated to study drug and injection procedure. There were no events of NAION reported in Study ISEE2008 up to month 24.

Systemic infection

Based on human PK data ($C_{max}=6.2$ nM) and in regards to an IC_{50} human of 0.6 nM, avacincaptad pegol release in the systemic circulation after IVT treatment, will inhibit the classical human complement activation pathway and could lead to an increase of susceptibility to infections (see *OC raised in PK section*).

In Cohort 1, comparable incidence was reported for the SOC of "infections and infestations" with 25.7% for the avacincaptad pegol 2 mg group and 24.1% for the sham group. Serious systemic events occurred in 3.1% of patients in the avacincaptad pegol 2 mg group and 3% of patients in the sham group. The incidence of upper respiratory tract infection was similar across groups (2.1% in the avacincaptad pegol 2 mg arm compared with 1.5% in the sham arm). The incidence of sepsis was slightly higher in the avacincaptad pegol 2 mg group (0.7% (2 patients) in the avacincaptad pegol 2 mg arm vs. 0 in the sham arm) and the incidence of nasopharyngitis and pneumonia was higher in the avacincaptad pegol 2 mg arm compared to the sham group (6.8% vs. 4.2% and 3.4% vs. 1.8%, respectively), but none of the TEAEs of nasopharyngitis, pneumonia and sepsis were deemed to be related to the study drug or injection procedure. No additional significant imbalances were noted. Up to month 18, similar tendencies were observed.

Although infections and infestations were only slightly more frequent up to month 12 in avacincaptad pegol 2 mg treated patients compared to the sham group, the frequency was markedly higher in the 4 mg group (sham: 24.1%, avacincaptad pegol 2 mg: 25.7%, avacincaptad pegol 4 mg: 28.9%), with relevant imbalances in upper respiratory tract infections (sham: 0.9%, avacincaptad pegol 2 mg: 1.4%, avacincaptad pegol 4 mg: 4.8%) and sepsis (sham: 0, avacincaptad pegol 2 mg: 0.3%, avacincaptad pegol 4 mg: 3.6%). In addition, serious infections and infestations were significantly higher in the 4 mg group (sham: 3.0%, 2 mg: 3.1%, 4 mg: 8.4%). An OC was raised in regard to this concern with bilateral systemic exposure. In study OPH2003, no non-ocular TEAEs linked to systemic infection were reported to be related to Zimura/Sham or to administration injection procedure up to Month 18.

Up to month 24 in ISEE2008, non-ocular infections and infestations were similar in both the avacincaptad pegol 2 mg group (overall) (40.9%) and the sham group (40.1%). The number of patients who experienced non-ocular infections and infestations (42.7% versus 45.2%, respectively) was comparable between avacincaptad pegol EM and EOM groups. The most commonly reported PT were "COVID-19" (32 patients (14.2%) in avacincaptad pegol group vs 36 patients (16.2%) in sham group)), "Urinary tract infection" (27 patients [12.2%] in sham vs 19 patients [8.4%] in avacincaptad pegol). One (0.4%) case of COVID-19 pneumonia was reported in the avacincaptad pegol treatment group. There were numerically more cases of pneumonia in the avacincaptad pegol group (8 patients; 3.6%) compared to the sham group (3 patients; 1.4%). There were 7 (3.2%) cases of herpes zoster reported in the sham group and 2 (0.9%) cases in the avacincaptad pegol 2 mg group.

Up to month 24 in ISEE2008, ocular infections and infestations occurred with similar frequency in the avacincaptad pegol group (7 patients; 3.1%) and the sham group (7 patients; 3.2%). These events included conjunctivitis, conjunctivitis viral, hordeolum, and one event of culture-positive endophthalmitis.

Drug hypersensitivity

No events of ocular and non-ocular hypersensitivity were assessed as related to avacincaptad pegol or sham. The reported events were for the majority post-injection events and related to the injection procedure such as conjunctival oedema, corneal oedema or eyelid oedema or events related to the injection preparation process, such as conjunctivitis due to betadine sensitivity.

Laboratory findings and vital signs

In Cohort 1, incidence of notable laboratory values was comparable between avacincaptad pegol and sham. Moreover, notable laboratory results were infrequent; none were reported as related to the study drugs, and none led to discontinuation from the study drug.

No clinically meaningful differences between the treatment groups for the pulse, systolic and diastolic blood pressure parameters were observed.

There were no clinically relevant differences in the nature of ECG changes between treatment groups and changes were consistent with those expected in the study population.

Similar tendencies were observed up to month 24.

Shift in ophthalmic examination from baseline to month 12 were comparable between treatment groups with no change compared to baseline and ophthalmic examinations were for the majority normal except for the macula which is consistent with the studied population. As anticipated, due to IVT volume effect in the avacincaptad pegol, volume effect in the avacincaptad pegol 2 mg (100 µL injection volume) and 4 mg (100 µL + 100 µL injection volume) groups, the mean post-first injection IOP values were higher compared to the mean pre-injection IOP values at each study visit.

Immunological events

No immunogenicity data issued from immunogenicity assays are available at this stage. In the ongoing study ISEE2009 (open extension study including patient who completed ISE2008), assessments of anti-drug antibodies (ADA) will be performed at pre-dose at Month 1, Month 2, Month 4, Month 7, Month 13, and Month 18. The applicant will submit an interim report on day 180 as the analysis of the sample is ongoing and a full data report after completion of study ISEE2009 which is endorsed. **The applicant refers to document ICDIM 722 Validation Report for the detailed methodology of a validated enzyme-linked immunosorbent assay which was designed to detect anti-avacincaptad pegol antibodies in human serum however the document ICDIM 722 Validation Report could not be found in the submitted file (OC).**

Safety related to drug-drug interactions and other

No dedicated clinical studies evaluating the drug-drug interaction potential of avacincaptad pegol have been conducted.

In study ISEE2008, patient who developed CNV remained in the study with continued study treatment and received concomitant IVT anti-VEGF therapy. According the applicant, no new safety concerns have been identified when patients who developed CNV continued with avacincaptad pegol 2 mg treatment and received concurrent IVT anti-VEGF therapy. However, the applicant was requested to further discuss on this topic.

Moreover, non-clinical data showed unexpected results for avacincaptad pegol effect on CYP3A4 substrate (midazolam) as discussed in the non-clinical AR (section pharmacokinetic drug interaction). A potential DDI between avacincaptad pegol and CYP3A4 substrates could not be ruled out and further investigation were requested (see OC in *Pharmacology section*) including conducting an in vitro induction study (using midazolam and testosterone as substrates).

Use in pregnancy and Lactation

There are no available data on avacincaptad pegol use in pregnant women to evaluate the drug-associated risks. Pregnant women were excluded from studies. Avacincaptad pegol has negligible systemic exposure following the intravitreal route of administration. Animal studies in rats and rabbits did not indicate harmful effects with respect to reproductive toxicity however, concerns exist as to the pharmacological relevance of these species (rat and rabbit).

From all avacincaptad pegol clinical trials, there were three reports of pregnancy in partners of male patients, which resulted in birth of three normal newborns, one of whom had a premature delivery. However, avacincaptad pegol is administered directly into the vitreous to exert local effects in the eye, avacincaptad pegol plasma concentrations are predicted to be approximately 7,000 fold lower than vitreal concentrations, and passage into the semen has not been studied, no consequences are anticipated for the foetus exposed via the father.

No information is available on the clinical use of avacincaptad pegol during breastfeeding, on the presence of avacincaptad pegol in human milk, on the effect on the breastfed infant, or effects on milk production. Because avacincaptad pegol is administered directly into the vitreous to exert local effects in the eye and avacincaptad pegol plasma concentrations are predicted to be approximately 7,000 fold lower than vitreal concentrations, the amount in milk is likely to be low. The elimination half-life is 12 days and is indicative of potential accumulation in infant.

Overdose, Drug Abuse, Withdrawal and Rebound

There is no known potential for abuse of Avacincaptad pegol and no abuse studies have been performed. Overdose and drug potential are unlikely as the drug is administered IVT by a physician in a clinic. All patients should be monitored for post-injection IOP increase and treatment initiated with paracentesis if necessary. There is unlikely to be a misuse problem with avacincaptad pegol as it does not affect the central nervous system. There is a low probability of any potential withdrawal syndrome since the elimination half-life of avacincaptad pegol is slow (12 days).

Effect on ability to drive or operate machine

Avacincaptad pegol can be associated to temporal visual disturbances that may affect a person's vision dependent ability to drive or operate machine.

Post-Marketing experience

Izelvay has been recently approved by the FDA in August 2023. The applicant provided post-marketing safety data (US) for the reporting period of 04 Aug 2023 to 03 Feb 2024 which provides 1070 patient-years or 12,841 patient-months of exposure to avacincaptad pegol. Overall, 32 events (including 13 serious event) were reported of which 8 were serious and unexpected. One event of retinal vasculitis as off-label use in a patient treated for Stargardt disease with pegcetacoplan (left eye) and avacincaptad pegol (right eye). The patient presented retinal vasculitis in both eyes. The outcome is unknown. One patient presented non-arteritic anterior ischemic optic neuropathy, vitritis, visual impairment geographic atrophy secondary to AMD progression after two injections of avacincaptad pegol (right eye). The outcome is unknown. Overall, based on the submitted post-marketing data, the safety profile of avacincaptad pegol seems similar to the profile seen in clinical trials. No new safety signal was identified.

3.3.9. Conclusions on clinical safety

The safety profile of avacincaptad compared to sham demonstrated a higher incidence of ocular adverse events with the most reported PT consisting of events assessed as related to IVT injection procedure such as conjunctival haemorrhage and IOP increase, while a smaller part was considered treatment related. All of these events, however, are regarded as important for the risk-benefit assessment, as injection related events may also lead to severe impact on visual acuity and negatively impact the quality of life. Moreover, the safety data provided up to 24 months for avacincaptad pegol demonstrated a better safety profile for the dosing regimen EOM (every other month) compared to EM (every month).

In particular, although there is a potential for patients with dry AMD to develop neovascularization and progress to (wet) exudative AMD, an unexpected higher rate of choroidal neovascularisation (CNV) was observed in patients treated with avacincaptad pegol in particular in the EM (every month) dosing

regimen during year 2. No issues were raised with concomitant use of anti-VEGF therapy and patients treated with avacincaptad pegol do not seem more at risk of developing a non-treatable or less treatable CNV. .

Additionally, as GA is generally bilateral, discussion will also be needed to address the conduct of bilateral treatment in clinical practice. Although not fully applicable, limited safety data on 4 mg avacincaptad pegol submitted in this application provide supportive data regarding the expected safety profile.

No non-ocular adverse events were identified that would pose a significant risk for patient treated with Avacincaptad pegol. However, based on human PK data avacincaptad pegol release in the systemic circulation after IVT treatment, will inhibit the classical human complement activation pathway and could lead to an increase of susceptibility to infections. The applicant was requested to further discuss on this concern in particular in regards of the higher expected systemic exposure with bilateral treatment.

Furthermore, based on the submitted post-marketing data, the safety profile of avacincaptad pegol seems similar to the profile seen in clinical trials. No new safety signal was identified.

3.4. Risk management plan

3.4.1. Safety specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 49: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Endophthalmitis Choroidal neovascularization Intraocular inflammation Transient intraocular pressure increased
Important potential risks	None
Missing information	Long-term safety

3.4.1.1. Discussion on safety specification

Two patients have experienced serious adverse events of endophthalmitis during the clinical development of avacincaptad pegol, which were deemed related to the injection procedure but not to the study drug by the investigator. In the pivotal studies, CNV was twice more frequent in the avacincaptad pegol 2 mg group (7.2%) compared to the sham group (3.6%) in patients with GA secondary to AMD. Both endophthalmitis and choroidal neovascularization can have an impact on the benefit-risk of the product. Therefore, the inclusion of “endophthalmitis” and “choroidal neovascularisation” as important identified risks is endorsed.

Across all clinical trials, a total of nine patients treated with avacincaptad pegol experienced a TEAE of intraocular inflammation in the study eye in the avacincaptad pegol clinical development program. Intraocular inflammation generally constitutes a serious condition, which may lead to generalized eye inflammation and risk of blindness. Intraocular inflammation has been associated with other intravitreal injection therapies.

Additionally, higher rates of “transient” increase in IOP were reported in the avacincaptad pegol 30,1% in 4 mg arm, 11,3% in 2 mg arm and 1,2% in sham. The majority of the events of IOP increased were

transient, mild or moderate, assessed as related to IVT injection procedure and resolved on the same day.

Currently, there are data available from study OPH2003 up to Month 18. Safety data up to 24 months were submitted during the response to LoQ1. Therefore, no data on safety beyond 2 years of treatment is available. This information is considered relevant, since patients with GA will require long-term and potentially life-long treatment for their disease. Therefore, the inclusion of "Long-term safety" as missing information is endorsed.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification It is agreed that the safety concerns listed by the applicant are appropriate.

3.4.1.3. Protected Personal Data (PPD) and Commercially Confidential Information (CCI) considerations for the RMP Safety Specification

The rapporteur did not identify PPD/CCI in the RMP parts other than Safety Specification.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in the updated RMP submitted with the responses.

3.4.2. Pharmacovigilance plan

3.4.2.1. Summary of additional pharmacovigilance activities

The applicant proposes the following pharmacovigilance plan:

Table 50: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Study ISEE2009: An Open-Label Extension (OLE) Phase 3 Trial to Assess the Safety of Intravitreal Administration of Avacincaptad Pegol (Complement C5 Inhibitor) in Patients with Geographic Atrophy Who Previously Completed Phase 3 Study ISEE2008 (GATHER2) Ongoing	The objectives of this trial are to assess the long-term safety of avacincaptad pegol monthly intravitreal administration for patients with GA who completed Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment (either avacincaptad pegol or sham). The safety endpoints include: 1. Adverse events 2. Ophthalmic variables • Best-corrected visual acuity (BCVA)	Long-term safety	First patient first visit Planned study completion Final clinical study report planned	27/09/2022 02/2025 08/2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	• Low luminance visual acuity (LL VA) • Intraocular pressure (IOP) • Ophthalmic examination 3. Immunogenicity and pharmacokinetics			

The applicant proposes that a long-term extension study (ISEE2009) addresses the missing information of long-term safety.

This study is an open-label, multicentre, one-arm extension study of phase 3 trial ISEE2008 (GATHER2). Approximately 400 patients with GA will participate regardless of whether they received treatment with avacincaptad pegol or sham previously in ISEE2008 study. Patients are treated with monthly administration of avacincaptad pegol in study eye in a dose of 2 mg and followed up for additional 1.5 years. Taken into account the previous follow up time of 2 years in ISEE2008 study, the total maximum follow up after this extension would be 3.5 years in avacincaptad pegol arm. The safety endpoints in this study include adverse events, ophthalmic variables, immunogenicity and pharmacokinetic parameters. This study is currently ongoing and planned to be completed in 2/2025.

Although this ongoing study ISEE2009 is a single arm study and descriptive in nature, it is considered appropriate to be included in the PhV plan to address missing information concerning long-term safety. As part of long-term safety, the adverse events of special interest (AESI) especially include endophthalmitis, choroidal neovascularisation (including "wet" AMD), intraocular inflammation (including retinal vasculitis) and increased intraocular pressure (IOP).

3.4.2.2. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

3.4.3. Plans for post-authorisation efficacy studies

3.4.3.1. Summary of Post authorisation efficacy development plan

There are no planned or ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

3.4.4. Risk minimisation measures

3.4.4.1. Summary of additional risk minimisation measures

Table 51: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Endophthalmitis	Routine risk minimization measures: - SmPC sections 4.2, 4.3, 4.4 and 4.8 - PL sections 2 and 4 and "The following information is intended for healthcare professionals only" - Prescription only medicine Additional risk minimization measures: - Educational materials for patients/carers	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - Assess as part of routine PSUR reporting Additional pharmacovigilance activities: - None
Choroidal neovascularization	Routine risk minimization measures: - SmPC sections 4.4 and 4.8 - PL sections 2 and 4 - Prescription only medicine Additional risk minimization measures: - No additional risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - Assess as part of routine PSUR reporting Additional pharmacovigilance activities: - None
Intraocular inflammation	Routine risk minimization measures: - SmPC sections 4.2, 4.3 and 4.8 - PL sections 2 and 4 - Prescription only medicine Additional risk minimization measures: - Educational materials for patients/carers	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - Assess as part of routine PSUR reporting Additional pharmacovigilance activities: - None
Transient IOP increased	Routine risk minimization measures: - SmPC sections 4.2, 4.4 and 4.8 - PL sections 2 and 4 - Prescription only medicine Additional risk minimization measures: - Educational materials for patients/carers	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - Assess as part of routine PSUR reporting Additional pharmacovigilance activities: - None
Long-term safety	Routine risk minimization measures: - Prescription only medicine Additional risk minimization measures: - None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - None Additional pharmacovigilance activities: - Ongoing long-term extension study ISEE2009

In accordance with previously authorised intravitreously administered medications, additional risk minimisation measures are in place informing patients about need to seek urgent attention in case of symptoms compatible with endophthalmitis, intraocular inflammation, or increased intraocular pressure.

However, PRAC Rapporteur proposes that list of key elements for additional risk minimisation measures (aRMM) in the RMP Annex 6 would be limited to following:

The key elements of the patient/carer guide:

- A description of the symptoms of endophthalmitis, intraocular inflammation, and increase in intraocular pressure
- Instructions for patients to seek urgent medical attention should these symptoms present themselves **(LoOI)**

3.4.4.2. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.4.5. Summary of the risk management plan

The public summary of the RMP does not require revision.

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.2 could be acceptable, if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

Having considered the data submitted in the application, it is not appropriate to conclude on pharmacovigilance system at this time.

3.5.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the EBD or IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the international birth date (IBD). The IBD is 4 August 2023.

4. Benefit risk assessment

4.1. Therapeutic context

4.1.1. Disease or condition

GA is associated with AMD and causes bilateral, progressive and irreversible loss of retinal tissue (photoreceptors, retinal pigment epithelium [RPE], and choriocapillaris) leading to a permanent loss of visual function and blindness (Lindner et al., 2019; Lindblad et al., 2009; Bonilha, 2008; Sunness et al., 1999).

The atrophic lesions tend to arise in the perifoveal regions initially, preserving the fovea ('foveal sparing'), before these lesions expand and coalesce to affect the fovea (Fleckenstein et al., 2018). Therefore, patients typically experience impaired vision with small pockets of remaining sight over the course of the disease. Although patients may temporarily compensate by utilizing remaining islands of

viable retinal tissue for sight, this can dramatically impact day-to-day activities, quality of life and independence (Sivaprasad et al., 2019), as described below.

Patients with GA associated with AMD experience major difficulties in key aspects of daily living and a wide range of social and manual activities. The limitations in daily activities include reading, driving, watching television, cooking, recognizing faces, and other daily activities, including self-care; 56% of patients report loss of independence (Sivaprasad et al., 2019). Moreover, patients with GA associated with AMD are more prone to falls with high risks of fractures caused by poor vision, and they experience significant reductions in quality of life due to living with the emotion of fear related to worsening vision and difficulties experienced with simple tasks (Sacconi et al., 2017).

4.1.2. Available therapies and unmet medical need

There is currently no approved treatment available for this vision-threatening disease in Europe. At present, patients with GA associated with AMD are followed by an ophthalmologist in a “watch and wait” approach, so that if nAMD develops, they can be treated with anti-VEGF therapies (Lai and Landa, 2015).

As there remains a lack of pharmacological or surgical interventions to treat, prevent, cure, or delay the progression of GA in Europe, other nonpharmacological interventions (i.e., supplementation with antioxidant cocktails including vitamin C, vitamin E, lutein/zeaxanthin, zinc, and cupric oxide) have been evaluated, but not proven to be effective

4.1.3. Main clinical studies

The main evidence of efficacy is based on 2 double blind Sham-controlled studies (GATHER 1 and GATHER 2) evaluating the safety and the efficacy of intravitreal administration of avacincaptad pegol compared to Sham injection in adult patient with geographic atrophy secondary to age-related macular degeneration.

GATHER 1 is a two-part design evaluating 3 avacincaptad pegol doses (1 mg, 2 mg, and 4 mg) versus sham. The study remained double-masked through Month 18.

GATHER 2 is an ongoing randomised, double-masked and controlled phase 3 trial investigating the efficacy and safety of intravitreal avacincaptad pegol therapy (2mg monthly) compared to sham at Month 12. During the second year patients received avacincaptad pegol 2 mg IVT monthly or every other month of treatment. The study is still ongoing and no data on the tested schedules are available. Therefore, only monthly posology is considered for the labelling.

The goal of therapy in GA is to stabilize the disease by slowing GA lesion growth, thereby preventing irreversible vision loss and blindness. The primary efficacy endpoint in both pivotal studies was based on GA area measured by FAF at three time points: Baseline, Month 6, and Month 12 and mean change in best corrected visual acuity (BCVA) and low luminance best corrected visual acuity (LL BCVA) were key secondary endpoints for GATHER 1 study and exploratory endpoints for GATHER 2 study.

4.2. Favourable effects

At **month 12** a statistically reduction of GA lesion growth was observed in favour of avacincaptad pegol in both studies.

In GATHER 1 study, the primary endpoint was statistically met for both arms (2 and 4 mg) versus sham. A reduction in the rate of GA growth compared to Sham of 27.38% ($p = 0.0072$) was observed in the 2 mg arm and a reduction of 27.81% ($p = 0.0051$) was observed in the 4 mg arm.

The treatment effect at month 12 is observed throughout month 18 in GATHER 1 study (28.11% (95% confidence interval [CI] = 0.066; 0.271) in the 2 mg group and 29.7% (95% confidence interval [CI] = 0.062; 0.273) in the 4 mg group).

Results from sub-group analysis (pre-defined demographic analysis) and rate of GA lesion change were generally consistent with the reduction in GA lesion growth observed relative to the sham combined group.

Results from the first key secondary endpoint (Mean change in BCVA (ETDRS letters) from Baseline to Month 12.) compared to Sham for the 2 mg group showed a difference of 1.39 (95% confidence interval [CI] = -3.34; 4.10).

In GATHER 2 study, a difference of 0.056 mm per year (95% confidence interval [CI] = 0.016; 0.096) in the mean rate of GA growth, in favour of Avacincaptad pegol, compared to Sham ($p = 0.0064$) was demonstrated. The treatment effect at Month 12, represents a 14.25% reduction in mean rate of GA area growth compared to Sham ($p = 0.0064$).

At Month 24, difference in mean growth (Slope) from baseline was statistically significant for the Izelvay arms compared to sham: 0.362 mm² per year (95% CI: 0.066, 0.657) for avacincaptad pegol EM, and 0.488 mm² per year (95% CI: 0.189, 0.788) for avacincaptad pegol EOM.

4.3. Uncertainties and limitations about favourable effects

Patients

- Only one eye (study eye) was treated in both studies. Patients with CNV in either eye were not allowed to enter.

Treatment

- In GATHER 2 Study patients received avacincaptad pegol 2 mg IVT monthly or every other month during the second year of treatment. However, the fact that the magnitude of the effect is numerically larger in the EOM group while patient have received half of the dosing during the second year is questioning; this is inconsistent with the frequency of injection. All secondary and exploratory analyses at Month 24 are not yet available for the EM and the EOM arms separately.

Long-term efficacy

- At Month 18 no effect on visual function was shown in avacincaptad pegol treated group with respect to sham group. No efficacy results are available beyond this time point. It cannot be determined at present how long the treatment will be required to detect an effect and if this effect will be of sufficient magnitude. This issue seems to be crucial to establish the benefit-risk relationship of the treatment (OC).

Primary endpoint

- The primary efficacy endpoint in both studies was based on GA area measured by FAF as primary endpoint. It is understood that GA lesion size is an important structural measure of progression in patients with GA secondary to dry AMD.
- It can be followed that best-corrected visual acuity (BCVA) have been not used as a primary endpoint. Indeed, considering that the disease usually progress following a foveal-sparing pattern until late in the course of the disease, BCVA may be not sensitive enough to assess disease progression within a reasonable time frame. Although the use of GA area for primary variable is acceptable, it needs to be demonstrated that it represents a valid surrogate measure for visual function and how change GA lesion size can translated into a clinical benefit for the

patient. In that perspective, in addition of a related justification, at least a positive effect of treatment in clinical outcomes are needed to anchor the effect seen in primary endpoint.

- The estimation of the magnitude of the anatomical size effect remains of concern. Indeed, the face to face comparison of the OPH2003 Study and the pivotal ISEE2008 Study shows that the size of the effect (reduction in lesion size compared with sham) was almost halved in ISEE2008. The applicant believe that the difference in the magnitude of the treatment effect is likely attributable to random variation. This raises the critical question, what is the true effect of the treatment. Thus beyond the need to demonstrate the surrogacy, there are uncertainties on the estimation of the anatomical effect.

Secondary endpoint

- An important issue in GATHER 2 is the absence of secondary endpoints with controlled of the alpha risk to assess the visual function. This drastically reduce the ability of the study to translate the effect size seen with the surrogate into a benefit for the patient. It would have been awaited the applicant would define secondary outcomes addressing the visual function such as: BCVA, Low Luminance Visual Acuity, Reading speed or Functional Reading Independence.
- Also in GATHER 2, separated analysis at Month 24 for the EM and the EOM arms are not available, while there is no scientific rational to conduct such a pooling. Indeed, between Month 12 and Month 24, one arm has received overall half a dosing than the other one.
- Mean change in BCVA and LL BCVA from Baseline to Month 12 compared to Sham were prespecified key secondary endpoint in GATHER 1. A trend of less deterioration was observed with the 2 mg arm but not in the 4 mg arm. However, the small amplitude of these differences raises questions about the clinical relevance of the effect observed. Moreover the change of the primary endpoint from a clinical endpoint to an anatomic endpoint while the study was already ongoing, is critical for the integrity of the trial and the interpretation of the endpoints.
- In GATHER 1, at Month 18 no effect on visual function was shown in avacincaptad pegol treated group with respect to sham group. No efficacy results are available beyond this time point. It cannot be determined at present how long the treatment will be required to detect an effect and if this effect will be of sufficient magnitude. This issue seems to be crucial to establish the benefit-risk relationship of the treatment (OC).
- GATHER 2 is considered to be the sole pivotal trial of this MAA. Indeed, major modifications were made to the design of GATHER 1 while the study was ongoing, which was not initially planned as a confirmatory trial but rather as an investigation of the most adequate dose regimen to be included in a subsequent phase 3 trial.
- The number of DSMB data looks as well as the final adjustment of the alpha-level for the primary analysis (derived from the number of DSMB looks) could not be found and should be clarified.
- Although some measures were taken to limit the extent of personnel being unmasked after the month 12 primary analysis, it is not possible to exclude a dissemination of information following the month 12 database lock. As a consequence, it is difficult to rule out data driven decisions leading to an updated plan of year 2 analyses after the initial unmasking of the year 1 database lock. Given that type I error control of the year 2 analyses cannot be ensured, they are considered exploratory in nature

4.4. Unfavourable effects

Ocular TEAE in the study eye were more reported in the avacincaptad pegol 2 mg group (Up to Year 1 51,0% vs 36,4% in sham Up to Year 2: 69.8% EM, 64.5% EOM and 48.8% sham) while ocular TEAE in the fellow eye were reported in comparable proportions between arms (18,7% in sham, 20,5% in 2 mg and 19,3% in 4 mg). The most reported SOC for ocular TEAE in the study eye consisted of "Eye disorders" and most reported PT with higher incidence in the avacincaptad pegol group were Intraocular pressure increased (Up to Year 1: 19.3% in 4 mg, 8.6% in 2 mg and 0.9% in sham, Up to Year 2: 14.6% EM, 11.8% EOM), Conjunctival haemorrhage (Up to Year 1: 12,7% in 2 mg vs 9% in sham, Up to Year 2: 17.7% EM, 17.2% EOM and 7.4% in sham), and Choroidal neovascularisation (Up to Year 1: 7,2% in 2 mg and 3,6% in sham Up to Year 2: 16.7% EM, 9.7% EOM and 9.9% sham)). Ocular TEAE in the 2 mg were assessed as related to injection procedure in 28,8% (20,8 % in the sham group) and to study drug in 1,4% (0,6% in sham) up to Year 1. Up to Year 2, ocular TEAE in the 2 mg were assessed as related to injection procedure in 38.5% in EM, 33.3% in EOM and 20.8% in sham and assessed as study drug related in 5.2% in EM, 2.2% in EOM and 1.0% in sham. TEAEs were mild to moderate in severity and severe ocular TEAE in the study eye were slightly more reported in avacincaptad pegol (2,4% in 2 mg and 0,6% in sham) up to year 1 and 7.3% in EM, 3.2% in EOM and 1.0% in sham up to Year 2.

In the avacincaptad pegol 2 mg arm, Choroidal neovascularisation, VA reduced transiently, and IOP increased were each reported up to Year 1 as severe ocular TEAEs in the study eye for two patients (0.7%) each. Severe ocular TEAEs of retinal artery occlusion (transient) were reported for study OPH2003 in two patients (one in 2 mg arm and one in 4 mg arm). One severe ocular SAE of endophthalmitis was also reported in Year 1. Up to Year 2, severe ocular TEAEs in the study eye occurred in eleven patients (4.9%) in the avacincaptad pegol group (7.3% in EM, 3.2% in EOM) and 2 patients (1.0%) in the sham group. Furthermore, 6 of these patients who received avacincaptad pegol had 16 events that were considered related to injection procedure.

Incidences of non-ocular TEAEs were comparable between arms (56,2% in 2 mg vs 55,7% in sham). Up to month 24, non-ocular TEAEs occurred in 74.0% of the patients in the avacincaptad pegol 2 mg EM group and 84.9% in the avacincaptad pegol 2 mg EOM group compared to 71.4% in the sham group. Up to Year 2, the most reported SOC consisted of being Infections and infestations (42.7% EM, 45.2% EOM and 41.9% sham), Musculoskeletal and connective tissue disorders (21.9% EOM vs 11.8% EM vs 17.2% sham), Cardiac disorders (19.4% EOM vs 13.5% EM vs 14.3% sham) and Injury, poisoning and procedural complications (21.9% in EM, 19.0% in EOM and 21.7% in sham). Some discrepancies could be observed for reported non-ocular TEAEs on a SOC level but they were consistent with the reported incidences of non-ocular medical history between the two different dosing regimens (EM and EOM) and compared to sham.

No non-ocular TEAEs were assessed as related to study drug or sham. Non-ocular TEAEs assessed as related to IVT injection-procedure were low. Non-ocular TEAEs were mainly mild to moderate in the 2 mg arm and comparable proportions of severe non-ocular TEAEs were reported between arms up to Year 1. Up to Year 2, in the EM group (14.6%). No severe non-ocular TEAE was reported to be related to the injection procedure, avacincaptad pegol, or sham.

Up to Year 1, serious TEAEs were reported with a higher incidence in the sham group and were for the majority non-ocular TEAE (12,3% in the 2 mg vs 16,6% in the sham). Serious ocular TEAEs in the study eye were reported with comparable incidence between group and were low ($\leq 1\%$). Up to Year 2, Ocular SAEs in the study eye at Month 24 were reported in 6 (1.3%) patients in total; 4 [1.8%] patients in avacincaptad pegol 2 mg group (CNV in one patients, endophthalmitis in one patient and device dislocation (posterior displacement of the intraocular lens) in one patient in EM group and CNV in one patient in EOM group) and 2 patients [0.9%] in sham group (Visual acuity reduced in two patients). Up to Year 2, non-ocular SAEs occurred in 24.4% of patients in the avacincaptad pegol group (overall) and in 22.1%

of patients in the sham group. The proportion of patients with at least 1 non-ocular SAE was numerically higher in the avacincaptad pegol EOM group (26.9%) compared to EM (20.8%). Serious non-ocular TEAEs occurred in $\geq 2\%$ in the avacincaptad pegol 2 mg EOM arm and consisted of Chest pain (2.2% $n=2$ vs 0% in avacincaptad pegol 2 mg EM arm and sham arm; Clostridium difficile infection 2.2% $n=2$ vs 0 in avacincaptad pegol 2 mg EM arm and sham arm, Cerebrovascular accident 2.2% $n=2$ vs 0 in avacincaptad pegol 2 mg EM arm and 2.0% $n=4$ in sham arm). During the entire study, there were no non-ocular SAEs related to the injection procedure, avacincaptad pegol, or sham.

In Cohort 1, up to 12 months, TEAE lead to patient's death in 4 patients (3 patient in 2 mg and 1 patient in the 4 mg arm) and no death were assessed as related to avacincaptad pegol treatment or the injection procedure. A total of sixteen deaths occurred during the study up to Month 24 of which nine of the deaths were due to TEAE. up to Year 1, discontinuation due to adverse event were slightly higher in avacincaptad pegol groups 2 mg (2,1%) and 4 mg (2,4%) than with sham (0,9%). Up to month 24, twenty (4.5%) patients in total discontinued the study due to a TEAE: 11 (4.9%) patients in the avacincaptad pegol group (overall) and 9 patients (4.1%) in the sham group. The proportion of patients with TEAEs leading to study discontinuation was comparable between avacincaptad pegol EM (3.1%) and EOM (2.2%) groups. No ocular and non-ocular TEAE leading to study discontinuation were related to study drug. Four patients in avacincaptad pegol 2 mg presented vitreous detachment and IOP increase up to Year 1 and CNV and device dislocation in Year 2 which were assessed as IVT injection procedure related which lead to study discontinuation. Non-ocular TEAEs leading to study drug discontinuation occurring in the avacincaptad pegol group were pneumonia, acute leukaemia, chronic cardiac failure, biliary obstruction, vascular dementia, chronic obstructive pulmonary disease, and neurogenic shock in one patient each (0.4%).

Up to Month 12, no event of endophthalmitis, retinal (including occlusive) vasculitis and rhegmatogenous retinal detachment were reported in Cohort 1. Two cases of endophthalmitis assessed as related to IVT injection-procedure were assessed, one case in study OPH002 and one case in Cohort 1 up to Month 18 in avacincaptad 2 mg EM assessed as related to injection procedure. Two events of retinal tears and of vitreous haemorrhage occurred and none were an SAE nor related to avacincaptad pegol. Severe events of transient retinal artery occlusion were reported up to Year 1 in two patients, one in the 2 mg arm and one in the 4 mg arm (both were assessed related to IVT injection, resolved on the same day, were not associated to an inflammation and with stable VA).

No concerns were raised regarding, safety in special population (subgroup analysis by age and sex), laboratory findings and vital signs

Up to month 12, proportion of patient presenting a transient IOP ≥ 30 mmHg was much higher in the avacincaptad pegol (11,3% in 2 mg arm and 1,2% in sham) which can be explained that the sham procedure simulated the pressure of an injection. The Mean IOP value change (mmHg) in the study eye were stable up to month 12 and 18 months. The majority of the events of IOP increased were transient, mild or moderate, assessed as related to IVT injection procedure and resolved on the same day. Up to month 24, 32 (7.2%) patients across treatment groups reported to have experienced a TEAE of increased IOP: 30 (13.3%) patients in the avacincaptad pegol group (overall) and 2 (0.9%) patients in the sham group. There were no events of increased IOP reported as related to the study drug. The proportion of patients in the avacincaptad pegol 2 mg EM and the avacincaptad pegol 2 mg EOM group that experienced increased IOP was similar (14 [14.6%] and 11 [11.8%]). Of these, 8.3% of patients in the avacincaptad pegol EM treatment group experienced a transient IOP ≥ 35 mmHg 30 minutes post-injection (0.693% of all injections) and 6.5% of patients in the avacincaptad pegol EOM treatment group (0.432% of all injections). Paracentesis was required in 3,1 % (2,90 per 1000 injections) of the patient in the 2 mg group up to Year 1 and over the 24-month treatment period, there were a total of 44 cases of post-injection paracentesis (0.982% per number of total injections)..

4.5. Uncertainties and limitations about unfavourable effects

The proposed dosing regimen is 2 mg administered by IVT injection every 4 weeks (studied in GATHER 1 and GATHER 2). GA is generally bilateral, in OPH2003 (GATHER 1), 83 patients were treated by twice the recommended dose (4 mg administered by 2 IVT of 2 mg), thus limited data are available and results are not considered as fully applicable to bilateral treatment but supportive of the expected safety profile. Overall, compared to the 2 mg dose, the 4 mg dose showed a worse safety profile. Therefore, even though bilateral treatment has not been specifically studied, an increased risk in adverse events with bilateral treatment seems likely. Further discussion was requested to the applicant regarding on how bilateral treatment is expected to be conducted in clinical practice and on the potential for an increase in ocular and non-ocular adverse events with bilateral treatment, in particular regarding the higher risk of infection due to inhibition of C5.

Up to Month 18, one serious not recovered/not resolved event of endophthalmitis of which culture was positive and deemed to be related with injection procedure (avacincaptad pegol 2 mg EM) was reported in study ISEE2008 up to month 18.

There is a potential for patients with non-exudative (dry) AMD to develop neovascularization and progress to (wet) exudative AMD. In ISEE2008, in case of CNV diagnosis patients could remain in the trial while receiving concomitant anti-VEGF therapy (aflibercept or ranibizumab) while in study OPH2003, patients were withdrawn from study per protocol. Indeed, up to Year 1, CNV was reported in higher incidence in the avacincaptad pegol 2 mg group (7.2%) compared to the sham group (3.6%) in patients with GA secondary to AMD. In study ISEE2008, up to Year 2, the incidence of CNV remained constant between the first year with 6.7% (vs 4.1% in sham) and 7.3% in the second year for the avacincaptad pegol 2 mg EM while being lower for the avacincaptad pegol 2 mg EOM with an incidence of 4.3% (lower compared to the sham 5.4%). Moreover, a higher rate could be observed for the avacincaptad pegol 4 mg 11.5 (vs 2.5 in sham) per 100 patient-years for the first year and 9.9 (vs 0 in sham) per patient-years for the second year (up to month 18) in study OPH2003.

The biological mechanism behind why development of CNV appears to increase with treatment of GA via complement inhibition is unclear. Indeed, both complement and VEGF demonstrated a role in latestage AMD pathobiology however at this stage it is unknown if any correlation can be made regarding the development of CNV in patient treated by avacincaptad pegol. The occurrence of CNV in 1 eye seems to be associated with a higher likelihood of occurrence of CNV in the contralateral eye regardless of the study treatment. Provided safety data suggest that patients treated with intravitreal avacincaptad pegol are not at risk of developing an untreatable (or less-treatable) CNV. Moreover, no new safety issue is raised regarding patient treated with avacincaptad pegol who presented CNV and received anti-VEGF therapy

Patients are expected to receive long-term treatment with avacincaptad pegol 2 mg monthly via intravitreal injection. This means that the risks associated with intravitreal injection will gradually increase with treatment duration and ocular events that have not been reported during the clinical development programme may occur. Moreover, the concomitant treatment of patients developing CNV with avacincaptad pegol and anti-VEGF therapies will further increase the risk of adverse events associated with intravitreal injections, such as endophthalmitis and intraocular inflammations, amongst others.

Despite the overall minor differences in non-ocular AEs which were consistent with the reported incidences of non-ocular medical history between the two different dosing regimens (EM and EOM) and compared to sham, some relevant imbalances between the avacincaptad pegol and the sham groups in certain infections (pneumonia, upper respiratory tract infection and sepsis) were discussed. None of the TEAEs of nasopharyngitis, pneumonia and sepsis were deemed to be related to the study drug or injection

procedure. However, concerns remain in particular in case of bilateral treatment since based on human PK data ($C_{max}=6.2$ nM) and in regards to an IC_{50} human of 0.6 nM, avacincaptad pegol release in the systemic circulation after IVT treatment, will inhibit the classical human complement activation pathway and could lead to an increase of susceptibility to infections

Moreover, non-clinical data showed unexpected results for avacincaptad pegol effect on CYP3A4 substrate (midazolam) for which discussion were from the applicant however a potential DDI between avacincaptad pegol and CYP3A4 substrates could not be ruled out and further investigation were requested (see OC in *Pharmacology section*) including conducting an in vitro induction study (using midazolam and testosterone as substrates).

No immunogenicity data issued from immunogenicity assays are available at this stage. The applicant will have to provide the methodology and the results up to the most recent cut-off date which are available for the patient enrolled in ISEE2009 (GATHER 2 extension study).

The safety data provided up to 24 months for avacincaptad pegol demonstrated a better safety profile for the dosing regimen EOM (every other month) compared to *EM* (every month).

4.6. Effects table

Table 52: Effects table for Izelvay

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Change from baseline to month 12 GA growth rate in the study eye based on FAF	mean (SD) change from baseline		0.336 (0.032)	Sham treatment 0.392 (0.033)	Difference between groups :0.056 (95% CI 0.016; 0.096) p= 0.0064	GATHER 2 Primary endpoint
Change from baseline to month 12 GA lesion in the study eye based on FAF	Change from baseline in total area of GA lesion, least-square mean (SD)		2 mg arm 0.292 (0.077) 4 mg arm 0.321 (0.074)	2 mg sham 0.402 (0.075) 4mg sham 0.444 (0.072)	Difference between groups : 2 mg: 27.38% (95% CI 0.030;0.190) (p = 0.0072) 4 mg: 27.81% (95% CI 0.018;0.209) (p = 0.0051)	GATHER 1 Primary endpoint
Unfavourable Effects						
Ocular TEAE	Conjunctival haemorrhage	%	12,7 17.7 (EM)/17.2 (EOM)	9,0 9.0	Know TEAE related to IVT injection	(1) (2)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	IOP increased	%	8,6 14.6 (EM)/11.8 (EOM)	0,9 0.9	Know TEAE related to IVT injection	(1) (2)
	Choroidal neovascularisation	%	7,2 16.7 (EM)/9.7 (EOM)	3,6 9.0	TEAE most reported with avacincaptad pegol	(1) (2)
	Serious ocular TEAE (study eye)	%	0,7 3.1 (EM)/1.1 (EOM)	0,6 1.0		(1) (2)
Non-ocular TEAE	Infection and infestations	%	25,7 42.7 (EM)/45.2 (EOM)	21,4 40.1	Most reported SOC, consistent with study population	(1) (2)
	Musculoskeletal and connective tissue disorders	%	9,9 21.9 (EM)/11.8 (EOM)	10,8 15.8	Most reported SOC, consistent with study population	(1) (2)
	Injury, poisoning and procedure complications	%	14,7 21.9 (EM)/19.0 (EOM)	13,6 20.7	Most reported SOC, consistent with study population	(1) (2)
	Cardiac disorders	%	13.5 (EM)/19.4 (EOM)	14.3	Most reported SOC, consistent with study population	(2)
	Serious non-ocular TEAE	%	11 26.9 (EM)/20.8% (EOM)	10,5 22.1		(1) (2)
	Deaths	%	0,7 1.0 (EM)/1.1 (EOM)	0,6 2.3		(1) (2)
	TEAE leading to study discontinuation	%	2,1 4.9 (overall)/3.1 (EM)/2.2 (EOM)	0,9 4.1		(1) (2)

Abbreviations:

Notes:

- 1) Pooled 2 mg data (GATHER 1 & GATHER 2) up to Month 12
- 2) Safety data up to Year 2 for both dose regimen EM every month and EOM every other month

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

The applicant provided 2 clinical studies, GATHER 1 and GATHER 2, to support the MAA of avacincaptad pegol for the treatment of adults with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

GATHER 2 is considered to be the sole pivotal trial of this MAA. Indeed, major modifications were made to the design of GATHER 1 while the study was ongoing, which was not initially planned as a

confirmatory trial but rather as an investigation of the most adequate dose regimen to be included in a subsequent phase 3 study.

The primary efficacy endpoint in both pivotal studies is an anatomical endpoint (GA area measured by FAF) and it need to be demonstrated that it represents a valid surrogate measure for visual function and how change GA lesion size can translated into a clinical benefit for the patient is critical.

In GATHER 2 study, a difference in rate of GA growth, in favour of Avacincaptad pegol, compared to Sham was statistically demonstrated at Month 12. The However in the absence of efficacy secondary endpoints with controlled of the alpha risk to assess the visual function, it is not possible to conclude how the effect size seen with the surrogate translates into a benefit for the patient.

In GATHER 1 study, the primary endpoint was statistically met versus sham but no meaningful differences in key clinical secondary endpoints (BCVA and LL BCVA NL-BCVA) were observed for visual function changes over 12 months.

The included GA patients in both studies reflect a population with a conserved visual acuity and the detection of a relevant clinical effect seems challenging in the timeframe tested. The anatomic changes observed after 1 year of Avacincaptad pegol treatment did not result in tangible benefits for patients in terms of visual function (normal and low luminance visual acuity) nor improved QoL. Month 18 data are not supportive in this regard. The long-term efficacy results in visual parameters and QoL from GATHER 2 at Month 12 are not further convincing.

The estimation of the magnitude of the anatomical size effect remains also of concern. Indeed, the face to face comparison of the OPH2003 Study and the pivotal ISEE2008 Study shows that the size of the effect (reduction in lesion size compared with sham) was almost halved in ISEE2008. The applicant believe that the difference in the magnitude of the treatment effect is likely attributable to random variation. This raises the critical question, what is the true effect of the treatment. Thus beyond the need to demonstrate the surrogacy, there are uncertainties on the estimation of the anatomical effect.

Overall, the safety profile of intravitreal avacincaptad pegol was shown to be worse than the safety profile of sham injections up to month 24. Up to Year 1, this was observed for the overall rate of AEs (79.5% vs. 69.6%), ocular AEs in the study eye (51.0% vs. 36.4%), AEs related to the injection procedure (29.1% vs. 20.8%), AEs related to the study drug (1.4% vs. 0.6%) and AEs leading to study drug discontinuation (2.1% vs. 0.9%). The safety profile of avacincaptad pegol 2 mg every 4 weeks compared to sham demonstrated a higher incidence of ocular adverse events with the most reported PT consisting of events assessed as related to IVT injection procedure. Important adverse events with imbalances between groups in the cohort 1 safety data were intraocular pressure increased (8.6% vs. 0.9%), choroidal neovascularisation (7.2% vs. 3.6%), visual impairment (2.4% vs. 1.2%), visual acuity reduced transiently (2.1% vs. 0.6%), ocular hypertension (1.7% vs. 0) and keratitis (1.4% vs. 0.3%). In particular, although there is a potential for patient with dry AMD to develop neovascularization and progress to (wet) exudative AMD, one of the major concerns regarding the safety profile of intravitreal avacincaptad pegol in the treatment of geographic atrophy is the unanticipated increased incidence of choroidal neovascularisation. No non-ocular adverse events were identified that would pose a significant risk for patient treated with Avacincaptad pegol. However, based on human PK data avacincaptad pegol release in the systemic circulation after IVT treatment, will inhibit the classical human complement activation pathway and could lead to an increase of susceptibility to infections. The applicant was requested to further discuss on this concern in particular in regards of the higher expected systemic exposure with bilateral treatment

Up to Year 2, safety of avacincaptad pegol which was shown to be worse than sham through 24 months of treatment (overall TEAEs: 92.4% Avacincaptad pegol 2 mg; 82.9% sham) and with a better overall safety profile for the every other month dosing regimen between the two proposed dosing regimen

avacincaptad pegol 2 mg during the second year (Ocular TEAEs: 69.8% EM, 64.5% EOM, 48.8% sham; non ocular TEAEs: 74.0% EM, 84.9% EOM, 71.4% sham); serious TEAEs: 26% EM, 26.9% EOM and 21.7% sham). These data cast doubts on the proposed EM posology and the related safety risks after the first year of treatment. The applicant should discuss whether EOM injections would be preferable, taking into account available safety data and patient burden associated with intravitreal injections. Additionally, as GA is generally bilateral, discussion will also be needed to address the conduct of bilateral treatment in clinical practice. Although not fully applicable, limited safety data on 4 mg avacincaptad pegol submitted in this application provide supportive data regarding the expected safety profile. Overall, compared to the 2 mg dose, the 4 mg dose showed a worse safety profile. Therefore, even though bilateral treatment has not been specifically studied, an increased risk in adverse events with bilateral treatment seems likely.

4.7.2. Balance of benefits and risks

A demonstration of clinical improvement is crucial to establish the benefit-risk relationship of the treatment especially for patients with slow progressing GA in whom their relatively good prognosis in terms of atrophy enlargement may question the need of treatment with potentially unsafe treatments.

In this Application, the applicant demonstrated a significant effect of avacincaptad pegol 2 mg every 4 weeks at month 12 in GA lesion growth reduction but failed to demonstrate whether this effect will manifest in a functional benefit for the patient in terms of visual acuity.

Moreover, there is a critical question on what is the true effect of the treatment.

Additionally, the safety profile of avacincaptad pegol 2 mg every 4 weeks compared to sham demonstrated a higher incidence of ocular adverse events related to IVT injections (Conjunctival haemorrhage, IOP increased...) but similar incidence of non-ocular adverse events. In Year 2, the safety profile of avacincaptad pegol administered every 8 weeks demonstrated a better safety profile compared to an administration every 4 weeks ((Ocular TEAEs: 69.8% EM, 64.5% EOM, 48.8% sham; non ocular TEAEs: 74.0% EM, 84.9% EOM, 71.4% sham); serious TEAEs: 26% EM, 26.9% EOM and 21.7% sham). In particular, higher observed rates of exudative AMD with avacincaptad pegol, uncertainties regarding bilateral exposure (as GA is generally bilateral) and long-term safety data (up to at least 2 years) in particular conserving doubts on the proposed EM posology and the related safety risks after the first year of treatment, taking into account available safety data and patient burden associated with intravitreal injections, contributes at this stage to a major concern regarding the benefit risk of avacincaptad pegol.

Overall, there are no demonstrated clinical benefits and the primary effect in GA lesion growth reduction does not justify the treatment-associated risks, such as development of choroidal neovascularisation, elevation of intraocular pressure, or endophthalmitis - all of which may lead to a worsening or complete loss of eyesight. Hence, the benefit/risk based on outcome data (efficacy and safety) from 12 months avacincaptad pegol 2 mg treatment is considered negative.

4.7.3. Additional considerations on the benefit-risk balance

4.8. Conclusions

The overall benefit /risk balance of avacincaptad pegol is negative.

Public Summary of the RMP

None

4.9. Pharmacovigilance

Other concerns