9 November 2023
EMA/538733/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eylea

International non-proprietary name: Aflibercept

Procedure No. EMEA/H/C/002392/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ADA	antidrug antibodies
AE	adverse event
AMD	Age-Related Macular Degeneration
ANCOVA	analysis of covariance
ATE	Arterial thromboembolic events
BCVA	best corrected visual acuity
BRVO	Branch Retinal Vein Occlusion
CI	confidence interval
COVID-19	coronavirus disease 2019
CRT	central retinal thickness
CRVO	Central Retinal Vein Occlusion
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
CST	Central subfield thickness
CNV	Choroidal Neovascularization
DME	diabetic macular edema
DR	diabetic retinopathy
EMA	European Medicines Agency
EoS	End of Study
ET	early termination
ETDRS	early treatment diabetic retinopathy study
EU	European Union
FA	Fluorescein Angiography
FDA	US Food & Drug administration
FAS	Full analysis set
FP	Fundus Photography
GCP	good clinical practice
HD	High-Dose
ICF	informed consent form
IOP	intra ocular pressure
IRF	Intra-retinal Fluid
ITT	intent to treat
IVT	intravitreal
LLOQ	lower limit of quantification
LOCF	Last Observation Carried Forward
MA	Marketing Authorization
MAH	Marketing-Authorization Holder
MedDRA	Medical dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NAb	neutralizing antibody
NPDR	non proliferative diabetic retinopathy
nAMD/wAMD	Neovascular Age-Related Macular Degeneration
OE	ophthalmological examination
OC	observed case

PCV	polypoidal choroidal vascularization
PD	pharmacodynamic
PDR	proliferative diabetic retinopathy
PEDF	pigment epithelium derived factor
PK	pharmacokinetic
PlGF	placental growth factor
PP	Per-protocol
PT	Preferred term
qX	X weeks
RoW	Rest of the World
RPE	retinal pigmented epithelium
SA	Scientific advice
SAP	statistical analysis plan
SCDRC	Sentinel Cohort Data Review Committee
SD	Standard deviation
SD-OCT	spectral domain - optical coherence tomography
SOC	System organ class
SRF	Sub-Retinal Fluid
TEAE	treatment-emergent adverse event
VEGF	Vascular endothelial growth factor

1. Background information on the procedure

1.1. Submission of the dossier

Bayer AG submitted on 2 February 2023 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
B.II.g.2	Introduction of a post approval change management protocol related to the finished product	II

Extension application to add a new strength of Aflibercept 114.3 mg/ml solution for injection (in a vial), to be indicated in adults for the (1) treatment of neovascular (wet) age-related macular degeneration (nAMD) and (2) visual impairment due to diabetic macular oedema (DME), grouped with a type II variation (B.II.g.2) to introduce a post-approval change management protocol to add a new presentation for Aflibercept solution 114.3 mg/ml in a single-use pre-filled syringe for intravitreal injection.

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Application of a change to an existing marketing authorisation referred to in annex I of Regulation (EC) No. 1234/2008 with the addition of a new strength (114.3 mg/ml).

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The MAH received Scientific advice from the CHMP on the development for the indication from the CHMP on 29 May 2019 (EMEA/H/SA/903/8/2019/III), 29 May 2019 (EMEA/H/SA/903/7/2019/III), 18 June 2019

(EMEA/H/SA/903/8/2019/III), 20 May 2021 (EMA/SA/0000057230) and 23 June 2022 (EMA/SA/0000086937). The Scientific advice pertained to quality, non-clinical, and clinical aspects.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jean-Michel Race Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Nathalie Gault

The application was received by the EMA on	2 February 2023
The procedure started on	23 February 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	24 May 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	24 May 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	N/A
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	24 May 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	22 June 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	11 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	15 September 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	12 October 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	17 October 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	25 October 2023

The outstanding issues were addressed by the MAH during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Eylea on	9 November 2023

2. Scientific discussion

2.1. About the product

Aflibercept as described in its SmPC is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation.

nAMD is characterised by leakage of blood and fluid from a pathological choroidal neovascularisation (CNV) that may cause retinal thickening or oedema and/or sub-/intra-retinal haemorrhage.

DME is a consequence of diabetic retinopathy and is characterised by increased vaso-permeability and damage to the retinal capillaries.

Both pathology results in loss of visual acuity that, if left untreated can lead to blindness. The current standard of care (SOC) include treatment by anti-VEGF marketed products in Europe (EYLEA® – aflibercept; LUCENTIS® – ranibizumab and biosimilars; BEOVU® – broculizumab; VABYSMO® – faricimab), laser photocoagulation and vitrectomy.

Currently, EYLEA (aflibercept) 40 mg/mL solution for injection in pre-filled syringe and in a vial are registered via Centralised Procedure (EMA/H/C/002392) and are indicated in adults for the treatment of:

- *neovascular (wet) age-related macular degeneration (AMD),*
- *visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO),*
- *visual impairment due to diabetic macular oedema (DME),*
- *visual impairment due to choroidal neovascularisation (myopic CNV).*

Although anti-VEGF therapy is the standard-of-care for nAMD and DME, the patients, physicians, and caregivers' burden remain consequent with regard to the long-term treatment and the related consequences related to the number of intravitreous (IVT) injections.

Therefore, the Applicant has developed a novel formulation (aflibercept 8mg) for IVT injections, which will have the potential to decrease the number of IVT injections and at the same time increase intervals of patient's visits in adults for the treatment of nAMD and DME.

2.2. Type of Application and aspects on development

The development programme/compliance with guidance/scientific advice

The purpose of this line extension application is to seek marketing approval of aflibercept with a new strength for some of the indications approved in EU (DME and nAMD).

The clinical development program of aflibercept 8 mg consisted of three studies including two considered as pivotal and one supportive:

- Study PHOTON (21091, VGFTe-HD-DME-1934): an on-going (with data through Week 60), multi-center, randomized, double-masked, active-controlled Phase 2/3 study in participants with DME.
- Study PULSAR (20968): an on-going (with data through Week 60), multi-center, randomized, double-masked, active-controlled Phase 3 study in participants with nAMD.
- Study CANDELA (21086, VGFTe (HD)-AMD-1905): completed (supportive study), multi-center, randomized, single-masked, active-controlled Phase 2 study in participants with nAMD.

The MAH obtained a scientific advice (EMA/CHMP/SAWP/277944/2019) discussed throughout this report.

General comments on compliance with GMP, GLP, GCP

The manufacturing and testing of EYLEA are conducted in accordance with the provisions of current Good Manufacturing and Clinical Practices.

2.3. Quality aspects

2.3.1. Introduction

The Applicant applied for a line extension application to the existing Eylea marketing authorisation for a new aflibercept strength of 114.3 mg/mL in a vial. Aflibercept solution for injection 114.3 mg/mL is a new formulation with the same active substance as in the currently approved finished product Aflibercept solution for injection 40 mg/mL.

The finished product is presented as a solution for intravitreous administration containing 114.3 mg/mL of aflibercept as active substance. Other ingredients are: arginine hydrochloride, histidine hydrochloride monohydrate, histidine, sucrose, polysorbate 20 and water for injections (WfI).

1 ml solution for injection contains 114.3 mg aflibercept. Each vial contains 30.1 mg aflibercept in 0.263 ml solution. This provides a usable amount to deliver a single dose of 0.07 ml containing 8 mg aflibercept.

The product is available in Type I glass vial, stoppered with an elastomeric stopper, and sealed with an aluminium seal cap.

2.3.2. Active Substance

2.3.2.1. General information

Aflibercept is a recombinant homodimeric glycoprotein with a molecular weight of approximately 115,000 Daltons. This fusion protein consists of two identical polypeptide chains, each comprising the second Ig domain of the human vascular endothelial growth factor (VEGF) receptor 1 and the third Ig domain of the human VEGF receptor 2, with both polypeptide chains fused to the Fc domain of human IgG1.

2.3.2.2. Manufacture, characterisation and process controls

Manufacturers

The activities of manufacturing and testing of Aflibercept FDS solution 114.3 mg/mL are conducted by Regeneron Pharmaceuticals, Inc., Rensselaer (USA). The manufacturing and testing sites are supported by valid GMP documentation.

Description of manufacturing process and process controls

Aflibercept formulated active substance (FDS) manufacturing process begins with the thawing and pooling of Aflibercept DSI, which is then further purified through chromatography and concentrated by ultrafiltration/diafiltration (UF/DF). The final concentrated pool (FCP) is then adjusted buffers to produce FDS with a target protein concentration of 114.3 mg/mL.

Description of FDS manufacturing process and process controls are appropriately detailed and consistent with information provided in other sections of the dossier . The FDS batch definition and scale are given.

It is stated that reprocessing is not part of the standard manufacturing process and can only occur under certain circumstances. The conditions where reprocessing would apply are satisfactorily described.

Control of critical steps

The in-process control (IPC) program developed for FDS manufacturing process is mainly based on that was registered for DSI manufacturing process. The Applicant clarified that the differences noted in the IPC Program classification reflect a change of historical approach and application of a new control strategy. The primary change is in terminology. Confirmation was given that there is no impact to the treatment of potential out of trend/specification. The justification provided is acceptable.

In addition, for both DSI and FDS manufacturing processes, certain parameters were classified as non-critical attributes for in-process samples although these attributes satisfy the critical attribute definition . The Applicant explained that these in-process tests are classified as non-critical in-process controls (IPC), and are performed during processing and that adequate control is maintained. Any IPC excursion will lead to an investigation and appropriate corrective and preventive actions (CAPA) will be taken. Excursions that pertain to safety will lead to batch rejection. Furthermore, it was reminded that release testing of these parameter is classified as a critical quality attribute (CQA) . Based on the justification provided, the proposed classification is considered acceptable.

Control of materials

Raw materials used in the FDS manufacturing process are given. Apart from chromatography resin and membrane filter, all raw materials are chemical and compendial grade. Additionally, a risk assessment was performed with regards to potential extractables and leachables that could be released in the process. No compounds of toxicological concern originated from the FDS manufacturing process were identified.

Process validation

Consecutive PPQ lots were successfully produced. The capability of the process to operate consistently was demonstrated through control and monitoring of operational and process performance parameters, as well as conformance to specifications. A supplemental validation was thereafter performed to take into account late process changes for the final purification step . The unit operation has been confirmed to remain in the validated state.

Levels of specific residual impurities were demonstrated to be reduced to acceptably low levels in the FDS.

The established process hold times for routine manufacturing are supported by suitable data, using a combination of microbial control studies and chemical stability studies.

Reprocessing is not routinely performed as part of the DS manufacturing process but repetition of the filtration step can occur . Reprocessing will be validated under concurrent validation protocol at commercial scale.

A maximum lifetime for chromatography resin was proposed. Data have been compiled and are provided with the response. The claim resin lifetime is appropriately demonstrated.

An overview of the studies which contribute to the development of the manufacturing process was provided. Comparability studies were performed to evaluate process optimisations made during development of Aflibercept solution 114.3 mg/mL. Process changes were limited to the final purification and the concentration

and diafiltration (UF/DF) steps. A summary of comparability assessment between historical and optimised process was presented.

Characterisation

A comprehensive set of state-of-the-art methods was applied to demonstrate that aflibercept solution 114.3 mg/mL has the expected structure and function. Characterisation studies were conducted on three aflibercept FDS lots. Overall, there is a high level of conformance and quality observed among aflibercept lots.

As no new impurities were introduced during the manufacture of FDS when compared to DSI, process validation originally performed on DSI that demonstrated the capability of the DSI manufacturing process to clear process-related impurities is still valid. Regarding product-related impurities, a comprehensive control strategy for size and charge variants is in place to ensure process consistency through the in-process control and monitoring, release, and stability testing programs.

2.3.2.3. Specification

The proposed FDS specifications include testing for appearance , pH, protein and polysorbate contents, osmolality, identity, potency, charge variants, purity, and microbial contaminants.

The FDS release and end-of-shelf-life acceptance criteria are supported by process capability as well as clinical experience or were established based on process capability and levels evaluated during formulation robustness studies or were leveraged from previously established acceptance criteria. In addition, some acceptance criteria were based on historical experience or based on regulatory safety criteria for intraocular fluids, process capability, and is in alignment with the clinical specification. The proposed specifications are acceptable.

Analytical procedures

The analytical methods were satisfactorily validated as per ICH QR2 requirements. In some cases, data derived from the initial validation with aflibercept solution 40 mg/mL was used to support suitability of methods for aflibercept solution 114.3 mg/mL. Supplemental validation was performed for some parameters to demonstrate that differences in protein concentration and formulation matrices does not impact the results. This information provided is adequate.

Batch analysis

Batch analysis results have been provided for several batches representative of the intended commercial process (including batches from optimised process). Results confirm consistency and uniformity of the batches, indicating that the process is under control.

Reference standards

The Applicant established appropriately characterised in-house primary and working reference materials, prepared from lots representative of production (either active substance 40 mg/mL or FDS 114.3 mg/mL). Working reference material used in the testing of production lots was calibrated against the primary reference material. Documentation of the qualification, storage conditions and stability program of primary and working reference materials was also described.

Container closure system

Aflibercept FDS is stored and shipped in specified bottles. The components materials comply with relevant European requirements. The container closure system was selected to pose low risk for extractables and leachables. Compatibility of the container with the formulated active substance is demonstrated through stability studies. The information provided is adequate and sufficient.

2.3.2.4. Stability

The proposed shelf-life and storage conditions for aflibercept formulated active substance solution 114.3 mg/mL is based on several batches for which manufacture and storage are representative of the manufacturing scale of production . Updated stability data have been provided . Results from the long-term studies met the acceptance criteria at all available time points, and no meaningful changes were observed.

Under accelerated and stress stability conditions, some degradations were observed, confirming that the analytical methods selected are able to detect significant changes in the quality of the product. The photostability study highlight that FDS light exposure should be limited during storage.

FDS samples were demonstrated stable after several cycles of freezing and thawing.

Based on updated data provided, the proposed shelf-life, and storage conditions when protected from light, for aflibercept solution 114.3 mg/mL can be granted.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Aflibercept 114.3 mg/mL is supplied as a solution in a vial for intravitreous administration. Each vial has a minimum extractable volume to allow delivering a dose of 0.07 mL (8 mg). The finished product contains no preservatives and is for single use only. The secondary packaging includes a filter needle for aspiration of the aflibercept 114.3 mg/mL finished product.

The commercial formulation is an aqueous solution containing 114.3 mg/mL aflibercept, histidine, pH 5.8, sucrose, arginine monohydrochloride , and polysorbate 20. This formulation was selected based on screening studies that demonstrate the formulation effectively stabilises liquid finished product during long-term storage at 2 – 8 °C .

The development of the manufacturing process was based on technical transfer documentation, previous experience with filling aflibercept, as well as development and process parameters studies. During development, the manufacturing process was transferred from the clinical site to the commercial site accompanied by additional changes. An analytical comparability exercise was performed - including in-process controls, release testing, extended characterisation data, and long-term, accelerated, and stress stability studies – the results showed the lots filled at both manufacturing sites have comparable quality profile.

Aflibercept finished product contains no preservatives. The microbiological quality complies with the European requirements for sterile products and is ensured by a combination of various measures - sterile product-contact components, sterile in-line filtration, environmental and media monitoring - and is confirmed by microbiological IPC testing as well as sterility release testing.

The finished product, aflibercept solution 114.3 mg/mL in a vial, is intended to be administered intravitreally. Studies were performed to assess compatibility of the finished product with the components that may be used for dose preparation and administration(18 gauge filter needle and 30 gauge administration needle). Physicochemical stability of the Aflibercept finished product was demonstrated under simulated in-use conditions.

2.3.3.2. Manufacture of the product and process controls

Manufacturers

Bayer AG (Germany) is responsible for EU batch certification. The name, address, and responsibility of each manufacturer and facility involved in the manufacturing and testing of the finished product were given. GMP documentation (QP declaration and GMP certificates) presented are suitable. The sites responsible to perform each release test have been stated.

Description of manufacturing process and process controls

The finished product manufacturing process is standard and starts with the thawing of formulated active substance. The finished product solution is then pooled and mixed, pre-filtrated, and sterilised by filtration immediately prior to filling. The vials are stoppered, crimped and a visual inspection is performed before labelling and secondary packaging.

The hold/storage times and batch size were defined.

Process controls

For each manufacturing step, in-process controls were determined and classified. Operating ranges were established based on product knowledge and process experience. Information given has been adequately harmonised.

Process validation

Validation of the Aflibercept finished product manufacturing process is based on the analysis of consecutive PPQ batches. The validation studies included control of process parameters and IPCs, and control of quality attributes. The results met the acceptance criteria and demonstrated that the manufacturing process remains consistent.

Further supportive validation studies were performed. Process hold times were validated. It was confirmed that validation of the aseptic processing is conducted periodically. The information provided in this section was acceptable.

2.3.3.3. Product specification

The proposed finished product specifications include testing for appearance , pH, protein, identity, potency, isoaspartate content, charge variants, purity, sterility, endotoxins and extractable volume.

The Applicant agreed to tighten some specifications to better reflect the actual data. Other acceptance criteria are considered appropriately justified.

The manufacturing process has been evaluated for nitrosamines risk, based on risk factors for biologicals. Confirmation that the overall manufacturing process presents low risk of nitrosamine impurities was provided.

No additional testing is considered necessary. Similarly, the risk for the presence of elemental impurities in aflibercept finished product was evaluated (ICH Q3D) and is considered low. Therefore, no additional controls for elemental impurities in the manufacture or storage of aflibercept are required. This is acceptable.

Batch analysis

Analytical results of several finished product batches manufactured at the commercial site were provided, alongside representative clinical batches manufactured at previous manufacturing site. All results met the acceptance criteria and showed consistency.

Batch information including the status, manufacturing date, batch size and genealogy, description, manufacturing site, and study usage was adequately presented.

Container closure system

The primary packaging consists of a vial (type I glass) with a grey rubber stopper sealed with an aluminium cap with white lid. The names of the suppliers have been included in the dossier as requested.

The choice of the container closure system is in line with pharmaceutical standards and the components comply with pharmacopeia requirements. To avoid potential mix-up between Eylea 40 mg/mL and Eylea 114.3 mg/mL, confirmation was given that different colour of cap is used between presentations. For Eylea 114.3 mg/mL the flip cap is white and for Eylea 40 mg/mL the flip cap is blue. The information on the specific colour for each strength is provided in the Product Information. Adequate protection from microbial contamination is verified via container closure integrity testing. The containers proposed for routine storage are those which have been used in the stability studies supporting the shelf life.

2.3.3.4. Stability of the product

A shelf-life of 24 months when stored at 2 °C-8 °C is claimed for the finished product.

Several Aflibercept 114.3 mg/mL finished product batches were manufactured at the clinical and commercial site and placed into the stability monitoring programs. As comparability were demonstrated between clinical materials and commercial batches, stability data derived from the clinical site are considered representative of the commercial process. The quality of the finished product clinical and PPQ batches placed into the stability program is monitored using analytical test procedures, which are similar to release testing. Container closure integrity test (CCIT) and sterility of the product was monitored to demonstrate that the container closure integrity remained intact throughout the duration of the studies.

The proposed shelf-life and storage conditions of 24 months at 2 °C-8 °C is based on real-time, real conditions stability data available for three batches. All results are within specification without any significant degradation trend.

Stability data obtained from accelerated (25 °C/60% RH) and stressed (37 °C) storage conditions were also presented as supportive data. Under these conditions, changes to purity levels were observed.

The photostability analysis indicates that the finished product is photosensitive and should be protected from light during storage. The secondary packaging designated for use with the finished product container closure system offers sufficient protection from light exposure.

In summary, the proposed shelf-life of 24 months at 2 °C-8 °C, protected from light, for Aflibercept solution 114.3 mg/mL in vial is supported.

2.3.3.5. Post approval change management protocol(s)

In addition to the registration of a new aflibercept formulation of 114.3 mg/mL solution in a vial, a post approval change management protocol (PACMP) is proposed for the pre-filled syringe (PFS) presentation of the new formulation.

The PACMP describes the process differences between the vial and the PFS and the studies that will be performed in support of the PFS presentation, including process validation and analytical comparability studies between Aflibercept solution 114.3 mg/mL finished product in PFS and in vials.

The justification for the target fill volume owas considered acceptable.

The process validation protocol is designed to qualify the proposed manufacturing sites for aseptic filling of Aflibercept solution 114.3 mg/mL in prefilled syringes, and for labelling, assembling, blistering, outer surface sterilization and final packaging. Validation of the manufacturing process will be conducted on consecutive batches. The list of operating parameters and additional testing that will be performed to demonstrate that the manufacturing process is controlled and consistent has been appropriately detailed.

In addition to the process validation, additional validation/qualification activities will be conducted.

The comparability study follows the principles outlined in ICH Q5E "Comparability of Biotechnological/ Biological Products Subject to Changes in their Manufacturing Process" and will compare data of PFS batches with data of vials,. A thorough analytical comparison including testing against the product specification, stability testing and extended characterisation is planned. Evaluation of all analytical test results is appropriately described and will be supported by provision of statistical analysis and representative chromatograms where applicable.

Overall, the process validation and analytical comparability studies that will be performed as part of PACMP is comprehensive. The PACMP is thus considered acceptable.

2.3.3.6. Adventitious agents

Aflibercept intermediate (DSI) is the same as for the authorised Aflibercept solution 40 mg/mL. The manufacturing operations performed at Regeneron Pharmaceuticals, Inc. to obtain Aflibercept 114.3 mg/mL formulated active substance are chromatography and UF/DF. These steps are not dedicated to remove/inactivate virus. Additionally, no materials with viral safety concern are introduced at this stage of the process.

Based on these considerations, adventitious agents safety evaluation that was performed for Aflibercept intermediate (DSI) remains valid and no new assessment is deemed necessary.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The Applicant applied for a line extension application to the existing Eylea marketing authorisation for a new aflibercept strength of 114.3 mg/mL with a new formulation, in a vial. Further, this extension application is grouped with a Type II variation for a PACMP for the Aflibercept 114.3 mg/mL in a prefilled syringe.

The Module 3 dossier presented is of good quality. Information on development, manufacture and control of Aflibercept 114.3 mg/mL solution is comprehensive and overall acceptable. No major concern has been identified. Some other concerns were raised and have been satisfactorily addressed.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Eylea 114.3 mg/mL is considered acceptable when used in accordance with the conditions as defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing relevant guidelines.

In conclusion, based on the review of the data provided, this line extension application for Eylea to add a new strength of 114.3 mg/mL is considered approvable from the quality point of view.

2.4. Non-clinical aspects

2.4.1. Introduction

Extensive pharmacological program was conducted to obtain MA for aflibercept 2mg. In order to validate the development of the new aflibercept 8 mg dose strength, a primary *in vivo* pharmacology study in a chronic retinal neovascularization (RNV) model in rabbits was conducted. No additional primary or secondary pharmacology studies were conducted with the new aflibercept 8 mg formulation.

2.4.2. Pharmacology

The MAH has conducted an additional in vivo study in a chronic retinal neovascularization model in rabbits, in order to validate the development of the new aflibercept 8 mg dose strength.

A single IVT dose of aflibercept was able to completely block retinal vascular leak and cause regression of pathological neovascularization in all treated animals beginning at 1 week following injection and persisting for 4 (0.5 mg group) or 6 (2 mg group) weeks. Compared to the 0.5 mg dose, the number of treated eyes in which leak was completely blocked was significantly greater in the 2mg dose group at all sampling times up to 18-weeks post-dosing. Overall, these results support the development of the new aflibercept 8 mg dose strength.

2.4.3. Toxicology

In addition to the toxicity studies conducted to support the authorized aflibercept 2 mg formulation, the MAH has conducted two GLP-compliant IVT bridging studies in Cynomolgus monkeys with high concentration formulation to support marketing authorization of aflibercept 8 mg: a 9-week or 6-month study with 3 different formulations (VGFT-TX-18169) and a 3-month study with aflibercept to support specification.

2.4.4. Discussion on non-clinical aspects

No additional preclinical PK studies were conducted with the high concentration formulation. Results of the toxicokinetic evaluation of the two new IVT bridging studies in monkeys utilizing the new aflibercept 8 mg formulation (Module 4.2.3.2, VGFT-TX- 18169 and VGFT-TX-20170) do not raise any concerns. A bioanalytical method to detect anti-VEGF Trap antibodies in monkey serum samples has been developed and validated (Report VGFT-AV-12112-VA-01) using electrochemiluminescence in a bridging assay format.

Study VGFT-TX-18169, did not identify any new toxicity finding in comparison with study VGFT-TX-05011 (submitted for aflibercept 2 mg MA approval). As such, an acute, transient, generally mild, dose-related anterior segment inflammatory response was generally reported at ophthalmological examination and was not associated with any treatment-related finding at ERG, ocular imaging, and microscopic evaluations. Microscopic examination reported erosion and/or ulceration and squamous metaplasia of the respiratory epithelium in the nasal turbinates with evidence of ongoing reversibility at the end of recovery period. Whereas squamous metaplasia was not considered as adverse, a NOAEL could not be determined considering epithelial erosion and/or ulceration in the nasal turbinates. Those nasal turbinates findings had been identified previously within studies supporting the currently approved formulation with a NOAEL of 0.5 mg/eye after 8-month treatment (3.3-fold the predicted exposure in patients treated with the new formulation). At the LOAEL of 4 mg/eye identified in the current study, systemic exposure was 80-fold (Cmax) and 67-fold (AUC) that predicted in patients.

Study VGFT-TX-20170 in male cynomolgus, which was designed to evaluate the toxicity and determine the toxicokinetics of VEGF-Trap formulations containing different amounts of impurities (formulation 1 and 2) to support specification has highlighted similar results for both dose groups. In both groups, animals were dosed at 5.6 mg/eye. Both formulations were well tolerated during the whole study and no effect on clinical observations, body weights, body weight change, qualitative food consumption, IOP, ocular photography, FA, ERG, VEPs, macroscopic findings, or clear test article-related changes in organ weight parameters were noticed. Whereas erosion and/or ulceration and squamous metaplasia of the respiratory epithelium in the nasal turbinates, previously observed in studies supporting the currently approved formulation (8 months IVT study VGFT-TX-05011) and also in study VGFT-TX-18169, did not affect any animal during the full course of the study. Absence of systemic findings at the nasal turbinates level was considered to be related to the lower dose volume of 40 µL used in study VGF-TX-20170 v*s.* 50 µL used in studies VGFT-TX-18169 and VGFT-TX-05011. Since volume vitreous ratio between cynomolgus and human is equals to 2, no post-injection reflux is expected in clinics at a dose of 8 mg with an injection volume of 80 µL. At ophthalmic examination, sporadic instances of mild (0.5 to 1+) aqueous cell or flare and more frequent instances of mild (0.5 to 1+) vitreous cell were observed in comparison with but resolved at recovery phase. Based on the results of study VGF-TX-20170, the NOAEL is 5.6 mg/eye with systemic exposures (141 and 131-fold Cmax; 112 and 105-fold AUC) higher than those predicted in patients.

To support the current line extension to a novel drug product delivering a higher dose of aflibercept, the MAH has conducted a review of the available relevant studies to assess any potential risk on fertility and embryo-fetal development. Exposure ratios were also revised taking into consideration the exposure levels estimated on treatment weeks 8-12 from a popPK model after one IVT injection of 8 mg aflibercept every 4 weeks in patients with nAMD or DME (mean Cmax of 0.154 µg/mL, mean $AUC_{0\text{-}28d}$ of 48.72 µg.h/mL).

Reversible effects shown on menstrual cycle, female hormone levels and sperm parameters were reported at all dose levels in the 6-month intravenous monkey study. Due to the increase in systemic exposure with the new 8 mg formulation compared to the approved 2 mg formulations, the exposure ratio at the LOAEL of 3 mg/kg decreased from 1500-fold to 91-fold. This is still considerable, however this should also be interpreted in relation to the absence of safety margin. The wording proposed for fertility data in SPC section 5.3 is identical to that approved for the approved 2 mg formulation with revised exposure ratios; this is acceptable. However, the deletion of the fertility subsection in SPC 4.6 was not endorsed. A wording similar to that approved for the 2 mg formulation was included but adapted to account for the increase in systemic exposure level and to report the absence of human data.

Embryo-fetal development toxicity studies were conducted in rabbits after either intravenous (3-60 mg/kg) or subcutaneous (0.1-1 mg/kg) administration. In the subcutaneous study, a teratogenic effect was reported at all doses. Taking into account the exposure levels estimated in patients on treatment weeks 8-12 from a popPK model, it is concluded that malformations were seen in rabbits from exposure levels below those reached at the recommended human dose (exposure ratio for free aflibercept were 1.7 and 0.89 based on Cmax and AUC, respectively, at the LOAEL). In view of the absence of safety margin for embryo-fetal development with this new formulation, and considering available clinical safety data, the wording for SPC 4.6 pregnancy subsection was adapted. In relation to this teratogenic liability, the MAH has provided acceptable justification that contraception of male patients is not required since the estimated exposure of their female partners would be negligible compared to that of treated patients and not likely to cause VEGF inhibition. In addition, a 4-month post-treatment contraception period is recommended for female patients based on the time required for free aflibercept concentration in plasma to reach LLOQ according to the popPK model with an additional buffer of 1 month.

Regarding ERA, the applicant has acknowledged that the new dose strength may potentially increase the emission of aflibercept into the environment. Nevertheless, aflibercept is a monoclonal antibody and is unlikely to result in significant risk to the environment.

2.4.5. Conclusion on the non-clinical aspects

The non-clinical part of the submission was adequate.

2.5. Clinical aspects

- **Tabular overview of clinical studies**

The clinical development program of aflibercept consists of two pivotal studies (PULSAR and PHOTON studies) and a third study (CANDELA study) considered as supportive depicted in Table 1.

Table 1: Summary of high dose aflibercept clinical studies included in this application

Study number Report location Study status	Study population	Study design Treatment duration	Study objectives	Treatment, dose, and regimen	Data included in this application
Neovascular age-related macular degeneration					
VGFTe (HD)-AMD-1905 (CANDELA) Study 21086 Module 5.3.5.1 CANDELA CSR Completed (completion date: 30 Nov 2021)	Men or women ≥ 50 years of age with active subfoveal CNV secondary to nAMD	Phase 2, multicenter, randomized, single-masked, active-controlled Treatment duration 44 weeks	**Primary:** – To determine the safety of HD aflibercept – To determine if HD aflibercept provides greater intraocular pharmacodynamic effect and/or longer duration of action compared to aflibercept 2 mg **Secondary:** There were no secondary objectives in this study	Aflibercept IVT: – 2 mg IAI: aflibercept 2 mg administered monthly as 3 initial injections (baseline, Weeks 4 and 8), followed by additional doses at Weeks 20 and 32[a] – HD: aflibercept 8 mg administered monthly for 3 initial injections (baseline, Weeks 4 and 8), followed by additional doses at Weeks 20 and 32	Safety and PK data through Week 44
Study 20968 (PULSAR) Module 5.3.5.1 PULSAR W48 CSR, PULSAR W60 CSR Last participant last visit for the Week 48 primary endpoint: 27 Jul 2022 DBL: 24 Aug 2022 Ongoing (Week 60 completed)	Men or women ≥ 50 years of age with active subfoveal CNV secondary to nAMD	Phase 3, multicenter, randomized (1:1:1), double-masked, active-controlled Treatment duration 96 weeks[b]	**Primary:** To determine if treatment with HD aflibercept at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to aflibercept 2 mg every 8 weeks in participants with nAMD **Secondary:** – To determine the effect of HD versus aflibercept 2 mg on other visual and anatomic measures of response – To assess the efficacy of 8 mg compared to aflibercept 2 mg on vision-related quality of life – To evaluate the safety of aflibercept – To evaluate the PK and immunogenicity of aflibercept	Aflibercept IVT: – 2q8: aflibercept 2 mg administered every 8 weeks after 3 initial monthly injections – HDq12: aflibercept 8 mg administered every 12 weeks after 3 initial monthly injections – HDq16: aflibercept 8 mg administered every 16 weeks after 3 initial monthly injections	Safety, efficacy, and PK data through Week 48 plus data through Week 60 required by the statistical testing sequence.

Diabetic macular edema					
Study 21091 (PHOTON) Module 5.3.5.1 PHOTON W48 CSR, PHOTON W60 CSR Last participant last visit for the Week 48 primary endpoint: 30 May 2022 DBL: 19 Aug 2022 Ongoing (Week 60 completed)	Men or women ≥ 18 years of age with type 1 or type 2 diabetes mellitus	Phase 2/3, multicenter, randomized (1:2:1), double-masked, active-controlled Treatment duration 96 weeks[b]	**Primary:** To determine if treatment with HD aflibercept at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to aflibercept 2 mg dosed every 8 weeks **Secondary:** – To determine the effect of HD versus aflibercept 2 mg on anatomic and other visual measures of response – To evaluate the safety, immunogenicity, and PK of aflibercept	Aflibercept IVT: – 2q8: aflibercept 2 mg administered every 8 weeks after 5 initial monthly injections – HDq12: aflibercept 8 mg administered every 12 weeks after 3 initial monthly injections – HDq16: aflibercept 8 mg administered every 16 weeks after 3 initial monthly injections	Safety, efficacy, and PK data through Week 48 plus data through Week 60 required by the statistical testing sequence.

2q8 = aflibercept 2 mg administered every 8 weeks; BCVA = best corrected visual acuity; HDq12 = aflibercept 8 mg administered every 12 weeks; HDq16 = aflibercept 8 mg administered every 16 weeks; IAI = intravitreal aflibercept injection; CNV = choroidal neovascularization; CSR = clinical study report; DBL = database lock; DME = diabetic macular edema; HD = high dose; IVT = intravitreal; nAMD = neovascular age-related macular degeneration; PK = pharmacokinetics; SAF = safety analysis set.

Module 5.3.5.1, CANDELA CSR.

[b] Studies are planned to be extended beyond Week 96 by approximately 1 year (60 weeks).

2.5.1. Clinical pharmacology

2.5.1.1. Pharmacokinetics

Absorption

Based on Population PK analysis, participants in the combined nAMD and DME dense PK substudy population who received an initial dose of 2 mg or 8 mg aflibercept IVT had a Population PK post-hoc estimated free aflibercept in plasma median tmax of 2.16 days and 2.89 days, respectively. The attainment of tmax for adjusted bound aflibercept in plasma was slower when compared to free aflibercept. The simulated median tmax was 13.7 days and 15.8 days for the 2 mg and 8 mg IVT aflibercept treatments, respectively.

Based on the Population PK analysis, the bioavailability of free aflibercept following intravitreal administration is estimated to be approximately 72%.

Distribution

Based on the Population PK analysis, the total volume of distribution of free aflibercept after IV administration is estimated to be approximately 7 L.

Elimination

- *Systemic elimination*

Like most therapeutic proteins, the large molecular weight of aflibercept (approximately 115 kDa) is expected to preclude elimination via the kidney, and its metabolism is expected to be limited to proteolytic catabolism to small peptides and individual amino acids. Following initial monthly IVT dose, the concentration-time profile

of free aflibercept in plasma is characterized by an initial phase of increasing concentrations as the drug is absorbed from the ocular space into the systemic circulation, followed by a mono-exponential elimination phase. The Population PK predicted median time for free aflibercept concentrations in plasma to reach LLOQ following 2 mg IVT aflibercept is 1.5 weeks compared to 3.5 weeks for HD aflibercept.

- *Ocular elimination*

Based on the Population PK analysis, HD aflibercept was estimated to have a 34% slower clearance from the ocular compartment compared to the lower IVT doses of aflibercept (≤ 4 mg doses).

Dose proportionality and time dependencies

PK of free aflibercept appears to be greater than dose proportional, and adjusted bound aflibercept less than dose proportional consistent with IV dose PK already known. There appears to be little accumulation of free aflibercept, and up to 2.2 fold accumulation of bound aflibercept.

Special populations

This new presentation of aflibercept was intended for two different target populations, patients with nAMD and DME. Although not a statistically significant covariate in the population PK model, the effects of disease population on systemic exposures to free and adjusted bound aflibercept were evaluated. PK in patients with nAMD and DME were slightly differing, but disease population was not a statistically significant covariate in the population PK model.

Amongst the covariates evaluated in the Population PK analysis, body weight was the covariate with the greatest impact on systemic exposures to free and adjusted bound aflibercept. For participants in the lowest quintile of body weight (38.1 kg to 64.5 kg), the predicted impact on systemic exposures (Cmax and AUCtau) was modest, with 27% to 39% higher exposures to free aflibercept and 25% to 27% higher exposures to adjusted bound aflibercept when compared to the reference body weight range (73.5 to 83.5 kg). The effects of other covariates (age, albumin, disease population, and race, which included evaluation of Japanese race) on systemic exposures (Cmax, AUCtau) to free and adjusted bound aflibercept were small (<25% increase in exposure for covariate subgroups relative to the reference group), with several of these other covariate effects correlating with a consistent trend in body weight.

No dosage adjustments of HD aflibercept are warranted based on the assessed covariates. Mild to severe renal impairment also had a small impact on free aflibercept systemic exposures, as the increase in free aflibercept Cmax and AUCtau in these participants was less than approximately 28% compared to participants with normal renal function. Adjusted bound aflibercept systemic exposures in participants with mild to severe renal impairment ranged from 13% to 39% higher compared to participants with normal renal function. Here too, the perceived impact of renal impairment is best explained by the associated decrease in body weight with increasing renal impairment. Mild hepatic impairment had no effect on systemic exposures to free and adjusted bound aflibercept. No dosage adjustments of aflibercept are warranted for these populations.

2.5.1.2. Pharmacodynamics

Concentration effect relationship

As the IVT dose increased from 2 mg of aflibercept to 8 mg of HD aflibercept, no further increase in PD effect (decrease in CRT) was observed 4 weeks after each initial q4w dose through 12 weeks, in either the nAMD or DME population. Despite 2 mg of aflibercept and 8 mg of HD aflibercept having similar PD effect during the initial q4w dosing period, the 8 mg HD aflibercept dose provided a longer duration of pharmacological effect in the maintenance phase compared to 2 mg aflibercept.

In nAMD participants, the small fluctuations in CRT or CST during a maintenance dosing interval attenuated over time for all dosing regimens, with only minor numerical differences observed between treatment groups.

For DME participants, a greater reduction in CRT was observed from weeks 16 to 20 for 2q8 compared to both HD aflibercept regimens (HDq12 and HDq16). This is attributable to a difference in the number of doses administered during this time period, with the 2q8 regimen receiving 2 additional initial q4w doses at weeks 12 and 16 compared to the HD aflibercept regimens which received their last initial q4w dose at week 8. These differences in CRT did not translate into any meaningful difference in mean BCVA response. The fluctuations in CRT response over the course of a maintenance dosing interval attenuated over time for all dosing regimens.

For participants with nAMD or DME, the HDq12 and HDq16 regimens provided rapid and durable response in CRT and BCVA over 48 weeks of treatment, with the majority of participants maintaining their randomized HDq12 (79% nAMD; 91% DME) and HDq16 (77% nAMD; 89% DME) treatment regimens, without the need for DRM.

Ocular clearance of free aflibercept and baseline CRT were identified as significant covariates contributing to the need for DRM. Higher ocular clearance of free aflibercept and higher baseline CRT (indicative of more severe disease) were associated with an increased rate of DRM.

The slower ocular clearance for HD aflibercept, attributable to a HD drug product effect, is estimated to result in a 20.6% lower rate of DRM compared to HD aflibercept if the same ocular clearance was observed as the 2 mg aflibercept.

2.5.2. Discussion on clinical pharmacology

Pharmacokinetics and PD

The presented PopPK and E-R models are developed to provide context on the generated results and are used primarily for descriptive purposes, not to simulate untested scenario, but also in NC, pregnancy and toxicology discussions.

Concerning elimination, the longer duration of systemic exposure to free aflibercept for HD aflibercept is attributed to not only a higher administered dose and nonlinear systemic target mediated elimination but also to a 34% slower ocular clearance of free aflibercept.

Simulations of the population PK model showed that slower ocular clearance of the HD aflibercept drug product resulted in maintained ocular concentrations of free aflibercept above a threshold for 6 weeks longer with 8

mg aflibercept compared to 2 mg aflibercept. In consequence, the HD formulation can be expected to provide a 6 weeks longer duration of efficacy.

2.5.3. Conclusions on clinical pharmacology

Distribution, elimination from the ocular compartment after IVT, overall elimination, and effect of high dose were well characterised. No adaptation of dose for special populations for PK reasons or immunogenicity reasons are foreseen. MSOEG was of advice that the VPCs showed enough discrepancies to ask for an update of the model, and eventual support of the SmPC section 5.2 by the NCAs results instead of the population PKPD modelling, this was applied.

2.5.4. Clinical efficacy

2.5.4.1. Main studies

PULSAR Study – 20968

Methods

Study design

This phase 3, multi-center, randomized, double-masked, active-controlled study will investigate the efficacy, safety, and tolerability of IVT administration of aflibercept 8 mg (HD) versus aflibercept 2 mg in participants with treatment-naïve nAMD.

The study consists of a screening/baseline period, followed by a treatment period with duration of 92 weeks, and an end of study visit at Week 96. An extension of the study is planned starting Week 96.

Subjects with nAMD were randomized to receive IVT injections in the study eye of aflibercept high-dosed (HD) or aflibercept 2 mg in 3 parallel treatment groups (1:1:1 ratio):

- 2q8: aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
- HDq12: aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. Participants in this group can move to q8 dosing regimen at Weeks 16 or 20, or up to q16 dosing regimen at week 52 according to pre-specified criteria.
- HDq16: aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. Participants in this group can move to q8 dosing regimen at Weeks 16 or 20, to q12 dosing regimen at Week 24, or up to q20 dosing regimen at week 52 according to pre-specified criteria.

The design of the study is depicted in Figure 1-1 and 1-2.

Figure 1–1 Study Flow Diagram

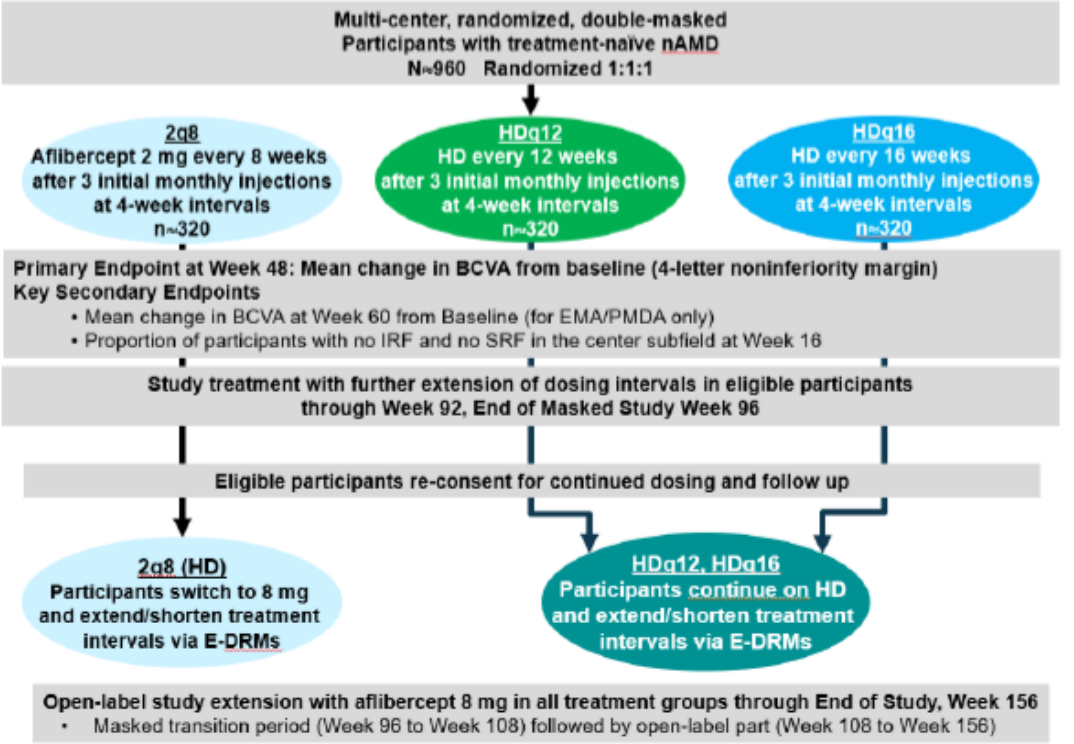


Figure 1–2 Dosing Schedule

	Day 1	Wk 4	Wk 8	Wk 12	Wk 16 (Key 2° Endpoint)	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48 (1° Endpoint)
2q8	X	X	X		X	o	X	o	X	o	X	o	X
HDq12	X	X	X		o[a]	X[a]	o	o	X[c]	o	o	X[c]	o
HDq16	X	X	X		o[b]	o[b]	X[b]	o	o	o	X[c]	o	o

	Wk 52	Wk 56	Wk 60 (Key 2° Endpoint)	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	
2q8	o	X	o	X	o	X	o	X	o	X	o	EOMS	Study extension on 8 mg
HDq12	o	X[d]	o	o	X[d]	o	o	X[d]	o	o	X[d]	EOMS	
HDq16	o	X[d]	o	o	o	X[d]	o	o	o	X[d]	o	EOMS	

Wk 96: Start of study extension

Mandatory monitoring visits to ensure that data collection occurs at least every 12 weeks

	Wk 96	Wk 100	Wk 104	Wk 108	Wk 110-Wk 118	Wk 120	Wk 122-Wk 130	Wk 132	Wk 134 Wk 142	Wk 144	Wk 146-Wk 152	Wk 156
2q8	8 mg	o	o[e]	X[e]	X[g]	X[g,h]	X[g]	X[g,h]	X[g]	X[g,h]	X[g]	EOS
HDq12	o	o	X[f]	o	X[g]	X[g,h]	X[g]	X[g,h]	X[g]	X[g,h]	X[g]	EOS
HDq16	o	o	X[f]	o	X[g]	X[g,h]	X[g]	X[g,h]	X[g]	X[g,h]	X[g]	EOS

Mandatory masked transition period | Open-label part

For masking purposes, DRM assessments will be performed in all participants at all visits (through the IXRS) starting from Week 16.

a HDq12 group: If DRM criteria are met, participants will continue on q8 rescue regimen.
b HDq16 group: If DRM criteria are met at Week 16 or 20, participant will continue on q8 rescue regimen. If DRM criteria are met at Week 24, participant will continue on q12 regimen.
c For participants remaining on a dosing interval of q12 or q16 weeks after Week 24, if DRM criteria are met at an active injection visit, the next dosing interval will be reduced by 4 weeks (to a minimum of q8).
d From Week 52, all participants in HD groups will be eligible for dose interval shortening (to a minimum of q8) or extension (by 4-week increments) according to pre-specified DRM criteria. If DRM criteria are met at an active injection visit, the next dosing interval will be changed by 4 weeks.
e Decision on treatment interval shortening at Week 104. If E-DRM shortening criteria in Year 3 are met, interval will be shortened to 8 weeks and the participants will be dosed with 8 mg at the same visit, and thus will not be dosed at Week 108.
f Aflibercept 8 mg will be administered according to individual participant response as determined by the E-DRM in Year 3.
g During the open-label part: aflibercept 8 mg will be administered according to individual participant response as determined by the E-DRM in Year 3. Visit windows will be increased to ±8 days (for mandatory visits by up to ±15 days) to allow merging visits 2 weeks apart. Decision on treatment interval shortening can be done at any visit: If E-DRM shortening criteria in Year 3 are met, dosing should be done at the same visit. Decision on treatment interval extension can only be done at treatment visits.
h Mandatory monitoring visits must be performed to ensure that data collection occurs at least every 12 weeks. They will be performed with or without treatment according to individual participant response as determined by the E-DRM in Year 3.

This figure does not reflect all available dosing options, once a participant's dose regimen is shortened or extended.

X=active injection, o=sham procedure
2q8=aflibercept 2 mg administered every 8 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 switch to aflibercept 8 mg every 12 weeks starting at Week 96; thereafter, aflibercept 8 mg administered according to individual participant response as determined by the E-DRM in Year 3. If the E-DRM criteria are met at Week 104, these participants will receive a dose at Week 104 and their subsequent treatment interval will be shortened to every 8 weeks.
HDq12=high dose aflibercept 8 mg administered every 12 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 receive aflibercept 8 mg according to individual participant response as determined by the E-DRM in Year 3.
HDq16=high dose aflibercept 8 mg administered every 16 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 receive aflibercept 8 mg according to individual participant response as determined by the E-DRM in Year 3.
1º=primary, 2º=secondary, DRM=dose regimen modification, E-DRM=dose regimen modification criteria for extension period, EOMS=end of masked study, HD=high dose, IXRS=Interactive Response System, q8=every 8 weeks, q12=every 12 weeks, q16=every 16 weeks, Wk=Week

Initially, approximately 960 patients were planned to be randomised. However, 1395 patients have actually been enrolled and randomized in a 1:1:1 ratio (337 in 2q8 arm, 336 in HDq12 and 338 in HDq16 arm respectively).

Study participants

The study population consisted of naïve male and female of ≥ 50 years patients with nAMD.

Key inclusion criteria

1. Active subfoveal CNV secondary to nAMD, including juxtafoveal lesions that affect the fovea as assessed in the study eye.

2. Total area of CNV (including both classic and occult components) must comprise greater than 50% of the total lesion area in the study eye.

3. BCVA ETDRS letter score of 78 to 24 (corresponding to a Snellen equivalent of approximately 20/32 to 20/320) in the study eye.

4. Decrease in BCVA determined to be primarily the result of nAMD in the study eye.

5. Presence of IRF and/or SRF affecting the central subfield of the study eye on OCT. The central subfield is defined as a circle with diameter 1 mm, centered on the fovea.

Key exclusion criteria

1. Causes of CNV other than nAMD in the study eye

2. Total lesion size >12 disc areas (30.5 mm2, including blood, scars, and neovascularization) as assessed by FA in the study eye.

3. Uncontrolled glaucoma (defined as IOP > 25 mmHg despite treatment with anti-glaucoma medication) in the study eye

4. Subretinal hemorrhage in the study eye ≥ 50% of the total lesion area, or if the blood under the fovea was ≥ 1 disc areas in size

5. Prior treatment of the study eye with anti-angiogenic drugs at any time

6. Uncontrolled blood pressure (defined as systolic > 160 mm Hg or diastolic > 95 mm Hg)

7. History or clinical evidence of diabetic retinopathy, diabetic macular edema, or any retinal vascular disease other than nAMD in either eye.

The comparator choice in naïve patients with nAMD was supported by the CHMP scientific advice. The chosen study population and related exams all along the study mimics the one from the randomised phase III VIEW1 and 2, which were the basis for the approval of aflibercept in nAMD patients and are in line with registrational studies for Eylea, therefore deemed acceptable.

Treatments

In PULSAR study, patients were randomized in a 1:1:1 ratio to receive monotherapy with either 2 mg aflibercept (administered every 8 weeks, after 3 initial injections at 4-week intervals) or aflibercept 8 mg administered every 12 or 16 weeks, after 3 initial injections at 4-week intervals as described in Table 2. Participants in the HD groups (HDq12 and HDq16) could benefit from a dose regimen modification and receive injections with a q8 dosing regimen at Weeks 16 or 20, or q12 dosing regimen (only for HDq16 treatment group) at Week 24, or up to or up to q16 (HDq12 group), q20 (HDq16 group) dosing regimen at week 52, according to pre-specified criteria listed in Table 3.

Each vial was for single eye use only. Medical devices used in this study include both devices that help prepare and deliver the study treatment (study drug and comparator), as well as devices that are used to gather additional clinical data. The devices were CE marked (or FDA cleared) according to the regulatory requirements specific for the country/region where the study site was located.

Treatment name	Aflibercept HD	Aflibercept 2 mg	Sham
Type	Drug	Drug	Not applicable
Dose formulation	Solution in vial	Solution in vial	Not applicable
Unit dose strengths	114.3 mg/mL	40 mg/mL	Not applicable
Dosage levels	8 mg (70 µL)	2 mg (50 µL)	Not applicable
Route of administration	IVT injection	IVT injection	Not applicable
Use	Experimental	Active comparator	Sham procedure
Packaging	Sterile 3 mL glass vials	Sterile 2 mL glass vials	Empty kit
Labeling	Each vial was labeled as required per country/region requirement		
Posology			
Initiation	All treatment arms: 3 initial injections at 4-week intervals		
Maintenance	HDq12: every 12 weeks HDq16: every 16 weeks	2q8: every 8 weeks	

HD = high dose, IVT = intravitreal
See Definition of terms for treatment group description.

Table 2 – Study treatment

		PULSAR
Year 1 (Baseline to Week 48)	**Shorten** dosing interval	• BCVA loss > 5 letters from Week 12, *AND* • > 25 µm increase in CRT from Week 12 *OR* new foveal hemorrhage *OR* new foveal neovascularization
Year 2 (Week 52 to Week 96)	**Shorten** dosing interval	Criteria as for Year 1
	Extend dosing interval	• BCVA loss <5 letters from Week 12, *AND* • No fluid at the central subfield on OCT, *AND* • No new onset foveal hemorrhage or foveal neovascularization

Table 3 - Dose regimen modification (DRM) criteria in PULSAR study during Year 1 and 2

Compared to the approved formulation of aflibercept 2mg, the dose tested is 4 times higher. It is to note that it is not clear why the 4 mg dose was not further investigated.

Permitted concomitant treatments:

Participants may not receive any standard or investigational agents for treatment of their nAMD in the study eye other than IVT aflibercept as specified in this protocol until they have completed the end of study/early termination visit assessments. This includes medications administered locally (e.g., IVT, by juxtascleral or periorbital routes), as well as those administered systemically with the intent of treating the fellow eye.

Any medication considered necessary for the participant's welfare, and that is not expected to interfere with the evaluation of the study intervention, may be given at the discretion of the investigator.

Any medication or vaccine (including any sedation, anesthesia, eye drops used for the study procedures, blood-derived products, prescription or over-the-counter medicines, probiotics, vitamins, and herbal supplements) that the participant is receiving at the time of enrolment or receives during the study was to be recorded.

If a pre-treatment concomitant medication is administered in the study eye before injection (e.g., antibiotic, topical anesthetic), it must be administered for sham procedures as well.

Dose delays or modifications: Assessments for dose regimen modification is to be performed in all participants at all visits starting from Week 16. Based on these assessments, participants in the HD groups may have their treatment intervals shortened or extended. The minimum interval between injections will be 8 weeks, which is considered a rescue regimen for participants randomized to HD groups who are unable to tolerate a dosing interval greater than every 8 weeks. Participants in the aflibercept 2 mg group will remain on fixed q8 dosing throughout the study until the end of masked study visit at Week 96 (i.e., will not have modifications of their treatment intervals regardless of the outcomes of the dose regimen modification assessments).

Treatment was to be discontinued in patients if any of the following reasons applied (but were not limited to):

• Relevant laboratory abnormality or SAEs, if the sponsor or investigator sees this as medical reason to warrant withdrawal.

• AE (ocular or nonocular) that, from the participant's or the investigator's view, is potent enough to require withdrawal from the study. The investigator must notify the sponsor immediately if a participant is withdrawn because of an AE/SAE.

• At the discretion of the treating investigator. The development of conditions, which would have prevented a participant's entry into the study according to the selection criteria, is no reason per se for withdrawal. However, the withdrawal in such cases remains at the discretion of the treating investigator.

• Decision by the investigator or sponsor that termination is in the participant's best medical interest or administrative decision for a reason other than an AE/SAE.

• A female participant becomes pregnant.

• Lost to follow-up.

• Decision by the sponsor to halt the entire study.

• Any treatment for nAMD other than study interventions in the study eye is considered a prohibited treatment, and participant must be withdrawn from the study.

• Systemic anti-angiogenic agents were taken by the participant during the study.

• If, in the investigator's opinion, continuation of the study would be harmful to the participant's well-being.

• At the specific request of the sponsor and in liaison with the investigator (e.g., obvious noncompliance or safety concerns).

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Participants who withdrew from the study were not replaced.

Objectives

Primary objective

To determine if treatment with aflibercept 8 mg (HD) at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to aflibercept 2 mg every 8 weeks in participants with nAMD

Secondary objectives

· To determine the effect of HD versus 2 mg aflibercept on other visual and anatomic measures of response

· To assess the efficacy of HD compared to 2 mg aflibercept on vision-related quality of life

Outcomes/endpoints

Primary efficacy endpoint

· Change from baseline in best corrected visual acuity (BCVA) (as measured by ETDRS letter score) at Week 48

Key secondary efficacy endpoints

· Change from baseline in BCVA measured by the ETDRS letter score at Week 60 (EP-SAP only)

· Proportion of Participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in Central Subfield at Week 16

Additional secondary endpoints

· Proportion of participants gaining ≥ 15 letters in BCVA from baseline at Week 48

· Proportion of participants with BCVA ≥ 69 letters at Week 48

· Change in CNV Size from Baseline to Week 48

· Change in Total Lesion Area from Baseline to Week 48

· Proportion of Participants with no IRF and no SRF in the Central Subfield at Week 48

· Change from baseline in CRT at Week 48

· Change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at Week 48

Exploratory endpoints

· Change from baseline in BCVA averaged over the period from Week 36 to Week 48

· Proportions of participants gaining and losing ≥ 5 or ≥ 10 letters at Week 48

· Proportion of participants losing ≥ 15 letters at Week 48

· Proportion of participants without leakage on FA at Week 48

· Proportion of participants randomized to HDq16 maintaining q16 dosing interval or longer through Weeks 48

· Proportion of participants randomized to HDq12 maintaining q12 dosing interval through Weeks 48

The primary objective and endpoint were discussed during the EMA Scientific Advice (SA) (EMA/CHMP/SAWP/277944/2019) and concerns were raised regarding the choice of an endpoint at 48 week in view of the increased intervals. Indeed, as stated in the SA there is a need to conclude on the durability of efficacy when extending the dosing intervals. A need for at least 64 week data, preferably supplemented with some 2-year data is foreseen to support the Q12 and/or Q16 dosing regimens as well as long-term safety. The MAH provided clinical results with a data cut-off at 60 weeks.

Sample size

The sample size of 960 subjects (3x320) was adequately estimated and included 10% possible dropout. It was based on a non-inferiority of two 8 mg dose-regimens aiming to consent a loss of efficacy over the 2 mg control regimen at 48 weeks not exceeding 4 characters of the EDTRS chart (i.e. one line of the chart), with 0.025 risk to a false positive non-inferiority and 94% chance to achieve the true positive non-inferiority.

Randomization

The randomization was performed with an interactive system for which it is not clear if it was through a web or a voice system or both. The 3 active arms were evenly distributed in the trial (1:1:1) and stratified over the geographical region (Japan vs Rest of the World) and the BCVA baseline (<60 vs ≥60). The granularity of the geographical stratification seems a bit wide given the heterogeneity of regions involved in the trial (Asia, Western Europe, Eastern Europe, North America and South America).

Blinding (masking)

As stated by the MAH, all study site personnel (except for those performing the unmasked roles as described in Table 7-2), were to remain masked to treatment assignment of participants in order to ensure an unbiased assessment of visual acuity, safety, and ancillary study measures. Masking continued until the end of the masked transition period of the study extension.

In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reactions related to the masked treatment, the participant's treatment code is usually to be unmasked before reporting to the health authorities, ethics committees and investigators.

The blinding of dose regimens was adequately guaranteed through sham injections in order to mask the difference in injection schedules. In addition, the unmasked investigator administering the study drug did not participate in any efficacy or safety endpoint evaluations apart from the reporting of AEs and device-related AEs/SAEs/deficiencies relating to filter needle, injection needle, or syringe during injection procedure and post-injection assessment. Therefore, no impact on study integrity is expected.

An overview of the masked and unmasked site personnel is presented in Table 4.

Study Procedure	Masked Study Staff [a]	Unmasked Study Staff [b]	Certification needed
Study intervention:			
Study intervention (study drug) accountability		X	
Injection-related procedures:			
IXRS access [c]	X	X	
(Pre-)injection procedures		X	
IVT injection (active, sham)		X	
Post-injection assessment (post-injection indirect ophthalmoscopy, and post-injection IOP)		X	
AE reporting:			
AEs and device-related AEs/SAEs/deficiencies relating to filter needle, injection needle, or syringe during injection procedure and post-injection assessment		X	
All other AEs, device-related AEs/SAEs/ deficiencies for devices used for gathering clinical data	X		
Ophthalmic assessment:			
BCVA examination BCVA recording in eCRF (different from BCVA examiner)	X X		X
Full ophthalmic examination (IOP, slit lamp, indirect ophthalmoscopy)	X		
FA, FP	X		X
SD-OCT	X		X
ICGA, if applicable	X		X
OCT-A, if applicable	X		X
NEI-VFQ-25 questionnaire	X		X
Other procedures:			
Informed consent	X [d]	X [d]	
Demography, medical and ocular history	X [d]	X [d]	
Record concomitant medications / treatments / interventions [e]	X		
Blood sampling (e.g., serum pregnancy test, immunogenicity, PK sampling)	X		
Blood pressure measurement	X		
Urine pregnancy test	X		

AE=adverse event, BCVA=best corrected visual acuity, eCRF=electronic case report form, FA=fluorescein angiography, FP=fundus photography, ICGA=indocyanine green angiography, IOP=intraocular pressure, IVT=intravitreal, IXRS=Interactive Response System, NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25, OCT-A=optical coherence tomography angiography, PK=pharmacokinetic, SAE=serious adverse event, SD-OCT=spectral domain optical coherence tomography.

a Includes masked investigator, masked study nurse/study coordinator, and study personnel for ocular assessments.

b Includes, unmasked investigator administering active/sham study intervention and assessing post-injection ocular assessments, and drug handler/pharmacist dispensing active/sham study intervention.

c For the purpose of treatment assignments/kit numbers, only the unmasked staff should have access to IXRS. Masked staff will have limited access to IXRS.

d Masked or unmasked personnel are allowed to do screening/baseline procedures such as initial informed consent. Reconsent must be undertaken by masked personnel.

e Except concomitant medications due to AE occurring during the injection or in the immediate post-injection period, which must be reported by unmasked investigator.

Table 4: Masked and Unmasked Site Personnel

Masked study intervention kits coded with a medication numbering system will be used. In order to maintain the mask, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Additionally, no emergency unblinding was required during the study.

Statistical methods

• Populations for statistical analyses

The full analysis set (FAS) included all randomized patients who received at least 1 dose of study medication; it was based on the treatment assigned to the patient at baseline (as randomized). FAS was the primary analysis set for efficacy endpoints.

The per-protocol set (PPS) was to include all patients in the FAS who had a baseline and at least 1 post-baseline assessment of BCVA, had any IRF or SRF affecting the central subfield at baseline and did not have any relevant important protocol violations that affect the primary efficacy variable. The final determination on the exclusion of patients from the PPS was to be made on the masked data prior to the first database lock and described in a separate document. Analysis of the PPS was to be performed according to the treatment the participant actually received (as treated). The PPS was used for supplementary analysis of change from baseline in BCVA (non-inferiority only) at week 48 (primary endpoint) and week 60 (key secondary endpoint).

Treatment assignment was based on the treatment received (as treated). In general, the randomized treatment group was to be considered as the actual treatment group, unless the patient has not been treated at all after randomization. Isolated incorrect treatments did not constitute a change in the "as treated" assignment but was considered as intercurrent events (refer to Section 5.6.1).

The safety analysis set (SAF) included all randomized patients who received any study treatment; it was based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables were analyzed using the SAF. The safety analysis was performed on the observed safety data.

The efficacy populations of analysis were acceptable, except for PPS which was planned to be analysed "as treated" while an error of treatment allocation should be considered as a major deviation to the protocol. Moreover, if the wrong treatment allocation occurred only at some specific time-points of the 48/60 weeks of exposure (this case is defined as an ICE), the rational for deciding which arm to assign to patient in the "as treated" strategy was initially unclear. As requested, clarifications have been brought by the Applicant regarding the "as treated" terminology used in the trial. Only 6 patients were concerned with the qualification of "as treated", whom only one subject underwent an error of treatment allocation. The other subjects were affected by deviations in the amount of volume injected or in the modalities of administration.

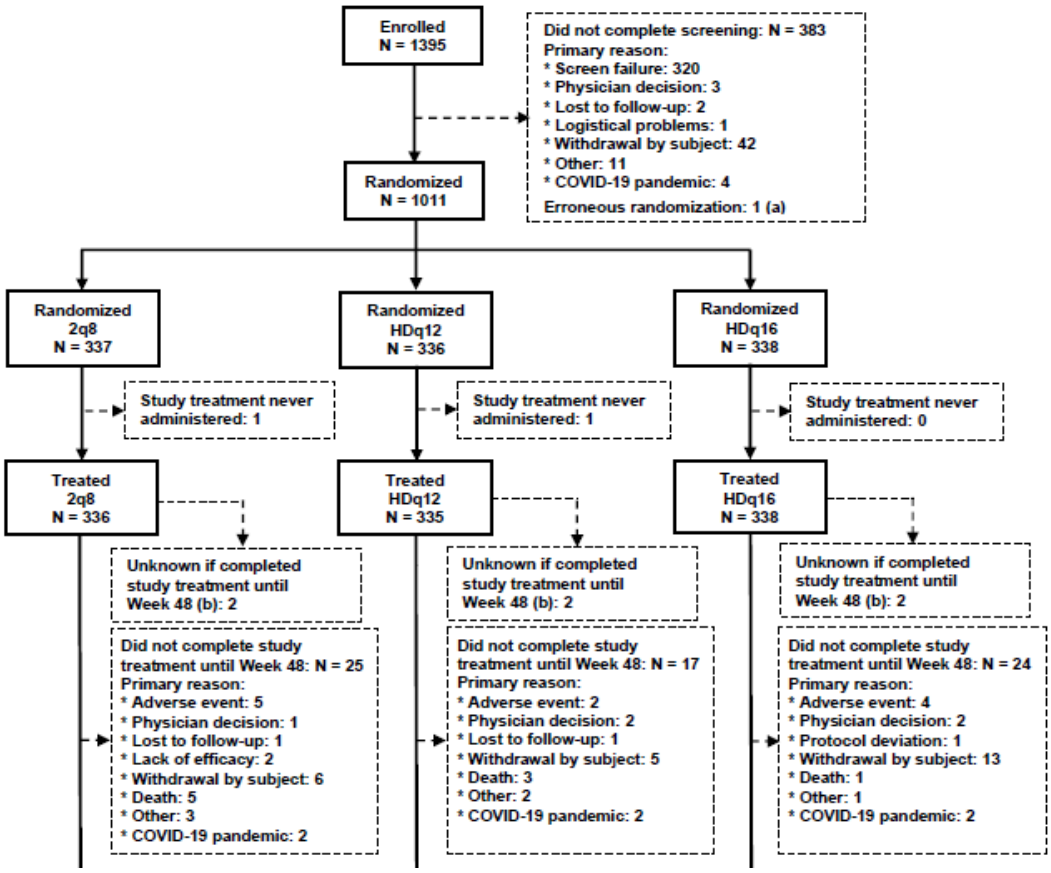
Overall, the issue could be considered as solved though the PP set do not reflect per-se the definition of such a population where patients presenting deviations in planned regimens potentially affecting the primary efficacy endpoint should be excluded.

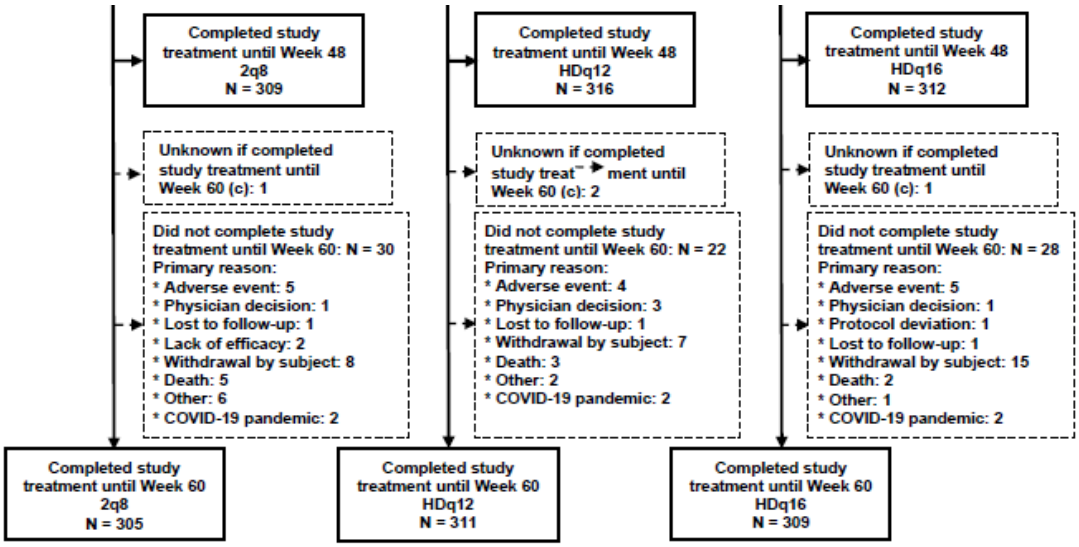
Results

Participant flow

The disposition of participants in the overall study through Week 48 and Week 60 is presented in Table 8-1. The MAH indicate that the number of participants who did not complete study shown in this table could differ from the number who did not complete study treatment in Figure 8-1, because participants who did not complete study treatment through Week 48 or Week 60 could have remained in the study (for other reasons of differences).

Figure 8-1: Disposition: Flow of participants through Week 60 (all enrolled participants)





COVID-19 = Coronavirus Disease 2019
(a) One participant was randomized in error after he/she had already discontinued from the study and was not considered as randomized in the datasets and study data analyses (see W48 Database errata in Section 16.4.2).
(b) 6 participants who had missing Week 48 information (i.e. they neither discontinued during Week 48 time frame, nor had Week 48 visit performed or marked as not done) were summarized as Unknown if completed study treatment until Week 48 (see W48 Database errata in Section 16.4.2).
(c) 4 participants who had missing Week 60 information (i.e. they neither discontinued during Week 60 time frame, nor had Week 60 visit performed or marked as not done) were summarized as Unknown if completed study treatment until Week 60 (see W60 Database errata in Section 16.4.2).
For some participants, the reason for premature discontinuation of treatment was inconsistently or not reported or the reason for end of screening was entered incorrectly (see W48 and W60 Database errata in Section 16.4.2).
Definition of Completed study treatment until Week 48/60 = did not discontinue study treatment prior to Week 48/60 visit.

Table 8-1: Disposition in overall study: Week 48 and Week 60 (all enrolled participants)

Number of subjects	2q8	HDq12	HDq16	All HD	Total
Week 48					
Enrolled, n					1395
Randomized, n (%)	337 (100%)	336 (100%)	338 (100%)	674 (100%)	1011 (100%)
Treated, n (%)	336 (99.7%)	335 (99.7%)	338 (100%)	673 (99.9%)	1009 (99.8%)
Completed study until Week 48, n (%)	309 (91.7%)	316 (94.0%)	312 (92.3%)	628 (93.2%)	937 (92.7%)
Unknown if completed study until Week 48[a], n (%)	3 (0.9%)	2 (0.6%)	1 (0.3%)	3 (0.4%)	6 (0.6%)
Did not complete study until Week 48, n (%)	25 (7.4%)	18 (5.4%)	25 (7.4%)	43 (6.4%)	68 (6.7%)
Primary reason[b]					
Adverse event	5 (1.5%)	1 (0.3%)	5 (1.5%)	6 (0.9%)	11 (1.1%)
Physician decision	1 (0.3%)	3 (0.9%)	2 (0.6%)	5 (0.7%)	6 (0.6%)
Non-compliance with study treatment	0	0	0	0	0
Pregnancy	0	0	0	0	0
Protocol deviation	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.2%)
Lost to follow-up	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Study terminated by sponsor	0	0	0	0	0
Lack of efficacy	2 (0.6%)	0	0	0	2 (0.2%)
Technical problems	0	0	0	0	0
Logistical problems	0	0	0	0	0
Withdrawal by subject	5 (1.5%)	5 (1.5%)	12 (3.6%)	17 (2.5%)	22 (2.2%)
Wish for pregnancy	0	0	0	0	0
Death	5 (1.5%)	3 (0.9%)	1 (0.3%)	4 (0.6%)	9 (0.9%)
Other	4 (1.2%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	8 (0.8%)
COVID-19 pandemic	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	6 (0.6%)
Subject decision: COVID-19 pandemic related	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	6 (0.6%)
Physician decision: COVID-19 pandemic related	0	0	0	0	0
Logistical reason: COVID-19 pandemic related	0	0	0	0	0
Other: COVID-19 pandemic related	0	0	0	0	0
Week 60					
Enrolled, n					1395
Randomized, n (%)	337 (100%)	336 (100%)	338 (100%)	674 (100%)	1011 (100%)
Treated, n (%)	336 (99.7%)	335 (99.7%)	338 (100%)	673 (99.9%)	1009 (99.8%)
Completed study until Week 60, n (%)	305 (90.5%)	310 (92.3%)	308 (91.1%)	618 (91.7%)	923 (91.3%)
Unknown if completed study until Week 60[c], n (%)	3 (0.9%)	3 (0.9%)	1 (0.3%)	4 (0.6%)	7 (0.7%)
Did not complete study until Week 60, n (%)	29 (8.6%)	23 (6.8%)	29 (8.6%)	52 (7.7%)	81 (8.0%)
Primary reason[d]					
Adverse event	6 (1.8%)	2 (0.6%)	5 (1.5%)	7 (1.0%)	13 (1.3%)
Physician decision	1 (0.3%)	4 (1.2%)	1 (0.3%)	5 (0.7%)	6 (0.6%)
Non-compliance with study treatment	0	0	0	0	0
Pregnancy	0	0	0	0	0
Protocol deviation	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.2%)
Lost to follow-up	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.4%)	4 (0.4%)
Study terminated by sponsor	0	0	0	0	0
Lack of efficacy	2 (0.6%)	0	0	0	2 (0.2%)
Technical problems	0	0	0	0	0
Logistical problems	0	0	0	0	0
Withdrawal by subject	6 (1.8%)	8 (2.4%)	14 (4.1%)	22 (3.3%)	28 (2.8%)
Wish for pregnancy	0	0	0	0	0
Death	5 (1.5%)	3 (0.9%)	2 (0.6%)	5 (0.7%)	10 (1.0%)
Other	6 (1.8%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	10 (1.0%)
COVID-19 pandemic	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	6 (0.6%)
Subject decision: COVID-19 pandemic related	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	6 (0.6%)
Physician decision: COVID-19 pandemic related	0	0	0	0	0

Logistical reason: COVID-19 pandemic related	0	0	0	0	0
Other: COVID-19 pandemic related	0	0	0	0	0

COVID-19 = Coronavirus Disease 2019.
a 6 participants who had missing Week 48 information (i.e. they neither discontinued during Week 48 time frame, nor had Week 48 visit performed or marked as not done) were summarized as Unknown if completed study until Week 48 (see W48 Database errata in Section 16.4.2).
b For some participants the reason for premature discontinuation of study was inconsistently reported (see W48 Database errata in Section 16.4.2).
c 7 participants who had missing Week 60 information (i.e. they neither discontinued during Week 60 time frame, nor had Week 60 visit performed or marked as not done) were summarized as Unknown if completed study until Week 60 (see W60 Database errata in Section 16.4.2).
d For some participants the reason for premature discontinuation of study was inconsistently reported (see W60 Database errata in Section 16.4.2).
Definition of completed study until Week 60 = did not answer NO to the question "Did the subject complete the study?" on the "End of study" form prior to Week 60 visit.
Number of subjects enrolled is the number of subjects who signed informed consent.
See Definition of terms for treatment group description.

Recruitment

Date first subject randomized: **20 Aug 2020**

Date last subject completed Week 60 / End of Study Visit: **04 Nov 2022**

The study was conducted at a total of in 19 EU countries, as well as in 6 APAC countries and 3 countries in American continent (Table 8-5).

Table 8-5: Number of participants by country/region (all randomized participants)

Pooled region	Country / Region	2q8 N = 337 (100%)	HDq12 N = 336 (100%)	HDq16 N = 338 (100%)	All HD N = 674 (100%)	Total N = 1011 (100%)
All	Total	337 (100%)	336 (100%)	338 (100%)	674 (100%)	1011 (100%)
APAC	Total	90 (26.7%)	81 (24.1%)	84 (24.9%)	165 (24.5%)	255 (25.2%)
	Australia	9 (2.7%)	7 (2.1%)	8 (2.4%)	15 (2.2%)	24 (2.4%)
	China	39 (11.6%)	31 (9.2%)	31 (9.2%)	62 (9.2%)	101 (10.0%)
	Japan	33 (9.8%)	32 (9.5%)	33 (9.8%)	65 (9.6%)	98 (9.7%)
	Korea	9 (2.7%)	11 (3.3%)	11 (3.3%)	22 (3.3%)	31 (3.1%)
	Singapore	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)
	Taiwan	0	0	0	0	0
Europe	Total	137 (40.7%)	162 (48.2%)	152 (45.0%)	314 (46.6%)	451 (44.6%)
	Austria	4 (1.2%)	2 (0.6%)	5 (1.5%)	7 (1.0%)	11 (1.1%)
	Bulgaria	10 (3.0%)	18 (5.4%)	7 (2.1%)	25 (3.7%)	35 (3.5%)
	Czech Republic	33 (9.8%)	31 (9.2%)	33 (9.8%)	64 (9.5%)	97 (9.6%)
	Estonia	2 (0.6%)	0	2 (0.6%)	2 (0.3%)	4 (0.4%)
	France	1 (0.3%)	6 (1.8%)	2 (0.6%)	8 (1.2%)	9 (0.9%)
	Georgia	1 (0.3%)	2 (0.6%)	6 (1.8%)	8 (1.2%)	9 (0.9%)
	Hungary	18 (5.3%)	34 (10.1%)	32 (9.5%)	66 (9.8%)	84 (8.3%)
	Israel	3 (0.9%)	5 (1.5%)	3 (0.9%)	8 (1.2%)	11 (1.1%)
	Italy	9 (2.7%)	9 (2.7%)	5 (1.5%)	14 (2.1%)	23 (2.3%)
	Latvia	7 (2.1%)	14 (4.2%)	3 (0.9%)	17 (2.5%)	24 (2.4%)
	Lithuania	9 (2.7%)	5 (1.5%)	12 (3.6%)	17 (2.5%)	26 (2.6%)
	Portugal	5 (1.5%)	7 (2.1%)	6 (1.8%)	13 (1.9%)	18 (1.8%)
	Russian Federation	4 (1.2%)	2 (0.6%)	3 (0.9%)	5 (0.7%)	9 (0.9%)
	Serbia	0	1 (0.3%)	0	1 (0.1%)	1 (0.1%)
	Slovakia	5 (1.5%)	14 (4.2%)	10 (3.0%)	24 (3.6%)	29 (2.9%)
	Spain	14 (4.2%)	7 (2.1%)	10 (3.0%)	17 (2.5%)	31 (3.1%)
	Switzerland	7 (2.1%)	2 (0.6%)	5 (1.5%)	7 (1.0%)	14 (1.4%)
	Ukraine	5 (1.5%)	3 (0.9%)	8 (2.4%)	11 (1.6%)	16 (1.6%)
Latin America	Total	2 (0.6%)	1 (0.3%)	4 (1.2%)	5 (0.7%)	7 (0.7%)
	Argentina	2 (0.6%)	1 (0.3%)	4 (1.2%)	5 (0.7%)	7 (0.7%)
North America	Total	108 (32.0%)	92 (27.4%)	98 (29.0%)	190 (28.2%)	298 (29.5%)
	Canada	0	2 (0.6%)	1 (0.3%)	3 (0.4%)	3 (0.3%)
	United States	108 (32.0%)	90 (26.8%)	97 (28.7%)	187 (27.7%)	295 (29.2%)

APAC = Asia Pacific
See Definition of terms for treatment group description.

Recruitment of subjects by country was overall balanced between treatment arms, except for Canada, Estonia, Serbia and Singapore where not all arms included patients due to the very low enrolment rate.

Conduct of the study

Protocol deviations

The frequency of participants with important protocol deviations through Week 60 was similar across the treatment groups (Table 8-2).

Overall, 355 (35.1%) participants reported important protocol deviations. The most frequent (≥ 5%) important protocol deviations were related to the categories: Procedure deviations, Treatment deviations, Time schedule deviations, and Informed consent.

Other protocol deviations were related to the COVID-19 pandemic (in 75 patients among them 1 not included in the Week 60 database) and Ukraine/Russian crisis (in 10 patients).

Considering that 35.1% of patients across the groups in PULSAR study reported important protocol deviations, the MAH was asked to discuss the impact of each of them on the efficacy analysis.

As requested, the Applicant has clarified what was meant by "important" protocol deviations in PULSAR study and described extensively the corresponding deviations as well as the decision rules that led to rule out from the primary analysis or the PPS analysis, all or part of data of patients presenting these deviations, depending on the way the might affect efficacy outcome and when they occurred. "Important" deviations to protocol were segmented in 3 categories: 1/ the ones not impacting the efficacy endpoints led to no exclusion from main efficacy analyses; 2/ deviations that might affect the efficacy endpoints and identified at screening led to excluding affected patients from the per-protocol set; 3/ deviations that might impact the efficacy and occurring after baselines measurements led to excluding from the main efficacy analyses partial data of affected patients. These last deviations were considered as intercurrent events and handled according to estimand strategies (mainly, hypothetical and treatment policy strategies, depending on the strength of the impact on efficacy data). Tables illustrating and justifying the updated definition and all concerned cases were provided and even though other approaches could have been considered, the proposed approach is reasonable.

However, in non-inferiority trials, it is well known that heterogeneity of data is a factor artificially favoring the non-inferiority, therefore, it would have been relevant to perform a per-protocol analysis excluding all patients presenting with "important" deviations impacting the primary endpoint within the 48 weeks treatment window, whatever the reason and the time of occurrence. This analysis, repeated on EU population would have been interesting too.

Table 8-2: Number of participants with important protocol deviations through Week 60 (all randomized participants)

Protocol deviation category	2q8 N = 337 (100%)	HDq12 N = 336 (100%)	HDq16 N = 338 (100%)	All HD N = 674 (100%)	Total N = 1011 (100%)
Subjects with any important deviation, n (%)	122 (36.2%)	113 (33.6%)	120 (35.5%)	233 (34.6%)	355 (35.1%)
Excluded concomitant medication treatment	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	3 (0.3%)
Subject received any standard or investigational agents for treatment of their nAMD in the study eye other than IVT aflibercept as specified in this protocol	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	3 (0.3%)
Inclusion/exclusion criteria not met but subject entered treatment [a]	8 (2.4%)	9 (2.7%)	11 (3.3%)	20 (3.0%)	28 (2.8%)
Exclusion Criteria: Subject has subretinal hemorrhage that is at least 50% of the total lesion area. or if the blood under the fovea is 1 or more disc areas in size in the study eye [b]	0	1 (0.3%)	0	1 (0.1%)	1 (0.1%)
Exclusion Criteria: Subject has a history or clinical evidence of diabetic retinopathy. diabetic macular edema. or any retinal vascular disease other than nAMD in either eye.	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Exclusion Criteria: Subject has known cardiac arrhythmia. based on medical history and/or outcome of ECG at screening. (Dense PK Substudy)	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Exclusion Criteria: Subject has uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg).	5 (1.5%)	6 (1.8%)	9 (2.7%)	15 (2.2%)	20 (2.0%)
Inclusion Criteria: Subject does not have BCVA ETDRS letter score of 78 to 24 at Baseline (corresponding to a Snellen equivalent of approximately 20/32 to 20/320) in the study eye (Left Eye).	1 (0.3%)	0	0	0	1 (0.1%)
Inclusion Criteria: Subject does not have BCVA ETDRS letter score of 78 to 24 at Baseline (corresponding to a Snellen equivalent of approximately 20/32 to 20/320) in the study eye (Right Eye).	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)
Inclusion Criteria: The patient does not have evidence of IRF and/or SRF affecting the central subfield of the study eye on OCT	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)
Informed consent	22 (6.5%)	20 (6.0%)	17 (5.0%)	37 (5.5%)	59 (5.8%)
Informed consent process not followed properly	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)
The Informed Consent is incomplete. The subject's signature/sign date are missing or partially signed or incorrect etc.	21 (6.2%)	20 (6.0%)	16 (4.7%)	36 (5.3%)	57 (5.6%)
The subject signed the ICF after starting his/her participation on the study (The ICF date is after the assessment date).	1 (0.3%)	0	0	0	1 (0.1%)
Other protocol deviations [c]	13 (3.9%)	14 (4.2%)	11 (3.3%)	25 (3.7%)	38 (3.8%)
Procedure deviations [c]	38 (11.3%)	55 (16.4%)	48 (14.2%)	103 (15.3%)	141 (13.9%)
Time schedule deviations [c, d]	23 (6.8%)	20 (6.0%)	29 (8.6%)	49 (7.3%)	72 (7.1%)
Treatment deviations	44 (13.1%)	20 (6.0%)	25 (7.4%)	45 (6.7%)	89 (8.8%)
Expired study drug administered to patient	8 (2.4%)	0	0	0	8 (0.8%)
Incorrect study drug kit administered to patient	0	1 (0.3%)	4 (1.2%)	5 (0.7%)	5 (0.5%)
Patient was randomized to the wrong stratum	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)

Study drug not administrated for reason other than documented medical issue.	16 (4.7%)	6 (1.8%)	3 (0.9%)	9 (1.3%)	25 (2.5%)
Received wrong dose treatment (high dose instead of low dose or vice versa; sham injection instead of active injection or vice versa)	19 (5.6%)	12 (3.6%)	13 (3.8%)	25 (3.7%)	44 (4.4%)
Regional Crisis Study drug not administered	2 (0.6%)	0	6 (1.8%)	6 (0.9%)	8 (0.8%)
Subject was given incorrect study treatment	0	1 (0.3%)	2 (0.6%)	3 (0.4%)	3 (0.3%)

BCVA = best corrected visual acuity, ECG = electrocardiogram, ETDRS = Early Treatment Diabetic Retinopathy Study, ICF = informed consent form, IRF = intraretinal fluid, nAMD = neovascular (wet) age-related macular degeneration, IVT = intravitreal, OCT = optical coherence tomography, PK = pharmacokinetics, PPS = per protocol set, SRF = subretinal fluid
Subjects could have more than one protocol deviation but are only counted once within each deviation category.
a A protocol deviation for 1 participant who was randomized and completed Day 1 assessments but did not receive study drug and was later found to meet Exclusion criterion 13 was not included in the Week 60 database (see W60 Database errata in Section 16.4.2).
b This protocol deviation, which was not included in the Week 48 analysis but was included in the Week 60 analysis, resulted in exclusion of the participant from the PPS (see W48 Database errata in Section 16.4.2 and Section 8.3).
c Subcategories are provided in source table.
d There was 1 protocol deviation related to "time schedule deviations" for missing Visit 15 related to the COVID-19 pandemic, which was not included in the analyses for Week 60 (see Section 8.2.1.1 and W60 Database errata in Section 16.4.2).
See Definition of terms for treatment group description.

Baseline data

Proportion of male and female were well balanced between the 3 arms, even if slightly more female patients were included in total (54,5%). Data were mostly well balanced across the treatment groups for the demographics and disease characteristics at baseline, except for discrepancies observed between groups for certain categories of age (<65, ≥ 65 to < 75 and ≥ 75 to < 80 years) and in patients with history of ischaemic heart disease and hepatic impairment (mild, severe, moderate).

Baseline disease characteristics of the study eye

The mean BCVA using ETDRS letter score averaged over all treatment groups at baseline was 59.6 letters; 86.2% of participants had an ETDRS letter score ≤ 73 and 41.7% of ≤ 60 letters. Individual values ranged from 24 and 78 letters overall and in each of the treatment groups at baseline, with mean values of 58.9, 59.9, and 60.0 in the 2q8, HDq12, and HDq16 groups, respectively.

The mean IOP in the study eye averaged over all treatment groups at baseline was 14.9 mmHg. Individual IOP values ranged from 6 to 25 mmHg overall and in the 2q8 group (from 7 to 25 mmHg in the HDq12 and HDq16 groups), with mean values of 14.8, 14.9, and 14.9 mmHg in the 2q8, HDq12, and HDq16 treatment groups, respectively.

The mean (SD) values of CST at baseline were 367.1 (133.6) µm in the 2q8 group, 370.3 (123.7) µm in the HDq12 group, and 370.7 (132.7) µm in the HDq16 group.

Medical and surgical history

The ocular medical and surgical history in the study eye mostly reported (> 10%) were AMD, Cataract and Cataract operation. Overall, baseline data for patient's medical and surgical history were comparable across the 3 groups, except for the cataract history were 101 (53.9) in the 2q8 group, 169 (50.4) in the HDq12 group,

and 206 (60.9) patients in the HDq16 group were observed, as well for patients with history of eyelid ptosis, retinal tear, vitreous disorder and asthenopia, in which no patient were included in all groups.

Table 8-8: Ocular medical history findings in the study eye occurring in > 1% of the participants in any treatment group (safety analysis set)

Primary system organ class Preferred term MedDRA version 25.0	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)	Total N = 1009 (100%)
Number (%) of subjects with at least one medical history finding, n (%)	335 (99.7%)	334 (99.7%)	337 (99.7%)	671 (99.7%)	1006 (99.7%)
Eye disorders	333 (99.1%)	334 (99.7%)	335 (99.1%)	669 (99.4%)	1002 (99.3%)
Neovascular age-related macular degeneration	249 (74.1%)	241 (71.9%)	251 (74.3%)	492 (73.1%)	741 (73.4%)
Cataract	181 (53.9%)	169 (50.4%)	206 (60.9%)	375 (55.7%)	556 (55.1%)
Age-related macular degeneration	69 (20.5%)	73 (21.8%)	71 (21.0%)	144 (21.4%)	213 (21.1%)
Dry age-related macular degeneration	46 (13.7%)	38 (11.3%)	41 (12.1%)	79 (11.7%)	125 (12.4%)
Vitreous detachment	30 (8.9%)	25 (7.5%)	32 (9.5%)	57 (8.5%)	87 (8.6%)
Dry eye	29 (8.6%)	20 (6.0%)	24 (7.1%)	44 (6.5%)	73 (7.2%)
Cataract nuclear	16 (4.8%)	23 (6.9%)	17 (5.0%)	40 (5.9%)	56 (5.6%)
Glaucoma	14 (4.2%)	10 (3.0%)	11 (3.3%)	21 (3.1%)	35 (3.5%)
Astigmatism	3 (0.9%)	4 (1.2%)	15 (4.4%)	19 (2.8%)	22 (2.2%)
Presbyopia	6 (1.8%)	9 (2.7%)	10 (3.0%)	19 (2.8%)	25 (2.5%)
Choroidal neovascularisation	12 (3.6%)	10 (3.0%)	8 (2.4%)	18 (2.7%)	30 (3.0%)
Open angle glaucoma	10 (3.0%)	8 (2.4%)	10 (3.0%)	18 (2.7%)	28 (2.8%)
Hypermetropia	6 (1.8%)	5 (1.5%)	11 (3.3%)	16 (2.4%)	22 (2.2%)
Macular degeneration	7 (2.1%)	9 (2.7%)	7 (2.1%)	16 (2.4%)	23 (2.3%)
Myopia	3 (0.9%)	6 (1.8%)	10 (3.0%)	16 (2.4%)	19 (1.9%)
Posterior capsule opacification	7 (2.1%)	7 (2.1%)	8 (2.4%)	15 (2.2%)	22 (2.2%)
Epiretinal membrane	4 (1.2%)	7 (2.1%)	5 (1.5%)	12 (1.8%)	16 (1.6%)
Retinal degeneration	4 (1.2%)	9 (2.7%)	3 (0.9%)	12 (1.8%)	16 (1.6%)
Dermatochalasis	3 (0.9%)	2 (0.6%)	8 (2.4%)	10 (1.5%)	13 (1.3%)
Retinopathy hypertensive	4 (1.2%)	5 (1.5%)	4 (1.2%)	9 (1.3%)	13 (1.3%)
Retinal drusen	1 (0.3%)	1 (0.3%)	7 (2.1%)	8 (1.2%)	9 (0.9%)
Exfoliation syndrome	3 (0.9%)	1 (0.3%)	6 (1.8%)	7 (1.0%)	10 (1.0%)
Vitreous floaters	2 (0.6%)	6 (1.8%)	1 (0.3%)	7 (1.0%)	9 (0.9%)
Cataract cortical	5 (1.5%)	4 (1.2%)	2 (0.6%)	6 (0.9%)	11 (1.1%)
Eyelid ptosis	0	2 (0.6%)	4 (1.2%)	6 (0.9%)	6 (0.6%)
Retinal tear	0	5 (1.5%)	1 (0.3%)	6 (0.9%)	6 (0.6%)
Vitreous disorder	1 (0.3%)	6 (1.8%)	0	6 (0.9%)	7 (0.7%)
Pterygium	2 (0.6%)	4 (1.2%)	1 (0.3%)	5 (0.7%)	7 (0.7%)
Vitreous degeneration	4 (1.2%)	3 (0.9%)	2 (0.6%)	5 (0.7%)	9 (0.9%)
Asthenopia	4 (1.2%)	1 (0.3%)	0	1 (0.1%)	5 (0.5%)
Surgical and medical procedures	114 (33.9%)	114 (34.0%)	106 (31.4%)	220 (32.7%)	334 (33.1%)
Cataract operation	83 (24.7%)	86 (25.7%)	75 (22.2%)	161 (23.9%)	244 (24.2%)
Intraocular lens implant	32 (9.5%)	31 (9.3%)	26 (7.7%)	57 (8.5%)	89 (8.8%)
Lens capsulotomy	6 (1.8%)	14 (4.2%)	5 (1.5%)	19 (2.8%)	25 (2.5%)
Blepharoplasty	1 (0.3%)	1 (0.3%)	10 (3.0%)	11 (1.6%)	12 (1.2%)
Keratomileusis	5 (1.5%)	4 (1.2%)	1 (0.3%)	5 (0.7%)	10 (1.0%)
Laser therapy	5 (1.5%)	4 (1.2%)	1 (0.3%)	5 (0.7%)	10 (1.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.2%)	6 (1.8%)	7 (2.1%)	13 (1.9%)	17 (1.7%)
Eye naevus	3 (0.9%)	4 (1.2%)	2 (0.6%)	6 (0.9%)	9 (0.9%)

MedDRA = Medical Dictionary for Regulatory Activities
A participant was counted only once within each primary system organ class/preferred term.
The threshold of > 1% was applied to any system organ class and any preferred term in any treatment group. System organ classes and preferred terms that met the threshold are sorted by decreasing order of frequency in the pooled HD groups. System organ classes that met the threshold but none of the underlying preferred terms, are not displayed. The number (%) of participants with at least one medical history finding overall and in each system organ class are without consideration for the threshold.

Regarding the non-ocular medical and surgical history in the study eye, the most commonly reported SOC (> 30%) were Vascular disorders, Metabolism and nutrition disorders, Surgical and medical procedures, and Musculoskeletal and connective tissue disorders.

Table 8-9: Non-ocular medical history findings occurring in > 3% of the participants in any treatment group (safety analysis set)

Primary system organ class Preferred term MedDRA version 25.0	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)	Total N = 1009 (100%)
Number (%) of subjects with at least one medical history finding, n (%)	303 (90.2%)	316 (94.3%)	310 (91.7%)	626 (93.0%)	929 (92.1%)
Vascular disorders	212 (63.1%)	226 (67.5%)	224 (66.3%)	450 (66.9%)	662 (65.6%)
Hypertension	195 (58.0%)	218 (65.1%)	207 (61.2%)	425 (63.2%)	620 (61.4%)
Metabolism and nutrition disorders	161 (47.9%)	178 (53.1%)	168 (49.7%)	346 (51.4%)	507 (50.2%)
Hypercholesterolaemia	49 (14.6%)	73 (21.8%)	56 (16.6%)	129 (19.2%)	178 (17.6%)
Hyperlipidaemia	56 (16.7%)	59 (17.6%)	49 (14.5%)	108 (16.0%)	164 (16.3%)
Type 2 diabetes mellitus	30 (8.9%)	39 (11.6%)	36 (10.7%)	75 (11.1%)	105 (10.4%)
Diabetes mellitus	11 (3.3%)	18 (5.4%)	19 (5.6%)	37 (5.5%)	48 (4.8%)
Dyslipidaemia	22 (6.5%)	11 (3.3%)	26 (7.7%)	37 (5.5%)	59 (5.8%)
Hyperuricaemia	12 (3.6%)	18 (5.4%)	18 (5.3%)	36 (5.3%)	48 (4.8%)
Gout	7 (2.1%)	10 (3.0%)	7 (2.1%)	17 (2.5%)	24 (2.4%)
Obesity	11 (3.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	15 (1.5%)
Surgical and medical procedures	117 (34.8%)	134 (40.0%)	124 (36.7%)	258 (38.3%)	375 (37.2%)
Hysterectomy	23 (6.8%)	20 (6.0%)	24 (7.1%)	44 (6.5%)	67 (6.6%)
Appendicectomy	10 (3.0%)	21 (6.3%)	16 (4.7%)	37 (5.5%)	47 (4.7%)
Cholecystectomy	5 (1.5%)	12 (3.6%)	11 (3.3%)	23 (3.4%)	28 (2.8%)
Tonsillectomy	15 (4.5%)	8 (2.4%)	14 (4.1%)	22 (3.3%)	37 (3.7%)
Coronary arterial stent insertion	7 (2.1%)	11 (3.3%)	8 (2.4%)	19 (2.8%)	26 (2.6%)
Musculoskeletal and connective tissue disorders	125 (37.2%)	123 (36.7%)	100 (29.6%)	223 (33.1%)	348 (34.5%)
Osteoarthritis	37 (11.0%)	27 (8.1%)	31 (9.2%)	58 (8.6%)	95 (9.4%)
Osteoporosis	39 (11.6%)	33 (9.9%)	24 (7.1%)	57 (8.5%)	96 (9.5%)
Arthritis	17 (5.1%)	17 (5.1%)	16 (4.7%)	33 (4.9%)	50 (5.0%)
Back pain	17 (5.1%)	11 (3.3%)	12 (3.6%)	23 (3.4%)	40 (4.0%)
Arthralgia	10 (3.0%)	9 (2.7%)	5 (1.5%)	14 (2.1%)	24 (2.4%)
Cardiac disorders	90 (26.8%)	100 (29.9%)	87 (25.7%)	187 (27.8%)	277 (27.5%)
Myocardial ischaemia	11 (3.3%)	26 (7.8%)	15 (4.4%)	41 (6.1%)	52 (5.2%)
Atrial fibrillation	28 (8.3%)	21 (6.3%)	18 (5.3%)	39 (5.8%)	67 (6.6%)
Coronary artery disease	15 (4.5%)	9 (2.7%)	15 (4.4%)	24 (3.6%)	39 (3.9%)
Angina pectoris	10 (3.0%)	11 (3.3%)	9 (2.7%)	20 (3.0%)	30 (3.0%)
Myocardial infarction	8 (2.4%)	12 (3.6%)	6 (1.8%)	18 (2.7%)	26 (2.6%)
Arrhythmia	10 (3.0%)	6 (1.8%)	8 (2.4%)	14 (2.1%)	24 (2.4%)
Gastrointestinal disorders	88 (26.2%)	88 (26.3%)	92 (27.2%)	180 (26.7%)	268 (26.6%)
Gastrooesophageal reflux disease	44 (13.1%)	42 (12.5%)	42 (12.4%)	84 (12.5%)	128 (12.7%)
Nervous system disorders	71 (21.1%)	66 (19.7%)	74 (21.9%)	140 (20.8%)	211 (20.9%)
Cerebrovascular accident	11 (3.3%)	8 (2.4%)	6 (1.8%)	14 (2.1%)	25 (2.5%)
Transient ischaemic attack	10 (3.0%)	3 (0.9%)	1 (0.3%)	4 (0.6%)	14 (1.4%)
Endocrine disorders	54 (16.1%)	62 (18.5%)	67 (19.8%)	129 (19.2%)	183 (18.1%)
Hypothyroidism	37 (11.0%)	45 (13.4%)	45 (13.3%)	90 (13.4%)	127 (12.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	58 (17.3%)	66 (19.7%)	62 (18.3%)	128 (19.0%)	186 (18.4%)
Breast cancer	14 (4.2%)	12 (3.6%)	10 (3.0%)	22 (3.3%)	36 (3.6%)
Prostate cancer	9 (2.7%)	10 (3.0%)	8 (2.4%)	18 (2.7%)	27 (2.7%)
Basal cell carcinoma	6 (1.8%)	4 (1.2%)	11 (3.3%)	15 (2.2%)	21 (2.1%)
Psychiatric disorders	64 (19.0%)	54 (16.1%)	72 (21.3%)	126 (18.7%)	190 (18.8%)
Depression	39 (11.6%)	20 (6.0%)	32 (9.5%)	52 (7.7%)	91 (9.0%)
Insomnia	14 (4.2%)	17 (5.1%)	24 (7.1%)	41 (6.1%)	55 (5.5%)
Anxiety	20 (6.0%)	18 (5.4%)	14 (4.1%)	32 (4.8%)	52 (5.2%)
Respiratory, thoracic and mediastinal disorders	57 (17.0%)	58 (17.3%)	51 (15.1%)	109 (16.2%)	166 (16.5%)
Asthma	14 (4.2%)	21 (6.3%)	17 (5.0%)	38 (5.6%)	52 (5.2%)
Chronic obstructive pulmonary disease	18 (5.4%)	16 (4.8%)	20 (5.9%)	36 (5.3%)	54 (5.4%)
Reproductive system and breast disorders	38 (11.3%)	46 (13.7%)	55 (16.3%)	101 (15.0%)	139 (13.8%)

Benign prostatic hyperplasia	23 (6.8%)	34 (10.1%)	35 (10.4%)	69 (10.3%)	92 (9.1%)
Immune system disorders	39 (11.6%)	38 (11.3%)	42 (12.4%)	80 (11.9%)	119 (11.8%)
Seasonal allergy	20 (6.0%)	23 (6.9%)	24 (7.1%)	47 (7.0%)	67 (6.6%)
Drug hypersensitivity	16 (4.8%)	18 (5.4%)	20 (5.9%)	38 (5.6%)	54 (5.4%)
Social circumstances	33 (9.8%)	31 (9.3%)	36 (10.7%)	67 (10.0%)	100 (9.9%)
Menopause	24 (7.1%)	20 (6.0%)	25 (7.4%)	45 (6.7%)	69 (6.8%)
Postmenopause	9 (2.7%)	13 (3.9%)	11 (3.3%)	24 (3.6%)	33 (3.3%)
Investigations	23 (6.8%)	26 (7.8%)	26 (7.7%)	52 (7.7%)	75 (7.4%)
Blood cholesterol increased	9 (2.7%)	8 (2.4%)	11 (3.3%)	19 (2.8%)	28 (2.8%)

MedDRA = Medical Dictionary for Regulatory Activities
A participant was counted only once within each primary system organ class preferred term.
The threshold of > 1% was applied to any system organ class and any preferred term in any treatment group. System organ classes and preferred terms that met the threshold are sorted by decreasing order of frequency in the pooled HD groups. System organ classes that met the threshold but none of the underlying preferred terms, are not displayed. The number (%) of participants with at least one medical history finding overall and in each system organ class are without consideration for the threshold.

Numbers analysed

Analysis sets of FAS and SAF were identical. The group size of the PPS was ≥ 95% of all randomized participants in all treatment groups at Week 48 and Week 60 (Table 8-3 and Table 8-4, respectively).

Table 8-3: Analysis sets and validity findings at Week 48 (all randomized participants)

	2q8 N = 337 (100%)	HDq12 N = 336 (100%)	HDq16 N = 338 (100%)	All HD N = 674 (100%)	Total N = 1011 (100%)
Subjects valid for FAS, n (%)	336 (99.7%)	335 (99.7%)	338 (100%)	673 (99.9%)	1009 (99.8%)
Excluded from FAS, n (%)	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Subjects valid for SAF, n (%)	336 (99.7%)	335 (99.7%)	338 (100%)	673 (99.9%)	1009 (99.8%)
Excluded from SAF, n (%)	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Subjects valid for PPS, n (%)	320 (95.0%)	325 (96.7%)	325 (96.2%)	650 (96.4%)	970 (95.9%)
Excluded from PPS, n (%)	17 (5.0%)	11 (3.3%)	13 (3.8%)	24 (3.6%)	41 (4.1%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No baseline BCVA value available	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No post-baseline BCVA value available	2 (0.6%)	2 (0.6%)	1 (0.3%)	3 (0.4%)	5 (0.5%)
No IRF or SRF in central subfield at baseline	14 (4.2%)	8 (2.4%)	11 (3.3%)	19 (2.8%)	33 (3.3%)
Violation of relevant inclusion / exclusion criteria [a, b]	2 (0.6%)	1 (0.3%)	3 (0.9%)	4 (0.6%)	6 (0.6%)
Subjects valid for PKS, n (%)	308 (91.4%)	313 (93.2%)	313 (92.6%)	626 (92.9%)	934 (92.4%)
Excluded from PKS, n (%)	29 (8.6%)	23 (6.8%)	25 (7.4%)	48 (7.1%)	77 (7.6%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No drug concentration measurement following the first dose of study intervention available	28 (8.3%)	22 (6.5%)	25 (7.4%)	47 (7.0%)	75 (7.4%)
Subjects valid for DPKS, n (%)	7 (2.1%)	10 (3.0%)	6 (1.8%)	16 (2.4%)	23 (2.3%)
Excluded from DPKS, n (%)	330 (97.9%)	326 (97.0%)	332 (98.2%)	658 (97.6%)	988 (97.7%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No drug concentration measurement (dense PK result) following the first dose of study intervention available	328 (97.3%)	324 (96.4%)	332 (98.2%)	656 (97.3%)	984 (97.3%)
Subjects valid for AAS, n (%)	260 (77.2%)	269 (80.1%)	264 (78.1%)	533 (79.1%)	793 (78.4%)
Excluded from AAS, n (%)	77 (22.8%)	67 (19.9%)	74 (21.9%)	141 (20.9%)	218 (21.6%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No result in the ADA assay following the first dose of study intervention available	76 (22.6%)	66 (19.6%)	74 (21.9%)	140 (20.8%)	216 (21.4%)
Subjects valid for NAbAS, n (%)	256 (76.0%)	267 (79.5%)	263 (77.8%)	530 (78.6%)	786 (77.7%)
Excluded from NAbAS, n (%) [c]	81 (24.0%)	69 (20.5%)	75 (22.2%)	144 (21.4%)	225 (22.3%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No result in the NAb assay following the first dose of study intervention available	80 (23.7%)	68 (20.2%)	75 (22.2%)	143 (21.2%)	223 (22.1%)

AAS = ADA analysis set, ADA = anti-drug antibody, BCVA = best corrected visual acuity, DPKS = dense pharmacokinetic analysis set, FAS = full analysis set, IRF = intraretinal fluid, NAb = neutralizing antibody, NAbAS = NAb analysis set, PK = pharmacokinetics, PKS = pharmacokinetic analysis set, PPS = per protocol set, SAF = safety analysis set, SRF = subretinal fluid

Number of subjects enrolled is the number of subjects who signed informed consent.

If a subject had more than one validity finding that excluded him/her from an analysis set, all of the findings are displayed.

a Relevant inclusion / exclusion criteria affected are provided in source table.

b One participant met Exclusion criterion #02a (data were updated after the Week 48 database release); this protocol deviation was considered important, and the participant should have been excluded from the PPS (see W48 Database errata in Section 16.4.2).

c 6 participants who were excluded should have been included in the NAbAS as they had pre-existing ADA response, were tested negative in ADA at post-dose and had their corresponding NAb results imputed as negative (see W48 Database errata in Section 16.4.2).

Table 8-4: Analysis sets and validity findings at Week 60 (all randomized participants)

	2q8 N = 337 (100%)	HDq12 N = 336 (100%)	HDq16 N = 338 (100%)	All HD N = 674 (100%)	Total N = 1011 (100%)
Subjects valid for FAS, n (%)	336 (99.7%)	335 (99.7%)	338 (100%)	673 (99.9%)	1009 (99.8%)
Excluded from FAS, n (%)	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Subjects valid for SAF, n (%)	336 (99.7%)	335 (99.7%)	338 (100%)	673 (99.9%)	1009 (99.8%)
Excluded from SAF, n (%)	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Subjects valid for PPS, n (%)	320 (95.0%)	324 (96.4%)[b]	325 (96.2%)	649 (96.3%)[b]	969 (95.8%)[b]
Excluded from PPS, n (%)	17 (5.0%)	12 (3.6%)[b]	13 (3.8%)	25 (3.7%)[b]	42 (4.2%)[b]
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No baseline BCVA value available	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No post-baseline BCVA value available	2 (0.6%)	2 (0.6%)	1 (0.3%)	3 (0.4%)	5 (0.5%)
No IRF or SRF in central subfield at baseline	14 (4.2%)	8 (2.4%)	11 (3.3%)	19 (2.8%)	33 (3.3%)
Violation of relevant inclusion / exclusion criteria [a]	2 (0.6%)	2 (0.6%)[b]	3 (0.9%)	5 (0.7%)[b]	7 (0.7%)[b]
Subjects valid for PKS, n (%)	308 (91.4%)	313 (93.2%)	313 (92.6%)	626 (92.9%)	934 (92.4%)
Excluded from PKS, n (%)	29 (8.6%)	23 (6.8%)	25 (7.4%)	48 (7.1%)	77 (7.6%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No drug concentration measurement following the first dose of study intervention available	28 (8.3%)	22 (6.5%)	25 (7.4%)	47 (7.0%)	75 (7.4%)
Subjects valid for DPKS, n (%)	7 (2.1%)	10 (3.0%)	6 (1.8%)	16 (2.4%)	23 (2.3%)
Excluded from DPKS, n (%)	330 (97.9%)	326 (97.0%)	332 (98.2%)	658 (97.6%)	988 (97.7%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No drug concentration measurement (dense PK result) following the first dose of study intervention available	328 (97.3%)	324 (96.4%)	332 (98.2%)	656 (97.3%)	984 (97.3%)
Exclude from Dense PK Substudy	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Subjects valid for AAS, n (%)	273 (81.0%)	283 (84.2%)	277 (82.0%)	560 (83.1%)	833 (82.4%)
Excluded from AAS, n (%)	64 (19.0%)	53 (15.8%)	61 (18.0%)	114 (16.9%)	178 (17.6%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No result in the ADA assay following the first dose of study intervention available	63 (18.7%)	52 (15.5%)	61 (18.0%)	113 (16.8%)	176 (17.4%)
Subjects valid for NAbAS, n (%)	273 (81.0%)	282 (83.9%)	277 (82.0%)	559 (82.9%)	832 (82.3%)
Excluded from NAbAS, n (%)	64 (19.0%)	54 (16.1%)	61 (18.0%)	115 (17.1%)	179 (17.7%)
Never took study intervention	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
No result in the NAb assay following the first dose of study intervention available	63 (18.7%)	53 (15.8%)	61 (18.0%)	114 (16.9%)	177 (17.5%)

AAS = ADA analysis set, ADA = anti-drug antibody, BCVA = best corrected visual acuity, DPKS = dense pharmacokinetic analysis set, FAS = full analysis set, IRF = intraretinal fluid, NAb = neutralizing antibody, NAbAS = NAb analysis set, PK = pharmacokinetics, PKS = pharmacokinetic analysis set, PPS = per protocol set, SAF = safety analysis set, SRF = subretinal fluid

Number of subjects enrolled is the number of subjects who signed informed consent.

If a subject had more than one validity finding that excluded him/her from an analysis set, all of the findings are displayed.

a Relevant inclusion / exclusion criteria affected are provided in source table.

b One participant who met Exclusion criterion #02a was not excluded from the PPS for the Week 48 analysis but was excluded from the PPS for the Week 60 analysis (because data were only updated after the Week 48 database release; see W48 Database errata in Section 16.4.2). Therefore, the PPS in the Week 48 database included a total of 970 (95.9%) participants, whereas the PPS in the Week 60 database included a total of 969 (95.8%) participants.

Outcomes and estimation

Overview of hierarchical testing procedure, corresponding test decisions and statistical conclusions

Table 9-6 provides a summary of the results compiled by the MAH for the primary and key secondary endpoints included in the hierarchical testing procedure, as per the EP-SAP. The first 5 confirmatory tests in the hierarchy (H10, H20, H30, H40, H50) were statistically significant at the alpha level of 0.025 (one-sided tests). Therefore, the following is concluded:

· Treatment of participants with nAMD with HDq12 is non-inferior to treatment with 2q8 with regard to the primary endpoint "change from baseline in BCVA at Week 48" and with regard to the key secondary endpoint "change from baseline in BCVA at Week 60" (p=0.0009 and p=0.0002, respectively)

· Treatment of participants with nAMD with HDq16 is non-inferior to treatment with 2q8 with regard to the primary endpoint "change from baseline in BCVA at Week 48" and with regard to the key secondary endpoint "change from baseline in BCVA at Week 60" (p=0.0011 and p < 0.0001, respectively)

· Treatment of participants with nAMD with HD is superior to treatment with 2q8 with regard to the key secondary endpoint "proportion of participants with no IRF and no SRF in central subfield at Week 16" (p = 0.0002)

The confirmatory test for superiority of HDq12 vs. 2q8 (H60) in the primary endpoint "change from baseline in BCVA at Week 48" was not statistically significant (p = 0.8437) and hence the hierarchical testing procedure was stopped at the H60 test (i.e. the confirmatory test for superiority of Week 60 HDq12 vs. 2q8, H70, must not be performed).

Table 9-6: Test decisions and statistical conclusions as per the EP-SAP (full analysis set)

Null hypothesis		p-value (one-sided test)	Estimate for contrast or Difference (two-sided 95% CI)	Test decision: H_{x0} rejected
Primary endpoint "Change from baseline in BCVA at Week 48" and key secondary endpoint "Change from baseline in BCVA at Week 60": Non-inferiority (at a margin of 4 letters)				
H_{10}: non-inferiority of HDq12 vs. 2q8 in primary endpoint	Week 48	0.0009	-0.97 (-2.87,0.92) letters [a]	Yes
H_{20}: non-inferiority of HDq12 vs. 2q8 in key secondary endpoint	Week 60	0.0002	-0.86 (-2.57,0.84) letters [a]	Yes
H_{30}: non-inferiority of HDq16 vs. 2q8 in primary endpoint	Week 48	0.0011	-1.14 (-2.97,0.69) letters [a]	Yes
H_{40}: non-inferiority of HDq16 vs. 2q8 in key secondary endpoint	Week 60	<0.0001	-0.92 (-2.51,0.66) letters [a]	Yes
Key secondary endpoint "Proportion of participants with no IRF and no SRF in central subfield at Week 16": Superiority				
H_{50}: superiority of pooled high dose vs. 2q8 in key secondary endpoint	Week 16	p = 0.0002	11.733% (5.263%, 18.204%) [b]	Yes
Primary endpoint "Change from baseline in BCVA at Week 48" and key secondary endpoint "Change from baseline in BCVA at Week 60": Superiority				
H_{60}: superiority of HDq12 vs. 2q8 in primary endpoint	Week 48	p = 0.8437	-0.97 (-2.87,0.92) letters [a]	No, and hierarchical testing procedure stopped
H_{70}: superiority of HDq12 vs. 2q8 in key secondary endpoint at	Week 60	p = 0.8393	-0.86 (-2.57,0.84) letters [a]	NA (test must not be performed)
H_{80}: superiority of HDq16 vs. 2q8 in primary endpoint	Week 48	p = 0.8884	-1.14 (-2.97,0.69) letters [a]	NA (test must not be performed)
H_{90}: superiority of HDq16 vs. 2q8 in key secondary endpoint at	Week 60	p = 0.8731	-0.92 (-2.51,0.66) letters [a]	NA (test must not be performed)

BCVA = best corrected visual acuity, CI = Confidence limits, EMA = European Medicines Agency, EP-SAP = EMA/PMDA statistical analysis plan, IRF = intraretinal fluid, MMRM = mixed model for repeated measurements, NA = not applicable, PMDA = Pharmaceuticals and Medical Devices Agency, SRF = Subretinal fluid

a Estimate for contrast based on the MMRM model, computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively, with two-sided 95% CIs.

b Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% CIs as described in SAP Section 6.2.3.1.2.

For the sake of completeness, when applying the hierarchical testing procedure defined in the G-SAP, the first 3 confirmatory tests in the hierarchy (H10, H30, H50) were statistically significant at the alpha level of 0.025 (one-sided tests) (W48 Table 14.2.1/1 and W48 Table 14.2.2/1 of the PH-42588 report section). Therefore, the following is concluded:

· Treatment of participants with nAMD with HDq12 is non-inferior to treatment with 2q8 with regard to the primary endpoint "change from baseline in BCVA at Week 48"

· Treatment of participants with nAMD with HDq16 is non-inferior to treatment with 2q8 with regard to the primary endpoint "change from baseline in BCVA at Week 48"

· Treatment of participants with nAMD with HD is superior to treatment with 2q8 with regard to the key secondary endpoint "proportion of participants with no IRF and no SRF in central subfield at Week 16".

The non-inferiority of each high dose over the control dose is formally demonstrated at 48 and 60 weeks of treatment in the ITT population, as well as the superiority of the pooled high doses at 16 weeks of treatment in the subgroup of patients without IRF and SRF in subfield central. No superiority can be claimed over the control dose for individual high doses.

Primary endpoint analysis

For the primary analysis of the primary efficacy endpoint, the MAH used a mixed model for repeated measurements (MMRM) with baseline BCVA measurement as a covariate and treatment group, visit, the stratification variables (geographic region [Japan vs. Rest of World], and baseline BCVA [< 60 vs. ≥ 60]) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit. The results of this analysis are presented in Table 9-2.

Change from baseline in BCVA measured by the ETDRS letter score at Week 48

The primary analysis of the change from baseline in BCVA resulted in LS mean changes from baseline to Week 48 (i.e. estimated, adjusted mean changes) of 7.03, 6.06 and 5.89 letters for the 2q8, HDq12 and HDq16 groups, respectively (Table 9-2).

The estimated difference in LS means changes from baseline to Week 48 in BCVA (with corresponding 95% CI) of HDq12 vs. 2q8 was -0.97 (-2.87, 0.92) letters and of HDq16 vs. 2q8 was -1.14 (-2.97, 0.69) letters (Table 9-2). The p-values for the non-inferiority test at a margin of 4 letters were 0.0009 (related to H10) for HDq12 vs. 2q8, and 0.0011 (related to H30) for HDq16 vs. 2q8; p-values for a superiority test were 0.8437 (related to H60) for HDq12 vs. 2q8 and of 0.8884 (related to H80) for HDq16 vs. 2q8 (W48 Table 14.2.1/1).

The arithmetic mean (SD) changes from baseline in BCVA to Week 48 (i.e. observed, unadjusted mean changes) were 7.6 (12.2), 6.7 (12.6), and 6.2 (11.7) letters for the 285, 299, and 289 participants with Week 48 data, i.e. excluding data after an ICE as handled by the hypothetical strategy, in the 2q8, HDq12, and HDq16 groups, respectively (Table 9-2).

The arithmetic mean changes from baseline in BCVA measured by the ETDRS letter score by visit, based on OC prior to ICE in the FAS, are graphically displayed in Figure 9-1; the corresponding LS mean changes (95% CIs) from baseline in BCVA by visit, based on MMRM in the FAS, are displayed in post-hoc Figure 9-2.

The analysis of the primary endpoint was repeated on the PPS from the Week 48 analysis as supplementary analysis and the results were consistent with those in the FAS W48 (Table 14.2.1/2).

Table 9-2: Change from baseline in BCVA measured by the ETDRS letter score at Week 48 and Week 60 in the study eye, MMRM (full analysis set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Week 48 (primary endpoint)			
Baseline mean (a)	58.9	59.9	60.0
Number of subjects with Week 48 data	285	299	289
Arithmetic mean (SD) change from baseline (a)	7.6 (12.2)	6.7 (12.6)	6.2 (11.7)
LS mean (SE) change from baseline	7.03 (0.74)	6.06 (0.77)	5.89 (0.72)
DF	/	622.1	647.7
Contrast (b)	/	HDq12 - 2q8	HDq16 - 2q8
t-value	/	3.14	3.07
p-value of one-sided test for non-inferiority at a margin of 4 letters	/	0.0009	0.0011
Estimate for Contrast and two-sided 95% CI (c)	/	-0.97 (-2.87,0.92)	-1.14 (-2.97,0.69)
Week 60 (key secondary endpoint, according to EP-SAP)			
Baseline mean (a)	58.9	59.9	60.0
Number of subjects with Week 60 data	268	283	282
Arithmetic mean (SD) change from baseline (a)	7.8 (12.6)	6.6 (13.6)	6.6 (11.7)
LS mean (SE) change from baseline	7.23 (0.68)	6.37 (0.74)	6.31 (0.66)
DF	/	896.3	928.7
Contrast (b)	/	HDq12 - 2q8	HDq16 - 2q8
t-value	/	3.61	3.81
p-value of one-sided test for non-inferiority at a margin of 4 letters	/	0.0002	<0.0001
Estimate for Contrast and two-sided 95% CI (c)	/	-0.86 (-2.57,0.84)	-0.92 (-2.51,0.66)

BCVA = best corrected visual acuity, CI = confidence interval, DF = degrees of freedom, ETDRS = Early Treatment Diabetic Retinopathy Study, LS = least squares, SAP = statistical analysis plan, SD = standard deviation, SE = standard error
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit.
A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured (for Week 48) and Toeplitz with heterogeneity (for Week 60).
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.
(a): Based on observed assessments.
(b): The contrast also includes the interaction term for treatment x visit (at Week 48 or Week 60, for details on the population-level summary see SAP Section 6.2.2.1).
(c): Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively, with two-sided 95% CIs.

Table 14.2.1 / 2 Change from baseline in BCVA measured by the ETDRS letter score at Week 48, MMRM (per protocol set)

Treatment	LS mean (SE) chg. from BL	Arith. mean (SD) chg. from BL (a)	Baseline mean(a)	Number of subjects with week 48 data	DF	Contrast(b)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(c)
HDq12 (N = 325)	6.08 (0.78)	6.7 (12.7)	59.8	290	601.6	HDq12 - 2q8	2.96	0.0016	0.8558	-1.06 (-3.01,0.90)
HDq16 (N = 325)	5.91 (0.75)	6.2 (11.9)	59.9	278	620.9	HDq16 - 2q8	2.87	0.0021	0.8975	-1.23 (-3.13,0.67)
2q8 (N = 320)	7.13 (0.77)	7.7 (12.4)	58.8	272						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SD Standard deviation. SE Standard error.
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.
Intercurrent events (ICE) will be handled according to primary estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.
(a) based on observed assessments.
(b) The contrast also includes the interaction term for treatment x visit (at week 48, for details on the population-level summary see SAP section 6.2.2.1).
(c) Estimate based on the MMRM model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Change from baseline in BCVA measured by the ETDRS letter score at Week 60 (key secondary efficacy endpoint)

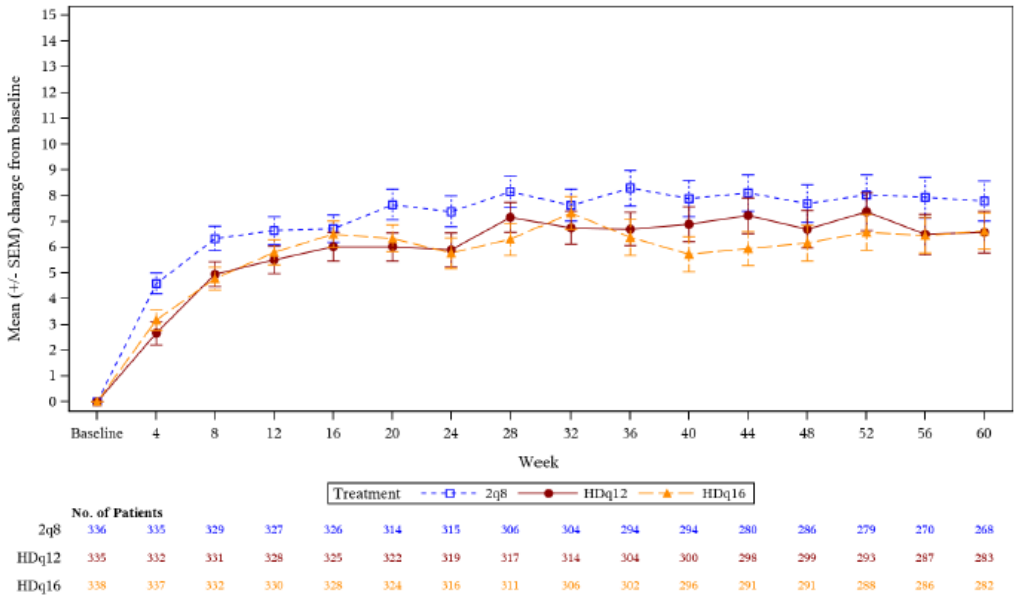
The analysis of this key secondary efficacy variable at Week 60 resulted in LS mean changes from baseline to Week 60 (i.e. estimated, adjusted mean changes) of 7.23, 6.37 and 6.31 letters for the 2q8, HDq12 and HDq16 groups, respectively (Table 9-2).

The estimated difference in LS means changes from baseline to Week 60 in BCVA (with corresponding 95% CI) of HDq12 vs. 2q8 was -0.86 (-2.57, 0.84) letters and of HDq16 vs. 2q8 was -0.92 (-2.51, 0.66) letters (Table 9-2). The p-values for the non-inferiority test at a margin of 4 letters were 0.0002 (related to H20) for HDq12 vs. 2q8, and < 0.0001 (related to H40) for HDq16 vs. 2q8; p-values for a superiority test were 0.8393 (related to H70) for HDq12 vs. 2q8 and of 0.8731 (related to H90) for HDq16 vs. 2q8 (W60 Table 14.2.2/31).

The arithmetic mean (SD) changes from baseline in BCVA to Week 60 (i.e. observed, unadjusted mean changes) were 7.8 (12.6), 6.6 (13.6), and 6.6 (11.7) letters for the 268, 283, and 282 participants with Week 60 data, i.e. excluding data after an ICE as handled by the hypothetical strategy, in the 2q8, HDq12, and HDq16 groups, respectively (Table 9-2).

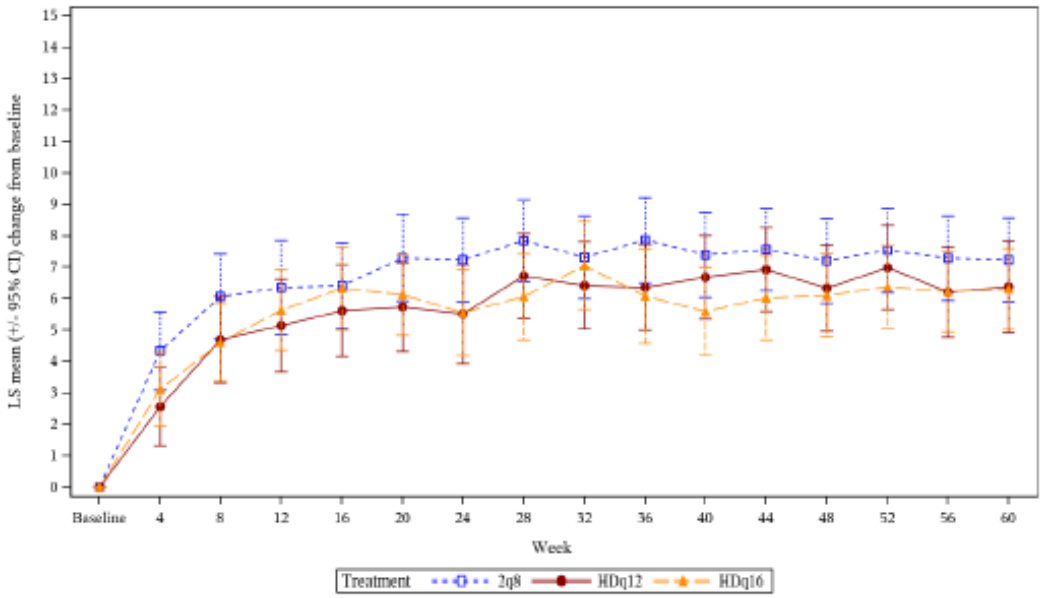
The arithmetic mean changes from baseline in BCVA measured by the ETDRS letter score by visit through Week 60, based on OC prior to ICE in the FAS, are graphically displayed in Figure 9-1; the corresponding LS mean changes (95% CIs) from baseline in BCVA by visit, based on MMRM in the FAS, are displayed in Figure 9-2. The mean as well as the LS mean increases in BCVA over time were similar across all groups through Week 60 with minor numerical differences not being considered of clinical relevance.

Figure 9-1: Mean change from baseline in BCVA measured by the ETDRS letter score in study eye by visit through Week 60, OC prior to ICE (full analysis set)



BCVA = best corrected visual acuity, ETDRS = Early Treatment Of Diabetic Retinopathy Study, SEM = standard error mean
OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded as described in the SAP.
Of note, in this by-visit analysis based on the Week 60 analysis, the number of participants in the 2q8 group is higher by 1 participant from Week 28 to Week 48 and in the HDq16 group is higher by 1 participant at Week 48 as compared to the Week 48 analysis (W48 Figure 14.2.1/1). The reason is that in the Week 48 analysis, a concomitant medication for these 2 participants was recorded as prohibited study eye treatment and thus as an ICE, which was actually fellow-eye treatment that was not prohibited and thus did not constitute an ICE. These errors were corrected in the Week 60 database and the data of these participants included in the Week 60 analysis (see W48 and W60 Database errata in Section 16.4.2, Section 8.7 and Section 9.2.1).

Figure 9-2: LSmean change from baseline in BCVA measured by the ETDRS letter score in study eye by visit through Week 60, MMRM (full analysis set)



BCVA = best corrected visual acuity, ETDRS = Early Treatment Of Diabetic Retinopathy Study, LS = least squares, SAP = statistical analysis plan, SEM= standard error of the LS mean
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: Toeplitz with heterogeneity.
Intercurrent events (ICE) were handled according to sensitivity estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.

The analysis of the key secondary endpoint was repeated on the PPS as supplementary analysis and the results were consistent with those in the FAS.

Overall, the primary and key secondary endpoint criteria, to know, the change from baseline in BCVA measured by the ETDRS letter score at Week 48 and 60 (non-inferiority of IVT aflibercept therapy HDq12 and HDq16 dosing regimen to the current authorized IVT aflibercept therapy 2q8 dosing regimen) is considered to be statistically met (95% credible interval for treatment difference with a non-inferiority margin of 4 letters with LS mean change from baseline in BCVA to Week 48), at Week 48 and 60.

However, even if the non-inferiority appear to be statistically met, given the longer intervals in the new proposed dosing regimen (HDq12 and HDq16), more long-term efficacy and safety results are awaited. Therefore, and as discussed in the previous scientific advice dated from 2019, in order to straighten the efficacy and safety results, the Applicant was requested to provide the 2 years data.

In response, the Applicant provides additional new long-term data from PULSAR study where around 80% of patients completed Week 96 and PHOTON study where 100% completed Week 96. Indeed, to respond to request for some 2-year data, a snapshot of PULSAR data up to Week 96 was performed in May 2023. This dataset comprises all patients (100%) enrolled in PULSAR. Of ongoing patients, approximately 80% (689 out of 875) had already completed the Week 96 visit and almost all had completed visits up to Week 88. More precisely, of the 1009 randomized patients included in the FAS and the SAF, 689 patients had completed the study through Week 96. 137 patients had discontinued prematurely. For 186 patients (18.4%), according to the Applicant, these patients constitute the ongoing patients at the time of the data snapshot.

The mean number of active injections in the Week 96 completers of the PULSAR SAF population was 12.8, 9.8 and 8.2 in the 2q8, HDq12 and HDq16 treatment groups, respectively, over the first 96 weeks of the study.

Of note, the proportions of Week 96 completers in the European subgroups were even higher than in the non-European subgroups given that the recruitment in Europe was completed earlier than in other regions.

For the PHOTON study, this later reached Week 96 LPLV in May 2023. Therefore, complete Week 96 key results for the DME indication are available in full for all study participants. Of the 660 randomized patients included in the FAS and the SAF, 534 patients completed the study through Week 96. However, 126 patients did not complete the study, with a higher proportion of patients in the HDq12 group (22.2% vs. 15.2% and 16.8%), mainly attributable to withdrawal of consent by subject, lost to follow-up and death. Of note, 31 (4.7%) patients were reported as lost to follow-up through Week 96. As for the PULSAR study, the mean number of active injections in the PHOTON SAF population of Week-96 completers was proportional to allocated interval dosing with a number of injections of 13.8, 9.5 and 7.8 in the 2q8, HDq12 and HDq16 treatment groups, respectively over the first 96 weeks of the study.

Overall and based on the provided long-term data, it appears that the product dosed every 12 weeks (HDq12) or every 16 weeks (HDq16) showed maintained non-inferior efficacy through Week 96 compared to 2 mg aflibercept, consistent with the results demonstrated at Week 48 and Week 60 with respect to improvement in BCVA and CST in patients with nAMD or DME. It is important to note that these W96 analysis are exploratory and should be interpreted with caution.

Additionally, the MAH was asked to further discuss clinical relevance of the chosen 4 letters margin rather than a smaller one as advised in the previous scientific advice.

The justification of the non-inferiority margin provided by the Applicant is consistent and clinically relevant. This margin ensures that any difference in visual acuity within one line of the ETDRS chart is not clinically meaningful. This 4-letters margin has been used in many non-inferiority trials investigating visual acuity.

Moreover, the MAH should further discuss and justify the initiation dosing regimen that appears to be 4 times higher exposure than the current regimen authorized and provide efficacy and safety results regarding that period for both PULSAR and PHOTON studies.

During the loading phase (up to Week 12), in PULSAR (3 monthly injections in all study arms) and PHOTON studies (5 monthly injections for 2q8 and 3 monthly injections for all HD) all treatment arms received active monthly injection with either 2 mg or 8 mg aflibercept at day 1, week 4 and week 8.

In PULSAR, comparable proportions of ocular TEAE were reported (17,3% for 2q8 vs 18,1% for all HD) and proportions of TEAE reported in more than 2 patients and with a difference $\geq$ 0.5% to the 2 mg arm (retinal haemorrhage, conjunctivitis, IOP increase and vitreous floaters) were low and comparable. Additionally, comparable proportions were reported for ocular safety topics (cataract, retinal detachment/tear, RPE tear, and intraocular inflammation) other than IOP increase for which event were all non-serious and without sustained IOP elevations. Non-ocular TEAE were reported in higher proportions for HD group (22.1% vs 16.7% in 2q8 arm). For SOC in which a difference of > 1% was observed and higher incidence in the HD arms (Infections and infestations and Vascular disorders), PT reported in more than 1 patient were Pulpitis dental, Upper respiratory and Urinary tract infection and Hypertension. Incidence for non-ocular safety topics were low and comparable between treatment arms.

In PHOTON, incidences of ocular TEAEs were higher in the HD group (2q8: 9.6%, all HD: 17.1%) however when compared to PULSAR studies a lower proportion of ocular TEAE was reported in 2q8 arm (PULSAR - 2q8: 17.3%, PHOTON – 2q8: 9.6%) and incidences for ocular TEAE in the HD group were nevertheless similar to

PULSAR. Events reported in more than 2 patients and with a difference ≥ 0.5% to the 2 mg arm consisted of cataract/cataract cortical, conjunctival hemorrhage, photopsia, punctate keratitis, and vitreous detachment for which no consistent trend were observed across studies. Proportions of ocular safety topics were low and comparable between treatment arms. Non-ocular event were reported in comparable proportions between treatment arms. For the SOC with a difference of > 1% and higher incidence in the HD arms (Gastrointestinal disorders, Infections and infestations, Nervous system disorders, Psychiatric disorders, Renal and urinary disorders and Respiratory, thoracic and mediastinal disorders), majority of PTs were reported in single patient with no consistent trend were observed across studies. Incidences for non-ocular safety topics were low and comparable.

Overall, although exposures to aflibercept in the HD treatment arms in both PULSAR and PHOTON studies were higher during the loading phase and that the incidence of ocular TEAE in the 2q8 arms in both groups were disparate, safety data are still reassuring and in favour of a comparable safety profile with ocular and non-ocular TEAE being reported in similar range between both studies. No consistent trend could be observed in both studies.

Subgroup analysis of change from baseline in BCVA measured by the ETDRS letter score at Week 48 and Week 60

Week 48

Subgroup analyses for changes from baseline in BCVA at Week 48 by age, sex, geographic region, ethnicity, race, baseline BCVA letters, and baseline PCV were performed by the MAH using MMRM in the FAS.

A tendency to higher mean increases in the HD groups compared to the 2q8 group may be considered for the Asian subgroup (N = 234), which showed estimated differences in LSmeans (95% CIs) of 2.30 (-1.82, 6.41) letters for HDq12 vs. 2q8 and of 1.57 (-1.96, 5.10) letters for HDq16 vs. 2q8 (W48 Table 14.2.1/10).

Table 14.2.1 / 10 Change from baseline in BCVA measured by the ETDRS letter score at Week 48 by race, MMRM (full analysis set)

Subgroup	Treatment	LS mean (SE) chg. from BL	Arith. mean (SD) chg. from BL (a)	Baseline mean (a)	Number of subjects with week 48 data	DF	Contrast(b)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(c)
White (N = 765)	HDq12 (N = 256)	5.11 (0.79)	5.5 (12.7)	60.3	232	488.7	HDq12 - 2q8	1.79	0.0367	0.9687	-2.04 (-4.19,0.11)
	HDq16 (N = 260)	5.19 (0.78)	5.5 (12.3)	60.7	228	492.0	HDq16 - 2q8	1.87	0.0312	0.9640	-1.96 (-4.11,0.18)
	2q8 (N = 249)	7.15 (0.77)	7.3 (11.9)	59.0	216						
Asian (N = 234)	HDq12 (N = 74)	9.77 (1.48)	10.9 (11.7)	57.7	62	120.1	HDq12 - 2q8	3.03	0.0015	0.1359	2.30 (-1.82,6.41)
	HDq16 (N = 77)	9.04 (1.04)	9.0 (8.5)	58.1	60	132.5	HDq16 - 2q8	3.12	0.0011	0.1904	1.57 (-1.96,5.10)
	2q8 (N = 83)	7.47 (1.46)	8.2 (13.2)	59.2	67						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SD Standard deviation. SE Standard error.
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.
Intercurrent events (ICE) will be handled according to primary estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.
(a) based on observed assessments.
(b) The contrast also includes the interaction term for treatment x visit (at week 48, for details on the population-level summary see SAP section 6.2.2.1).
(c) Estimate based on the MMRM model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

A similar tendency was observed for the Japanese subgroup (N = 97), with differences of 1.83 (-5.62, 9.29) letters for HDq12 vs. 2q8 and 3.19 (-2.63, 9.00) letters for HDq16 vs. 2q8 (Table 14.2.1/8).

Table 14.2.1 / 8 Change from baseline in BCVA measured by the ETDRS letter score at Week 48 by geographic region, MMRM (full analysis set)

Subgroup	Treatment	LS mean (SE) chg. from BL	Arith. mean (SD) chg. from BL (a)	Baseline mean (a)	Number of subjects with week 48 data	DF	Contrast(b)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(c)
Japan (N = 97)	HDq12 (N = 31)	6.14 (2.63)	8.7 (12.2)	61.5	28	31.7	HDq12 - 2q8	1.59	0.0604	0.3099	1.83 (-5.62,9.29)
	HDq16 (N = 33)	7.49 (1.40)	8.3 (7.4)	59.5	32	46.5	HDq16 - 2q8	2.49	0.0082	0.1377	3.19 (-2.63,9.00)
	2q8 (N = 33)	4.30 (2.58)	5.1 (14.9)	60.6	31						
Rest of the World (N = 912)	HDq12 (N = 304)	6.20 (0.73)	6.5 (12.6)	59.7	271	580.5	HDq12 - 2q8	2.69	0.0037	0.9088	-1.33 (-3.28,0.63)
	HDq16 (N = 305)	5.86 (0.71)	6.0 (12.1)	60.1	257	584.5	HDq16 - 2q8	2.37	0.0090	0.9549	-1.67 (-3.60,0.26)
	2q8 (N = 303)	7.53 (0.69)	7.9 (11.8)	58.8	254						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SD Standard deviation. SE Standard error.
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variable (baseline BCVA [<60 vs. ≥60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.
Intercurrent events (ICE) will be handled according to primary estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.
(a) based on observed assessments.
(b) The contrast also includes the interaction term for treatment x visit (at week 48, for details on the population-level summary see SAP section 6.2.2.1).
(c) Estimate based on the MMRM model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Week 60

The tendency to higher mean increases in the HD groups compared to the 2q8 group noted for the Asian (N = 234) and the Japanese (N = 97) subgroups at Week 48 (see above) was less pronounced at Week 60: in the Asian subgroup, the estimated differences in LS means (95% CIs) were 1.64 (-1.83, 5.11) letters for HDq12 vs. 2q8 and 0.54 (-2.32, 3.40) letters for HDq16 vs. 2q8 (W60 Table 14.2.2/40);

Table 14.2.2 / 40 Change from baseline in BCVA measured by the ETDRS letter score at Week 60 by race, MMRM (full analysis set)

Subgroup	Treatment	LS mean (SE) chg. from BL	Arith. mean (SD) chg. from BL (a)	Baseline mean (a)	Number of subjects with week 60 data	DF	Contrast(b)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(c)
White (N = 765)	HDq12 (N = 256)	5.15 (0.75)	5.3 (13.8)	60.3	221	680.1	HDq12 - 2q8	2.30	0.0109	0.9513	-1.68 (-3.66,0.31)
	HDq16 (N = 260)	5.49 (0.68)	5.9 (12.4)	60.7	222	671.9	HDq16 - 2q8	2.75	0.0030	0.9168	-1.34 (-3.24,0.56)
	2q8 (N = 249)	6.83 (0.70)	7.3 (12.5)	59.0	206						
Asian (N = 234)	HDq12 (N = 74)	10.05 (1.31)	11.3 (12.1)	57.7	57	191.0	HDq12 - 2q8	3.21	0.0008	0.1763	1.64 (-1.83,5.11)
	HDq16 (N = 77)	8.95 (0.86)	9.0 (8.4)	58.1	59	213.4	HDq16 - 2q8	3.13	0.0010	0.3548	0.54 (-2.32,3.40)
	2q8 (N = 83)	8.41 (1.17)	9.0 (12.8)	59.2	60						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SD Standard deviation. SE Standard error.
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: Toeplitz with heterogeneity.
Intercurrent events (ICE) will be handled according to primary estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.
(a) based on observed assessments.
(b) The contrast also includes the interaction term for treatment x visit (at week 60, for details on the population-level summary see SAP section 6.2.2.1).
(c) Estimate based on the MMRM model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

In the Japanese subgroup, the corresponding differences were 0.28 (-6.20, 6.76) letters for HDq12 vs. 2q8 and 1.59 (-3.09, 6.27) letters for HDq16 vs. 2q8 (W60 Table 14.2.2/38).

Table 14.2.2 / 38 Change from baseline in BCVA measured by the ETDRS letter score at Week 60 by geographic region, MMRM (full analysis set)

Subgroup	Treatment	LS mean (SE) chg. from BL	Arith. mean (SD) chg. from BL (a)	Baseline mean (a)	Number of subjects with week 60 data	DF	Contrast(b)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(c)
Japan (N = 97)	HDq12 (N = 31)	5.86 (2.49)	8.5 (13.3)	61.5	27	49.7	HDq12 - 2q8	1.33	0.0954	0.4660	0.28 (-6.20,6.76)
	HDq16 (N = 33)	7.17 (1.18)	8.0 (7.8)	59.5	31	76.4	HDq16 - 2q8	2.38	0.0099	0.2501	1.59 (-3.09,6.27)
	2q8 (N = 33)	5.58 (2.09)	6.5 (14.5)	60.6	31						
Rest of the World (N = 912)	HDq12 (N = 304)	6.33 (0.68)	6.4 (13.6)	59.7	256	827.2	HDq12 - 2q8	3.21	0.0007	0.8803	-1.07 (-2.86,0.72)
	HDq16 (N = 305)	6.17 (0.61)	6.5 (12.1)	60.1	251	814.5	HDq16 - 2q8	3.19	0.0007	0.9222	-1.23 (-2.94,0.47)
	2q8 (N = 303)	7.41 (0.62)	8.0 (12.4)	58.8	237						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SD Standard deviation. SE Standard error.
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variable (baseline BCVA [<60 vs. ≥60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: Toeplitz with heterogeneity.
Intercurrent events (ICE) will be handled according to primary estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.
(a) based on observed assessments.
(b) The contrast also includes the interaction term for treatment x visit (at week 60, for details on the population-level summary see SAP section 6.2.2.1).
(c) Estimate based on the MMRM model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

The results presented for the changes from baseline in BCVA at Week 48 and 60 were similar with the overall population. Tendency for higher mean increases in the HD groups compared to the 2q8 group were noted for the Asian and Japanese subgroups at Week 48 and 60 in PULSAR study. However, given the smaller size of these subgroups, the validity of these comparisons is limited.

Sensitivity analysis for change from baseline in BCVA score at Week 48 and Week 60

Week 48

Different sensitivity analyses were performed by the MAH for the primary endpoint, change from baseline in BCVA measured by the ETDRS letter score at Week 48, one using an ANCOVA with LOCF (Table 14.2.1/3) and one using an ANCOVA after applying MI in the FAS (Table 14.2.1/4).

Table 14.2.1 / 3 Change from baseline in BCVA measured by the ETDRS letter score at Week 48, ANCOVA, LOCF (full analysis set)

Treatment	LS mean (SE) chg. from BL	Arith. mean (SD) chg. from BL (a)	Baseline mean (b)	Number of subjects with week 48 data	DF	Contrast(c)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(d)
HDq12 (N = 335)	5.95 (0.85)	6.1 (13.2)	59.9	334	1000.0	HDq12 - 2q8	3.12	0.0009	0.8758	-1.08 (-2.92,0.76)
HDq16 (N = 338)	5.81 (0.84)	5.9 (11.8)	60.0	337	1000.0	HDq16 - 2q8	2.96	0.0016	0.9057	-1.23 (-3.07,0.61)
2q8 (N = 336)	7.04 (0.85)	7.5 (12.0)	58.9	335						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SD Standard deviation. SE Standard error.
An analysis of covariance (ANCOVA) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors.
LOCF (last observation carried forward): last available observed value prior to ICE will be used to impute missing data.
Intercurrent events (ICE) will be handled according to sensitivity estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.
(a) based on a mix of observed and imputed assessments.
(b) based on observed assessments.
(c) For details on the population-level summary see SAP section 6.2.2.2.1.
(d) Estimate based on the ANCOVA model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Table 14.2.1 / 4 Change from baseline in BCVA measured by the ETDRS letter score at Week 48, ANCOVA, MI (full analysis set)

Treatment	LS mean (SE) chg. from BL	DF	Contrast(a)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(b)
HDq12 (N = 335)	6.27 (0.86)	5255.4	HDq12 - 2q8	3.23	0.0006	0.8343	-0.93 (-2.79,0.94)
HDq16 (N = 338)	6.07 (0.86)	2017.5	HDq16 - 2q8	2.98	0.0015	0.8782	-1.13 (-3.02,0.77)
2q8 (N = 336)	7.20 (0.87)						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SE Standard error.
An analysis of covariance (ANCOVA) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors.
MI (multiple imputation) method is to generate multiple copies of the original dataset by replacing missing values using appropriate stochastic model (10 times and seeds 12345) using SAS procedure "PROC MI".
Intercurrent events (ICE) will be handled according to sensitivity estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.
(a) For details on the population-level summary see SAP section 6.2.2.2.1.
(b) Estimate based on the ANCOVA model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

The results of these sensitivity analyses were consistent with those of the primary analysis using MMRM in the FAS:

The estimated differences (95% CIs) in LS means were -1.08 (-2.92, 0.76) for the comparison HDq12 vs. 2q8 and were -1.23 (-3.07, 0.61) letters for the comparison HDq16 vs. 2q8 when using ANCOVA with LOCF (Table 14.2.1/3).

The estimated differences (95% CIs) in LS means were -0.93 (-2.79, 0.94) for the comparison HDq12 vs. 2q8 and were -1.13 (-3.02, 0.77) letters for the comparison HDq16 vs. 2q8 when using ANCOVA after applying MI (Table 14.2.1/4).

In order to check robustness of the results if the missing data are not MAR, also a tipping point analysis was conducted by the MAH based on the MI analysis and the results are provided in Table 14.2.1/5. The results of this analysis show that the smallest shift parameter (delta) used as penalty for participants with missing data in the HD groups, for which non-inferiority could not be shown anymore (with a 1-sided t-test at a significance level of 0.025), i.e. the "tipping point" that significantly reversed the analysis result, was delta = -11 letters for HDq12 vs. 2q8 and delta = -7 letters for HDq16 vs. 2q8 (Table 14.2.1/5).

Table 14.2.1 / 5 Change from baseline in BCVA measured by the ETDRS letter score at Week 48, ANCOVA, MI with tipping point analysis (full analysis set)

Delta (letters)	Treatment	LS mean (SE) chg. from BL	DF	Contrast(a)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(b)
1	HDq12 (N = 335)	6.19 (0.86)	5267.0	HDq12 - 2q8	3.11	0.0009	0.8606	-1.03 (-2.90,0.84)
	HDq16 (N = 338)	5.95 (0.86)	2027.8	HDq16 - 2q8	2.83	0.0024	0.9059	-1.27 (-3.17,0.62)
	2q8 (N = 336)	7.22 (0.87)						
2	HDq12 (N = 335)	6.10 (0.86)	5335.1	HDq12 - 2q8	2.99	0.0014	0.8837	-1.14 (-3.01,0.73)
	HDq16 (N = 338)	5.82 (0.86)	2042.0	HDq16 - 2q8	2.67	0.0038	0.9285	-1.42 (-3.31,0.48)
	2q8 (N = 336)	7.24 (0.87)						
3	HDq12 (N = 335)	6.01 (0.86)	5413.5	HDq12 - 2q8	2.87	0.0020	0.9038	-1.25 (-3.13,0.63)
	HDq16 (N = 338)	5.70 (0.86)	2060.1	HDq16 - 2q8	2.51	0.0060	0.9465	-1.56 (-3.46,0.34)
	2q8 (N = 336)	7.26 (0.87)						
4	HDq12 (N = 335)	5.93 (0.86)	5502.5	HDq12 - 2q8	2.75	0.0030	0.9210	-1.36 (-3.24,0.53)
	HDq16 (N = 338)	5.57 (0.86)	2082.1	HDq16 - 2q8	2.36	0.0093	0.9606	-1.71 (-3.62,0.20)
	2q8 (N = 336)	7.28 (0.87)						
5	HDq12 (N = 335)	5.84 (0.87)	5632.2	HDq12 - 2q8	2.63	0.0042	0.9356	-1.46 (-3.35,0.42)
	HDq16 (N = 338)	5.45 (0.87)	2106.5	HDq16 - 2q8	2.20	0.0140	0.9714	-1.86 (-3.77,0.06)
	2q8 (N = 336)	7.30 (0.88)						
6	HDq12 (N = 335)	5.76 (0.87)	5773.6	HDq12 - 2q8	2.51	0.0060	0.9479	-1.57 (-3.46,0.32)
	HDq16 (N = 338)	5.32 (0.87)	2142.3	HDq16 - 2q8	2.04	0.0206	0.9796	-2.00 (-3.92,-0.08)
	2q8 (N = 336)	7.33 (0.88)						
7	HDq12 (N = 335)	5.67 (0.87)	5931.0	HDq12 - 2q8	2.39	0.0083	0.9581	-1.68 (-3.58,0.22)
	HDq16 (N = 338)	5.20 (0.87)	2181.3	HDq16 - 2q8	1.89	0.0297	0.9856	-2.15 (-4.07,-0.22)
	2q8 (N = 336)	7.35 (0.88)						
8	HDq12 (N = 335)	5.59 (0.88)	6085.5	HDq12 - 2q8	2.27	0.0115	0.9665	-1.78 (-3.69,0.13)
	HDq16 (N = 338)	5.08 (0.88)	2225.2	HDq16 - 2q8	1.73	0.0419	0.9899	-2.29 (-4.23,-0.36)
	2q8 (N = 336)	7.37 (0.89)						
9	HDq12 (N = 335)	5.50 (0.88)	6253.1	HDq12 - 2q8	2.15	0.0156	0.9733	-1.89 (-3.81,0.03)
	HDq16 (N = 338)	4.95 (0.88)	2273.6	HDq16 - 2q8	1.58	0.0577	0.9931	-2.44 (-4.38,-0.50)
	2q8 (N = 336)	7.39 (0.89)						
10	HDq12 (N = 335)	5.42 (0.88)	6434.5	HDq12 - 2q8	2.04	0.0209	0.9788	-2.00 (-3.93,-0.07)
	HDq16 (N = 338)	4.83 (0.88)	2326.6	HDq16 - 2q8	1.42	0.0778	0.9953	-2.59 (-4.54,-0.63)
	2q8 (N = 336)	7.42 (0.90)						
11	HDq12 (N = 335)	5.33 (0.89)	6630.1	HDq12 - 2q8	1.92	0.0277	0.9833	-2.10 (-4.04,-0.17)
	HDq16 (N = 338)	4.71 (0.89)	2384.5	HDq16 - 2q8	1.27	0.1026	0.9968	-2.73 (-4.69,-0.77)
	2q8 (N = 336)	7.44 (0.90)						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SE Standard error.
An analysis of covariance (ANCOVA) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors.
MI (multiple imputation) method is to generate multiple copies of the original dataset by replacing missing values using appropriate stochastic model (10 times and seeds 12345) using SAS procedure "PROC MI".
Intercurrent events (ICE) will be handled according to sensitivity estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.
(a) For details on the population-level summary see SAP section 6.2.2.2.1.
(b) Estimate based on the ANCOVA model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.
The BCVA values in the high dose arms, which have been imputed with the multiple imputation procedure will be reduced by a delta of 1, 2, 3,.. letters until non-inferiority cannot be shown anymore.
The smallest delta, for which non-inferiority (in terms of unadjusted p-value < 0.025) cannot be shown anymore, will be the "tipping point".

The "tipping point" values of -11 letters and -7 letters requiring such a large difference in BCVA at Week 48 between HDq16 and HDq12 vs. 2q8, respectively, do not seem plausible.

Therefore, the primary analysis of non-inferiority conclusion based on MMRM method is robust to the departure of the MAR assumption according to the MAH.

Week 60

Different sensitivity analyses were performed for the key secondary endpoint, change from baseline in BCVA measured by the ETDRS letter score at Week 60, one using an ANCOVA with LOCF (Table 14.2.2/33) and one using an ANCOVA after applying MI in the FAS (Table 14.2.2/34).

Table 14.2.2 / 33 Change from baseline in BCVA measured by the ETDRS letter score at Week 60, ANCOVA, LOCF (full analysis set)

Treatment	LS mean (SE) chg. from BL	Arith. mean (SD) chg. from BL (a)	Baseline mean (b)	Number of subjects with week 60 data	DF	Contrast(c)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(d)
HDq12 (N = 335)	6.04 (0.87)	6.2 (13.9)	59.9	334	1000.0	HDq12 - 2q8	3.05	0.0012	0.8668	-1.07 (-2.96,0.82)
HDq16 (N = 338)	5.97 (0.87)	6.1 (11.8)	60.0	337	1000.0	HDq16 - 2q8	2.97	0.0015	0.8828	-1.14 (-3.03,0.74)
2q8 (N = 336)	7.11 (0.88)	7.6 (12.3)	58.9	335						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SD Standard deviation. SE Standard error.
An analysis of covariance (ANCOVA) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors.
LOCF (last observation carried forward): last available observed value prior to ICE will be used to impute missing data.
Intercurrent events (ICE) will be handled according to sensitivity estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.
(a) based on a mix of observed and imputed assessments.
(b) based on observed assessments.
(c) For details on the population-level summary see SAP section 6.2.2.2.1.
(d) Estimate based on the ANCOVA model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Table 14.2.2 / 34 Change from baseline in BCVA measured by the ETDRS letter score at Week 60, ANCOVA, MI (full analysis set)

Treatment	LS mean (SE) chg. from BL	DF	Contrast(a)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(b)
HDq12 (N = 335)	6.24 (0.90)	2465.4	HDq12 - 2q8	2.91	0.0018	0.8679	-1.11 (-3.06,0.84)
HDq16 (N = 338)	6.18 (0.88)	2238.4	HDq16 - 2q8	2.85	0.0022	0.8785	-1.16 (-3.11,0.79)
2q8 (N = 336)	7.35 (0.92)						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SE Standard error.
An analysis of covariance (ANCOVA) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors.
MI (multiple imputation) method is to generate multiple copies of the original dataset by replacing missing values using appropriate stochastic model (10 times and seeds 12345) using SAS procedure "PROC MI".
Intercurrent events (ICE) will be handled according to sensitivity estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.
(a) For details on the population-level summary see SAP section 6.2.2.2.1.
(b) Estimate based on the ANCOVA model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

The results of these sensitivity analyses were consistent with those of the primary analysis using MMRM in the FAS and similar to the corresponding analyses for Week 48 (see above):

The estimated differences (95% CIs) in LS means were -1.07 (-2.96, 0.82) for the comparison HDq12 vs. 2q8 and were -1.14 (-3.03, 0.74) letters for the comparison HDq16 vs. 2q8 when using ANCOVA with LOCF (Table 14.2.2/33).

The estimated differences (95% CIs) in LS means were -1.11 (-3.06, 0.84) for the comparison HDq12 vs. 2q8 and were -1.16 (-3.11, 0.79) letters for the comparison HDq16 vs. 2q8 when using ANCOVA after applying MI (Table 14.2.1/34).

In order to check robustness of the results if the missing data are not MAR, a tipping point analysis was also conducted based on the MI analysis for Week 60 and the results were similar to those at Week 48 (Table 14.2.2/35).

Table 14.2.2 / 35 Change from baseline in BCVA measured by the ETDRS letter score at Week 60, ANCOVA, MI with tipping point analysis (full analysis set)

Delta (letters)	Treatment	LS mean (SE) chg. from BL	DF	Contrast(a)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(b)
1	HDq12 (N = 335)	6.10 (0.90)	2486.9	HDq12 - 2q8	2.74	0.0031	0.8983	-1.27 (-3.22,0.69)
	HDq16 (N = 338)	6.04 (0.88)	2253.1	HDq16 - 2q8	2.68	0.0037	0.9091	-1.33 (-3.28,0.62)
	2q8 (N = 336)	7.37 (0.92)						
2	HDq12 (N = 335)	5.97 (0.90)	2494.9	HDq12 - 2q8	2.58	0.0050	0.9231	-1.42 (-3.38,0.53)
	HDq16 (N = 338)	5.90 (0.89)	2273.4	HDq16 - 2q8	2.50	0.0062	0.9333	-1.50 (-3.46,0.46)
	2q8 (N = 336)	7.40 (0.92)						
3	HDq12 (N = 335)	5.84 (0.90)	2507.9	HDq12 - 2q8	2.42	0.0079	0.9428	-1.58 (-3.54,0.38)
	HDq16 (N = 338)	5.76 (0.89)	2298.6	HDq16 - 2q8	2.33	0.0100	0.9521	-1.67 (-3.63,0.29)
	2q8 (N = 336)	7.43 (0.92)						
4	HDq12 (N = 335)	5.72 (0.90)	2520.8	HDq12 - 2q8	2.25	0.0122	0.9581	-1.74 (-3.71,0.23)
	HDq16 (N = 338)	5.61 (0.89)	2329.4	HDq16 - 2q8	2.15	0.0157	0.9663	-1.84 (-3.81,0.13)
	2q8 (N = 336)	7.45 (0.92)						
5	HDq12 (N = 335)	5.59 (0.91)	2538.5	HDq12 - 2q8	2.09	0.0184	0.9698	-1.89 (-3.87,0.08)
	HDq16 (N = 338)	5.47 (0.89)	2365.5	HDq16 - 2q8	1.98	0.0241	0.9767	-2.01 (-3.98,-0.03)
	2q8 (N = 336)	7.48 (0.93)						
6	HDq12 (N = 335)	5.46 (0.91)	2561.2	HDq12 - 2q8	1.93	0.0271	0.9785	-2.05 (-4.04,-0.07)
	HDq16 (N = 338)	5.33 (0.90)	2406.8	HDq16 - 2q8	1.80	0.0358	0.9841	-2.18 (-4.16,-0.19)
	2q8 (N = 336)	7.51 (0.93)						
7	HDq12 (N = 335)	5.33 (0.91)	2588.6	HDq12 - 2q8	1.76	0.0390	0.9849	-2.21 (-4.20,-0.21)
	HDq16 (N = 338)	5.19 (0.90)	2444.0	HDq16 - 2q8	1.63	0.0519	0.9894	-2.34 (-4.34,-0.35)
	2q8 (N = 336)	7.53 (0.93)						
8	HDq12 (N = 335)	5.20 (0.92)	2620.9	HDq12 - 2q8	1.60	0.0547	0.9896	-2.36 (-4.37,-0.36)
	HDq16 (N = 338)	5.05 (0.91)	2486.3	HDq16 - 2q8	1.45	0.0730	0.9930	-2.51 (-4.52,-0.51)
	2q8 (N = 336)	7.56 (0.94)						
9	HDq12 (N = 335)	5.07 (0.92)	2657.8	HDq12 - 2q8	1.44	0.0750	0.9928	-2.52 (-4.54,-0.50)
	HDq16 (N = 338)	4.91 (0.91)	2521.7	HDq16 - 2q8	1.28	0.0999	0.9954	-2.68 (-4.70,-0.67)
	2q8 (N = 336)	7.59 (0.94)						
10	HDq12 (N = 335)	4.94 (0.93)	2685.4	HDq12 - 2q8	1.28	0.1003	0.9951	-2.68 (-4.70,-0.65)
	HDq16 (N = 338)	4.77 (0.92)	2562.1	HDq16 - 2q8	1.11	0.1331	0.9970	-2.85 (-4.88,-0.82)
	2q8 (N = 336)	7.62 (0.95)						
11	HDq12 (N = 335)	4.81 (0.93)	2717.8	HDq12 - 2q8	1.12	0.1310	0.9967	-2.83 (-4.87,-0.79)
	HDq16 (N = 338)	4.63 (0.92)	2607.2	HDq16 - 2q8	0.94	0.1728	0.9981	-3.02 (-5.06,-0.98)
	2q8 (N = 336)	7.64 (0.95)						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SE Standard error.
An analysis of covariance (ANCOVA) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors.
MI (multiple imputation) method is to generate multiple copies of the original dataset by replacing missing values using appropriate stochastic model (10 times and seeds 12345) using SAS procedure "PROC MI".
Intercurrent events (ICE) will be handled according to sensitivity estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.
(a) For details on the population-level summary see SAP section 6.2.2.2.1.
(b) Estimate based on the ANCOVA model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.
The BCVA values in the high dose arms, which have been imputed with the multiple imputation procedure will be reduced by a delta of 1, 2, 3,.. letters until non-inferiority cannot be shown anymore.
The smallest delta, for which non-inferiority (in terms of unadjusted p-value < 0.025) cannot be shown anymore, will be the "tipping point".

Change from baseline in BCVA measured by ETDRS letter score at Week 96

- ***PULSAR study***

Table 5 PULSAR: Change from baseline in BCVA measured by the ETDRS letter score at Week 48, Week 60 and Week 96, MMRM (FAS)

		2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Baseline mean (a)		58.9	59.9	60.0
Week 48	Number of subjects with Week 48 data	285	299	289
Primary efficacy endpoint	Arithmetic mean (SD) change from baseline [a]	7.6 (12.2)	6.7 (12.6)	6.2 (11.7)
	LS mean (SE) change from baseline	7.03 (0.74)	6.06 (0.77)	5.89 (0.72)
	Contrast [b]		HDq12 - 2q8	HDq16 - 2q8
	Estimate for Contrast and two-sided 95% CI c		-0.97 (-2.87,0.92)	-1.14 (-2.97,0.69)
	p-value of one-sided test for non-inferiority at a margin of 4 letters		0.0009	0.0011
Week 60	Number of subjects with Week 60 data	268	283	282
Key secondary efficacy endpoint	Arithmetic mean (SD) change from baseline [a]	7.8 (12.6)	6.6 (13.6)	6.6 (11.7)
	LS mean (SE) change from baseline	7.23 (0.68)	6.37 (0.74)	6.31 (0.66)
	DF		896.3	928.7
	Contrast [b]		HDq12 - 2q8	HDq16 - 2q8
	Estimate for Contrast and two-sided 95% CI c		-0.86 (-2.57,0.84)	-0.92 (-2.51,0.66)
	p-value of one-sided test for non-inferiority at a margin of 4 letters		0.0002	< 0.0001
Week 96	Number of subjects with Week 96 data	206	213	228
Exploratory efficacy endpoint	Arithmetic mean (SD) change from baseline [a]	7.5 (13.3)	4.7 (14.4)	6.0 (13.5)
	LS mean (SE) change from baseline	6.49 (0.74)	5.46 (0.79)	5.60 (0.76)
	DF		953.5	928.2
	Contrast [b]		HDq12 - 2q8	HDq16 - 2q8
	Estimate for Contrast and two-sided 95% CI [c]		-1.02 (-2.88,0.83)	-0.89 (-2.72,0.94)
	p-value of one-sided test for non-inferiority at a margin of 4 letters		0.0008	0.0004

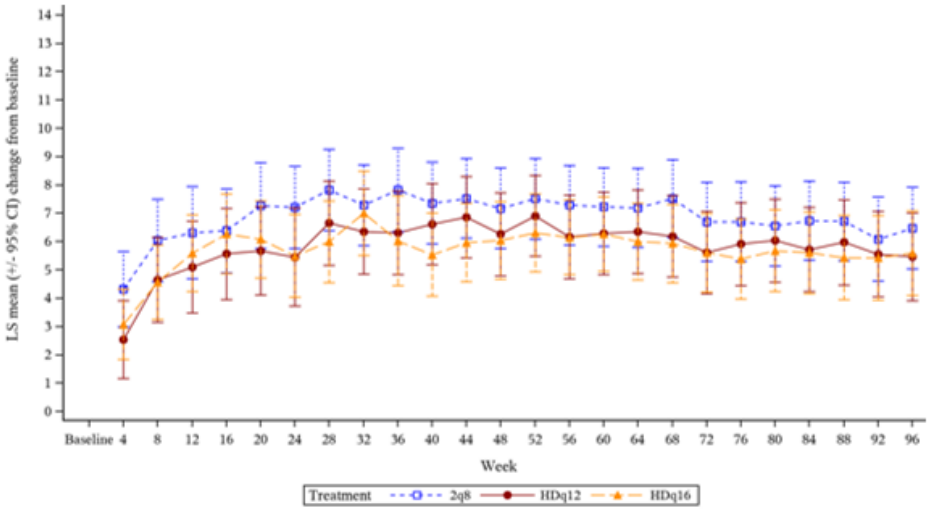
BCVA = best corrected visual acuity, CI = Confidence interval, DF = Degrees of freedom, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS = Full analysis set, LS = Least Square, SD = Standard deviation, SE = Standard error

A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit.

A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.

Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.

Figure 1 PULSAR: LS-mean change from baseline in BCVA measured by the ETDRS letter score by visit through Week 96, MMRM (FAS)



BCVA = best corrected visual acuity, ETDRS = Early Treatment Of Diabetic Retinopathy Study, FAS = Full analysis set, LS = least squares, SAP = statistical analysis plan

A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: Toeplitz with heterogeneity.

OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded as described in the SAP.

2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals.

HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals.

HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals.

Source: Module 5.3.5.1, PULSAR TLF EMA CHMP Day-120 Question 20, 45, 61, Figure 2.1.1

As indicted in the table and figure above, The LS mean of BCVA gains appears to be stable over time and similar across all groups, with minor numerical differences not being considered as clinically relevant.

Secondary key endpoint analysis

Proportion of participants with no IRF and no SRF in central subfield at Week 16

This key secondary efficacy endpoint describes the proportion of all participants with no IRF and no SRF in central subfield at Week 16 as assessed by the reading center. The results of the analysis for this endpoint based on data using LOCF are presented by the MAH in Table 9-3.

As both HD groups and the 2 mg group were all treated identically with 3 initial monthly doses prior to Week 16, the pooled HDq12 and HDq16 were compared to the 2q8 group for this endpoint. At Week 16, 63.3% of participants in the pooled HD groups had no retinal fluid (no IRF and no SRF) compared to 51.6% in the 2q8 treatment group. The difference (95% CI) between pooled HD groups vs. 2q8 treatment was 11.733% points (5.263%, 18.204%) superiority. The p-value of the 1-sided Cochran-Mantel-Haenszel (CMH) test for superiority was 0.0002 (Table 9-3).

Table 9-3: Proportion of participants with no IRF and no SRF in central subfield at Week 16, LOCF (full analysis set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338	All HD N = 673
Subjects who had no IRF and no SRF, Num/Den (%)	173/335 (51.6%)	205/333 (61.6%)	217/334 (65.0%)	422/667 (63.3%)
Contrast	/	/	/	All HD - 2q8
Difference (a) % (two-sided 95% CI)	/	/	/	11.733 (5.263, 18.204)
CMH test (b) p-value	/	/	/	0.0002

BCVA = best corrected visual acuity, CI = confidence interval, CMH = Cochran-Mantel-Haenszel, ICE = intercurrent events, IRF = intraretinal fluid, LOCF = last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan, SRF = subretinal fluid
LOCF method for the last available observed value prior to ICE was carried forward to impute missing data.
ICE were handled according to primary estimand strategy for binary endpoints as described in Table 9-13 in Section 9.5 of the SAP.
(a): Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% CIs as described in SAP Section 6.2.3.1.2.
(b): p-value for the one-sided Cochran-Mantel-Haenszel (CMH) test for superiority.

Of note, the observation that 3.6% of the participants in the 2q8 and the pooled HD groups, respectively, in the FAS had no IRF and no SRF in central subfield at screening with similar proportions at baseline (see W48 Table 14.2.2/15), although Inclusion criterion 6 required the presence of IRF and/or SRF, can be explained by the fact that the eligibility criteria were assessed by the investigators at screening based on preliminary data, whereas the above observations of no retinal fluid (no IRF and no SRF) in some participants were based on updated reading center data. The reading center provided eligibility assessment for all participants based on imaging exams performed at screening, while the investigator confirmed eligibility based on imaging exams performed at randomization. The imaging exams performed at screening, baseline and every other visit subsequently underwent detailed grading by the reading center, independently from the eligibility check. Based on this detailed grading, a very small number of discrepancies were noted in the assessment of fluid in screening OCTs.

Table 14.2.2 / 15 Summary statistics for proportion of subjects with no IRF and no SRF in central subfield by visit, LOCF (full analysis set)

Visit	Fluid status	2q8 N = 336 Num/Den(%)	HDq12 N = 335 Num/Den(%)	HDq16 N = 338 Num/Den(%)	All HD N = 673 Num/Den(%)
Screening	Dry	12/336 (3.6%)	15/335 (4.5%)	9/337 (2.7%)	24/672 (3.6%)
	Not Dry	324/336 (96.4%)	320/335 (95.5%)	328/337 (97.3%)	648/672 (96.4%)
	IRF only	43/336 (12.8%)	35/335 (10.4%)	28/337 (8.3%)	63/672 (9.4%)
	SRF only	169/336 (50.3%)	171/335 (51.0%)	175/337 (51.9%)	346/672 (51.5%)
	IRF and SRF	112/336 (33.3%)	114/335 (34.0%)	125/337 (37.1%)	239/672 (35.6%)
	Missing or undetermined	0	0	1	1
	IRF missing or undetermined (and SRF=No)	0	0	0	0
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	0	0	1	1
Baseline	Dry	13/336 (3.9%)	8/335 (2.4%)	9/336 (2.7%)	17/671 (2.5%)
	Not Dry	323/336 (96.1%)	327/335 (97.6%)	327/336 (97.3%)	654/671 (97.5%)
	IRF only	48/336 (14.3%)	38/335 (11.3%)	28/336 (8.3%)	66/671 (9.8%)
	SRF only	170/336 (50.6%)	168/335 (50.1%)	172/336 (51.2%)	340/671 (50.7%)
	IRF and SRF	105/336 (31.3%)	121/335 (36.1%)	127/336 (37.8%)	248/671 (37.0%)
	Missing or undetermined	0	0	2	2
	IRF missing or undetermined (and SRF=No)	0	0	0	0
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	0	0	2	2
Week 12	Dry	235/334 (70.4%)	258/333 (77.5%)	263/335 (78.5%)	521/668 (78.0%)
	Not Dry	99/334 (29.6%)	75/333 (22.5%)	72/335 (21.5%)	147/668 (22.0%)
	IRF only	40/334 (12.0%)	41/333 (12.3%)	36/335 (10.7%)	77/668 (11.5%)
	SRF only	54/334 (16.2%)	29/333 (8.7%)	26/335 (7.8%)	55/668 (8.2%)
	IRF and SRF	5/334 (1.5%)	5/333 (1.5%)	10/335 (3.0%)	15/668 (2.2%)
	Missing or undetermined	2	2	3	5
	IRF missing or undetermined (and SRF=No)	0	0	0	0
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	2	2	3	5
Week 16	Dry	173/335 (51.6%)	205/333 (61.6%)	217/334 (65.0%)	422/667 (63.3%)
	Not Dry	162/335 (48.4%)	128/333 (38.4%)	117/334 (35.0%)	245/667 (36.7%)
	IRF only	45/335 (13.4%)	46/333 (13.8%)	41/334 (12.3%)	87/667 (13.0%)
	SRF only	98/335 (29.3%)	68/333 (20.4%)	61/334 (18.3%)	129/667 (19.3%)
	IRF and SRF	19/335 (5.7%)	14/333 (4.2%)	15/334 (4.5%)	29/667 (4.3%)
	Missing or undetermined	1	2	4	6
	IRF missing or undetermined (and SRF=No)	0	0	0	0
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	1	2	4	6
Week 20	Dry	228/334 (68.3%)	165/333 (49.5%)	162/335 (48.4%)	327/668 (49.0%)
	Not Dry	106/334 (31.7%)	168/333 (50.5%)	173/335 (51.6%)	341/668 (51.0%)
	IRF only	45/334 (13.5%)	51/333 (15.3%)	53/335 (15.8%)	104/668 (15.6%)
	SRF only	53/334 (15.9%)	86/333 (25.8%)	95/335 (28.4%)	181/668 (27.1%)
	IRF and SRF	8/334 (2.4%)	31/333 (9.3%)	25/335 (7.5%)	56/668 (8.4%)
	Missing or undetermined	2	2	3	5
	IRF missing or undetermined (and SRF=No)	1	0	0	0
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	1	2	3	5
Week 24	Dry	177/335 (52.8%)	239/332 (72.0%)	136/334 (40.7%)	375/666 (56.3%)
	Not Dry	158/335 (47.2%)	93/332 (28.0%)	198/334 (59.3%)	291/666 (43.7%)
	IRF only	53/335 (15.8%)	44/332 (13.3%)	59/334 (17.7%)	103/666 (15.5%)
	SRF only	86/335 (25.7%)	40/332 (12.0%)	109/334 (32.6%)	149/666 (22.4%)
	IRF and SRF	19/335 (5.7%)	9/332 (2.7%)	30/334 (9.0%)	39/666 (5.9%)
	Missing or undetermined	1	3	4	7
	IRF missing or undetermined (and SRF=No)	0	0	0	0
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	1	3	4	7

Week 28	Dry	226/335 (67.5%)	196/332 (59.0%)	236/335 (70.4%)	432/667 (64.8%)
	Not Dry	109/335 (32.5%)	136/332 (41.0%)	99/335 (29.6%)	235/667 (35.2%)
	IRF only	46/335 (13.7%)	60/332 (18.1%)	51/335 (15.2%)	111/667 (16.6%)
	SRF only	58/335 (17.3%)	64/332 (19.3%)	42/335 (12.5%)	106/667 (15.9%)
	IRF and SRF	5/335 (1.5%)	12/332 (3.6%)	6/335 (1.8%)	18/667 (2.7%)
	Missing or undetermined	1	3	3	6
	IRF missing or undetermined (and SRF=No)	0	0	0	0
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	1	3	3	6
Week 32	Dry	185/335 (55.2%)	171/332 (51.5%)	220/334 (65.9%)	391/666 (58.7%)
	Not Dry	150/335 (44.8%)	161/332 (48.5%)	114/334 (34.1%)	275/666 (41.3%)
	IRF only	51/335 (15.2%)	59/332 (17.8%)	47/334 (14.1%)	106/666 (15.9%)
	SRF only	84/335 (25.1%)	83/332 (25.0%)	56/334 (16.8%)	139/666 (20.9%)
	IRF and SRF	15/335 (4.5%)	19/332 (5.7%)	11/334 (3.3%)	30/666 (4.5%)
	Missing or undetermined	1	3	4	7
	IRF missing or undetermined (and SRF=No)	0	0	1	1
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	1	3	3	6
Week 36	Dry	236/335 (70.4%)	236/331 (71.3%)	177/335 (52.8%)	413/666 (62.0%)
	Not Dry	99/335 (29.6%)	95/331 (28.7%)	158/335 (47.2%)	253/666 (38.0%)
	IRF only	42/335 (12.5%)	45/331 (13.6%)	60/335 (17.9%)	105/666 (15.8%)
	SRF only	54/335 (16.1%)	40/331 (12.1%)	76/335 (22.7%)	116/666 (17.4%)
	IRF and SRF	3/335 (0.9%)	10/331 (3.0%)	22/335 (6.6%)	32/666 (4.8%)
	Missing or undetermined	1	4	3	7
	IRF missing or undetermined (and SRF=No)	0	0	0	0
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	1	4	3	7
Week 40	Dry	190/334 (56.9%)	204/331 (61.6%)	170/334 (50.9%)	374/665 (56.2%)
	Not Dry	144/334 (43.1%)	127/331 (38.4%)	164/334 (49.1%)	291/665 (43.8%)
	IRF only	48/334 (14.4%)	50/331 (15.1%)	58/334 (17.4%)	108/665 (16.2%)
	SRF only	80/334 (24.0%)	66/331 (19.9%)	80/334 (24.0%)	146/665 (22.0%)
	IRF and SRF	16/334 (4.8%)	11/331 (3.3%)	26/334 (7.8%)	37/665 (5.6%)
	Missing or undetermined	2	4	4	8
	IRF missing or undetermined (and SRF=No)	0	0	1	1
	SRF missing or undetermined (and IRF=No)	1	0	0	0
	Both missing or undetermined	1	4	3	7
Week 44	Dry	232/335 (69.3%)	172/332 (51.8%)	227/335 (67.8%)	399/667 (59.8%)
	Not Dry	103/335 (30.7%)	160/332 (48.2%)	108/335 (32.2%)	268/667 (40.2%)
	IRF only	49/335 (14.6%)	66/332 (19.9%)	44/335 (13.1%)	110/667 (16.5%)
	SRF only	51/335 (15.2%)	77/332 (23.2%)	50/335 (14.9%)	127/667 (19.0%)
	IRF and SRF	3/335 (0.9%)	17/332 (5.1%)	14/335 (4.2%)	31/667 (4.6%)
	Missing or undetermined	1	3	3	6
	IRF missing or undetermined (and SRF=No)	0	0	0	0
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	1	3	3	6
Week 48	Dry	199/335 (59.4%)	236/332 (71.1%)	223/334 (66.8%)	459/666 (68.9%)
	Not Dry	136/335 (40.6%)	96/332 (28.9%)	111/334 (33.2%)	207/666 (31.1%)
	IRF only	52/335 (15.5%)	47/332 (14.2%)	53/334 (15.9%)	100/666 (15.0%)
	SRF only	73/335 (21.8%)	42/332 (12.7%)	48/334 (14.4%)	90/666 (13.5%)
	IRF and SRF	11/335 (3.3%)	7/332 (2.1%)	10/334 (3.0%)	17/666 (2.6%)
	Missing or undetermined	1	3	4	7
	IRF missing or undetermined (and SRF=No)	0	0	1	1
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	1	3	3	6

LOCF method for the last available observed value prior to ICE will be carried forward to impute missing data.
Intercurrent events (ICE) will be handled according to primary estimand strategy for binary endpoints as described in table 9-13 in section 9.5 of the SAP.
IRF Intraretinal fluid. SRF Subretinal fluid.
Dry = defined as no IRF nor SRF detected; Not dry = defined as IRF and/or SRF detected.

This observation did not appear to have a major impact on the results: The analysis of this key secondary endpoint was repeated on the PPS as supplementary analysis by the MAH, in which participants with no IRF and no SRF in central subfield at baseline were excluded, and the results were consistent with those obtained in the FAS (W48 Table 14.2.2/2).

Table 14.2.2 / 2 Proportion of subjects with no IRF and no SRF in central subfield at Week 16, LOCF (per protocol set)

Treatment	Subjects who had no IRF and no SRF Num/Den (%)	Contrast	Difference(a) % (two-sided 95% CI)	CMH test(b) p-value
HDq12 (N = 325)	197/324 (60.8%)			
HDq16 (N = 325)	208/324 (64.2%)			
All HD (N = 650)	405/648 (62.5%)	All HD - 2q8	12.327 (5.726, 18.929)	0.0001
2q8 (N = 320)	161/320 (50.3%)			

CI Confidence interval. CMH Cochran-Mantel-Haenszel. IRF Intraretinal fluid. LOCF Last observation carried forward. SRF Subretinal fluid.
LOCF method for the last available observed value prior to ICE will be carried forward to impute missing data.
Intercurrent events (ICE) will be handled according to primary estimand strategy for binary endpoints as described in table 9-13 in section 9.5 of the SAP.
(a) Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (<60 vs. ≥60) and is displayed with two-sided 95% CIs as described in SAP section 6.2.3.1.2.
(b) p-value for the one-sided Cochran-Mantel-Haenszel (CMH) test for superiority.

At Week 16, 62.5% of participants in the pooled HD groups had no retinal fluid (no IRF and no SRF) compared to 50.3% in the 2q8 treatment group. The difference (95% CI) between the pooled HD groups and the 2q8 group, using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60), was 12.327% points (5.726%, 18.929%).

Subgroup analysis for proportion of participants with no IRF and no SRF in central subfield at Week 16

The proportions of participants with no IRF and no SRF in central subfield at Week 16 by subgroups age, sex, geographic region, ethnicity, race, baseline BCVA, and baseline polypoidal choroidal vascularization (PCV) are presented by the MAH in the following Table:

Subgroup	Treatment	Subjects who had no IRF or SRF Num/Den (%)	Contrast	Difference(a) % (two-sided 95% CI)	CMH test(b) p-value
<65 years (N = 114)	HDq12 (N = 26)	11/ 26 (42.3%)			
	HDq16 (N = 43)	23/ 42 (54.8%)			
	All HD (N = 69)	34/ 68 (50.0%)	All HD - 2q8	-1.610 (-20.578, 17.358)	0.5658
	2q8 (N = 45)	24/ 45 (53.3%)			
>= 65 to < 75 years (N = 387)	HDq12 (N = 137)	87/137 (63.5%)			
	HDq16 (N = 124)	75/122 (61.5%)			
	All HD (N = 261)	162/259 (62.5%)	All HD - 2q8	15.695 (5.084, 26.305)	0.0019
	2q8 (N = 126)	59/125 (47.2%)			
>= 75 to < 80 years (N = 212)	HDq12 (N = 77)	44/ 77 (57.1%)			
	HDq16 (N = 66)	40/ 66 (60.6%)			
	All HD (N = 143)	84/143 (58.7%)	All HD - 2q8	10.171 (-4.161, 24.503)	0.0852
	2q8 (N = 69)	34/ 69 (49.3%)			
>= 80 to < 85 years (N = 184)	HDq12 (N = 59)	38/ 58 (65.5%)			
	HDq16 (N = 66)	49/ 65 (75.4%)			
	All HD (N = 125)	87/123 (70.7%)	All HD - 2q8	19.089 (4.200, 33.979)	0.0053
	2q8 (N = 59)	31/ 59 (52.5%)			
>= 85 years (N = 112)	HDq12 (N = 36)	25/ 35 (71.4%)			
	HDq16 (N = 39)	30/ 39 (76.9%)			
	All HD (N = 75)	55/ 74 (74.3%)	All HD - 2q8	2.529 (-15.897, 20.956)	0.3912
	2q8 (N = 37)	25/ 37 (67.6%)			
Male (N = 459)	HDq12 (N = 153)	89/151 (58.9%)			
	HDq16 (N = 158)	104/156 (66.7%)			
	All HD (N = 311)	193/307 (62.9%)	All HD - 2q8	8.749 (-0.986, 18.485)	0.0374
	2q8 (N = 148)	80/147 (54.4%)			
Female (N = 550)	HDq12 (N = 182)	116/182 (63.7%)			
	HDq16 (N = 180)	113/178 (63.5%)			
	All HD (N = 362)	229/360 (63.6%)	All HD - 2q8	14.473 (5.775, 23.171)	0.0005
	2q8 (N = 188)	93/188 (49.5%)			
Japan (N = 97)	HDq12 (N = 31)	19/ 30 (63.3%)			
	HDq16 (N = 33)	29/ 33 (87.9%)			
	All HD (N = 64)	48/ 63 (76.2%)	All HD - 2q8	9.469 (-10.147, 29.084)	0.1631
	2q8 (N = 33)	22/ 33 (66.7%)			
Rest of the world (N = 912)	HDq12 (N = 304)	186/303 (61.4%)			
	HDq16 (N = 305)	188/301 (62.5%)			
	All HD (N = 609)	374/604 (61.9%)	All HD - 2q8	11.977 (5.128, 18.826)	0.0003
	2q8 (N = 303)	151/302 (50.0%)			

Not Hispanic or Latino (N = 970)	HDq12 (N = 322)	199/320 (62.2%)			
	HDq16 (N = 326)	208/322 (64.6%)			
	All HD (N = 648)	407/642 (63.4%)	All HD - 2q8	11.856 (5.251, 18.461)	0.0002
	2q8 (N = 322)	166/321 (51.7%)			
Hispanic or Latino (N = 28)	HDq12 (N = 7)	3/ 7 (42.9%)			
	HDq16 (N = 9)	7/ 9 (77.8%)			
	All HD (N = 16)	10/ 16 (62.5%)	All HD - 2q8	11.803 (-27.597, 51.203)	0.2710
	2q8 (N = 12)	7/ 12 (58.3%)			
White (N = 765)	HDq12 (N = 256)	156/255 (61.2%)			
	HDq16 (N = 260)	155/256 (60.5%)			
	All HD (N = 516)	311/511 (60.9%)	All HD - 2q8	14.932 (7.402, 22.461)	<.0001
	2q8 (N = 249)	114/248 (46.0%)			
Asian (N = 234)	HDq12 (N = 74)	46/ 73 (63.0%)			
	HDq16 (N = 77)	61/ 77 (79.2%)			
	All HD (N = 151)	107/150 (71.3%)	All HD - 2q8	5.323 (-7.123, 17.769)	0.2012
	2q8 (N = 83)	55/ 83 (66.3%)			
<= 73 letters (N = 870)	HDq12 (N = 293)	181/291 (62.2%)			
	HDq16 (N = 290)	189/287 (65.9%)			
	All HD (N = 583)	370/578 (64.0%)	All HD - 2q8	13.308 (6.307, 20.308)	<.0001
	2q8 (N = 287)	145/286 (50.7%)			
> 73 letters (N = 139)	HDq12 (N = 42)	24/ 42 (57.1%)			
	HDq16 (N = 48)	28/ 47 (59.6%)			
	All HD (N = 90)	52/ 89 (58.4%)	All HD - 2q8	3.433 (-13.976, 20.843)	0.3480
	2q8 (N = 49)	28/ 49 (57.1%)			
Yes (N = 141)	HDq12 (N = 45)	26/ 45 (57.8%)			
	HDq16 (N = 42)	33/ 42 (78.6%)			
	All HD (N = 87)	59/ 87 (67.8%)	All HD - 2q8	4.538 (-11.465, 20.542)	0.2914
	2q8 (N = 54)	34/ 54 (63.0%)			
No (N = 153)	HDq12 (N = 54)	30/ 54 (55.6%)			
	HDq16 (N = 46)	37/ 46 (80.4%)			
	All HD (N = 100)	67/100 (67.0%)	All HD - 2q8	19.529 (2.294, 36.763)	0.0105
	2q8 (N = 53)	24/ 53 (45.3%)			

CI Confidence interval. CMH Cochran-Mantel-Haenszel. IRF Intraretinal fluid. LOCF Last observation carried forward. SRF Subretinal fluid.
LOCF method for the last available observed value prior to ICE will be carried forward to impute missing data.
Intercurrent events (ICE) will be handled according to primary estimand strategy for binary endpoints as described in table 9-13 in section 9.5 of the SAP.
(a) Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (<60 vs ≥60) and is displayed with two-sided 95% CIs as described in SAP section 6.2.3.1.2.
(b) p-value for the one-sided Cochran-Mantel-Haenszel (CMH) test for superiority.

Discrepancies in results of absence of IRF/SRF in central subfield at Week 16 in the HD groups compared to the 2q8 group appeared in the following subgroups of patients: < 65 years, ≥ 65 to < 75 years, ≥ 80 to < 85 years, females, from Rest of the world, not Hispanic or Latino, White, with a baseline BCVA ≤ 73 letters, and no PCV at baseline. However, given the smaller size of these subgroups, the validity of these comparisons appears limited.

Sensitivity analysis for proportion of participants with no IRF and no SRF in central subfield at Week 16

For a sensitivity analysis of the key secondary efficacy variable, proportion of participants with no IRF and no SRF in central subfield at Week 16 in the FAS, a Cochran-Mantel-Haenszel test was calculated by the MAH based on OC only (W48 Table 14.2.2/3).

Table 14.2.2 / 3 Proportion of subjects with no IRF and no SRF in central subfield at Week 16, OC (full analysis set)

Treatment	Subjects who had no IRF and no SRF Num/Den (%)	Contrast	Difference(a) % (two-sided 95% CI)	CMH test(b) p-value
HDq12 (N = 335)	197/325 (60.6%)			
HDq16 (N = 338)	211/325 (64.9%)			
All HD (N = 673)	408/650 (62.8%)	All HD - 2q8	11.985 (5.423, 18.547)	0.0002
2q8 (N = 336)	166/326 (50.9%)			

CI Confidence interval. CMH Cochran-Mantel-Haenszel. IRF Intraretinal fluid. OC Observed cases. SRF Subretinal fluid.
OC: only subjects with available data prior to ICE included. No imputation of missing values after occurrence of ICEs was done.
Intercurrent events (ICE) will be handled according to primary estimand strategy for binary endpoints as described in table 9-13 in section 9.5 of the SAP.
(a) Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (<60 vs. ≥60) and is displayed with two-sided 95% CIs as described in SAP section 6.2.3.1.2.
(b) p-value for the one-sided Cochran-Mantel-Haenszel (CMH) test for superiority.

The results of this sensitivity analysis were similar to the results using LOCF in the FAS:

At Week 16, 62.8% of participants in the pooled HD groups had no retinal fluid (no IRF and no SRF) compared to 50.9% in the 2q8 treatment group. The difference (95% CI) between the pooled HD groups and the 2q8 group, using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60), was 11.985% points (5.423%, 18.547%).

Proportion of participants with no IRF and no SRF in the center subfield at Week 48 (additional secondary efficacy variable) and through Week 60

The proportion of participants with no retinal fluid (no IRF and no SRF) in the center subfield at Week 48 was numerically higher in the HDq12 and HDq16 groups (71.1% and 66.8%, respectively) compared to the 2q8 treatment group 59.4%, based on LOCF in the FAS. The pairwise differences (95% CI) for the 2-sided tests, using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60), of 11.725% points (4.527%, 18.923%) for HDq12 vs. 2q8 and 7.451% points (0.142%, 14.760%) for HDq16 vs. 2q8 were both in favor of HD treatment (Table 9-4).

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Subjects who had no IRF and no SRF, Num/Den (%)	199/335 (59.4%)	236/332 (71.1%)	223/334 (66.8%)
Contrast	/	HDq12 - 2q8	HDq16 - 2q8
Difference (a) % (two-sided 95% CI)	/	11.725 (4.527, 18.923)	7.451 (0.142, 14.760)
CMH test (b) p-value	/	0.0015	0.0458

BCVA = best corrected visual acuity, CI = Confidence interval, CMH = Cochran-Mantel-Haenszel, IRF = Intraretinal fluid, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan, SRF = Subretinal fluid
LOCF method for the last available observed value prior to ICE were carried forward to impute missing data.
Intercurrent events (ICE) were handled according to primary estimand strategy for binary endpoints as described in Table 9-13 in Section 9.5 of the SAP.
(a) Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% CIs as described in SAP Section 6.2.3.1.2.
(b) Nominal p-value for the two-sided Cochran-Mantel-Haenszel (CMH) test.

Even larger differences in favor of HD treatment were obtained using OC prior to ICE for the pairwise comparisons in the FAS, providing differences of 15.417% points (7.664%, 23.170%) for HDq12 vs. 2q8 and 11.397% points (3.452%, 19.343%) for HDq12 vs. 2q8 (W48 Table 14.2.3/18 of the PH-42588 report section).

Summary statistics for the proportion of participants with no IRF and no SRF in central subfield at baseline, Week 16, Week 48, and Week 60, using LOCF for the FAS, are presented in Table 9-5. As can be seen from this table, the proportions of participants with no retinal fluid were > 50% at both Week 16 and Week 48 and numerically higher at Week 48 than at Week 16 in all 3 treatment groups and the pooled HD groups. At Week 60, the proportions of participants with no retinal fluid were > 70% and similar in all 3 treatment groups and the pooled HD groups.

Table 9-4: Proportion of participants with no IRF and no SRF in the central subfield at Week 48, LOCF (full analysis set)

Table 9-5: Summary statistics for proportion of participants with no IRF and no SRF in central subfield by visit through Week 60, LOCF (full analysis set)

Visit	Fluid status	2q8 N = 336 Num/Den(%)	HDq12 N = 335 Num/Den(%)	HDq16 N = 338 Num/Den(%)	All HD N = 673 Num/Den(%)
Baseline	Dry [a]	13/336 (3.9%)	8/335 (2.4%)	9/336 (2.7%)	17/671 (2.5%)
	Not dry [b]	323/336 (96.1%)	327/335 (97.6%)	327/336 (97.3%)	654/671 (97.5%)
	Missing or undetermined	0	0	2	2
Week 16	Dry [a]	173/335 (51.6%)	205/333 (61.6%)	217/334 (65.0%)	422/667 (63.3%)
	Not dry [b]	162/335 (48.4%)	128/333 (38.4%)	117/334 (35.0%)	245/667 (36.7%)
	Missing or undetermined	1	2	4	6
Week 48	Dry [a]	199/335 (59.4%)	236/332 (71.1%)	223/334 (66.8%)	459/666 (68.9%)
	Not dry [b]	136/335 (40.6%)	96/332 (28.9%)	111/334 (33.2%)	207/666 (31.1%)
	Missing or undetermined	1	3	4	7
Week 60	Dry [a]	249/334 (74.6%)	247/331 (74.6%)	242/335 (72.2%)	489/666 (73.4%)
	Not dry [b]	85/334 (25.4%)	84/331 (25.4%)	93/335 (27.8%)	177/666 (26.6%)
	Missing or undetermined	2	4	3	7

ICE = intercurrent events, IRF = intraretinal fluid, LOCF = last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan, SRF = subretinal fluid
LOCF method for the last available observed value prior to ICE was carried forward to impute missing data.
Intercurrent events (ICE) were handled according to primary estimand strategy for binary endpoints as described in Table 9-13 in Section 9.5 of the SAP.
a Dry = defined as no IRF nor SRF detected
b Not dry = defined as IRF and/or SRF detected

The second key secondary endpoint concerned the proportion of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in Central Subfield at Week 16. All arms received the 3 initial monthly doses prior to week 16. At week 16, 51.6% in the 2q8 treatment group compared to 63.3% of participants in the pooled HD groups (61.6% in HDq12 and 65% in HDq16) had no retinal fluid (no IRF and no SRF) with a difference (95% CI) between pooled HD groups vs. 2q8 treatment of 11.733% points (5.263%, 18.204%) superiority and a p-value of the 1-sided CMH test for superiority of 0.0002. The key secondary endpoint appears to be statistically met for both HD groups at week 16 and data at 48 and 60 weeks to numerically confirm results in favour of the HD groups.

Other secondary endpoints

Proportion of participants gaining at least 15 letters in BCVA

From baseline to Week 48

The proportions of participants gaining at least 15 letters in BCVA from baseline at Week 48, using LOCF in the FAS, are described in Table 9-7: 20.7% and 21.7% of patients in HDq12 and HDq16 arms respectively, compared 22.1% in the 2q8 treatment group with differences (95% CI) for the 2-sided tests of -1,748 letters (-7.784, 4.287, p-value= 0.5704) for HDq12 vs. 2q8 and -0.939 letters (-6.997, 5.119, P-value= 0.7611) for HDq16 vs. 2q8 at week 48 were observed.

Table 9-7: Proportion of participants who gained at least 15 letters in BCVA from baseline at Week 48, LOCF (full analysis set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Week 48 (additional secondary efficacy variable)			
Subjects who gained ≥ 15 letters, Num/Den (%)	74/335 (22.1%)	69/334 (20.7%)	73/337 (21.7%)
Contrast	/	HDq12 - 2q8	HDq16 - 2q8
Difference (a) % (two-sided 95% CI)	/	-1.748 (-7.784, 4.287)	-0.939 (-6.997, 5.119)
CMH test (b) p-value	/	0.5704	0.7611

BCVA = best corrected visual acuity, CI = Confidence interval, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan
LOCF method for the last available observed value prior to ICE was carried forward to impute missing data.
Intercurrent events (ICE) were handled according to sensitivity estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP (applied on BCVA).
(a) Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% CIs as described in SAP Section 6.2.3.1.2.
(b) Nominal p-value for the two-sided Cochran-Mantel-Haenszel (CMH) test.

From baseline to Week 60

The proportions of participants who gained at least 15 letters in BCVA from baseline reached values > 20% at Week 20 (2q8), Week 28 (HDq12), or Week 32 (HDq16) and remained at that level with similar values in all 3 treatment groups at Week 48 (20.7% to 22.1%) and at Week 60 (23.1% to 23.7%) as presented in Table 14.2.3/3.

Table 14.2.3 / 3 Summary statistics for proportion of subjects who gained at least 15 letters in BCVA from baseline by visit, LOCF (full analysis set)

Visit	2q8 N = 336 Num/Den(%)	HDq12 N = 335 Num/Den(%)	HDq16 N = 338 Num/Den(%)
Week 4	27/335 (8.1%)	17/332 (5.1%)	15/337 (4.5%)
Week 8	47/335 (14.0%)	38/334 (11.4%)	34/337 (10.1%)
Week 12	61/335 (18.2%)	46/334 (13.8%)	43/337 (12.8%)
Week 16	63/335 (18.8%)	50/334 (15.0%)	55/337 (16.3%)
Week 20	73/335 (21.8%)	61/334 (18.3%)	56/337 (16.6%)
Week 24	76/335 (22.7%)	62/334 (18.6%)	59/337 (17.5%)
Week 28	80/335 (23.9%)	73/334 (21.9%)	65/337 (19.3%)
Week 32	72/335 (21.5%)	69/334 (20.7%)	82/337 (24.3%)
Week 36	79/335 (23.6%)	70/334 (21.0%)	71/337 (21.1%)
Week 40	76/335 (22.7%)	77/334 (23.1%)	66/337 (19.6%)
Week 44	79/335 (23.6%)	75/334 (22.5%)	73/337 (21.7%)
Week 48	74/335 (22.1%)	69/334 (20.7%)	73/337 (21.7%)
Week 52	84/335 (25.1%)	74/334 (22.2%)	70/337 (20.8%)
Week 56	84/335 (25.1%)	80/334 (24.0%)	70/337 (20.8%)
Week 60	78/335 (23.3%)	79/334 (23.7%)	78/337 (23.1%)

LOCF (last observation carried forward): last available observed value prior to ICE will be used to impute missing data.
Intercurrent events (ICE) will be handled according to sensitivity estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP (applied on BCVA).

Proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent)

Week 48

The proportions of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 48 using LOCF in the FAS are presented in Table 9-8.

Table 9-8: Proportion of participants who achieved an ETDRS letter score of at least 69 at Week 48, LOCF (full analysis set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Subjects who achieved ≥ 69 letters, Num/Den (%)	194/335 (57.9%)	190/334 (56.9%)	183/337 (54.3%)
Contrast	/	HDq12 - 2q8	HDq16 - 2q8
Difference (a) % (two-sided 95% CI)	/	-0.182 (-6.565, 6.200)	-2.221 (-8.435, 3.994)
CMH test (b) p-value	/	0.9554	0.4834

BCVA = best corrected visual acuity, CI = Confidence interval, ETDRS = Early Treatment Of Diabetic Retinopathy Study, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan
LOCF method for the last available observed value prior to ICE was carried forward to impute missing data
Intercurrent events (ICE) were handled according to sensitivity estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP (applied on BCVA).
(a) Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% CIs as described in SAP Section 6.2.3.1.2.
(b) Nominal p-value for the two-sided Cochran-Mantel-Haenszel (CMH) test.

Week 60

The proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at week 60: 58.2%, 56.3% and 54.6% of patients achieved at least 69 letters (ETDRS score) in 2q8, HDq12 and HDq16 groups respectively.

Table 14.2.3 / 7 Summary statistics for proportion of subjects who achieved an ETDRS letter score of at least 69 by visit, LOCF (full analysis set)

Visit	2q8 N = 336 Num/Den(%)	HDq12 N = 335 Num/Den(%)	HDq16 N = 338 Num/Den(%)
Baseline	99/336 (29.5%)	114/335 (34.0%)	96/338 (28.4%)
Week 4	158/335 (47.2%)	140/332 (42.2%)	147/337 (43.6%)
Week 8	174/335 (51.9%)	165/334 (49.4%)	166/337 (49.3%)
Week 12	174/335 (51.9%)	174/334 (52.1%)	168/337 (49.9%)
Week 16	173/335 (51.6%)	177/334 (53.0%)	188/337 (55.8%)
Week 20	185/335 (55.2%)	175/334 (52.4%)	177/337 (52.5%)
Week 24	187/335 (55.8%)	178/334 (53.3%)	174/337 (51.6%)
Week 28	191/335 (57.0%)	187/334 (56.0%)	181/337 (53.7%)
Week 32	189/335 (56.4%)	186/334 (55.7%)	194/337 (57.6%)
Week 36	192/335 (57.3%)	194/334 (58.1%)	181/337 (53.7%)
Week 40	187/335 (55.8%)	192/334 (57.5%)	176/337 (52.2%)
Week 44	190/335 (56.7%)	189/334 (56.6%)	177/337 (52.5%)
Week 48	194/335 (57.9%)	190/334 (56.9%)	183/337 (54.3%)
Week 52	192/335 (57.3%)	194/334 (58.1%)	184/337 (54.6%)
Week 56	193/335 (57.6%)	193/334 (57.8%)	179/337 (53.1%)
Week 60	195/335 (58.2%)	188/334 (56.3%)	184/337 (54.6%)

LOCF (last observation carried forward): last available observed value prior to ICE will be used to impute missing data.
Intercurrent events (ICE) will be handled according to sensitivity estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP (applied on BCVA).
2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals.

Change in CNV size from baseline

Week 48

The mean CNV size at baseline was similar ranging from 6.0 to 6.5 mm² across the 3 treatment groups. Mean changes from baseline at Week 48 showed mean decreases in the HD groups and the 2q8 group. The estimated contrasts (95% CI) for the 2-sided test, using the MMRM in the FAS, of -1.22 (-1.94, -0.51) mm² for HDq12 vs. 2q8 and of -0.48 (-1.22, 0.27) mm² for HDq16 vs. 2q8 were both numerically in favor of HD treatment (Table 9-9).

Table 9-9: Change from baseline in CNV size (mm^2) at Week 48, MMRM (full analysis set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
LS mean (SE) change from baseline	-2.43 (0.31)	-3.65 (0.28)	-2.91 (0.29)
Arithmetic mean (SD) change from baseline (a)	-2.4 (5.3)	-3.5 (5.0)	-2.9 (5.3)
Baseline mean (a)	6.4	6.0	6.5
Number of subjects with Week 48 data	276	285	274
DF	/	614.0	609.2
Contrast (b)	/	HDq12-2q8	HDq16-2q8
t-value	/	-3.35	-1.26
P-value(c)	/	0.0009	0.2076
Estimate for Contrast and two-sided 95% CI (d)	/	-1.22 (-1.94,-0.51)	-0.48 (-1.22,0.27)

BCVA = best corrected visual acuity, CI = confidence interval, CNV = choroidal neovascularization, DF = degrees of freedom, LS = least squares, SAP = statistical analysis plan, SD = standard deviation, SE = standard error
A mixed model for repeated measurements (MMRM) was used with baseline CNV measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline CNV and visit and the interaction between treatment and visit.
A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.
(a) Based on observed assessments.
(b) The contrast also includes the interaction term for treatment x visit (at Week 48, for details on the population-level summary, see SAP Section 6.2.2.1).
(c) p-value for the two-sided test.
(d) Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Week 60

Summary statistics for the CNV size at baseline, Week 12, Week 48, and Week 60 based on OC prior to ICE in the FAS, are presented in Table 9-10.

The mean (SD) CNV size at baseline ranged from 5.9768 (4.8306) mm^2 to 6.5459 (5.5315) mm^2 across the 3 treatment groups. Numerical mean and median decreases from baseline were observed in all 3 treatment groups at Week 12, Week 48, and Week 60. At Week 60, the mean (SD) decreases in CNV size from baseline were of similar extent in all 3 treatment groups ranging from -3.6610 (5.6624) mm^2 to -3.8795 (5.4295) mm^2.

Table 9-10: Summary statistics for choroidal neovascularization size (mm^2) by visit, OC prior to ICE (full analysis set)

		Value at visit				Change from baseline			
Treatment	Visit	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
2q8 (N = 336)	Baseline	336	6.3593 (5.0394)	4.9970	0.148, 24.129	/	/	/	/
	Week 12	314	5.2107 (5.4069)	3.7455	0.000, 29.362	314	-1.1702 (3.4604)	-0.4930	-22.149, 11.671
	Week 48	280	4.1366 (5.5680)	1.6195	0.000, 27.675	280	-2.3934 (5.2421)	-1.3125	-24.129, 16.636
	Week 60	250	2.7613 (4.5855)	0.0000	0.000, 24.233	250	-3.8795 (5.4295)	-2.5440	-24.129, 12.664
HDq12 (N = 335)	Baseline	335	5.9768 (4.8306)	4.8990	0.115, 30.023	/	/	/	/
	Week 12	312	4.3936 (4.6561)	3.0690	0.000, 30.212	312	-1.4886 (3.6500)	-0.5530	-21.998, 11.890
	Week 48	287	2.4733 (4.6964)	0.0000	0.000, 27.034	287	-3.5530 (5.0074)	-2.5760	-21.998, 15.501
	Week 60	249	2.1483 (4.2820)	0.0000	0.000, 26.051	249	-3.8080 (4.9944)	-2.7740	-21.998, 12.783
HDq16 (N = 338)	Baseline	337	6.5459 (5.5315)	4.6980	0.000, 28.650	/	/	/	/
	Week 12	313	4.8923 (5.1756)	3.3660	0.000, 27.081	313	-1.5729 (4.2200)	-0.4950	-25.133, 16.628
	Week 48	279	3.5367 (5.1716)	0.7110	0.000, 28.936	279	-2.9790 (5.3189)	-1.4060	-25.354, 15.869
	Week 60	258	2.6576 (4.7255)	0.0000	0.000, 30.991	258	-3.6610 (5.6624)	-2.1700	-26.231, 16.769

Max = maximum, Min = minimum, SAP = statistical analysis plan, SD = standard deviation
OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded as described in the SAP.
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.

Change in total lesion area from baseline

Week 48

The mean total lesion area at baseline was similar across the 3 treatment groups, ranging from 6.4 to 6.9 mm². Mean changes from baseline at Week 48 showed mean decreases in the HD groups but a mean increase in the 2q8 group. The estimated contrasts (95% CI) for the 2-sided test, using the MMRM in the FAS, of -0.55 (-1.04, -0.06) mm² for HDq12 vs. 2q8 and of -0.44 (-0.94, 0.06) mm² for HDq16 vs. 2q8 were numerically in favor of HD treatment (Table 9-11).

The corresponding analysis using an ANCOVA with LOCF in the FAS provided mean changes from baseline to Week 48 and estimated contrasts (95% CIs) for the 2-sided tests between the HD groups and the 2q8 group that were numerically also in favor of HD treatment and thus consistent with the results from the analysis using MMRM (Table 14.2.3/14 of the PH-42588 report section). The corresponding summary statistics for total lesion area by visit using LOCF are presented in Table 14.2.3/16 of the PH-42588 report section.

Table 9-11: Change in total lesion area (mm²) from baseline to Week 48, MMRM (full analysis set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Baseline mean (a)	6.9	6.4	6.9
Number of subjects with Week 48 data	277	285	273
Arithmetic mean (SD) change from baseline (a)	0.1 (3.6)	-0.4 (2.9)	-0.2 (3.1)
LS mean (SE) change from baseline	0.09 (0.22)	-0.46 (0.19)	-0.35 (0.20)
DF	/	631.4	640.4
Contrast (b)	/	HDq12-2q8	HDq16-2q8
t-value	/	-2.19	-1.71
P-value (c)	/	0.0287	0.0870
Estimate for Contrast and two-sided 95% CI (d)	/	-0.55 (-1.04,-0.06)	-0.44 (-0.94,0.06)

BCVA = best corrected visual acuity, CI = confidence interval, DF = degrees of freedom, LS = least squares, SAP = statistical analysis plan, SD = standard deviation, SE = standard error
A mixed model for repeated measurements (MMRM) was used with baseline total lesion area as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline total lesion area and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.
(a) Based on observed assessments.
(b) The contrast also includes the interaction term for treatment x visit (at Week 48, for details on the population-level summary, see SAP Section 6.2.2.1).
(c) Nominal p-value for the two-sided test.
(d) Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Week 60

Summary statistics for the total lesion area at baseline, Week 12, Week 48, and Week 60 based on OC prior to ICE in the FAS, are presented in Table 9-12. The mean (SD) total lesion area at baseline ranged from 6.3820 (5.0664) mm² to 6.8814 (5.6514) mm² across the 3 treatment groups.

Numerical mean and median decreases in total lesion area from baseline were observed in all 3 treatment groups from Week 12 to Week 60, except for a numerical mean increase in the 2q8 group at Week 48. At Week 60, the mean (SD) decreases in total lesion area from baseline were of similar extent in all 3 treatment groups ranging from -0.3095 (3.1708) mm² to -0.5199 (2.8399) mm².

Table 9-12: Summary statistics for total lesion area (mm^2) by visit, OC prior to ICE (full analysis set)

		Value at visit				Change from baseline			
Treatment	Visit	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
2q8 (N = 336)	Baseline	336	6.8647 (5.4145)	5.4120	0.148, 27.409	/	/	/	/
	Week 12	314	6.6722 (5.4651)	4.8480	0.271, 29.362	314	-0.2130 (2.4653)	-0.1510	-11.233, 13.520
	Week 48	281	7.2282 (6.1106)	5.5800	0.271, 35.332	281	0.1110 (3.5498)	-0.2690	-11.242, 24.641
	Week 60	250	6.8963 (5.7963)	5.1360	0.379, 30.953	250	-0.3095 (3.1708)	-0.3715	-11.494, 15.885
HDq12 (N = 335)	Baseline	335	6.3820 (5.0664)	5.0260	0.185, 30.023	/	/	/	/
	Week 12	312	5.8133 (4.7055)	4.9645	0.154, 30.212	312	-0.4475 (2.2635)	-0.2345	-8.654, 10.872
	Week 48	287	6.0700 (5.2298)	4.9800	0.110, 30.259	287	-0.3628 (2.8917)	-0.2550	-8.719, 13.190
	Week 60	249	5.8150 (5.2904)	4.4550	0.138, 31.583	249	-0.5199 (2.8399)	-0.3180	-11.011, 14.006
HDq16 (N = 338)	Baseline	336	6.8814 (5.6514)	5.0685	0.180, 28.650	/	/	/	/
	Week 12	312	6.3994 (5.2627)	5.0060	0.180, 27.081	312	-0.3923 (2.6320)	-0.1355	-11.856, 16.628
	Week 48	278	6.5391 (5.5705)	4.9190	0.137, 28.936	278	-0.2856 (3.1628)	-0.0460	-13.105, 15.869
	Week 60	257	6.2872 (5.6288)	4.5190	0.134, 34.294	257	-0.3530 (3.2158)	-0.1350	-12.755, 16.769

Max = maximum, Min = minimum, SAP = statistical analysis plan, SD = standard deviation
OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded as described in the SAP.
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.

Change from baseline in CST

Week 48

The mean values of CST at baseline were ranging from 367.1 to 370.7 µm across the 3 treatment groups. Mean decreases from baseline were observed in all treatment groups at Week 48, which were higher in the HD groups than in the 2q8 group. The estimated contrasts (95% CIs) for the 2-sided tests, using the MMRM in the FAS, of -11.12 (-21.06,-1.18) µm for HDq12 vs. 2q8 and of -10.51 (-20.12,-0.90) µm for HDq16 vs. 2q8 were both numerically in favor of HD treatment (Table 9-13).

Table 9-13: Change from baseline in CST (µm) at Week 48, MMRM (full analysis set)

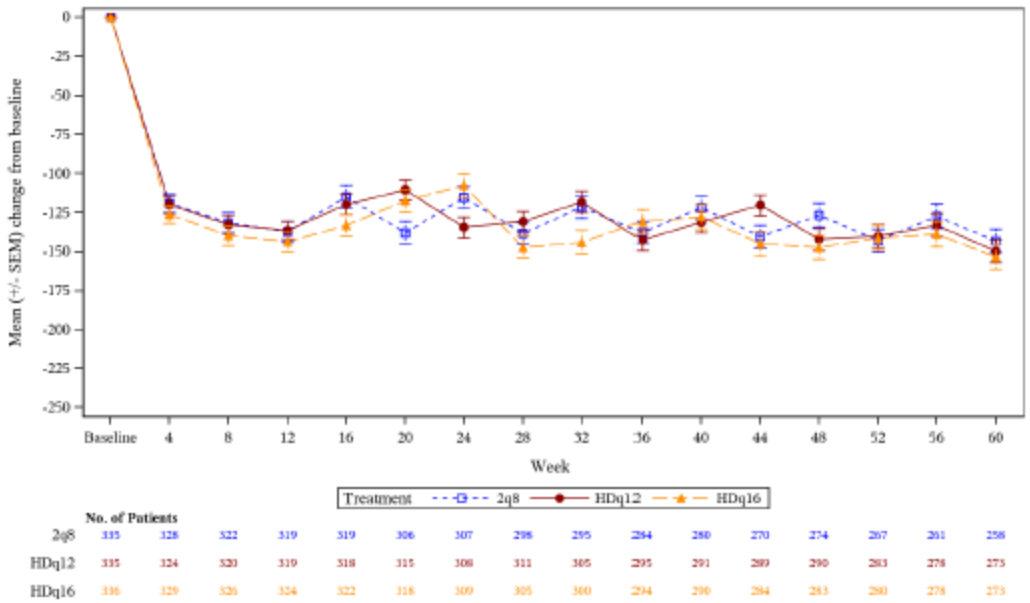
	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
LS mean (SE) change from baseline	-136.25 (4.24)	-147.37 (4.01)	-146.76 (3.76)
Arithmetic mean (SD) change from baseline (a)	-126.3 (124.3)	-141.9 (120.1)	-147.1 (131.2)
Baseline mean (a)	367.1	370.3	370.7
Number of subjects with Week 48 data	273	289	282
DF	/	626.1	608.6
Contrast (b)	/	HDq12-2q8	HDq16-2q8
t-value	/	-2.20	-2.15
P-value(c)	/	0.0283	0.0321
Estimate for Contrast and two-sided 95% CI (d)	/	-11.12 (-21.06,-1.18)	-10.51 (-20.12,-0.90)

BCVA = best corrected visual acuity, CI = confidence interval, CST = central subfield retinal thickness, DF = degrees of freedom, LS = least squares, SAP = statistical analysis plan, SD = standard deviation, SE = standard error
A mixed model for repeated measurements (MMRM) was used with baseline CST as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline CST and visit and the interaction between treatment and visit.
A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.
(a) Based on observed assessments.
(b) The contrast also includes the interaction term for treatment x visit (at Week 48, for details on the population-level summary see SAP Section 6.2.2.1).
(c) P-value for the two-sided test.
(d) Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Week 60

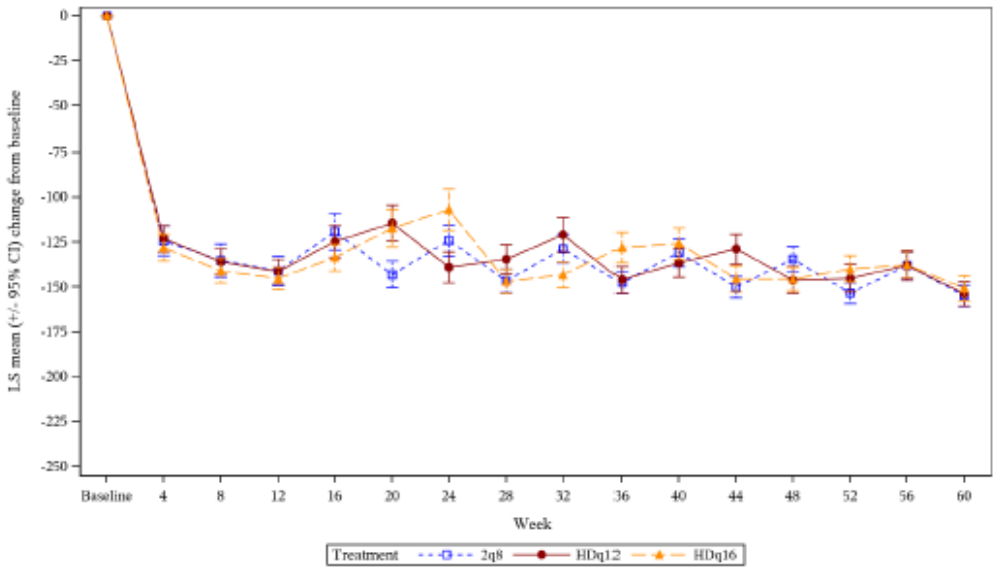
Mean changes from baseline in CST (µm) by visit through Week 60, based on OC prior to ICE in the FAS, are graphically displayed in post-hoc Figure 9-3; the LSmean (95% CIs) changes from baseline in CST (µm) by visit through Week 48, based on MMRM in the FAS, are graphically displayed in Figure 9-4.

Figure 9-3: Mean change from baseline in CST (µm) by visit through Week 60, OC prior to ICE (full analysis set)



CST = central subfield retinal thickness, SAP = statistical analysis plan, SEM = standard error mean
OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded as described in the SAP.

Figure 9-4: LSmean change from baseline in CST (µm) by visit through Week 60, MMRM (full analysis set)



BCVA = best corrected visual acuity, CI = confidence interval, CST = central subfield retinal thickness, LS = least squares, SAP = statistical analysis plan
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit.
A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: Toeplitz with heterogeneity.
Intercurrent events (ICE) were handled according to sensitivity estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.

Change from baseline in CST at <u>Week 96</u>

- ***PULSAR study***

Table 7 PULSAR: Change from baseline in CST (µm) at Week 48, Week 60, and Week 96 MMRM (FAS)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Baseline mean [a]	367.1	370.3	370.7
Week 48 (Additional secondary efficacy endpoint)			
Number of subjects with Week 48 data	273	289	282
Arithmetic mean (SD) change from baseline [a]	-126.3 (124.3)	-141.9 (120.1)	-147.1 (131.2)
LS mean (SE) change from baseline	-136.25 (4.24)	-147.37 (4.01)	-146.76 (3.76)
Contrast [b]		HDq12-2q8	HDq16-2q8
Estimate for Contrast and two-sided 95% CI [d]		-11.12 (-21.06,-1.18)	-10.51 (-20.12,-0.90)
p-value [c]		0.0283	0.0321
Week 60 (Exploratory efficacy endpoint)			
Number of subjects with Week 60 data	258	273	273
Arithmetic mean (SD) change from baseline [a]	-143.0 (120.9)	-149.7 (121.0)	-153.4 (134.1)
LS mean (SE) change from baseline	-154.83 (3.07)	-153.67 (3.53)	-150.69 (3.55)
Contrast [b]		HDq12-2q8	HDq16-2q8
Estimate for Contrast and two-sided 95% CI [d]		1.16 (-6.75,9.07)	4.14 (-3.87,12.14)
p-value [c]		0.7739	0.3104
Week 96 (Exploratory efficacy endpoint)			
Number of subjects with Week 96 data	129	119	131
Arithmetic mean (SD) change from baseline [a]	-124.2 (115.9)	-148.0 (128.8)	-153.6 (137.3)
LS mean (SE) change from baseline	-147.07 (3.90)	-151.01 (4.16)	-146.65 (4.21)
Contrast [b]		HDq12-2q8	HDq16-2q8
Estimate for Contrast and two-sided 95% CI [d]		-3.94 (-14.19,6.31)	0.42 (-9.95,10.80)
p-value [c]		0.4506	0.9364

CI = Confidence interval, CST = Central subfield retinal thickness, LS = Least Square, SD = Standard deviation, SE = Standard error, FAS = full analysis set

A mixed model for repeated measurements (MMRM) was used with baseline CST as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline CST and visit and the interaction between treatment and visit.

A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.

Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.

a Based on observed assessments.

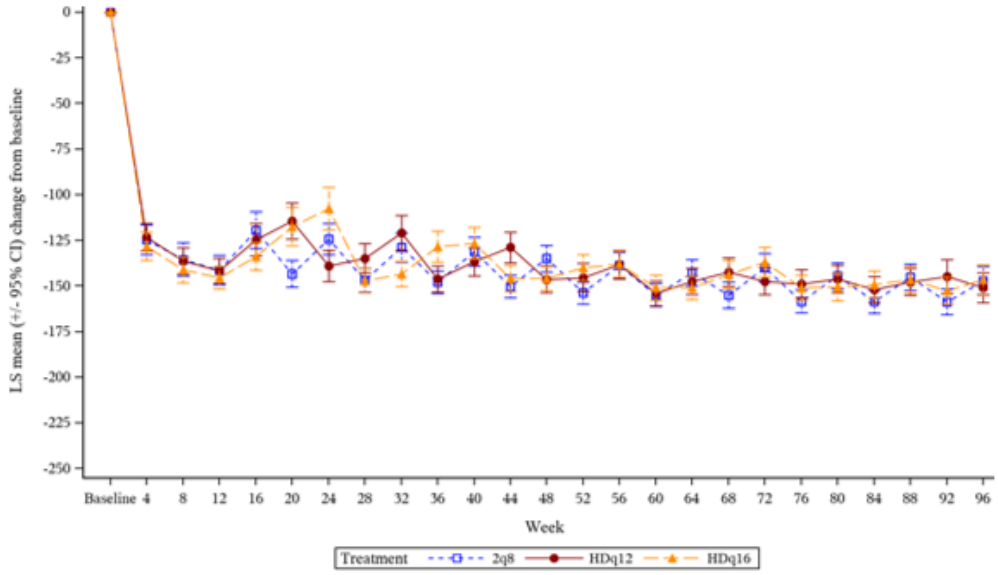
b The contrast also includes the interaction term for treatment x visit (at Week 48 or Week 60, respectively; for details on the population-level summary see SAP Section 6.2.2.1).

c Nominal p-value for the two-sided test.

d Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Source: Module 5.3.5.1, PULSAR W60 CSR PH-42588, W48 Table 14.2.3/19 and W60 Table 14.2.3/19, and Module 5.3.5.1, PULSAR TLF EMA CHMP Day-120 Question 20, 45, 61, Table 2.2.1

Figure 4 PULSAR: LS-mean change in CST (µm) by visit through Week 96, MMRM (FAS)



BCVA = best corrected visual acuity, CI = confidence interval, CST = central subfield retinal thickness, LS = least squares, SAP = statistical analysis plan
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: Toeplitz with heterogeneity. LS = Least squares
OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded as described in the SAP.
2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals.
HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals.
program location:
Source: Module 5.3.5.1, PULSAR TLF EMA CHMP Day-120 Question 20, 45, 61, Figure 2.2.1

As noted in table above, mean decreases from baseline in CST were observed in all treatment groups at Week 96, with arger mean decreases in the HD groups than in the 2q8, except for HDq16. Overall, the mean decreases from baseline in CST over time seems to be maintained and similar across all groups with generally minor numerical differences that could be considered as not clinically meaningful. Although exploratory, it should be noted that contrary to BCVA analysis, the results on CST are not statistically significant.

Change from baseline in NEI-VFQ-25 total score

Week 48

The mean values of the NEI-VFQ-25 total score at baseline across the 3 treatment groups were similar and ranging from 76.4 to 77.8. Mean increases from baseline were observed in all groups at Week 48, which were numerically lower in the HD groups than in the 2q8 group (Table 9-14).

Table 9-14: Change from baseline in NEI-VFQ-25 total score at Week 48, MMRM (full analysis set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Baseline mean (a)	77.8	76.4	77.7
Number of subjects with Week 48 data	266	285	266
Arithmetic mean (SD) change from baseline (a)	4.6 (11.0)	4.1 (10.4)	3.4 (10.8)
LS mean (SE) change from baseline	4.22 (0.70)	3.50 (0.70)	3.35 (0.72)
DF	/	571.7	540.3
Contrast (b)	/	HDq12-2q8	HDq16-2q8
t-value	/	-0.88	-1.02
P-value (c)	/	0.3817	0.3070
Estimate for Contrast and two-sided 95% CI (d)	/	-0.72 (-2.35,0.90)	-0.87 (-2.55,0.80)

CI = confidence interval, DF = degrees of freedom, LS = least squares, NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25, SAP = statistical analysis plan, SD = standard deviation, SE = standard error
A mixed model for repeated measurements (MMRM) was used with baseline NEI-VFQ-25 total score as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline NEI-VFQ-25 total score and visit and the interaction between treatment and visit.
A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.
(a) Based on observed assessments.
(b) The contrast also includes the interaction term for treatment x visit (at Week 48, for details on the population-level summary see SAP Section 6.2.2.1).
(c) Nominal p-value for the two-sided test.
(d) Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Week 60

The mean NEI-VFQ-25 total score at baseline across the 3 treatment groups were ranging from 76.36 to 77.81. The mean changes from baseline in NEI-VFQ-25 total score over time, based on OC prior to ICE, were all mean increases, which were numerically lower in the HD groups than in the 2q8 group at Week 24, Week 48, and Week 60. The mean (SD) increases from baseline at Week 60, which ranged from 3.65 (12.08) in the HDq12 group to 5.10 (11.38) in the 2q8 group, were similar to those at Week 48 (Table 14.2.3/25).

Table 14.2.3 / 25 Summary statistics for NEI-VFQ-25 total score by visit, OC prior to ICE (full analysis set)

			Value at visit						Change from baseline						
Treatment	Visit	n	Mean	SD	Q1	Median	Q3	Min , Max	n	Mean	SD	Q1	Median	Q3	Min , Max
2q8 (N = 336)	Baseline	317	77.81	14.42	68.64	80.45	89.24	36.92, 99.43							
	Week 24	297	82.41	12.91	74.02	85.95	92.95	37.73, 100.00	297	4.50	9.99	-1.21	3.67	9.63	-25.80, 44.05
	Week 48	269	82.47	13.56	75.91	85.87	93.08	31.38, 100.00	269	4.64	11.01	-1.52	3.33	9.77	-33.79, 43.71
	Week 60	254	83.26	13.53	76.83	87.48	94.25	38.30, 100.00	254	5.10	11.38	-1.40	3.24	10.49	-34.50, 45.95
HDq12 (N = 335)	Baseline	321	76.36	15.12	67.46	79.51	88.60	24.21, 98.18							
	Week 24	304	80.08	15.35	71.30	85.73	91.88	22.23, 99.43	304	3.16	10.76	-1.88	2.92	8.40	-37.54, 47.83
	Week 48	283	81.30	14.96	73.21	85.38	92.88	32.92, 100.00	283	3.99	10.31	-1.33	3.07	9.58	-27.33, 38.92
	Week 60	268	81.39	15.93	74.73	85.94	93.67	18.67, 100.00	268	3.65	12.08	-2.29	3.85	10.97	-58.00, 44.92
HDq16 (N = 338)	Baseline	316	77.67	15.40	68.63	81.85	89.92	16.17, 98.18							
	Week 24	293	81.28	13.87	74.20	84.70	92.01	27.21, 100.00	293	3.21	11.41	-2.73	2.27	8.86	-50.75, 43.67
	Week 48	269	81.77	14.59	74.54	85.79	92.58	16.71, 100.00	269	3.40	10.74	-2.27	2.27	8.56	-37.38, 39.66
	Week 60	257	82.29	14.77	74.96	86.52	93.83	27.42, 99.43	257	3.84	11.89	-2.35	2.29	9.73	-39.20, 47.50

OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded as described in the SAP.
Intercurrent events (ICE) will be handled according to primary estimand strategy for continuous endpoints as described in table 9-12 in section 9.5 of the SAP.

Overall, secondary efficacy endpoints results for HD groups (HDq12 and HDq16) in PULSAR study appears to be following the same tendency as for the 2q8 group with a slight numerical superiority in favour to the HDq12 regimen compared to the HDq16. Therefore the MAH should further discuss the clinical relevance of the secondary endpoint results with regards to the two new proposed dosing regimen.

As requested, the applicant provides a comprehensive discussion regarding the clinical relevance of the Secondary efficacy endpoints results for HD groups (HDq12 and HDq16) in PULSAR study (functional and anatomical response based on Change from baseline in BCVA measured by the ETDRS letter, Proportion of participants with no IRF and no SRF in central subfield, Proportion of participants gaining ≥ 15 letters in BCVA, Change from baseline in CST...).

Overall, the functional measures show similar outcomes across the 3 treatment groups, with non-inferiority demonstrated in the key secondary endpoint of change from baseline in BCVA at Week 60, in line with the primary endpoint results at Week 48. Between the two HD groups, numerical differences in other secondary endpoints are small, and not always in favour of HDq12 (e.g. proportion of patients gaining at least 15 letters in BCVA from baseline to Week 48). In conclusion, the results of the secondary efficacy endpoints in PULSAR are globally in line with the primary analysis and seem clinically relevant for demonstrating the value of aflibercept for the treatment of nAMD.

Exploratory endpoints

Change from baseline in BCVA averaged over the period from Week 36 to Week 48 and from Week 48 to Week 60

Mean (SD) values in BCVA were similar among treatment groups in the FAS at baseline across all treatment groups. The observed mean (SD) changes from baseline in BCVA averaged over the period from Week 36 to Week 48 and from Week 48 to Week 60 were similar to those for the primary endpoint (Table 9-15).

Table 9-15: Summary statistics for averaged BCVA in ETDRS letter score, OC prior to ICE (full analysis set)

		Averaged value for period				Change from baseline			
Treatment	Visit / Period	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
2q8 (N = 336)	Baseline	336	58.94 (14.02)	62.00	24.00, 78.00	/	/	/	/
	Average BCVA over the period from Week 36 to Week 48	299	66.88 (15.59)	72.25	10.50, 92.00	299	7.78 (11.42)	8.25	-44.75, 47.50
	Average BCVA over the period from Week 48 to Week 60	300	66.93 (15.60)	72.25	10.50, 92.00	300	7.88 (11.53)	8.25	-44.75, 47.50
HDq12 (N = 335)	Baseline	335	59.85 (13.37)	62.00	24.00, 78.00	/	/	/	/
	Average BCVA over the period from Week 36 to Week 48	313	66.87 (15.02)	71.50	13.25, 91.00	313	6.85 (11.58)	6.25	-58.75, 46.25
	Average BCVA over the period from Week 48 to Week 60	313	66.87 (15.02)	71.50	13.25, 91.00	313	6.85 (11.58)	6.25	-58.75, 46.25
HDq16 (N = 338)	Baseline	338	60.04 (12.38)	61.00	24.00, 78.00	/	/	/	/
	Average BCVA over the period from Week 36 to Week 48	308	66.21 (14.85)	69.75	6.75, 94.00	308	6.21 (11.14)	6.75	-43.25, 39.50
	Average BCVA over the period from Week 48 to Week 60	308	66.20 (14.85)	69.75	6.75, 94.00	308	6.20 (11.15)	6.75	-43.25, 39.50

BCVA = best corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, Max = maximum, Min = minimum, SAP = statistical analysis plan, SD = standard deviation
OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded as described in the SAP.
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.

Proportions of participants gaining and losing at least 5 or at least 10 letters in BCVA from baseline at Week 48 and Week 60

Overall, the proportions of participants gaining or losing at least 5 or 10 letters in BCVA from baseline at Week 48 are presented in Table 9-16.

The proportion of participants gaining at least 10 letters or at least 5 letters in BCVA from baseline at Week 48 were numerically higher in the 2q8 group than in the HDq12 and HDq16 treatment groups, based on LOCF in the FAS. In contrast, the proportion of participants who showed any gain (> 0 letters) in BCVA from baseline was similar in the HDq16 and 2q8 groups and lower in the HDq12 group. Similar results for the proportions of participants gaining at least 10 letters, at least 5 letters, or any gain (> 0 letters) in BCVA from baseline were observed at Week 60.

The numerical differences in the proportion of participants who lost at least 5 or 10 letters across the treatment groups were generally small, with the lowest proportions observed in the 2q8 group at Week 48 as well as at Week 60.

Table 9-16: Proportion of participants who gained or lost at least 5, 10 or 15 letters in BCVA from baseline at Week 48 and Week 60, LOCF (full analysis set)

Response category	Treatment	Subjects with response category, Num/Den (%)	
		Week 48	Week 60
Gained ≥ 15 letters	2q8 (N = 336)	74/335 (22.1%)	78/335 (23.3%)
	HDq12 (N = 335)	69/334 (20.7%)	79/334 (23.7%)
	HDq16 (N = 338)	73/337 (21.7%)	78/337 (23.1%)
Gained ≥ 10 letters	2q8 (N = 336)	142/335 (42.4%)	143/335 (42.7%)
	HDq12 (N = 335)	130/334 (38.9%)	137/334 (41.0%)
	HDq16 (N = 338)	130/337 (38.6%)	126/337 (37.4%)
Gained ≥ 5 letters	2q8 (N = 336)	213/335 (63.6%)	216/335 (64.5%)
	HDq12 (N = 335)	186/334 (55.7%)	191/334 (57.2%)
	HDq16 (N = 338)	196/337 (58.2%)	204/337 (60.5%)
Gained > 0 letters (any gain)	2q8 (N = 336)	255/335 (76.1%)	266/335 (79.4%)
	HDq12 (N = 335)	240/334 (71.9%)	233/334 (69.8%)
	HDq16 (N = 338)	258/337 (76.6%)	253/337 (75.1%)
Lost ≥ 5 letters	2q8 (N = 336)	37/335 (11.0%)	35/335 (10.4%)
	HDq12 (N = 335)	44/334 (13.2%)	45/334 (13.5%)
	HDq16 (N = 338)	48/337 (14.2%)	50/337 (14.8%)
Lost ≥ 10 letters	2q8 (N = 336)	21/335 (6.3%)	26/335 (7.8%)
	HDq12 (N = 335)	27/334 (8.1%)	30/334 (9.0%)
	HDq16 (N = 338)	31/337 (9.2%)	30/337 (8.9%)
Lost ≥ 15 letters	2q8 (N = 336)	14/335 (4.2%)	14/335 (4.2%)
	HDq12 (N = 335)	18/334 (5.4%)	22/334 (6.6%)
	HDq16 (N = 338)	18/337 (5.3%)	17/337 (5.0%)

BCVA = best corrected visual acuity, Num/Den = numerator/denominator, SAP = statistical analysis plan
LOCF (last observation carried forward): last available observed value prior to ICE was used to impute missing data.
Intercurrent events (ICE) were handled according to sensitivity estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP (applied to BCVA).

Proportions of participants losing at least 15 letters in BCVA from baseline at Week 48 and Week 60

The proportion of participants who lost at least 15 letters in BCVA from baseline was < 6.0% at Week 48 and < 7.0% at Week 60 in all 3 treatment groups, based on LOCF in the FAS can be seen in Table 9-16.

Proportions of patients gaining and losing ≥ 5, ≥ 10 or ≥ 15 letters in BCVA from baseline at Week 96

- *PULSAR study*

Table 6 PULSAR: Proportion of patients who gained or lost ≥ 5, 10, or 15 letters in BCVA from baseline through Week 48, Week 60 and Week 96, LOCF (FAS)

		Subjects with response category, Num/Den (%)		
Response category	Treatment	Week 48	Week 60	Week 96
Gained ≥ 15 letters	2q8 (N = 336)	74/335 (22.1%)	78/335 (23.3%)	80/335 (23.9%)
	HDq12 (N = 335)	69/334 (20.7%)	79/334 (23.7%)	79/334 (23.7%)
	HDq16 (N = 338)	73/337 (21.7%)	78/337 (23.1%)	77/337 (22.8%)
Gained ≥ 10 letters	2q8 (N = 336)	142/335 (42.4%)	143/335 (42.7%)	146/335 (43.6%)
	HDq12 (N = 335)	130/334 (38.9%)	137/334 (41.0%)	131/334 (39.2%)
	HDq16 (N = 338)	130/337 (38.6%)	126/337 (37.4%)	137/337 (40.7%)
Gained ≥ 5 letters	2q8 (N = 336)	213/335 (63.6%)	216/335 (64.5%)	208/335 (62.1%)
	HDq12 (N = 335)	186/334 (55.7%)	191/334 (57.2%)	182/334 (54.5%)
	HDq16 (N = 338)	196/337 (58.2%)	204/337 (60.5%)	186/337 (55.2%)
Lost ≥ 5 letters	2q8 (N = 336)	37/335 (11.0%)	35/335 (10.4%)	52/335 (15.5%)
	HDq12 (N = 335)	44/334 (13.2%)	45/334 (13.5%)	54/334 (16.2%)
	HDq16 (N = 338)	48/337 (14.2%)	50/337 (14.8%)	60/337 (17.8%)
Lost ≥ 10 letters	2q8 (N = 336)	21/335 (6.3%)	26/335 (7.8%)	26/335 (7.8%)
	HDq12 (N = 335)	27/334 (8.1%)	30/334 (9.0%)	34/334 (10.2%)
	HDq16 (N = 338)	31/337 (9.2%)	30/337 (8.9%)	42/337 (12.5%)
Lost ≥ 15 letters	2q8 (N = 336)	14/335 (4.2%)	14/335 (4.2%)	19/335 (5.7%)
	HDq12 (N = 335)	18/334 (5.4%)	22/334 (6.6%)	25/334 (7.5%)
	HDq16 (N = 338)	18/337 (5.3%)	17/337 (5.0%)	25/337 (7.4%)

BCVA = best corrected visual acuity; FAS = Full analysis set, ICE = intercurrent events; LOCF = last observation carried forward; SAP = statistical analysis plan.

LOCF (last observation carried forward): last available observed value prior to ICE was used to impute missing data.

Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP (applied to BCVA).

Source: Module 5.3.5.1, PULSAR W60 CSR PH-42588, W48 Table 14.2.4/4 (Week 48), W60 Table 14.2.4/4 (Week 60), Module 5.3.5.1, PULSAR TLF EMA CHMP Day-120 Question 20, 45, 61, Tables 2.1.14, 2.1.24 to 2.1.28 (Week 96)

As a general comment, it appears that like for Week 48 and Week 60, across all treatment groups, more participants gained letters in BCVA at Week 96, compared to those losing letters in BCVA. Although numerically slightly different, a similar proportion of patients in the HDq12 and HDq16 groups gained ≥ 10 letters or ≥ 15 letters through Week 96 compared to the 2q8 group.

The proportions of patients who gained ≥ 15 letters in BCVA from baseline reached values > 20% at Week 20 (2q8), Week 28 (HDq12) and Week 32 (HDq16), respectively, and remained at that level with similar values in all 3 treatment groups at Week 48 (20.7% to 22.1%), Week 60 (23.1% to 23.7%) and Week 96 (22.8% to 23.9%).

Proportion of participants without retinal fluid (total fluid, IRF, and/or SRF) and subRPE fluid in central subfield at Week 48 and Week 60

The proportion of participants without subRPE fluid in central subfield at Week 48 using LOCF in the FAS increased to values > 90% in both HD treatment groups and 86.2% in the 2q8 group. At Week 60, the proportion of participants without subRPE fluid in central subfield increased to values > 90% in all treatment groups (Table 9-17).

The proportion of participants with both no subRPE fluid and no retinal fluid (no IRF and no SRF) in central subfield increased from approximately 2% in each treatment group at baseline to proportions > 60% in both HD treatment groups and of 54.6% in the 2q8 group at Week 48.

At Week 60, the proportion of participants with both no subRPE fluid and no retinal fluid in central subfield increased further to values of approximately 69% to 71% in all treatment groups (Table 9-17).

Table 9-17: Proportion of participants without retinal fluid and subretinal pigment epithelium fluid in central subfield by visit, LOCF (full analysis set)

Visit	Fluid status	2q8 N = 336 Num/Den(%)	HDq12 N = 335 Num/Den(%)	HDq16 N = 338 Num/Den(%)
Baseline	No SubRPE fluid	237/335 (70.7%)	225/334 (67.4%)	236/336 (70.2%)
	Dry	7/335 (2.1%)	5/334 (1.5%)	6/336 (1.8%)
	Not dry (IRF and/or SRF)	230/335 (68.7%)	220/334 (65.9%)	230/336 (68.5%)
	Both IRF and SRF missing or undetermined	0/335	0/334	0/336
	SubRPE fluid present	98/335 (29.3%)	109/334 (32.6%)	100/336 (29.8%)
	Dry	6/335 (1.8%)	3/334 (0.9%)	3/336 (0.9%)
	Not dry (IRF and/or SRF)	92/335 (27.5%)	106/334 (31.7%)	97/336 (28.9%)
	Both IRF and SRF missing or undetermined	0/335	0/334	0/336
	SubRPE missing or undetermined	1	1	2
Week 48	No SubRPE fluid	281/326 (86.2%)	298/325 (91.7%)	308/330 (93.3%)
	Dry	178/326 (54.6%)	216/325 (66.5%)	207/330 (62.7%)
	Not dry (IRF and/or SRF)	103/326 (31.6%)	82/325 (25.2%)	100/330 (30.3%)
	Both IRF and SRF missing or undetermined	0/326	0/325	0/330
	SubRPE fluid present	45/326 (13.8%)	27/325 (8.3%)	22/330 (6.7%)
	Dry	17/326 (5.2%)	16/325 (4.9%)	14/330 (4.2%)
	Not dry (IRF and/or SRF)	28/326 (8.6%)	11/325 (3.4%)	8/330 (2.4%)
	Both IRF and SRF missing or undetermined	0/326	0/325	0/330
	SubRPE missing or undetermined	10	10	8
Week 60	No SubRPE fluid	296/326 (90.8%)	305/328 (93.0%)	309/331 (93.4%)
	Dry	226/326 (69.3%)	232/328 (70.7%)	228/331 (68.9%)
	Not dry (IRF and/or SRF)	70/326 (21.5%)	72/328 (22.0%)	81/331 (24.5%)
	Both IRF and SRF missing or undetermined	0/326	0/328	0/331
	SubRPE fluid present	30/326 (9.2%)	23/328 (7.0%)	22/331 (6.6%)
	Dry	18/326 (5.5%)	12/328 (3.7%)	13/331 (3.9%)
	Not dry (IRF and/or SRF)	12/326 (3.7%)	11/328 (3.4%)	9/331 (2.7%)
	Both IRF and SRF missing or undetermined	0/326	0/328	0/331
	SubRPE missing or undetermined	10	7	7

IRF = Intraretinal fluid, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan, SRF = Subretinal fluid, subRPE = subretinal pigment epithelium fluid
LOCF: last available observed value prior to ICE was used to impute missing data.
Intercurrent events (ICE) were handled according to primary estimand strategy for binary endpoints as described in Table 9-13 in Section 9.5 of the SAP.
Dry = defined as no IRF nor SRF in central subfield detected; Not dry = defined as IRF and/or SRF in central subfield detected.

Time to fluid-free retina over 48 weeks and over 60 weeks (total fluid in the central subfield)

There were no clinically meaningful pairwise differences between the HD treatment groups and the 2q8 group in the median time to fluid-free retina (no IRF and no SRF), median time to IRF-free retina, or median time to SRF-free retina over 48 weeks in the FAS (Table 14.2.4/7, Table 14.2.4/8, and Table 14.2.4/9 of the PH-42588 report section, respectively).

There were also no clinically meaningful pairwise differences between the HD treatment groups and the 2q8 group in the median time to fluid-free retina (no IRF and no SRF), median time to IRF-free retina, or median time to SRF-free retina over 60 weeks in the FAS (Table 14.2.4/7, Table 14.2.4/8, and Table 14.2.4/9 of the PH-42588 report section, respectively).

Proportion of participants with sustained fluid-free retina over 48 weeks and over 60 weeks (total fluid in the central subfield)

There were no clinically meaningful pairwise differences between the HD treatment groups and the 2q8 group in the median time to sustained fluid-free retina (no IRF and no SRF), median time to IRF-free retina, or median time to SRF-free retina over 48 weeks in the FAS (Table 14.2.4/13, Table 14.2.4/14, and Table 14.2.4/15 of the PH-42588 report section, respectively).

There were also no clinically meaningful pairwise differences between the HD treatment groups and the 2q8 group in the median time to sustained fluid-free retina (no IRF and no SRF), median time to IRF-free retina, or median time to SRF-free retina over 60 weeks in the FAS (Table 14.2.4/13, Table 14.2.4/14, and Table 14.2.4/15 of the PH-42588 report section, respectively).

The proportions of participants with sustained fluid-free retina, IRF-free retina, and SRF-free retina can be found in Table 14.2.4/10 to Table 14.2.4/12 (over 48 weeks) and Table 14.2.4/10 to Table 14.2.4/12 (and over 60 weeks) of the PH-42588 report section.

Proportion of participants without leakage on FA at Week 48 and Week 60

The proportion of participants without leakage on FA increased in all groups over time reaching values of > 40% in the HDq16 and the 2q8 groups and > 60% in the HDq12 group at Week 48. At Week 60, the proportion of participants without leakage on FA increased further, reaching values of > 50% in the HDq16 and the 2q8 groups and > 60% in the HDq12 group. The number of participants with an undetermined leakage status was generally small and similar across the treatment groups over time (Table 9-18).

Table 9-18: Proportion of participants without leakage on FA by visit, LOCF (full analysis set)

Visit	Leakage status	2q8 N = 336 Num/Den(%)	HDq12 N = 335 Num/Den(%)	HDq16 N = 338 Num/Den(%)
Baseline	No leakage	0/336	0/335	1/337 (0.3%)
	Any leakage	336/336 (100%)	335/335 (100%)	336/337 (99.7%)
	Undetermined	0	0	1
Week 12	No leakage	61/308 (19.8%)	70/305 (23.0%)	67/307 (21.8%)
	Any leakage	247/308 (80.2%)	235/305 (77.0%)	240/307 (78.2%)
	Undetermined	9	8	7
Week 48	No leakage	136/322 (42.2%)	193/319 (60.5%)	140/319 (43.9%)
	Any leakage	186/322 (57.8%)	126/319 (39.5%)	179/319 (56.1%)
	Undetermined	8	9	8
Week 60	No leakage	178/320 (55.6%)	195/318 (61.3%)	169/316 (53.5%)
	Any leakage	142/320 (44.4%)	123/318 (38.7%)	147/316 (46.5%)
	Undetermined	10	10	10

ICE = Intercurrent events, FA = fluorescein angiography, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan
LOCF: last available observed value prior to ICE was used to impute missing data.
ICE were handled according to primary estimand strategy for binary endpoints as described in Table 9-13 in Section 9.5 of the SAP.

Proportion of participants with q12 or q16 or longer treatment intervals

Proportion of participants with q16 or longer treatment interval through Week 48 and Week 60 in HDq16 group

The proportion of completers who maintained q16 dosing intervals prior to Week 48 was 76.6% and 74.1% prior to Week 60 in the HDq16 group (Table 10-2).

Proportion of participants with q12 or longer interval through Week 48 and Week 60 in the HDq12 and HDq16 groups

The proportion of completers in the HD treatment groups who maintained q12 or longer dosing intervals prior to Week 48 was 79.4% and 87.2% in the HDq12 and HDq16 groups, respectively. In the pooled HD groups, 83.3% maintained q12 or longer dosing intervals.

The proportion of completers in the HD treatment groups who maintained q12 or longer dosing intervals prior to Week 60 was 77.8% and 85.4% in the HDq12 and HDq16 groups, respectively. In the pooled HD groups, 81.6% maintained q12 or longer dosing intervals (Table 10-2).

Proportion of participants with q12 or q16 or longer treatment interval as the last intended interval at Week 48 and Week 60 in HDq12 and HDq16 groups, respectively

The proportion of participants with q12 or longer treatment interval as the last intended interval at Week 48 was 79.4% in the HDq12 and 86.9% in the HDq16 group, and 83.1% in the pooled HD groups. The proportion of participants with q16 or longer treatment interval as the last intended interval at Week 48 was 76.6% in the HDq16 group (Table 10-2).

The proportion of participants with q12 or longer treatment interval as the last intended interval at Week 60 was 84.6% in the HDq12 and 90.0% in the HDq16 group, and 87.3% in the pooled HD groups. The proportion of participants with q16 or longer treatment interval as the last intended interval at Week 60 was 77.3% in the HDq16 group (Table 10-2).

Table 10-2: Exposure to study treatment through Week 48 and Week 60 – Dosing intervals (safety analysis set, only participants considered as completers for Week 48)

Through Week 48 (a)	2q8 N = 309 (100%)	HDq12 N = 316 (100%)	HDq16 N = 312 (100%)	All HD N = 628 (100%)
Subjects with q12 or longer dosing interval (b), n (%)	/	251 (79.4%)	272 (87.2%)	523 (83.3%)
Subjects with q16 dosing interval (c), n (%)	/	/	239 (76.6%)	/
Subjects with q12 or longer dosing interval as the last intended dosing interval (d), n (%)	/	251 (79.4%)	271 (86.9%)	522 (83.1%)
Subjects with q16 dosing interval as the last intended dosing interval (d), n (%)	/	/	239 (76.6%)	/
Subjects shortened to q8 dosing interval at Week 16, n (%)	/	17 (5.4%)	10 (3.2%)	27 (4.3%)
Subjects shortened to q8 dosing interval at Week 20, n (%)	/	25 (7.9%)	21 (6.7%)	46 (7.3%)
Subjects shortened anytime, n (%)	/	65 (20.6%)	73 (23.4%)	138 (22.0%)
Subjects shortened to q8 dosing interval anytime, n (%)	/	65 (20.6%)	40 (12.8%)	105 (16.7%)
Subjects shortened to q12 dosing interval anytime, n (%) (without shortening to q8)	/	/	33 (10.6%)	/

Through Week 60 (e)	2q8 N = 305 (100%)	HDq12 N = 311 (100%)	HDq16 N = 309 (100%)	All HD N = 620 (100%)
Subjects maintained with q12 or longer dosing interval (f), n (%)	/	242 (77.8%)	264 (85.4%)	506 (81.6%)
Subjects maintained with q16 or longer dosing interval (g), n (%)	/	/	229 (74.1%)	/
Subjects with q12 or longer dosing interval as the last intended dosing interval (h), n (%)	/	263 (84.6%)	278 (90.0%)	541 (87.3%)
Subjects with q16 or longer dosing interval as the last intended dosing interval (h), n (%)	/	134 (43.1%)	239 (77.3%)	373 (60.2%)
Subjects with q20 dosing interval as the last intended dosing interval (h), n (%)	/	/	119 (38.5%)	/
Subjects shortened to q8 dosing interval at Week 16, n (%)	/	17 (5.5%)	10 (3.2%)	27 (4.4%)
Subjects shortened to q8 dosing interval at Week 20, n (%)	/	25 (8.0%)	20 (6.5%)	45 (7.3%)
Subjects shortened anytime, n (%)	/	69 (22.2%)	80 (25.9%)	149 (24.0%)
Subjects shortened to q8 dosing interval anytime, n (%)	/	69 (22.2%)	45 (14.6%)	114 (18.4%)
Subjects shortened to q12 dosing interval anytime (without shortening to q8), n (%)	/	/	35 (11.3%)	/
Subjects never extended dosing interval, n (%) (i)	/	159 (51.1%)	174 (56.3%)	333 (53.7%)
Subjects extended dosing interval anytime, n (%) (j)	/	152 (48.9%)	135 (43.7%)	287 (46.3%)

DRM = dose regimen modification

/ indicates categories that do not apply.

a Study interventions given at Week 48 or beyond are not included in this table.

b All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 44] prior to Week 48.

c All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 44] prior to Week 48.

d Based on DRM criteria assessed at the last visit on or before Week 48.

e Study interventions given at Week 60 or beyond are not included in this table.

f All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 56] prior to Week 60.

g All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 56] prior to Week 60.

h Based on DRM criteria assessed at the last visit on or before Week 60.

i All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 56] prior to Week 60.

j All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 56] prior to Week 60.

Table 10-1: Exposure to study treatment: through Week 48 and Week 60 (safety analysis set)

	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Week48				
Total number of active injections, n	2267	1986	1703	3689
Total number of sham injections, n	1212	1515	1793	3308
Number of active injections, n (%)				
1	1 (0.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
2	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
3	4 (1.2%)	3 (0.9%)	9 (2.7%)	12 (1.8%)
4	6 (1.8%)	7 (2.1%)	22 (6.5%)	29 (4.3%)
5	6 (1.8%)	22 (6.6%)	263 (77.8%)	285 (42.3%)
6	29 (8.6%)	260 (77.6%)	11 (3.3%)	271 (40.3%)
7	288 (85.7%)	39 (11.6%)	29 (8.6%)	68 (10.1%)
8	1 (0.3%)	0	0	0
Number of active injections				
n	336	335	337	672
Mean (SD)	6.7 (0.8)	5.9 (0.8)	5.1 (0.8)	5.5 (0.9)
Median	7.0	6.0	5.0	6.0
Min, Max	1,8	1,7	1,7	1,7
Number of sham injections, n (%)				
1	7 (2.1%)	4 (1.2%)	3 (0.9%)	7 (1.0%)
2	15 (4.5%)	4 (1.2%)	8 (2.4%)	12 (1.8%)
3	46 (13.7%)	17 (5.1%)	5 (1.5%)	22 (3.3%)
4	258 (76.8%)	63 (18.8%)	40 (11.8%)	103 (15.3%)
5	1 (0.3%)	240 (71.6%)	45 (13.3%)	285 (42.3%)
6	0	0	229 (67.8%)	229 (34.0%)
Number of sham injections				
n	327	328	330	658
Mean (SD)	3.7 (0.7)	4.6 (0.7)	5.4 (1.0)	5.0 (1.0)
Median	4.0	5.0	6.0	5.0
Min, Max	1,5	1,5	1,6	1,6
Duration of treatment (weeks)				
n	336	335	337	672
Mean (SD)	46.28 (6.62)	46.54 (6.56)	46.18 (6.97)	46.36 (6.77)

Median	48.00	48.00	48.00	48.00
Min, Max	4,50.9	4,52	4,53.3	4,53.3
Week 60				
Total number of active injections, n	2854	2324	2018	4342
Total number of sham injections, n	1502	2080	2380	4460
Number of active injections, n (%)				
1	1 (0.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
2	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
3	4 (1.2%)	3 (0.9%)	9 (2.7%)	12 (1.8%)
4	6 (1.8%)	7 (2.1%)	10 (3.0%)	17 (2.5%)
5	5 (1.5%)	5 (1.5%)	20 (5.9%)	25 (3.7%)
6	9 (2.7%)	24 (7.2%)	255 (75.4%)	279 (41.5%)
7	6 (1.8%)	239 (71.3%)	11 (3.3%)	250 (37.1%)
8	43 (12.8%)	38 (11.3%)	21 (6.2%)	59 (8.8%)
9	260 (77.4%)	15 (4.5%)	8 (2.4%)	23 (3.4%)
10	1 (0.3%)	0	0	0
Number of active injections				
n	336	335	337	672
Mean (SD)	8.5 (1.3)	6.9 (1.1)	6.0 (1.1)	6.5 (1.2)
Median	9.0	7.0	6.0	6.0
Min, Max	1,10	1,9	1,9	1,9
Number of sham injections, n (%)				
1	5 (1.5%)	4 (1.2%)	3 (0.9%)	7 (1.0%)
2	12 (3.6%)	2 (0.6%)	8 (2.4%)	10 (1.5%)
3	15 (4.5%)	5 (1.5%)	2 (0.6%)	7 (1.0%)
4	48 (14.3%)	12 (3.6%)	5 (1.5%)	17 (2.5%)
5	246 (73.2%)	34 (10.1%)	19 (5.6%)	53 (7.9%)
6	1 (0.3%)	58 (17.3%)	31 (9.2%)	89 (13.2%)
7	0	213 (63.6%)	42 (12.4%)	255 (37.9%)
8	0	0	220 (65.1%)	220 (32.7%)
Number of sham injections				
n	327	328	330	658
Mean (SD)	4.6 (0.9)	6.3 (1.2)	7.2 (1.5)	6.8 (1.4)
Median	5.0	7.0	8.0	7.0
Min, Max	1,6	1,7	1,8	1,8
Duration of treatment (weeks)				
n	336	335	337	672
Mean (SD)	57.23 (9.56)	57.74 (9.12)	57.44 (9.80)	57.59 (9.46)
Median	60.00	60.00	60.00	60.00
Min, Max	4,64.7	4,63.3	4,63.6	4,63.6

Max = maximum, Min = minimum, SD = standard deviation
Duration (weeks) = [(date of last study treatment) – (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study.
Study interventions given at Week 60 or beyond are not included in this table.

In addition to the shortening of the intervals of IVT injections, some patients were eligible starting week 52 to extend up by 4 week the interval based on DRM criteria assessed in HD groups and at 60 weeks (patients in HDq12 group could be injected with a q16 interval and patients in HDq16 group could be injected with a q20 interval). Moreover, the sponsor proposed the following wording for the posology in the SmPC:

"**4.2 Posology and method of administration**

Eylea must only be administered by a qualified physician experienced in intravitreal injections.

Posology

The recommended dose is 8 mg aflibercept, equivalent to 0.07 ml solution.

Eylea treatment is initiated with 1 injection per month for 3 consecutive doses. Injection intervals may then be extended up to every 16 weeks based on the physician's judgement of visual and/or anatomic outcomes. Subsequently, the treatment intervals may be further adjusted based on the physician's judgement of visual and/or anatomic outcomes up to every 5 months.

Eylea treatment intervals of 1 month for more than 3 consecutive doses have not been studied. There are limited data for treatment intervals longer than 5 months.

There is no requirement for monitoring between injections. Based on the physician's judgement the schedule of monitoring visits may be more frequent than the injection visits."

Overall, the efficacy results issued from PULSAR study are very limited to support the 5 months injection interval during the maintenance phase and more data was requested.

The applicant provides additional exposure data regarding the 20q dosing interval. Through Week 96, up to 47% and 44.3% of HD patients extended their treatment interval to q20 or longer intervals in the PULSAR and PHOTON study respectively. Numerically, this corresponds to a total of 185 patients completed at least one q20 interval before Week 96 in PULSAR and 133 patients in PHOTON study.

At Week 96, the proportion of patients with q20 or longer as the last intended dosing interval in the PULSAR was 36.8% in the HDq12 group and 54.9% in the HDq16 group. Of 216 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24 (i.e. 53 and 127 HD patients, respectively); only a few patients were shortened back to q16 (i.e. 3 HD patients).

For the PHOTON study, at Week 96 the proportion of patients with q20 or longer as the last intended dosing interval was 42.2% in the HDq12 group and 45.3% in the HDq16 group. Of 177 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24.

Moreover, all participants in HD groups were eligible for dose interval shortening (to a minimum of q8) as of Week 16 or extension (by 4-week increments) as of Week 52 according to the pre-specified DRM criteria. Due to this option for treatment individualization, by the end of Year 2, the HDq12 and HDq16 groups were allocated into a range of treatment intervals from 8 to 24 weeks. No patient had yet completed a 24-week interval by Week 96, but patients could have completed one or two q20 intervals. As for the requested 2-year data, the Applicant provided exposure details for patients who extended their treatment interval to q20 or longer. Through Week 96, up to 47% and 44.3% of HD patients extended their treatment interval to q20 or longer intervals in the PULSAR and PHOTON study respectively. Numerically, this corresponds to a total of 185 patients completed at least one q20 interval before Week 96 in PULSAR and 133 patients in PHOTON study.

At Week 96, the proportion of patients with q20 or longer as the last intended dosing interval in the PULSAR was 36.8% in the HDq12 group and 54.9% in the HDq16 group. Of 216 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24 (i.e. 53 and 127 HD patients, respectively); only a few patients were shortened back to q16 (i.e. 3 HD patients).

For the PHOTON study, at Week 96 the proportion of patients with q20 or longer as the last intended dosing interval was 42.2% in the HDq12 group and 45.3% in the HDq16 group. Of 177 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24.

Thus, in both studies, a high proportion of patients in the HD groups (48% and 56% respectively in the PHOTON and PULSAR HDq16 groups) extended their treatment intervals to q20 or longer while only a very few patients extended to intervals of q20 required a subsequent shortening of the treatment interval. However, even low, details on the reasons that lead to dosing interval shortening were needed.

Further discussion was required on the absence of visits between two injections during the maintenance phase.

The Applicant provided some clarifications regarding the relevance of absence of visits between two injections during the maintenance phase for patients allocated to HD intervals.

As discussed above, considering that the HDq12 and HDq16 treatment regimens have overall demonstrated BCVA gains non-inferior compared to 2q8, it is supported that modification of treatment intervals is not needed between doses and therefore monitoring visits are not a requirement for these regimens. Nevertheless, in line with the current practice regarding aflibercept 2 mg and the information included in the SmPC for aflibercept 2 mg, the Applicant proposes that event for the HD intervals, the frequency of monitoring visits may be higher than the dosing frequency, based on the discretion of the treating physician. As for validated regimen, the applicant proposal to leave need for monitoring visits to the physician´s discretion seems to be acceptable.

Issue could be considered as solved mainly on the basis that the HDq12 and HDq16 treatment regimens have overall demonstrated BCVA gains non-inferior compared to 2q8 at W96.

The MAH was asked to should provide a Table that could clearly identify the patient's dosing interval of treatment in each arm at Week 48 and 60 (q8, q12, q16 and q20) which is presented below.

Table 51 Actual dosing intervals at Week 48 and 60 by assigned treatment arm - PULSAR and PHOTON

Figures denote number (%) of subjects

		PULSAR			PHOTON		
		2q8	HDq12	HDq16	2q8	HDq12	HDq16
Week 48 completers		N=309 (100%)	N=316 (100%)	N=312 (100%)	N=157 (100%)	N=300 (100%)	N=156 (100%)
Interval at Week 48	q8	309 (100%)	65 (20.6%)	40 (12.8%)	157 (100%)	27 (9.0%)	6 (3.8%)
	q12	NA	251 (79.4%)	33 (10.6%)	NA	273 (91.0%)	11 (7.1%)
	q16	NA	NA	239 (76.6%)	NA	NA	139 (89.1%)
Week 60 completers		N=305 (100%)	N=311 (100%)	N=309 (100%)	N=155 (100%)	N=289 (100%)	N=152 (100%)
Interval at Week 60	q8	305 (100%)	51 (16.4%)	33 (10.7%)	155 (100%)	23 (8.0%)	8 (5.3%)
	q12	NA	126 (40.5%)	42 (13.6%)	NA	138 (47.8%)	12 (7.9%)
	q16	NA	134 (43.1%)	116 (37.5%)	NA	128 (44.3%)	77 (50.7%)
	Q20	NA	NA	118 (38.2%)	NA	NA	55 (36.2%)

Manually calculated from swimmer plots shown in Figure 18 to Figure 25.

As noted above, the participant's dosing intervals in each treatment arm at Week 48 for PULSAR study indicated that:

In the HDq12 arm (N=316 Week 48 completers):

- 251 participants (79.4%) maintained their originally assigned q12 dosing interval
- 65 participants (20.6%) were shortened to q8. Of these:
    - 17 participants (5.4%) were shortened at Week 16 and
    - 25 participants (7.9%) were shortened at Week 20.
    - The remaining 23 participants (7.3%) were shortened at later timepoints through Week 48, i.e. at Week or 32 or Week 44

In the HDq16 arm (N=312 Week 48 completers):

- 239 participants (76.6%) maintained their originally assigned q16

- 33 participants (10.6%) were shortened to q12;
- 40 participants (12.8%) were shortened to q8. Of these:
    - 10 participants (3.2%) were shortened from q16 to q8 at Week 16.
    - 21 participants (6.7%) were shortened from q16 to q8 at Week 20.
    - The remaining 9 participants (2.9%) were shortened from q16 to q12 at Week 24, and further shortened to q8 in a subsequent step through Week 48.

In the HDq12 arm (N=311 Week 60 completers):

- 134 participants (43.1%) were extended to a q16 dosing interval until Week 60.
- 126 participants (40.5%) were on a q12 dosing interval at Week 60.
- 51 participants (16.4%) were on a q8 dosing interval at Week 60

In the HDq16 arm (N=309 Week 60 completers):

- 118 participants (38.2%) were extended to a q20 dosing interval until Week 60.
- 116 participants (37.5%) were on a q16 dosing interval at Week 60.
- 42 participants (13.6%) were on a q12 dosing interval at Week 60.
- 33 participants (10.7%) were on a q8 dosing interval at Week 60

PHOTON study

In the HDq12 arm (N=300 Week 48 completers):

- 273 participants (91.0%) maintained their originally assigned q12 dosing.
- 27 participants (9.0%) shortened from q12 to q8.
    - 3 participants (1.0%) were shortened at Week 16,
    - 12 participants (4.0%) were shortened at Week 20,
    - The remaining 12 participants (4.0%) were shortened at later timepoints through Week 48, i.e. at Week or 32 or Week 44.

In the HDq16 arm (N=156 Week 48 completers):

- 139 participants (89.1%) maintained their originally assigned q16 dosing interval
- 11 participants (7.1%) were shortened to q12;
- 6 participants (3.8%) were shortened to q8.
    - 1 participant (0.6%) were shortened from q16 to q8 at Week 16,
    - 3 participants (1.9%) were shortened from q16 to q8 at Week 20,
    - the remaining 2 participants (1.3%) were shortened from q16 to q12 at Week 24, and further shortened to q8 in a subsequent step through Week 48

In the HDq12 arm (N=289 Week 60 completers):

- 128 participants (44.3%) were extended to a q16 dosing interval until Week 60.

- 138 participants (47.8%) were on a q12 dosing interval at Week 60.
- 23 participants (8.0%) were on a q8 dosing interval at Week 60.

In the HDq16 arm (N=152 Week 60 completers, see Figure 25):
- 55 participants (36.2%) were extended to a q20 dosing interval until Week 60.
- 77 participants (50.7%) were on a q16 dosing interval at Week 60.
- 12 participants (7.9%) were on a q12 dosing interval at Week 60.
- 8 participants (5.3%) were on a q8 dosing interval at Week 60

The Applicant has adequately provided the requested patient's dosing interval of treatment in each arm at Week 48 and 60 (q8, q12, q16 and q20) in both PULSAR and PHOTON studies.

For PULSAR study, it appears that the majority of patients were rather maintained on their originally assigned interval or extended to a greater interval (eg, from q12 to q16 interval) both on W48 and W60 completers. However, even low, it should be noted that a certain proportion of patients were shortened their treatment interval (less than 20% in both HDq12 and HDq16 arm at W48 and W60). In the meantime, and as discussed above, a proportion of patients were extended from their original assignment (43.1% of HDq12 arm were extended to a q16 dosing interval and 38.2% of HDq16 arm were extended to a q20 dosing interval)

For PHOTON study, the proportion of patients who maintained their original interval was greater with around 90% of patients maintained their originally assigned q12 or q16 dosing at W48 and W60 and around 10% who shortened the originally assigned interval. In parallel, 43.3% and 36.2% of patients were extended to a q16 and q20 dosing interval for HDq12 and HDq16 arm respectively.

PHOTON Study - 21091, VGFTe-HD-DME-1934

Methods

Study design

This phase 2/3, multi-center, randomized, double-masked, study aim to investigate the efficacy, safety, of IVT administration of aflibercept 8 mg (HD) versus aflibercept 2 mg in participants with DME involving the center of the macula (Figure 1 and 2).

The study consists of a screening/baseline period, a treatment period with duration of 92 weeks, and an end of study visit at Week 96. An extension of the study is planned starting Week 96 for 60 weeks with an end of study visit at week 156.

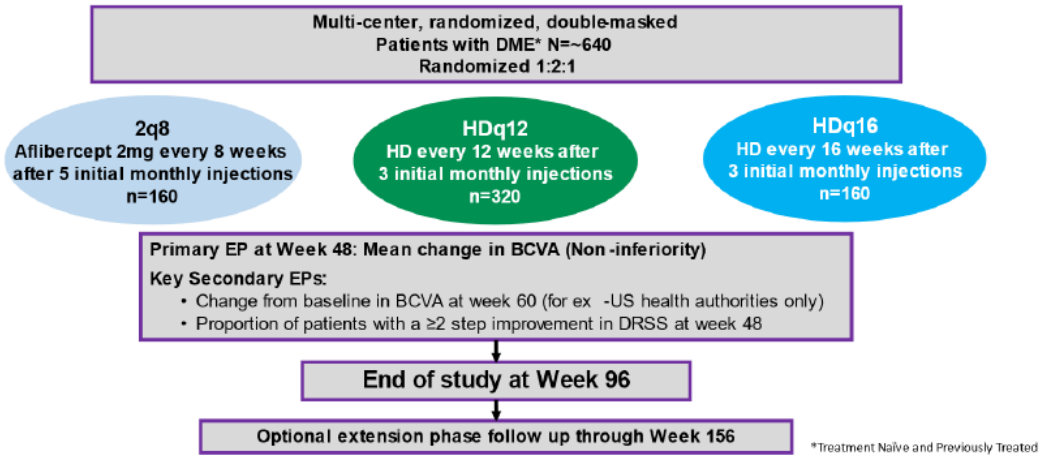
Subjects with nAMD were randomized to receive IVT injections in the study eye of HD or 2 mg in a 1:2:1 ratio to 3 parallel treatment groups:

• 2q8: aflibercept 2 mg administered every 8 weeks, after 5 initial injections doses at 4-week intervals.

• HDq12: aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. Participants in this group can move to q8 dosing regimen at Weeks 16 or 20, or up to q16 dosing regimen at week 52 according to pre-specified criteria.

• HDq16: aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. Participants in this group can move to q8 dosing regimen at Weeks 16 or 20, to q12 dosing regimen at Week 24, or up to q20 dosing regimen at week 52 according to pre-specified criteria.

Figure 1: Study Flow Diagram



Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HD=high dose aflibercept (8 mg aflibercept); HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; BCVA=Best corrected visual acuity; DME=diabetic macular edema; EP=Endpoint; DRSS=Diabetic Retinopathy Severity Scale.

Figure 2: Dosing Schedule

PHOTON: Dosing Schedule

	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24*	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48 (1° Endpoint)
2q8	X	X	X	X	X	o	X	o	X	o	X	o	X
HDq12	X	X	X	o	o^	X^	o	o	X[a]	o	o	X[a]	o
HDq16	X	X	X	o	o*	o*	X*	o	o	o	X[a]	o	o

X=active injection
o=sham injections

Dose Regimen Modifications in Year 1
^Q12 group: If criteria are met, patients will continue q8.
*HDq16 group: If criteria are met at week 16 or 20, patient will continue q8. If criteria are met at week 24, patient will continue q12.
[a]For patients on a dosing interval of q12 or q16 weeks, DRM criteria will be assessed at dosing visits and if DRM criteria are met the next dosing interval will be reduced by 4 weeks.

	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96
2q8	o	X	o	X	o	X	o	X	o	X	o	
HDq12	o	X[a]	o	o	X[a]	o	o	X[a]	o	o	X[a]	
HDq16	o	X[a]	o	o	o	X[a]	o	o	o	X[a]	o	

Dose Regimen Modifications in Year 2
[a]Patients that continue on a dosing interval >8 weeks will be assessed at their dosing visits for DRM criteria for both shortening and extension of the interval by 4 week increments

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HD=high dose; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4 week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; DRM=Dose regimen modification.

Note: Figure does not reflect all dosing options once a patient is shortened or extended

Study participants

The study population consisted of naïve male and female of ≥ 18 years patients with DME.

Key inclusion criteria

1. Type 1 or type 2 diabetes mellitus

2. DME with central involvement in the study eye (CRT ≥ 300 µm)

3. BCVA ETDRS letter score 78 to 24

Key exclusion criteria

1. Evidence of macular edema due to any cause other than diabetes mellitus in either eye

2. Active proliferative diabetic retinopathy in the study eye

3. IOP ≥ 25 mmHg in the study eye

4. IVT anti-VEGF treatment in the study eye within 12 weeks of screening

5. Uncontrolled BP (systolic > 160 mm Hg or diastolic > 95 mm Hg)

6. Uncontrolled diabetes mellitus (HbA1c > 12%)

The proposed study treatment compared to the current treatment in patients with DME was supported by the CHMP scientific advice. The chosen study population and related exams all along the study are similar the one from the randomised phase III VIVID and VISTA, which was the basis for the approval of aflibercept in DME patients which is deemed acceptable.

Treatments

In PHOTON study, patients were randomized in a 1:2:1 ratio to receive monotherapy with either 2 mg aflibercept (administered every 8 weeks, after 5 initial injections at 4-week intervals) or aflibercept 8 mg administered every 12 or 16 weeks, after 5 initial injections at 4-week intervals. Participants in these groups can move to q8 dosing regimen at Weeks 16 or 20, q12 dosing regimen at Week 24, or up to or up to q16 (HDq12 group), q20 (HDq16 group) dosing regimen at week 52, if both criteria were met:

° >10 letter loss in BCVA from week 12 in association with persistent or worsening DME

° >50 µm increase in CRT from week 12 (It should be noted that the change in CRT for these criteria will be assessed at the site.)

Each vial was for single eye use only. No dosing modification for an individual patient is allowed.

Permitted concomitant treatments:

Participants may not receive any standard or investigational agents for treatment of their DME in the study eye other than IVT aflibercept as specified in this protocol until they have completed the end of study/early termination visit assessments. This includes medications administered locally (e.g., IVT, by juxtascleral or periorbital routes), as well as those administered systemically with the intent of treating the fellow eye.

Patients may receive any medication considered necessary for the participant's welfare, and that is not expected to interfere with the evaluation of the study intervention, may be given at the discretion of the investigator.

Any medication or vaccine (including any sedation, anesthesia, eye drops used for the study procedures, blood-derived products, prescription or over-the-counter medicines, probiotics, vitamins, and herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded.

If the fellow eye has DME, or any other approved indication, 2 mg aflibercept will be allowed. Once the fellow eye receives only aflibercept 2 mg therapy during the study.

If a pre-treatment concomitant medication is administered in the study eye before injection (e.g., antibiotic, topical anesthetic), it must be administered for sham procedures as well.

Dose delays or modifications: Assessments for dose regimen modification is to be performed in all participants at all visits starting from Week 16. Based on these assessments, participants in the HD groups may have their treatment intervals shortened or extended. The minimum interval between injections will be 8 weeks, which is considered a rescue regimen for participants randomized to HD aflibercept who are unable to tolerate a dosing interval greater than every 8 weeks. Participants in the aflibercept 2 mg group will remain on fixed q8 dosing throughout the study until the end of masked study visit at Week 96 (i.e., will not have modifications of their treatment intervals regardless of the outcomes of the dose regimen modification assessments).

Treatment was to be discontinued if any of the following reasons applied (but were not limited to):

• Relevant laboratory abnormality or SAEs, if the sponsor or investigator sees this as medical reason to warrant withdrawal.

• AE (ocular or nonocular) that, from the participant's or the investigator's view, is potent enough to require withdrawal from the study. The investigator must notify the sponsor immediately if a participant is withdrawn because of an AE/SAE.

• At the discretion of the treating investigator. The development of conditions, which would have prevented a participant's entry into the study according to the selection criteria, is no reason per se for withdrawal. However, the withdrawal in such cases remains at the discretion of the treating investigator.

• Decision by the investigator or sponsor that termination is in the participant's best medical interest or administrative decision for a reason other than an AE/SAE.

• A female participant becomes pregnant.

• Lost to follow-up.

• Decision by the sponsor to halt the entire study.

• If any treatment for DME other than study interventions is given in the study eye.

• Systemic anti-angiogenic agents were taken by the participant during the study.

• If, in the investigator's opinion, continuation of the study would be harmful to the participant's well-being.

• At the specific request of the sponsor and in liaison with the investigator (e.g., obvious non-compliance or safety concerns).

Patients who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments.

Objectives

Primary objective

To determine if treatment with HD aflibercept at intervals of 12 or 16 weeks provides non-inferior BCVA compared to 2 mg aflibercept dosed every 8 weeks.

Secondary objectives

· To determine the effect of HD versus 2 mg aflibercept on other visual and anatomic measures of response

· To evaluate the safety, immunogenicity, and pharmacokinetics (PK) of aflibercept (HD and 2 mg)

Outcomes/endpoints

Primary efficacy endpoint

· Change from baseline in best corrected visual acuity (BCVA) (as measured by ETDRS letter score) at Week 48

Key secondary efficacy endpoints

· Proportion of patients with a ≥ 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) at week 48

· Change from baseline in BCVA (as measured by ETDRS letter score) at Week 60 (EP-SAP only)

Additional secondary endpoints

· Proportion of participants gaining ≥ 15 letters in BCVA from baseline at Week 48

· Proportion of participants with BCVA ≥ 69 letters at Week 48

· Proportion of participants without fluid at foveal center at Week 48

· Change from baseline in CRT at Week 48

· Proportion of participants without leakage on fluorescein angiography (FA) at Week 48

· Change from baseline in NEI-VFQ-25 total score at Week 48

Exploratory endpoints

· Proportion of participants without retinal fluid (total fluid in center subfield at Week 48 (FC is already secondary)

· Proportion of participants with a ≥ 3-step improvement in DRSS at Week 48

· Change from baseline in BCVA averaged over the period from Week 36 to Week 48

· Proportions of participants gaining and losing ≥ 5 or ≥ 10 letters at Week 48

· Proportion of participants losing ≥ 15 letters at Week 48

· Proportion of participants randomized to HDq16 maintaining q16 dosing interval or longer through Weeks 48

· Proportion of participants randomized to HDq12 maintaining q12 dosing interval through Weeks 48

As discussed for the PULSAR study in patient with nAMD, the primary objective and endpoint of PHOTON study were also discussed during the SA (EMA/CHMP/SAWP/277944/2019) and concerns was raised regarding the choice of an endpoint at 48 week in view of the increased intervals and the need for at least 64 week data, preferably supplemented with some 2-year data is foreseen to support the Q12 and/or Q16 dosing regimens as well as long-term safety.

Sample size

The sample size of 640 subjects (2x160+320) was adequately estimated with and included 19% possible dropout. The HDq12 dose regiment had twice the size of the two other doses due to regulatory requirements. It was based on the non-inferiority of the 8 mg dose-regimens aiming to consent a loss of efficacy over the 2 mg control regimen at 48 weeks not exceeding 4 characters of the EDTRS chart (i.e. one line of the chart), with 0.025 type-one error and with more than 90% power to achieve non-inferiority for both dose.

Randomization

The randomization was performed with an interactive web system. The 3 active arms (2q8, 8q12 and 8q16) were distributed in the trial according to the ratio 1:2:1, showing at the randomisation level, the preference of the sponsor to the high dose regimen every 12 weeks enrolling twice as more subjects as in the 2 other dose regimens. Patients were stratified on the geographical region (Japan vs Rest of the World) and the CRT baseline (<400µm vs ≥400 µm) and prior DME treatment (yes/no).

The EU population constituted the largest cohort of subjects included in the trial (39%), followed mainly by cohorts from North America (30%) and Asia (23%), representing a total of 92% of the study population.

Homogeneous treatment responses in these 3 major subgroups should be expected.

Blinding (masking)

Overall, relatively the same measures are followed as in the PULSAR Study.

Sham injections were aimed to mask the difference between dose regimen schedules in patients. In addition, the unmasked investigator administering the study drug did not participate in any efficacy or safety endpoint evaluations apart from the reporting of AEs and device-related AEs/SAEs/deficiencies relating to filter needle, injection needle, or syringe during injection procedure and post-injection assessment. Therefore, no impact on study integrity is expected.

An overview of the masked and unmasked site personnel is presented in Table 1.

Table 1: Responsibilities of the Masked and Unmasked Personnel

Masked or Unmasked Personnel
• Performs all screening procedures up until randomization • Assesses inclusion/exclusion criteria • Obtains medical/ophthalmic history • Obtains informed consent • Collects samples for laboratory testing and antibody sampling • Performs electrocardiograms (ECGs) and transfers to reading center
Masked Personnel
• Assesses AEs, including severity and relationship • Assesses efficacy • Performs ophthalmic examinations, including IOP, at all study visits (except post-dose examinations immediately after treatment) • Evaluates all safety, including vital signs and review of images for safety concerns (except those immediately after IVT injection) • May perform fellow eye injections at any unscheduled visits where only the fellow eye is treated • Tests refraction and BCVA (no exceptions will be granted) • Performs and assesses OCT, fundus photography (FP), and FA images and transfers them to reading centers
Unmasked Personnel
• Coordinates randomization • Performs receipt and accountability of study drug • Performs study drug (HD or 2 mg aflibercept) or sham injections in study eye • Performs fellow eye injection (if treatment is administered bilaterally/in conjunction with study eye treatment) • Observes safety through the end of the observation period (approximately 30 minutes following study treatment) • Checks IOP post-dose (study eye) before the end of the approximately 30-minute observation period • Checks indirect ophthalmoscopy post-dose (study eye)

Unmasking of treatment assignment for a patient could have been necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug had to be discontinued for patients whose treatment has been unmasked.

Additionally, no emergency unblinding was required during the study.

Statistical methods

• Populations for statistical analyses

The full analysis set (FAS) was planned to include all randomized patients who received at least 1 dose of study medication; it was based on the treatment assigned to the patient at baseline (as randomized). FAS was the primary analysis set for efficacy endpoints.

The per protocol set (PPS) was planned to include all patients in the FAS who had a baseline and at least 1 post-baseline assessment of BCVA, and did not have any relevant important protocol violations that affect the primary efficacy variable. The final determination on the exclusion of patients from the PPS was to be made on the masked data prior to the first database lock and described in a separate document. The PPS was used for

supplementary analysis of change from baseline in BCVA (non-inferiority only) at week 48 (primary endpoint) and week 60 (key secondary endpoint).
Treatment assignment was based on the treatment received (as treated). In general, the randomized treatment group was to be considered as the actual treatment group, unless the patient has not been treated at all after randomization. Isolated incorrect treatments did not constitute a change in the "as treated" assignment but were considered as intercurrent events.

The safety analysis set (SAF) was including all randomized patients who received any study treatment; it was based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables were analyzed using the SAF. The safety analysis was performed on the observed safety data.

The efficacy populations of analysis are acceptable, except for PPS which was planned to be analysed "as treated" while an error of treatment allocation should be considered as a major deviation to the protocol. However, it was not an issue in this trial where only one wrong treatment allocation was reported.

- Definition of estimands

The estimand was specified through the following definitions of population, variable, treatment condition, intercurrent events, and population-level summary:

- Population: Defined by the inclusion/exclusion criteria. All efficacy analyses were conducted using the FAS.
- Variable: Change from baseline to week 48 in BCVA
- Treatment condition: Intention to treat with HD aflibercept administered every 12 weeks (HDq12) after 3 initial monthly injections or every 16 weeks (HDq16) after 3 initial monthly injections each versus aflibercept 2 mg administered every 8 weeks (2q8) after 5 initial monthly injections; dose regimen modifications did not affect patient's assigned ITT regimen.
- Intercurrent events: Premature discontinuation from treatment; missed injections; use of prohibited medication; wrong study intervention administered, as displayed in Table 1.
- Population-level summary: Difference in least-square (LS) mean change from baseline to week 48 in BCVA between HDq12 and 2q8 (and HDq16 and 2q8) resulting from a mixed-model for repeated measurements (MMRM).

The estimand proposal is similar to the Pulsar trial and is acceptable with the same interrogation on the hypothetical strategy which looks like the while on treatment strategy.

Table 1: Strategies for occurrence of intercurrent events (ICE)

Potential post-randomization event	Intercurrent event (yes/no)	Estimand strategy	Analysis strategy
Premature discontinuation of study intervention before Week 48			
- Discontinuation of study at the same time	Yes	Hypothetical	Non-observed data beyond discontinuation will be covered implicitly in the MMRM
- Continuation of study beyond discontinuation of study intervention^	Yes	Hypothetical	Observed data beyond last active injection prior to discontinuation + current treatment interval + 5 days will be excluded from analysis. Missing and excluded data will be covered by the MMRM.
Missed injection for any reason before Week 48			
- Planned to be sham	Yes, but no impact	N/A	All observed data will be included in the analysis
- Planned to be active, make-up given at next visit	Yes	Treatment policy	All observed data will be included in the analysis
- Planned to be active, make-up or scheduled active injection not given at next visit	Yes	Hypothetical	Observed data beyond last active injection prior to the missed dose + current treatment interval + 5 days will be excluded from analysis. Missing and excluded data will be covered by the MMRM.
Shortening of dosing interval according to DRM criteria before Week 48	No, DRM is considered part of the treatment regimen	N/A	
Use of a prohibited medication after the first dose of study medication (	Yes	Hypothetical	Observed data beyond first administration of prohibited medicine will be excluded from analysis. Missing and excluded data will be covered by the MMRM.
Wrong study intervention before Week 48			
- Active injection given instead of sham	Yes	Treatment policy	All observed data will be included in the analysis
- Sham injection instead of active	Yes	Hypothetical	Observed data beyond last active injection prior to the wrong dose + current treatment interval + 5 days will be excluded from analysis. Missing and excluded data will be covered by the MMRM.
- Wrong dose level given (eg, 2mg given instead of 8mg)	Yes	Treatment policy	All observed data will be included in the analysis

^ This ICE will be handled in the same way as "Missed injection: Planned to be active, make-up or scheduled active injection not given at next visit, since the info of discontinuation from study intervention was not collected in the database.

The following 2 hypotheses were tested in the primary analysis:

- HDq12 was non-inferior to 2q8 regarding the mean change in BCVA from baseline to week 48 using a non-inferiority margin of 4 letters:

H_{10}: $\mu_1 \leq \mu_0 - 4$ vs. H_{11}: $\mu_1 > \mu_0 - 4$, where μ_0, μ_1, were the mean change from baseline in BCVA at week 48 for 2q8 and HDq12, respectively.

- HDq16 was non-inferior to 2q8 regarding the mean change in BCVA from baseline to week 48 using a non-inferiority margin of 4 letters:

H_{30}: $\mu_2 \leq \mu_0 - 4$ vs. H_{31}: $\mu_2 > \mu_0 - 4$, where μ_0, μ_2 were the mean change from baseline in BCVA at week 48 for 2q8, and HDq16, respectively.

For the analysis of the primary efficacy variable, a mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate and treatment group (HDq16 vs. 2q8 and HDq12 vs. 2q8) and baseline CRT category (<400 µm, ≥400 µm), prior DME treatment (yes, no), geographical region (Rest of world, Japan), and visit as fixed effects as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. Further, an unstructured covariance structure was used. If the model did not converge, an appropriate covariance structure would be used instead. Only data up to Week 48 were used in this analysis.

$$Y_{ijk} = \beta_0 + \beta_{baseBCVA}\, x_i + \beta_{treat}^{(k)} + \beta_{base\_CRT}^{(n)} + \beta_{pDME}^{(l)} + \beta_{reg}^{(m)} + \beta_{visit}^{(j)} + \beta_{treat*visit}^{(k,j)} + \beta_{base*visit}^{(j)}\, x_i + \epsilon_{ijk},$$

where:

Y_{ijk} is the change from baseline BCVA for i^{th}patient at j^{th}visit for k^{th} treatment group,

β_0 is an intercept term,

$\beta_{baseBCVA}$ is the regression coefficient of the covariate,

x_i for the baseline BCVA of i^{th} patient,

$\beta_{treat}^{(k)}$ is the fixed effect of treatment group k

$\beta_{base\_CRT}^{(n)}$ is the fixed effect of categorized baseline CRT n,

$\beta_{pDME}^{(l)}$ is the fixed effect of prior DME treatment l,

$\beta_{reg}^{(m)}$ is the fixed effect of region m,

$\beta_{visit}^{(j)}$ is the fixed effect of visit j,

$\beta_{base*visit}^{(j)}$ the interaction between baseline BCVA and visit j,

$\beta_{treat*visit}^{(k,j)}$ the interaction between treatment k and visit j,

ϵ_{ijk} is the residual error with $\epsilon_{ijk} \sim N(0, \sigma^2)$ and $corr(\epsilon_{ijk}, \epsilon_{ij'k,}) = \rho^{(k)}\_\{i, j'\}$, or 0 otherwise.

In terms of the estimators the population-level summary of the estimands (ie, the treatment effect at week 48) can then be expressed as

$$D_{HDQ12} = \left[\beta_{treat}^{(HDQ12)} + \beta_{treat*visit}^{(HDQ12,w48)}\right] - \left[\beta_{treat}^{(2Q8)} + \beta_{treat*visit}^{(2Q8,w48)}\right]$$

and

$$D_{HDQ16} = \left[\beta_{treat}^{(HDQ16)} + \beta_{treat*visit}^{(HDQ16,w48)}\right] - \left[\beta_{treat}^{(2Q8)} + \beta_{treat*visit}^{(2Q8,w48)}\right].$$

The hierarchical procedure proposed to control for multiplicity hypothesis testing is endorsed. As in Pulsar, the hierarchy targets preferably the 8 mg every 12 weeks dose regimen (HDq12). If this regimen passed the non-inferiority tests in BCVA at 48 and 60 weeks treatment, the HDq16 week regimen will be then tested in BCVA non-inferiority. The HDq12 dose regimen will be then tested for non-inferiority in DRSS score ≥ 2-step. If these steps are positively past, the high doses will be tested for superiority.

- Control of Multiplicity

The overall family-wise type 1 error was controlled at 0.025 (one-sided tests) for testing the primary and key secondary endpoints. Adjustment for multiple comparisons in the primary and key secondary endpoints were made with a hierarchical testing procedure. This approach allowed the confirmatory testing of a hypothesis at the full alpha level of 0.025 after successful rejection of the hypotheses which were ranked higher in the hierarchy. The hypotheses were tested in the order as specified in Table 2 for G-SAP and EP-SAP, respectively.

Table 2: The Testing Order of Hierarchical Testing Procedure[a] in G-SAP and EP-SAP

G-SAP	EP-SAP
H_{10} : Q12 BCVA Week 48 non-inferiority	H_{10} : Q12 BCVA Week 48 non-inferiority
	H_{20} : Q12 BCVA Week 60 non-inferiority
H_{30} : Q16 BCVA Week 48 non-inferiority	H_{30} : Q16 BCVA Week 48 non-inferiority
	H_{40} : Q16 BCVA Week 60 non-inferiority
H_{50} : Q12 DRSS Week 48 non-inferiority	H_{50} : Q12 DRSS Week 48 non-inferiority
H_{60} : Q16 DRSS Week 48 non-inferiority	H_{60} : Q16 DRSS Week 48 non-inferiority
H_{70} : Q12 BCVA Week 48 superiority	H_{70} : Q12 BCVA Week 48 superiority
	H_{80} : Q12 BCVA Week 60 superiority
H_{90} : Q16 BCVA Week 48 superiority	H_{90} : Q16 BCVA Week 48 superiority
	H_{100} : Q16 BCVA Week 60 superiority

[a] for comparisons with 2q8 study treatment group

• Subgroup analyses

Analyses were performed in the following subgroups:

• Sex: male, female
• Age at enrollment: <55 years, ≥55 years to <65 years, ≥65 years to < 75 years, ≥75 years
• Race (only subgroups with sufficient sample size): White, Black or African American, Asian
• Ethnicity: Not Hispanic or Latino, Hispanic or Latino
• Baseline BCVA (≤73 letters, >73 letters)
• Geographic region: Japan, Rest of the world
• Baseline CRT category (<400 µm, ≥400 µm)
• Prior DME treatment (yes, no)

Subgroup analyses were performed using the same model as the one mentioned for the primary analysis, except for those subgroups that were also stratification factors (geographic region, baseline CRT category, and prior DME treatment), where these terms were individually removed from the model (leaving the other 2 factors in).

Regarding the subgroup analyses, the geographical region segmentation (Japan vs RoW), should be considered for sensitivity analyses. As for Pulsar trial, the primary analysis was reiterated using the region fixed effect, stratified as follows: Japan, Europe including Czech Rep, Germany, Hungary and UK, North America including Canada and USA . In addition, the primary endpoint was documented in the European and North America regions as mentioned above .

As for Pulsar trial, a new geographical region analysis was requested. The main cohort in this trial comes from North America with 462 patients (70%), followed by Europe (19%) and Japan (11%). Results across the new segmentation of regions seem more consistent in the Photon trial with a non-inferiority confirmed in the North America subgroup. The smaller size of EU and Japan subgroups make their results a bit less reliable.

• Sensitivity analyses

Sensitivity analyses included an analysis of covariance with missing data imputed by last observation carried forward (LOCF), a multiple imputation (MI) analysis, and a tipping point analysis; and supplementary analyses included an MMRM model for the primary endpoint using the PPS.

The hierarchical procedure proposed to control for multiplicity hypothesis testing is endorsed. As in PULSAR, the hierarchy targets preferably the 8 mg every 12 weeks dose regimen (HDq12). If this regimen passed the non-inferiority tests in BCVA at 48 and 60 weeks treatment, the HDq16 week regimen will be then tested in BCVA non-inferiority. The HDq12 dose regimen will be then tested for non-inferiority in DRSS score ≥ 2-step. If these steps are positively past, the high doses will be tested for superiority.

Results

Participant flow

There were 660 enrolled participants (970 patients screened with 310 screening failure) at 138 sites in 7 countries (Canada, Czech Republic, Germany, Hungary, Japan, United Kingdom, and the United States). Most participants in each of the 3 groups (2q8: 94.0%, HDq12: 91.2%, and HDq16: 95.1%) completed their Week 48 analysis visit. The disposition of participants through Week 60 and further through Week 60 is presented in Table-4. **Of note, as requested the Applicant provides a participant flow figure for the PHOTON study.**

Table 4: Summary of Participant Disposition Through Week 60 (All Randomized Participants)

	2q8 (N=167)	HDq12 (N=329)	HDq16 (N=164)	All HD (N=493)	Total (N=660)
Week 48					
Number of patients who completed Week 48	157 (94.0%)	300 (91.2%)	156 (95.1%)	456 (92.5%)	613 (92.9%)
Number of patients who discontinued prior to Week 48	10 (6.0%)	29 (8.8%)	8 (4.9%)	37 (7.5%)	47 (7.1%)
Reasons for discontinuation prior to Week 48					
Noncompliance with protocol by the subject	1 (0.6%)	0	0	0	1 (0.2%)
Adverse event	0	4 (1.2%)	1 (0.6%)	5 (1.0%)	5 (0.8%)
Decision by the investigator/sponsor	0	4 (1.2%)	1 (0.6%)	5 (1.0%)	5 (0.8%)
Withdrawal of consent by subject	4 (2.4%)	7 (2.1%)	2 (1.2%)	9 (1.8%)	13 (2.0%)
Lost to follow-up	1 (0.6%)	5 (1.5%)	1 (0.6%)	6 (1.2%)	7 (1.1%)
Death	4 (2.4%)	9 (2.7%)	3 (1.8%)	12 (2.4%)	16 (2.4%)
Due to COVID-19	0	0	0	0	0
Week 60					
Number of patients who completed Week 60	155 (92.8%)	289 (87.8%)	152 (92.7%)	441 (89.5%)	596 (90.3%)
Number of patients who discontinued prior to Week 60	12 (7.2%)	40 (12.2%)	12 (7.3%)	52 (10.5%)	64 (9.7%)
Reasons for discontinuation prior to Week 60					
Noncompliance with protocol by the subject	1 (0.6%)	1 (0.3%)	0	1 (0.2%)	2 (0.3%)
Adverse event	0	4 (1.2%)	2 (1.2%)	6 (1.2%)	6 (0.9%)
Decision by the investigator/sponsor	0	6 (1.8%)	2 (1.2%)	8 (1.6%)	8 (1.2%)
Withdrawal of consent by subject	4 (2.4%)	12 (3.6%)	2 (1.2%)	14 (2.8%)	18 (2.7%)
Lost to follow-up	2 (1.2%)	8 (2.4%)	2 (1.2%)	10 (2.0%)	12 (1.8%)
Death	5 (3.0%)	9 (2.7%)	4 (2.4%)	13 (2.6%)	18 (2.7%)
Due to COVID-19	0	0	0	0	0

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12=High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16=High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; All HD=Pooled HDq12 and HDq16 groups; COVID-19=Coronavirus Disease 2019.
The percentage was based on the number of patients in each treatment group as denominator.
Definition of completed Week 48 = did not answer NO to the question "Did the subject complete the study?" on the "Study Completion" form prior to Week 48 visit.
Definition of completed Week 60 = did not answer NO to the question "Did the subject complete the study?" on the "Study Completion" form prior to Week 60 visit.

Recruitment

Date first subject randomized: **29 Jun 2020**

Date last subject completed Week 60 / End of Study Visit: **07 Oct 2022.**

The study was conducted at a total of 7 countries (Canada, Czech Republic, Germany, Hungary, Japan, United Kingdom, and the United States).

Conduct of the study

Protocol deviations

Overall, 36 (35.1%) participants reported important protocol deviations (Table 5). The most frequent (≥ 5%) important protocol deviations were related to the initiation of study procedures without re-consenting participants to the amended Informed consent (17 participants) and followed by initiation of study procedures without consenting/prior to consenting of participants to the ICF (9 participants overall). Globally, the frequency of participants with important protocol deviations through Week 60 is considered similar across the treatment groups.

Other protocol deviation were related to the COVID-19 pandemic (in 17 patients without any exclusion in the Week 60 database).

Table 5: Summary of Important Protocol Deviations Through Week 48 (All Randomized Participants)

	2q8 (N=167)	HDq12 (N=329)	HDq16 (N=164)	All HD (N=493)	Total (N=660)
Number of Important Protocol Deviations	7	18	11	29	36
Patients with Any Important Protocol Deviation	7 (4.2%)	18 (5.5%)	11 (6.7%)	29 (5.9%)	36 (5.5%)
Type of Important Protocol Deviation					
Subject did not re-consent to amended ICF and study procedures initiated (never signed amended ICF or signed after procedure)	4 (2.4%)	6 (1.8%)	7 (4.3%)	13 (2.6%)	17 (2.6%)
Ex #07 met but subject randomized. [a]	3 (1.8%)	2 (0.6%)	0	2 (0.4%)	5 (0.8%)
Ex #08 met but subject randomized. [b]	0	1 (0.3%)	0	1 (0.2%)	1 (0.2%)
Inc #03 not met but subject randomized. [c]	0	3 (0.9%)	1 (0.6%)	4 (0.8%)	4 (0.6%)
Subject did not sign ICF and study procedures were initiated (never signed ICF or signed after procedure performed)	0	6 (1.8%)	3 (1.8%)	9 (1.8%)	9 (1.4%)

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12=8 mg aflibercept administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16=8 mg aflibercept administered every 16 weeks after 3 initial injections at 4-week intervals; All HD=Pooled HDq12 and HDq16 groups; BCVA =best corrected visual acuity; DME= diabetic macular edema; ETDRS= Early Treatment Diabetic Retinopathy Study; Ex= exclusion criterion; ICF= informed consent form; Inc= inclusion criterion; IVT= intravitreal.

The percentage for each analysis set was based on the number of randomized patients in each treatment group as denominator.

[a] Exclusion criterion #7: Prior use of intraocular or periocular corticosteroids in study eye within 16 weeks/112 days of screening or ILUVIEN® or OZURDEX® IVT implants at any time

[b] Exclusion criterion #8: History of vitreoretinal surgery (including scleral buckle) in the study eye

[c] Inclusion criterion #3: Subject didn't satisfy BCVA ETDRS score of 78-24 (Snellen equivalent of 20/32 - 20/320) in study eye with decreased vision determined to be result of DME.

Minor deviations

• 1 participant in HDq16 met exclusion criterion #01 Evidence of macular edema due to any cause other than diabetes mellitus in the fellow eye

• 5 participants met exclusion criterion #28 Uncontrolled diabetes mellitus as defined by HbA1c > 12% (3 in 2q8, 1 in HDq12, 1 in HDq16)

– All 5 participants had values undetermined at baseline.

• 52 participants met exclusion criterion #29 Uncontrolled BP (systolic > 160 mmHg or diastolic > 95 mmHg); treated with up to 3 agents known to have anti-hypertensive effects for arterial hypertension to achieve adequate blood pressure control; changes in BP medications must be stable for 12 weeks (84 days prior to screening)

– 52 participants were randomized despite having systolic blood pressure (SBP) or diastolic blood pressure (DBP) above of the protocol-specified range (11 in 2q8, 24 in HDq12, 17 in HDq16)

– 25 participants were randomized despite being treated with > 3 BP medications (7 in 2q8, 10 in HDq12, 7 in HDq16)

– 1 participant in 2q8 group was randomized despite having BP medication regimen changed within 12 weeks of screening

The following protocol deviations were not captured correctly in the PD listing:

• 1 participant met exclusion criteria #4: IVT anti-VEGF treatment (aflibercept, ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium) in the study eye within 12 weeks (84 days) of the screening visit, but this deviation was not captured in the PD listing

• 1 participant met exclusion criteria #1 for the dense PK substudy: Prior treatment with IVT aflibercept in the fellow eye within 12 weeks (84 days) of the screening visit, but this deviation was not captured in the PD listing

• 6 participants had data entered in IWRS that did not match the data entered in EDC for prior DME treatment, but these deviations were not captured in the PD listing

• 9 participants had a deviation reported incorrectly for "incorrect data entered into IWRS at randomization visit (eg, CRT, BCVA, or prior DME treatment)" for prior DME treatment; IWRS and EDC data are consistent

Amendment to the protocol

Amendment 1 (06 Dec 2019)

The purpose of this amendment was to address feedback received from European Union (EU) regulatory agencies as part of the Voluntary Harmonisation Procedure (VHP). The requested revisions include: addition of information on criteria for study and study drug discontinuation, specification that collection of adverse events (AEs) and serious adverse events (SAEs) will begin at the time of informed consent, clarification on assessment of laboratory values as AEs, clarification of some of the statistical considerations, and other minor revisions as requested.

Amendment 2 (14 Feb 2020)

The primary purpose of this amendment was to update details of the study design, combining rescue treatment with Dose Regimen Modification (DRM) assessments in both year 1 and year 2. Patients in the HDq12 and

HDq16 groups will now be eligible for a rescue regimen (8 mg aflibercept every 8 weeks) beginning at week 16.

Amendment 3 (07 May 2020)

The primary purposes for this amendment were to clarify the machine-specific values for CRT (measured on spectral domain optical coherence tomography [SD-OCT]) defined in the inclusion criteria for the reading center's determination of eligibility, and to describe the continuity plan for conducting clinical study activities and study oversight activities during the public health emergency due to Coronavirus Disease 2019 (COVID-19).

Amendment 4 (28 Apr 2022)

The primary purpose for this amendment was to simplify and extend the confirmatory testing hierarchy:

To remove the initial Bonferroni-based split of the overall significance level (which had been introduced originally to allow simultaneous testing of the 2 hypotheses (8 mg aflibercept every 12 weeks [HDq12] vs 2 mg aflibercept every 8 weeks [2q8] and 8 mg aflibercept every 16 weeks [HDq16] vs 2q8) of the primary endpoint at a significance level of 0.0125 [1-sided] each) and to assign the full significance level of 0.025 (1-sided) to the first hypothesis (HDq12 vs 2q8). The reason for this change is to adjust the testing sequence to the perceived clinical probability of success, ie, since HDq12 is more likely to succeed than HDq16 (due to the higher dosing frequency after the loading phase).

1. To remove the subsequent splitting of the remaining alpha levels between 2 hypotheses, and replace it by a simpler hierarchical testing procedure in both the global statistical analysis plan (G-SAP) and the statistical analysis plan for EMA and PMDA (EP-SAP).

This change allows sequential testing of hypotheses at the full significance level after successful rejection of the hypotheses which are ranked higher in the hierarchy. The reason for this change is to prioritize testing of hypotheses which are deemed to be clinically more relevant.

2. To allow formal statistical testing for superiority of the change from baseline in best corrected visual acuity (BCVA) at week 48 (and week 60, in the EP-SAP only) that controls the overall family-wise type 1 error. The formal statistical testing for superiority is added at the end of the revised testing hierarchy. Hence the testing hierarchy is extended.

3. To remove the endpoint of "Proportion of patients without retinal fluid at the foveal center at week 12" as a key secondary endpoint in the testing hierarchy (it remains as a secondary endpoint assessed at week 48). Based on recent data from another, completed study, it was determined that week 12 is not a reasonable time point to assess this endpoint. Analysis of this endpoint will be more informative at week 48 after a year of treatment.

Of note, the updated confirmatory testing hierarchy still controls the overall family-wise type 1 error at 0.025 level (1-sided). These changes will be implemented after the end of enrolment but before database lock and before any unmasking occurs.

Amendment 5 (14 Sept 2022)

The primary purpose for this amendment was to add an optional 1 year extension phase to the current study at select countries and sites. During the extension phase, all patients will be treated with HD aflibercept including those originally assigned to the aflibercept 2 mg every 8 week (2q8) group.

The treatment intervals for all groups will be adjusted according to individual responses as determined by extension phase dose regimen modification (E-DRM) criteria.

Baseline data

Baseline data are presented in Table 7.

The following differences were noted by the MAH between the 2q8 group and the pooled HD groups (these characteristics were similar between the HDq12 and HDq16 groups):

• Although most participants in all treatment groups were between the ages of 55 and 75, slightly more participants younger than age 55 were in the pooled HD groups compared to the 2q8 group (23.4% vs 17.4%, respectively).

• More participants in all treatment groups were male; however, more males were in the pooled HD groups compared to the 2q8 group (62.9% vs 55.1%, respectively).

• A history of cerebrovascular disease was less prevalent in the pooled HD groups compared to the 2q8 group (6.3% vs 11.4%, respectively). However, across all treatment groups, most participants did not have a history of cerebrovascular disease.

Table 7: Demographics and Baseline Characteristics (Full Analysis Set)

	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)	Total (N=658)
Age (years)					
n	167	328	163	491	658
Mean (SD)	63.0 (9.78)	62.1 (11.13)	61.9 (9.50)	62.0 (10.61)	62.3 (10.41)
Median	64.0	63.0	62.0	63.0	63.0
Q1 : Q3	56.0 : 70.0	55.0 : 70.0	55.0 : 68.0	55.0 : 70.0	56.0 : 70.0
Min : Max	38 : 90	24 : 87	37 : 83	24 : 87	24 : 90
Age category, n (%)					
<55 years	29 (17.4%)	77 (23.5%)	38 (23.3%)	115 (23.4%)	144 (21.9%)
≥55 - <65 years	63 (37.7%)	108 (32.9%)	54 (33.1%)	162 (33.0%)	225 (34.2%)
≥65 - <75 years	54 (32.3%)	107 (32.6%)	57 (35.0%)	164 (33.4%)	218 (33.1%)
≥75 years	21 (12.6%)	36 (11.0%)	14 (8.6%)	50 (10.2%)	71 (10.8%)
Ethnicity, n (%)					
Hispanic or Latino	31 (18.6%)	54 (16.5%)	34 (20.9%)	88 (17.9%)	119 (18.1%)
Not Hispanic or Latino	133 (79.6%)	266 (81.1%)	126 (77.3%)	392 (79.8%)	525 (79.8%)
Not Reported	3 (1.8%)	8 (2.4%)	3 (1.8%)	11 (2.2%)	14 (2.1%)
Race, n (%)					
American Indian or Alaska Native	0	2 (0.6%)	0	2 (0.4%)	2 (0.3%)
Asian	30 (18.0%)	48 (14.6%)	23 (14.1%)	71 (14.5%)	101 (15.3%)
Black or African American	18 (10.8%)	35 (10.7%)	9 (5.5%)	44 (9.0%)	62 (9.4%)
Native Hawaiian or Other Pacific Islander	0	1 (0.3%)	0	1 (0.2%)	1 (0.2%)
White	112 (67.1%)	231 (70.4%)	128 (78.5%)	359 (73.1%)	471 (71.6%)
Other	0	1 (0.3%)	0	1 (0.2%)	1 (0.2%)
Not Reported	4 (2.4%)	6 (1.8%)	1 (0.6%)	7 (1.4%)	11 (1.7%)
Sex, n (%)					
Female	75 (44.9%)	118 (36.0%)	64 (39.3%)	182 (37.1%)	257 (39.1%)
Male	92 (55.1%)	210 (64.0%)	99 (60.7%)	309 (62.9%)	401 (60.9%)
Geographical region, n (%)					
Japan	20 (12.0%)	37 (11.3%)	17 (10.4%)	54 (11.0%)	74 (11.2%)
Rest of World	147 (88.0%)	291 (88.7%)	146 (89.6%)	437 (89.0%)	584 (88.8%)

BMI (kg/m^2)					
N	167	327	163	490	657
Mean (SD)	29.91 (6.525)	30.44 (6.156)	31.02 (6.123)	30.63 (6.145)	30.45 (6.247)
Median	28.70	29.40	30.00	29.65	29.40
Q1 : Q3	25.10 : 34.10	26.00 : 33.90	26.40 : 34.70	26.20 : 34.20	25.90 : 34.10
Min : Max	17.7 : 48.6	17.7 : 52.1	20.1 : 58.5	17.7 : 58.5	17.7 : 58.5
SBP at baseline (mmHg) [a]					
N	167	328	163	491	658
Mean (SD)	135.92 (14.792)	134.06 (14.627)	133.47 (13.766)	133.86 (14.335)	134.39 (14.469)
Median	137.00	134.00	133.50	134.00	135.00
Q1 : Q3	126.00 : 147.00	123.00 : 146.00	123.67 : 144.50	123.50 : 145.50	123.67 : 146.00
Min : Max	97.0 : 167.0	98.5 : 170.0	102.0 : 167.0	98.5 : 170.0	97.0 : 170.0
DBP at baseline (mmHg) [a]					
N	167	328	163	491	658
Mean (SD)	75.35 (8.928)	75.21 (9.445)	75.29 (9.216)	75.24 (9.361)	75.27 (9.246)
Median	76.00	75.50	75.50	75.50	75.50
Q1 : Q3	69.50 : 82.00	68.50 : 82.00	69.00 : 82.50	69.00 : 82.00	69.00 : 82.00
Min : Max	47.5 : 91.5	46.5 : 108.5	50.5 : 95.5	46.5 : 108.5	46.5 : 108.5
Hemoglobin A1c at baseline (%)					
N	166	326	161	487	653
Mean (SD)	8.14 (1.482)	7.94 (1.546)	7.84 (1.502)	7.91 (1.531)	7.97 (1.521)
Median	7.90	7.60	7.60	7.60	7.60
Q1 : Q3	7.20 : 9.10	6.80 : 8.90	6.90 : 8.50	6.80 : 8.70	6.90 : 8.80
Min : Max	5.5 : 13.6	5.1 : 13.6	4.5 : 12.0	4.5 : 13.6	4.5 : 13.6
Hemoglobin A1c at baseline category, n (%)					
≤8%	90 (53.9%)	193 (58.8%)	106 (65.0%)	299 (60.9%)	389 (59.1%)
>8%	76 (45.5%)	133 (40.5%)	55 (33.7%)	188 (38.3%)	264 (40.1%)
Missing	1	2	2	4	5
History of renal impairment, n (%)					
Normal	111 (66.5%)	217 (66.2%)	112 (68.7%)	329 (67.0%)	440 (66.9%)
Mild	38 (22.8%)	72 (22.0%)	38 (23.3%)	110 (22.4%)	148 (22.5%)
Moderate	13 (7.8%)	22 (6.7%)	8 (4.9%)	30 (6.1%)	43 (6.5%)
Severe	4 (2.4%)	11 (3.4%)	5 (3.1%)	16 (3.3%)	20 (3.0%)
Missing	1	6	0	6	7
History of hepatic impairment, n (%)					
Yes	4 (2.4%)	12 (3.7%)	4 (2.5%)	16 (3.3%)	20 (3.0%)
No	163 (97.6%)	316 (96.3%)	159 (97.5%)	475 (96.7%)	638 (97.0%)
History of cerebrovascular disease, n (%)					
Yes	19 (11.4%)	21 (6.4%)	10 (6.1%)	31 (6.3%)	50 (7.6%)
No	148 (88.6%)	307 (93.6%)	153 (93.9%)	460 (93.7%)	608 (92.4%)
History of ischaemic heart disease, n (%)					
Yes	28 (16.8%)	64 (19.5%)	22 (13.5%)	86 (17.5%)	114 (17.3%)
No	139 (83.2%)	264 (80.5%)	141 (86.5%)	405 (82.5%)	544 (82.7%)
Duration of diabetes (years) [b]					
N	167	327	162	489	656
Mean (SD)	15.9 (10.04)	15.1 (9.96)	15.7 (10.67)	15.3 (10.20)	15.5 (10.15)
Median	15.2	14.0	14.4	14.2	14.5
Q1 : Q3	8.9 : 21.0	7.2 : 21.3	6.3 : 22.1	6.9 : 21.3	7.2 : 21.3
Min : Max	1 : 61	0 : 51	0 : 54	0 : 54	0 : 61
Diabetes type, n (%)					
Type I	11 (6.6%)	18 (5.5%)	9 (5.5%)	27 (5.5%)	38 (5.8%)
Type II	156 (93.4%)	310 (94.5%)	154 (94.5%)	464 (94.5%)	620 (94.2%)
Insulin Dependent	84 (50.3%)	150 (45.7%)	85 (52.1%)	235 (47.9%)	319 (48.5%)
Non-Insulin Dependent	73 (43.7%)	160 (48.8%)	68 (41.7%)	228 (46.4%)	301 (45.7%)
NEI-VFQ-25 total score at baseline					
N	166	328	163	491	657
Mean (SD)	76.65 (15.889)	76.79 (17.316)	77.86 (15.578)	77.15 (16.751)	77.02 (16.527)
Median	79.62	81.41	80.79	81.40	80.64
Q1 : Q3	66.44 : 90.17	66.54 : 90.74	68.45 : 90.49	67.08 : 90.68	67.08 : 90.42
Min : Max	29.2 : 98.2	15.1 : 100.0	18.6 : 99.4	15.1 : 100.0	15.1 : 100.0

Abbreviations: 2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HD=high dose; HDq12: aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; All HD: Pooled HD12 and HDq16 groups; BMI=body mass index; BP = blood pressure; DBP = diastolic blood pressure; mmHg=millimeters of mercury; max=maximum; min=minimum; N,n=number; NEI-VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; Q1=quartile 1; Q3=quartile 3; SD=standard deviation; SBP=systolic blood pressure.

The percentage was based on the number of patients in each treatment group as denominator.

[a] The Baseline for BP was defined as the average of all valid measurements taken prior to administration of study drug.

[b] Date of randomization – date of initial diagnosis.

Baseline Disease Characteristics in the Study Eye

Demographics and baseline characteristics appears to be unbalanced across the groups for the following groups: age category (<55, ≥ 55 to < 65), race (Black or African American, White), Hemoglobin A1c at baseline category (percentage of patients with ≤8% and ≥ 8%), patients with history of cerebrovascular disease, history of ischaemic heart disease and diabetes type II (Non/insulin dependent).

Table 8: Baseline Disease Characteristics in the Study Eye (Full Analysis Set)

	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)	Total (N=658)
BCVA (ETDRS letter score)					
N	167	328	163	491	658
Mean (SD)	61.5 (11.22)	63.6 (10.10)	61.4 (11.76)	62.9 (10.72)	62.5 (10.86)
Median	63.0	65.0	64.0	65.0	65.0
Q1 : Q3	54.0 : 70.0	57.0 : 72.0	55.0 : 71.0	56.0 : 71.0	56.0 : 71.0
Min : Max	24 : 78	27 : 79	29 : 78	27 : 79	24 : 79
Baseline BCVA category					
≤73 letters	147 (88.0%)	269 (82.0%)	140 (85.9%)	409 (83.3%)	556 (84.5%)
>73 letters	20 (12.0%)	59 (18.0%)	23 (14.1%)	82 (16.7%)	102 (15.5%)
CRT (microns)					
N	167	327	163	490	657
Mean (SD)	457.2 (144.00)	449.1 (127.39)	460.3 (117.84)	452.9 (124.29)	454.0 (129.48)
Median	417.0	431.0	432.0	431.0	430.0
Q1 : Q3	346.0 : 532.0	359.0 : 518.0	371.0 : 540.0	362.0 : 526.0	360.0 : 528.0
Min : Max	260 : 1014	229 : 1309	255 : 926	229 : 1309	229 : 1309
Missing	0	1	0	1	1
CRT category per reading center[a]					
<400 microns	72 (43.1%)	134 (40.9%)	65 (39.9%)	199 (40.5%)	271 (41.2%)
≥400 microns	95 (56.9%)	194 (59.1%)	98 (60.1%)	292 (59.5%)	387 (58.8%)
CRT category per IWRS (used for stratification)[b]					
<400 microns	69 (41.3%)	138 (42.1%)	69 (42.3%)	207 (42.2%)	276 (41.9%)
≥400 microns	98 (58.7%)	190 (57.9%)	94 (57.7%)	284 (57.8%)	382 (58.1%)
Intraocular pressure (mmHg)					
N	167	328	163	491	658
Mean (SD)	15.9 (2.99)	15.3 (3.24)	14.9 (3.25)	15.2 (3.25)	15.4 (3.20)
Median	16.0	15.0	15.0	15.0	15.0
Q1 : Q3	14.0 : 18.0	13.0 : 18.0	13.0 : 17.0	13.0 : 17.0	13.0 : 18.0
Min : Max	8 : 23	8 : 24	7 : 24	7 : 24	7 : 24

Diabetic Retinopathy Severity Score (DRSS)					
10	0	1 (0.3%)	2 (1.2%)	3 (0.6%)	3 (0.5%)
12	0	2 (0.6%)	0	2 (0.4%)	2 (0.3%)
14	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)	3 (0.5%)
15	1 (0.6%)	0	0	0	1 (0.2%)
20	3 (1.8%)	13 (4.0%)	2 (1.2%)	15 (3.1%)	18 (2.7%)
35	66 (39.5%)	121 (36.9%)	66 (40.5%)	187 (38.1%)	253 (38.4%)
43	34 (20.4%)	59 (18.0%)	36 (22.1%)	95 (19.3%)	129 (19.6%)
47	17 (10.2%)	46 (14.0%)	15 (9.2%)	61 (12.4%)	78 (11.9%)
53	22 (13.2%)	34 (10.4%)	11 (6.7%)	45 (9.2%)	67 (10.2%)
61	9 (5.4%)	20 (6.1%)	9 (5.5%)	29 (5.9%)	38 (5.8%)
65	4 (2.4%)	11 (3.4%)	9 (5.5%)	20 (4.1%)	24 (3.6%)
71	1 (0.6%)	1 (0.3%)	2 (1.2%)	3 (0.6%)	4 (0.6%)
75	0	1 (0.3%)	0	1 (0.2%)	1 (0.2%)
90 (non-gradable)	9 (5.4%)	18 (5.5%)	10 (6.1%)	28 (5.7%)	37 (5.6%)
Prior DME treatment per EDC, n (%) [c]					
Yes	74 (44.3%)	143 (43.6%)	71 (43.6%)	214 (43.6%)	288 (43.8%)
No	93 (55.7%)	185 (56.4%)	92 (56.4%)	277 (56.4%)	370 (56.2%)
Prior DME treatment per IWRS (used for stratification), n (%)[d]					
Yes	76 (45.5%)	149 (45.4%)	72 (44.2%)	221 (45.0%)	297 (45.1%)
No	91 (54.5%)	179 (54.6%)	91 (55.8%)	270 (55.0%)	361 (54.9%)

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; All HD= Pooled HDq12 and HDq16 groups; BCVA=best corrected visual acuity; CRT=central retinal thickness; DME=Diabetic macular edema; DRSS=Diabetic Retinopathy Severity Score; EDC=electronic data capture; ETDRS=early treatment diabetic retinopathy study; HD=high dose; IWRS=interactive web response system; max=maximum; min=minimum; N,n=number; Q1=quartile 1; Q3=quartile 3; SD=standard deviation.

[a] Baseline values; used for subgroup analyses

[b] Reflects site's entry of reading center values from screening visit into IWRS; 10 patients were stratified incorrectly, based on incorrect data entry in IWRS.

[c] Used for week 48 subgroup analyses. However, before the week 60 database lock, the prior DME treatment status was changed from No to Yes for 2 participants in the HDq12 group; the updated status was used for week 60 analyses.

[d] Reflects entry of prior DME treatment information by site into IWRS; 47 patients had data entered inconsistently between IWRS and EDC.

The percentage was based on the number of patients in each treatment group as denominator.

Medical History

The ocular medical and surgical history in the study eye mostly reported (> 10%) were AMD, Cataract, cataract nuclear, cataract operation and retinal laser coagulation. Overall, baseline data for patient's medical and surgical history were comparable across the 3 groups, except for the cataract history, as well for patients with vitreous detachment and intraocular lens implant (Table 9).

Moreover, non-ocular medical and surgical history in the study eye baseline data presented in Table 9 were not comparable across the 3 groups for the following SOC: metabolism and nutrition disorders (Hyperlipidaemia, Hypercholesterolaemia, and diabetes mellitus), gastrointestinal disorders (gastroesophageal reflux disease), immune system disorders (seasonal allergy and drug hypersensitivity) and endocrine disorders (hypothyroidism).

Table 9: Ocular Medical or Surgical History in Study Eye in Overall ≥ 5% Participants (Safety Analysis Set)

Primary System Organ Class Preferred Term MedDRA Version 25.0	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)	Total (N=658)
Number (%) of patients with at least one finding or surgery	165 (98.8%)	326 (99.4%)	163 (100%)	489 (99.6%)	654 (99.4%)
Eye disorders	165 (98.8%)	326 (99.4%)	163 (100%)	489 (99.6%)	654 (99.4%)
Diabetic retinal oedema	163 (97.6%)	320 (97.6%)	162 (99.4%)	482 (98.2%)	645 (98.0%)
Diabetic retinopathy	118 (70.7%)	233 (71.0%)	112 (68.7%)	345 (70.3%)	463 (70.4%)
Cataract	56 (33.5%)	113 (34.5%)	64 (39.3%)	177 (36.0%)	233 (35.4%)
Cataract nuclear	26 (15.6%)	56 (17.1%)	29 (17.8%)	85 (17.3%)	111 (16.9%)
Dry eye	13 (7.8%)	29 (8.8%)	10 (6.1%)	39 (7.9%)	52 (7.9%)
Vitreous detachment	19 (11.4%)	29 (8.8%)	10 (6.1%)	39 (7.9%)	58 (8.8%)
Retinopathy hypertensive	9 (5.4%)	22 (6.7%)	14 (8.6%)	36 (7.3%)	45 (6.8%)
Retinal haemorrhage	7 (4.2%)	18 (5.5%)	7 (4.3%)	25 (5.1%)	32 (4.9%)
Surgical and medical procedures	47 (28.1%)	101 (30.8%)	49 (30.1%)	150 (30.5%)	197 (29.9%)
Cataract operation	20 (12.0%)	47 (14.3%)	20 (12.3%)	67 (13.6%)	87 (13.2%)
Retinal laser coagulation	19 (11.4%)	41 (12.5%)	22 (13.5%)	63 (12.8%)	82 (12.5%)
Intraocular lens implant	16 (9.6%)	18 (5.5%)	12 (7.4%)	30 (6.1%)	46 (7.0%)

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. All HD=pooled HDq12 and HDq16 groups; MedDRA= Medical Dictionary for Regulatory Activities.
The percentage was based on the number of patients in each treatment group as denominator.

Table 10: Non-ocular Medical History Overall ≥ 5% Participants (SAF)

Primary System Organ Class Preferred Term MedDRA Version 25.0	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)	Total (N=658)
Number (%) of patients with at least one finding or surgery	167 (100%)	328 (100%)	163 (100%)	491 (100%)	658 (100%)
Metabolism and nutrition disorders	167 (100%)	328 (100%)	162 (99.4%)	490 (99.8%)	657 (99.8%)
Type 2 diabetes mellitus	126 (75.4%)	250 (76.2%)	131 (80.4%)	381 (77.6%)	507 (77.1%)
Hyperlipidaemia	45 (26.9%)	98 (29.9%)	59 (36.2%)	157 (32.0%)	202 (30.7%)
Hypercholesterolaemia	52 (31.1%)	84 (25.6%)	49 (30.1%)	133 (27.1%)	185 (28.1%)
Diabetes mellitus	24 (14.4%)	57 (17.4%)	20 (12.3%)	77 (15.7%)	101 (15.3%)
Obesity	9 (5.4%)	19 (5.8%)	10 (6.1%)	29 (5.9%)	38 (5.8%)
Type 1 diabetes mellitus	12 (7.2%)	20 (6.1%)	9 (5.5%)	29 (5.9%)	41 (6.2%)
Vascular disorders	132 (79.0%)	256 (78.0%)	131 (80.4%)	387 (78.8%)	519 (78.9%)
Hypertension	128 (76.6%)	248 (75.6%)	124 (76.1%)	372 (75.8%)	500 (76.0%)
Surgical and medical procedures	68 (40.7%)	151 (46.0%)	58 (35.6%)	209 (42.6%)	277 (42.1%)
Hysterectomy	17 (10.2%)	35 (10.7%)	14 (8.6%)	49 (10.0%)	66 (10.0%)
Cholecystectomy	10 (6.0%)	19 (5.8%)	9 (5.5%)	28 (5.7%)	38 (5.8%)
Nervous system disorders	61 (36.5%)	107 (32.6%)	58 (35.6%)	165 (33.6%)	226 (34.3%)
Diabetic neuropathy	18 (10.8%)	46 (14.0%)	23 (14.1%)	69 (14.1%)	87 (13.2%)
Neuropathy peripheral	18 (10.8%)	27 (8.2%)	13 (8.0%)	40 (8.1%)	58 (8.8%)
Musculoskeletal and connective tissue disorders	34 (20.4%)	72 (22.0%)	41 (25.2%)	113 (23.0%)	147 (22.3%)
Arthritis	10 (6.0%)	18 (5.5%)	8 (4.9%)	26 (5.3%)	36 (5.5%)
Gastrointestinal disorders	50 (29.9%)	75 (22.9%)	35 (21.5%)	110 (22.4%)	160 (24.3%)
Gastrooesophageal reflux disease	28 (16.8%)	38 (11.6%)	18 (11.0%)	56 (11.4%)	84 (12.8%)
Cardiac disorders	41 (24.6%)	76 (23.2%)	27 (16.6%)	103 (21.0%)	144 (21.9%)
Myocardial infarction	8 (4.8%)	20 (6.1%)	12 (7.4%)	32 (6.5%)	40 (6.1%)
Coronary artery disease	10 (6.0%)	23 (7.0%)	7 (4.3%)	30 (6.1%)	40 (6.1%)
Psychiatric disorders	33 (19.8%)	59 (18.0%)	30 (18.4%)	89 (18.1%)	122 (18.5%)
Depression	17 (10.2%)	28 (8.5%)	12 (7.4%)	40 (8.1%)	57 (8.7%)
Anxiety	12 (7.2%)	18 (5.5%)	8 (4.9%)	26 (5.3%)	38 (5.8%)
Immune system disorders	39 (23.4%)	44 (13.4%)	23 (14.1%)	67 (13.6%)	106 (16.1%)
Seasonal allergy	22 (13.2%)	23 (7.0%)	6 (3.7%)	29 (5.9%)	51 (7.8%)
Drug hypersensitivity	15 (9.0%)	17 (5.2%)	11 (6.7%)	28 (5.7%)	43 (6.5%)
Endocrine disorders	17 (10.2%)	42 (12.8%)	24 (14.7%)	66 (13.4%)	83 (12.6%)
Hypothyroidism	11 (6.6%)	37 (11.3%)	18 (11.0%)	55 (11.2%)	66 (10.0%)
Social circumstances	25 (15.0%)	30 (9.1%)	16 (9.8%)	46 (9.4%)	71 (10.8%)
Postmenopause	16 (9.6%)	20 (6.1%)	10 (6.1%)	30 (6.1%)	46 (7.0%)

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. All HD=pooled HDq12 and HDq16 groups; MedDRA= Medical Dictionary for Regulatory Activities; SAF= safety analysis set.

The percentage was based on the number of patients in each treatment group as denominator.

The MAH was asked to discuss the clinical relevance of the observed baseline disease characteristics discrepancies in PHOTON study (in patients of different age category (<55, ≥ 55 to < 65), race (Black or African American, White), percentage of Hemoglobin A1c at baseline category (≤8% and ≥ 8%), patients with history

of cerebrovascular disease, history of ischaemic heart disease and diabetes type II (Non/insulin dependent), BCVA category (≤73 and ≥ 73 letters) CRT, DRSS, cataract history, vitreous detachment, intraocular lens implant, metabolism and nutrition disorders (Hyperlipidaemia, Hypercholesterolaemia, diabetes mellitus), gastrointestinal disorders (gastroesophageal reflux disease), immune system disorders (seasonal allergy and drug hypersensitivity) and endocrine disorders (hypothyroidism)).

Regarding the age, in the age group < 55 there were 17.4%, 23.5% and 23.3% subjects and in the ≥ 55 to < 65 group there were 37.7%, 32.9% and 33.1% subjects in the 2q8, HDq12 and HDq16 group respectively. Based on the mean and median age including the standard deviation, the Applicant concluded that there was a similar distribution of age for the treatment groups and thus the minor numerical differences at baseline with regards to age groups are not considered clinically relevant. Due to the lower sample size per subgroup these did show some minor variability but did not reveal clinically meaningful differences between the subgroup populations and the total population.

For the ethnicity and Hemoglobin A1c differences, the observed imbalance among these subgroups is due to their relatively small sample sizes and is therefore not considered clinically relevant. Indeed, the Applicant considers that the primary and secondary endpoints are calculated based on the entire population (and not subgroups), such differences are judged as not clinically relevant.

Regarding the Medical history, the numerical imbalances in the distribution is also explained by the small number of patients and are not considered clinically relevant

Numbers analysed

The number of participants included in each analysis set and a summary of participants excluded from the respective analysis sets is provided in Table 6.

Two participants who did not receive treatment were excluded from all analyses (SAF, FAS, and PPS; 1 participant each in HDq12 and HDq16). An additional 9 participants were excluded from the PPS for the reasons presented in Table 6.

Table 6: Study Analysis Sets Analysis Sets by Treatment Group (All Randomized Participants)

	2q8 (N=167)	HDq12 (N=329)	HDq16 (N=164)	All HD (N=493)	Total (N=660)
Patients included in the Safety Set (SAF), n(%)	167 (100%)	328 (99.7%)	163 (99.4%)	491 (99.6%)	658 (99.7%)
Patients excluded from SAF (Not Treated), n(%)	0	1 (0.3%)	1 (0.6%)	2 (0.4%)	2 (0.3%)
Patients included in the Full Analysis Set (FAS), n(%)	167 (100%)	328 (99.7%)	163 (99.4%)	491 (99.6%)	658 (99.7%)
Patients excluded from FAS (not treated), n(%)	0	1 (0.3%)	1 (0.6%)	2 (0.4%)	2 (0.3%)
Patients included in the Per Protocol Set (PPS), n(%)	164 (98.2%)	322 (97.9%)	163 (99.4%)	485 (98.4%)	649 (98.3%)
Patients in FAS who were excluded from PPS, n(%)	3 (1.8%)	6 (1.8%)	0	6 (1.2%)	9 (1.4%)
Exclusion #07 met but subject randomized	3 (1.8%)	2 (0.6%)	0	2 (0.4%)	5 (0.8%)
Exclusion #08 met but subject randomized	0	1 (0.3%)	0	1 (0.2%)	1 (0.2%)
Inclusion #03 not met but subject randomized	0	1 (0.3%)	0	1 (0.2%)	1 (0.2%)
No post-baseline assessment of BCVA	0	2 (0.6%)	0	2 (0.4%)	2 (0.3%)
Patients included in the Pharmacokinetic Analysis Set, n(%)	163 (97.6%)	323 (98.2%)	162 (98.8%)	485 (98.4%)	648 (98.2%)
Patients included in the dense Pharmacokinetic Analysis Set, n(%)	12 (7.2%)	18 (5.5%)	5 (3.0%)	23 (4.7%)	35 (5.3%)
Patients included in the Immunogenicity Analysis Set, n(%)	137 (82.0%)	263 (79.9%)	141 (86.0%)	404 (81.9%)	541 (82.0%)
Patients included in the NAb Analysis Set, n(%)	137 (82.0%)	263 (79.9%)	141 (86.0%)	404 (81.9%)	541 (82.0%)

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= 8 mg aflibercept administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= 8 mg aflibercept administered every 16 weeks after 3 initial injections at 4-week intervals; All HD=Pooled HDq12 and HDq16 groups; BCVA= Best corrected visual acuity; DME= Diabetic macular edema; ETDRS= Early Treatment Diabetic Retinopathy Study; FAS=Full analysis set; NAb=neutralizing antibody; PPS=Per protocol set; SAF=Safety set.
The percentage for each analysis set was based on the number of randomized patients in each treatment group as denominator.
Exclusion criterion #7: Prior use of intraocular or periocular corticosteroids in study eye within 16 weeks/112 days of screening or ILUVIEN® or OZURDEX® IVT implants at any time; Exclusion criterion #8: History of vitreoretinal surgery (including scleral buckle) in the study eye; Inclusion criterion #3: BCVA ETDRS score of 78-24 (Snellen equivalent of 20/32 - 20/320) in study eye with decreased vision determined to be result of DME.

Outcomes and estimation

Overview of Hierarchical Testing Procedure

Table 18 provides a summary of the results for the primary and key secondary endpoints included in the hierarchical testing procedure according to the EP-SAP.

The first 5 confirmatory tests in the hierarchy (H10, H20, H30, H40, H50) were statistically significant at the alpha level of 0.025 (1-sided tests). Therefore, the following is concluded by the MAH:

• Treatment of participants with HDq12 is non-inferior to 2q8 with regard to the primary endpoint "change from baseline in BCVA at week 48" and with regard to the key secondary endpoint "change from baseline BCVA at week 60"

• Treatment of participants with HDq16 is non-inferior to 2q8 with regard to the primary endpoint "change from baseline in BCVA at week 48" and with regard to the key secondary endpoint "change from baseline in BCVA at week 60"

• Treatment of participants with HDq12 is non-inferior to 2q8 with regard to the key secondary endpoint "proportion of participants with a ≥ 2-step improvement in DRSS score at week 48"

The confirmatory test for non-inferiority of HDq16 vs. 2q8 (H60) in the key secondary endpoint "proportion of participants with a ≥ 2 step improvement in DRSS score at week 48" did not meet the non-inferiority margin of 15%; therefore, the hierarchical testing procedure was stopped at the H60 test.

Table 18: Test Decisions and Statistical Conclusions for EP-SAP Analysis (Full Analysis Set)

Null hypothesis		p-value (1-sided test)	2-sided 95% CI	Test decision (H_{x0} rejected)
Change from baseline in BCVA				
H_{10}: non-inferiority of HDq12 vs. 2q8 in primary endpoint	Week 48	$p < 0.0001$ [a]	-2.26, 1.13	Yes
H_{20}: non-inferiority of HDq12 vs. 2q8 in key secondary endpoint	Week 60	$p = 0.0003$ [a]	-2.67, 0.91	Yes
H_{30}: non-inferiority of HDq16 vs. 2q8 in primary endpoint	Week 48	$p = 0.0031$ [a]	-3.27, 0.39	Yes
H_{40}: non-inferiority of HDq16 vs. 2q8 in key secondary endpoint	Week 60	$p = 0.0122$ [a]	-3.71, 0.19	Yes
Proportion of patients with a ≥ 2-step improvement in DRSS score				
H_{50}: non-inferiority of HDq12 vs. 2q8 in key secondary endpoint	Week 48	NA	-6.61, 10.57 [b]	Yes
H_{60}: non-inferiority of HDq16 vs. 2q8 in key secondary endpoint	Week 48	NA	-16.88, 1.84 [b]	No, and hierarchical testing procedure stopped
Change from baseline in BCVA				
H_{70}: superiority of HDq12 vs. 2q8 in primary endpoint	Week 48	NA		NA
H_{80}: superiority of HDq12 vs. 2q8 in key secondary endpoint	Week 60	NA		NA
H_{90}: superiority of HDq16 vs. 2q8 in primary endpoint	Week 48	NA		NA
H_{100}: superiority of HDq16 vs. 2q8 in key secondary endpoint	Week 60	NA		NA

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. BCVA=best corrected visual acuity; CI=confidence interval; DRSS=Diabetic Retinopathy Severity Scale; EP-SAP= EMA/PMDA Statistical Analysis Plan; NA= not applicable

[a] p-value for the 1-sided non-inferiority test at a margin of 4 letters.

[b] The non-inferiority margin was set at 15%.

For the sake of completeness, when applying the hierarchical testing procedure defined in the G-SAP, the first 3 confirmatory tests in the hierarchy (H10, H30, H50) were statistically significant at the alpha level of 0.025 (1-sided tests) at week 48.

Therefore, the following was concluded by the MAH:

• Treatment of participants with HDq12 is non-inferior to 2q8 with regard to the primary endpoint "change from baseline in BCVA at week 48"

• Treatment of participants with HDq16 is non-inferior to 2q8 with regard to the primary endpoint "change from baseline in BCVA at week 48"

• Treatment of participants with HDq12 is non-inferior to 2q8 with regard to the key secondary endpoint "proportion of participants with a ≥ 2-step improvement in DRSS score"

The non-inferiority in BCVA of individual high doses over the control dose is formally demonstrated at 48 and 60 weeks of treatment in the ITT population, as well as the non-inferiority in DRSS score ≥ 2-step for the HDq12 at 48 weeks of treatment. No superiority can be claimed over the control dose for individual high doses.

Primary endpoint analysis

Change from Baseline in BCVA (as Measured by ETDRS Letter Score)

The primary objective of this study was to determine if treatment with higher dose aflibercept at intervals of 12 or 16 weeks provided non-inferior BCVA compared to 2 mg aflibercept dosed every 8 weeks.

The primary endpoint was the change from baseline in BCVA (as measured by ETDRS letter score) at week 48. A key secondary endpoint (as per the EP-SAP) was the change from baseline in BCVA (as measured by ETDRS letter score) at week 60.

Change from Baseline in BCVA (as Measured by ETDRS Letter Score) at Week 48

Both HDq12 and HDq16 demonstrated non-inferiority to 2q8 with respect to the primary efficacy endpoint (change from baseline in BCVA at week 48; H10 and H30 in the statistical testing hierarchy) using the non-inferiority margin of 4 letters with LS mean change from baseline in BCVA of 8.10 letters (HDq12) and 7.23 letters (HDq16) versus 8.67 letters in the 2q8 group (Table 14). The differences in LS mean changes from baseline in BCVA (95% CI) were -0.57 (- 2.26, 1.13) and -1.44 (-3.27, 0.39) for HDq12 and HDq16, respectively compared to 2q8 (Table 14). The p-values for the non-inferiority test at a margin of 4 letters were <0.0001 (related to H10) for HDq12 vs. 2q8, and 0.0031 (related to H30) for HDq16 vs. 2q8. The lower confidence limits were greater than -4, allowing the conclusion of non-inferiority at week 48 timepoint.

The non-inferiority tests regarding the BCVA changes from baseline was first performed by the MAH for the primary endpoint in HDq12 group (H10) at Week 48, followed by the non-inferiority test for the key secondary endpoint in HDq12 Week 60 (H20) and continued with the non-inferiority test for the primary endpoint in HDq16 (H30) at Week 48, and finally the key secondary endpoint in HDq16 at Week 60 (H40).

Table 14: Primary Endpoint -- Change from Baseline in BCVA (ETDRS Letters) at Week 48 in the Study Eye, MMRM (Full Analysis Set)

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 48 data	DF	Contrast [a]	t-value	1-sided NI p-value [b]	1-sided superiority p-value	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=328)	8.10 (0.61)	8.77 (8.95)	63.63	277	351.5	HDq12 - 2q8	3.9881	<0.0001	0.7447	-0.57 (-2.26, 1.13)
HDq16 (N=163)	7.23 (0.71)	7.86 (8.38)	61.44	149	315.0	HDq16 - 2q8	2.7533	0.0031	0.9388	-1.44 (-3.27, 0.39)
2q8 (N=167)	8.67 (0.73)	9.21 (8.99)	61.47	150						

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; BCVA=Best corrected visual acuity; CRT=Central retinal thickness; DME=Diabetic macular edema; ETDRS=Early Treatment Diabetic Retinopathy Study; EDC=electronic data capture; BL=baseline; CI=confidence interval; DF=degrees of freedom; NI=non-inferiority; LS=least square; SAP=statistical analysis plan; SE=standard error; SD=standard deviation

A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT from reading center [<400µm vs. ≥400µm], prior treatment for DME per EDC; [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom.

Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1).

[a] The contrast also included the interaction term for treatment x visit.

[b] p-value for the 1-sided non-inferiority (NI) test at a margin of 4 letters.

[c] Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with 2-sided 95% CIs.

Results of the analysis in the PPS were consistent with the FAS (Table 14.2.1.2) and LS mean change from baseline in BCVA by visit in the PPS was also consistent with the FAS (Figure 14.2.1.2 of the r-14238 report section).

Table 14.2.1.2 Statistical Analysis of Change from Baseline in BCVA Score at Week 48 (MMRM)
(Per Protocol Set)

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 48 data	DF	Contrast [a]	t-value	1-sided NI p-value [b]	1-sided superiority p-value	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=322)	8.14 (0.61)	8.81 (8.96)	63.69	273	342.9	HDq12 - 2q8	3.8950	<0.0001	0.7554	-0.60 (-2.32, 1.11)
HDq16 (N=163)	7.24 (0.71)	7.86 (8.38)	61.44	149	311.2	HDq16 - 2q8	2.6605	0.0041	0.9452	-1.50 (-3.35, 0.34)
2q8 (N=164)	8.75 (0.74)	9.27 (9.02)	61.63	147						

Change from Baseline in BCVA (as Measured by ETDRS Letter Score) at Week 60

Both HDq12 and HDq16 demonstrated non-inferiority to 2q8 with respect to this key secondary endpoint (change from baseline in BCVA at week 60) using the non-inferiority margin of 4 letters with LS mean change from baseline in BCVA of 8.52 letters (HDq12) and 7.64 letters (HDq16) versus 9.40 letters in the 2q8 group (Table 15). The differences in LS mean changes from baseline in BCVA (95% CI) were: -0.88 (-2.67, 0.91) and -1.76 (-3.71, 0.19) for HDq12 and HDq16, respectively, compared to 2q8. The p-values for the non-inferiority test at a margin of 4 letters were 0.0003 (related to H20) for HDq12 vs. 2q8, and 0.0122 (related to H40) for HDq16 vs. 2q8. The lower confidence limits were greater than -4, allowing the conclusion of non-inferiority at week 60 timepoint.

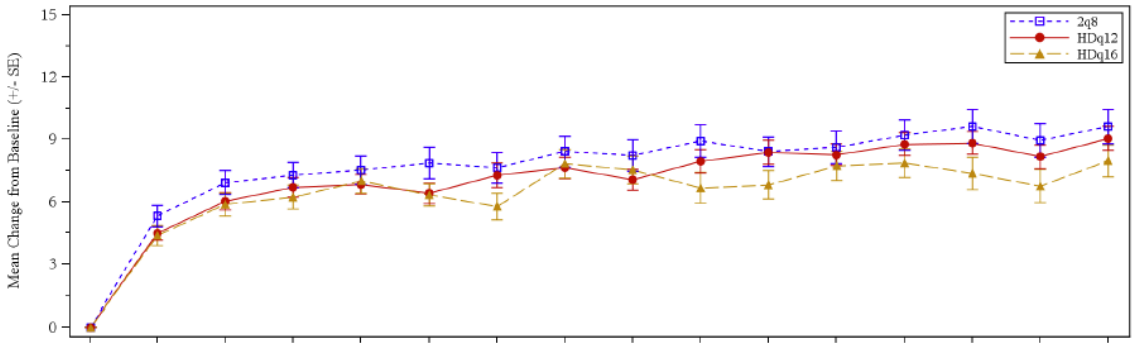
Table 15: Key Secondary Endpoint -- Change from Baseline in BCVA (ETDRS Letters) at Week 60 in the Study Eye, MMRM (Full Analysis Set)

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 60 data	DF	Contrast [a]	t-value	1-sided NI p-value [b]	1-sided superiority p-value	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=328)	8.52 (0.63)	9.05 (9.27)	63.63	252	342.4	HDq12 - 2q8	3.4242	0.0003	0.8325	-0.88 (-2.67, 0.91)
HDq16 (N=163)	7.64 (0.75)	7.96 (9.14)	61.44	138	315.5	HDq16 - 2q8	2.2625	0.0122	0.9619	-1.76 (-3.71, 0.19)
2q8 (N=167)	9.40 (0.77)	9.62 (9.58)	61.47	133						

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
BL=baseline; CI=confidence interval; CRT= Central retinal thickness (or, central subfield retinal thickness); DF=degrees of freedom; DME=diabetic macular edema; NI=non-inferiority; LS=least square; SAP=statistical analysis plan; SE=standard error; SD=standard deviation
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT from reading center [<400µm vs. ≥400µm], prior treatment for DME per EDC; [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1).
[a] The contrast also included the interaction term for treatment x visit.
[b] p-value for the 1-sided non-inferiority (NI) test at a margin of 4 letters.
[c] Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with 2-sided 95% CIs.

The mean changes from baseline in BCVA measured by the ETDRS letter score by visit through week 60 using OC, are graphically displayed in Figure 3; the corresponding LS mean changes from baseline in BCVA using MMRM in the FAS, are displayed in Figure 4. The mean increases in BCVA over time were generally similar across all groups, with small fluctuations consistent with the dosing intervals.

Figure 3: **Mean Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye Through Week 60, OC (Full Analysis Set)**

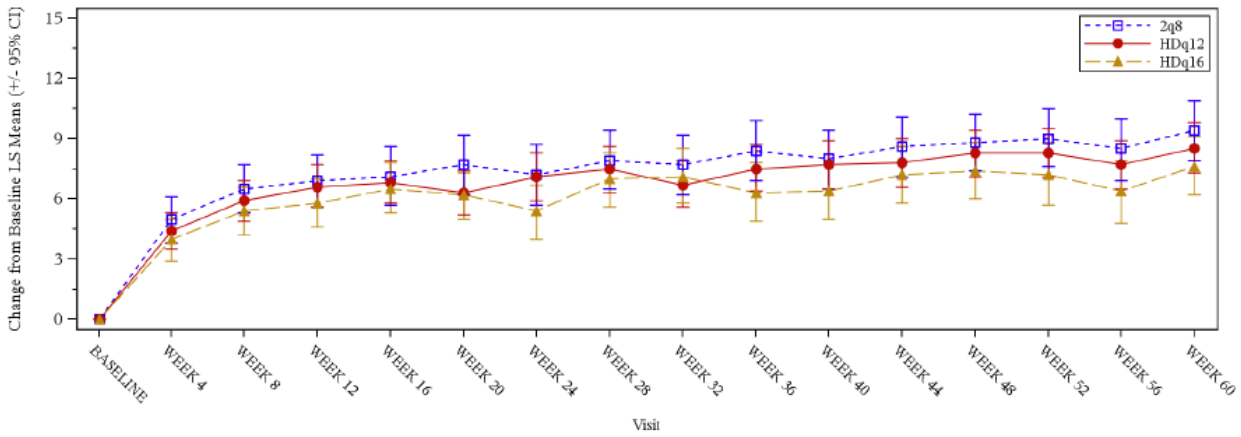


Number of Patients

2q8	167	163	163	165	163	147	160	150	159	142	152	141	150	144	144	133
HDq12	328	326	317	314	299	304	272	285	287	271	267	280	277	255	266	252
HDq16	163	163	161	160	159	152	155	144	149	146	151	145	149	137	142	138

Abbreviations: 2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
BCVA=best corrected visual activity; ETDRS=Early Treatment of Diabetic Retinopathy Study; HD=high dose; OC=observed cases, SE=standard error.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). OC: Observations after an ICE defined for the primary estimand were excluded.

Figure 4: **Least Square Mean Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye Through Week 60 (Full Analysis Set)**



Abbreviations: 2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
BCVA=best corrected visual activity; CI=confidence interval; CRT= central retinal thickness (or, central subfield retinal thickness); DME=diabetic molecular edema; EDC=electronic data capture; ETDRS=Early Treatment of Diabetic Retinopathy Study; HD=high dose; LS=least square; OC=observed cases;SAP=statistical analysis plan.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1).
Least square mean (LSM) was generated from a mixed model for repeated measurements (MMRM) with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.

Sensitivity Analysis for Change from Baseline in BCVA Score at Week 48 and Week 60

The results of the sensitivity analyses of the primary efficacy endpoint for assessing non-inferiority using an ANCOVA with LOCF and ANCOVA with MI were consistent with the primary analysis and are presented in Tables 14.2.1.3 and 14.2.1.4 for week 48 and Tables 14.2.1.3a and 14.2.1.4a for week 60.

Table 14.2.1.3 Statistical Analysis of Change from Baseline in BCVA Score at Week 48 (ANCOVA, LOCF)
(Full Analysis Set)

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 48 data	DF	Contrast	t-value	1-sided NI p-value [a]	Estimate for contrast and 2-sided 95% CI [b]
HDq12 (N=328)	7.49 (0.67)	7.85 (10.27)	63.63	326	647.0	HDq12 - 2q8	3.4813	0.0003	-0.95 (-2.67, 0.77)
HDq16 (N=163)	6.91 (0.85)	7.71 (8.18)	61.44	163	647.0	HDq16 - 2q8	2.4428	0.0074	-1.54 (-3.52, 0.44)
2q8 (N=167)	8.45 (0.83)	9.17 (8.89)	61.47	165					

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI = Confidence interval. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. LS = Least Square. BL = Baseline.
An analysis of covariance (ANCOVA) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World], baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors.
Intercurrent events (ICE) were handled according to Table 1 of SAP. LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data.
[a] p-value for the one-sided non-inferiority (NI) test at a margin of 4 letters.
[b] Estimate based on the ANCOVA model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Table 14.2.1.4 Statistical Analysis of Change from Baseline in BCVA Score at Week 48 (ANCOVA, MI)
(Full Analysis Set)

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 48 data	DF	Contrast	t-value	1-sided NI p-value [a]	Estimate for contrast and 2-sided 95% CI
HDq12 (N=328)	7.90 (0.66)	8.35 (9.55)	63.63	328	27628.7	HDq12 - 2q8	4.0807	<0.0001	-0.52 (-2.19, 1.16)
HDq16 (N=163)	6.95 (0.83)	7.87 (8.32)	61.44	163	19946.9	HDq16 - 2q8	2.5629	0.0052	-1.46 (-3.40, 0.47)
2q8 (N=167)	8.42 (0.81)	9.25 (8.94)	61.47	167					

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI = Confidence interval. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. LS = Least Square. BL = Baseline.
An analysis of covariance (ANCOVA) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World], baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors.
MI (multiple imputation) method was to generate multiple copies of the original dataset by replacing missing values using appropriated stochastic model (50 times and seed 01934) using SAS procedure =PROC MI|
Intercurrent events (ICE) were handled according to Table 1 of SAP
[a] p-value for the one-sided non-inferiority (NI) test at a margin of 4 letters.

Table 14.2.1.3a Statistical Analysis of Change from Baseline in BCVA Score at Week 60 (ANCOVA, LOCF)
(Full Analysis Set)

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 60 data	DF	Contrast	t-value	1-sided NI p-value [a]	Estimate for contrast and 2-sided 95% CI [b]
HDq12 (N=328)	8.00 (0.70)	7.99 (10.60)	63.63	326	647.0	HDq12 - 2q8	3.2222	0.0007	-1.07 (-2.86, 0.71)
HDq16 (N=163)	7.35 (0.88)	7.88 (8.73)	61.44	163	647.0	HDq16 - 2q8	2.1801	0.0148	-1.72 (-3.77, 0.33)
2q8 (N=167)	9.07 (0.86)	9.56 (9.34)	61.47	165					

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4'week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4'week intervals.
CI = Confidence interval. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. LS = Least Square. BL = Baseline.
An analysis of covariance (ANCOVA) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World], baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME [yes vs. no]) as fixed factors.
Intercurrent events (ICE) were handled according to Table 1 of SAP. LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data.
[a] p-value for the one-sided non-inferiority (NI) test at a margin of 4 letters.
[b] Estimate based on the ANCOVA model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Table 14.2.1.4a Statistical Analysis of Change from Baseline in BCVA Score at Week 60 (ANCOVA, MI)
(Full Analysis Set)

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 60 data	DF	Contrast	t-value	1-sided NI p-value [a]	Estimate for contrast and 2-sided 95% CI
HDq12 (N=328)	8.44 (0.69)	8.57 (9.88)	63.63	328	3539.0	HDq12 - 2q8	3.5023	0.0002	-0.77 (-2.58, 1.04)
HDq16 (N=163)	7.50 (0.86)	8.21 (8.99)	61.44	163	9380.1	HDq16 - 2q8	2.2003	0.0139	-1.72 (-3.75, 0.32)
2q8 (N=167)	9.21 (0.85)	9.86 (9.41)	61.47	167					

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4'week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4'week intervals.
CI = Confidence interval. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. LS = Least Square. BL = Baseline.
An analysis of covariance (ANCOVA) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World], baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME [yes vs. no]) as fixed factors.
MI (multiple imputation) method was to generate multiple copies of the original dataset by replacing missing values using appropriated stochastic model (50 times and seed 01934) using SAS procedure =PROC MI|
Intercurrent events (ICE) were handled according to Table 1 of SAP
[a] p-value for the one-sided non-inferiority (NI) test at a margin of 4 letters.

In order to check robustness of the results if the missing data are not MAR (missing at random), a tipping point analysis was conducted based on the MI analysis and the results are provided in Table 14.2.1.5 of the r-14238 report section for week 48. The results of this analysis showed that the smallest shift parameter (delta) used as penalty for participants with missing data in the HD groups, for which non-inferiority could not be shown anymore (with a 1-sided t-test at a significance level of 0.025), ie, the "tipping point" that significantly reversed the analysis result, was delta= -11 letters for HDq12 vs. 2q8 and delta = -7 letters for HDq16 vs. 2q8 at week 48.

The "tipping point" values of -11 letters and -7 letters, requiring such a large difference in BCVA between HDq12 and HDq16 vs. 2q8, respectively, did not seem plausible at week 48. Therefore, the primary analysis of non-inferiority conclusion based on MMRM method was robust to the departure of the MAR (missing at random) assumption. The same analyses have been performed by the MAH at week 60 and are supportive (Tables 14.2.1.3a to 14.2.1.5a of the r-14238 report section).

Subgroup Analysis of Change from Baseline in BCVA Score at Week 48 and Week 60 (MMRM)

Subgroup analyses were performed by the MAH for change from baseline in BCVA at week 48 and week 60 by sex, age group, race, ethnicity, baseline BCVA, geographic region, baseline CRT category, and prior DME treatment (Tables 14.2.1.9 to 14.2.1.16 for week 48 and Tables 14.2.1.9a to 14.2.1.16a for week 60).

In the results presented for the following subgroups discrepancies in PHOTON study were noted in patients of ≥65 - <75 years, Black or African American and with a BCVA ≥73 letters across the 3 treatment arms at Week 48 and 60. However, given the smaller size of these subgroups, the validity of these comparisons appeared limited.

Tables 14.2.1.9 to 14.2.1.16 Subgroup Analysis of Change from Baseline in BCVA Score at Week 48 (MMRM) (FAS)

Subgroup	Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 48 data	Contrast [a]	Estimate for contrast and 2-sided 95% CI [b]
Male (N=401)	HDq12 (N=210)	7.57 (0.71)	8.35 (8.94)	63.62	179	HDq12 - 2q8	-0.89 (-2.93, 1.15)
	HDq16 (N=99)	7.32 (0.94)	8.26 (8.64)	61.96	91	HDq16 - 2q8	-1.14 (-3.50, 1.22)
	2q8 (N=92)	8.46 (0.89)	8.73 (8.72)	63.08	83		
Female (N=257)	HDq12 (N=118)	9.25 (1.06)	9.55 (8.96)	63.65	98	HDq12 - 2q8	0.34 (-2.56, 3.24)
	HDq16 (N=64)	6.99 (1.08)	7.22 (8.00)	60.64	58	HDq16 - 2q8	-1.92 (-4.86, 1.03)
	2q8 (N=75)	8.91 (1.24)	9.81 (9.35)	59.51	67		
<55 years (N=144)	HDq12 (N=77)	9.67 (1.28)	10.17 (10.68)	65.04	69	HDq12 - 2q8	-1.86 (-5.78, 2.07)
	HDq16 (N=38)	10.04 (1.40)	11.05 (8.12)	63.16	37	HDq16 - 2q8	-1.49 (-5.50, 2.53)
	2q8 (N=29)	11.53 (1.70)	12.96 (9.44)	62.45	28		
>=55 - <65 years (N=225)	HDq12 (N=108)	6.95 (1.33)	8.00 (9.16)	64.83	91	HDq12 - 2q8	-3.26 (-6.16, -0.37)
	HDq16 (N=54)	6.76 (1.41)	7.06 (9.15)	61.48	52	HDq16 - 2q8	-3.45 (-6.46, -0.45)
	2q8 (N=63)	10.21 (1.13)	10.25 (8.06)	61.70	53		
>=65 - <75 years (N=218)	HDq12 (N=107)	9.36 (0.90)	9.22 (7.76)	61.73	87	HDq12 - 2q8	2.67 (-0.38, 5.72)
	HDq16 (N=57)	7.42 (1.18)	7.04 (8.12)	60.67	47	HDq16 - 2q8	0.73 (-2.67, 4.12)
	2q8 (N=54)	6.69 (1.45)	6.90 (9.77)	61.91	50		
>=75 years (N=71)	HDq12 (N=36)	6.14 (1.22)	6.60 (6.59)	62.69	30	HDq12 - 2q8	-0.52 (-4.19, 3.16)
	HDq16 (N=14)	4.71 (1.03)	4.92 (3.75)	59.79	13	HDq16 - 2q8	-1.95 (-5.41, 1.52)
	2q8 (N=21)	6.66 (1.40)	6.89 (6.47)	58.33	19		
White (N=471)	HDq12 (N=231)	8.96 (0.67)	9.50 (9.17)	63.45	195	HDq12 - 2q8	-0.19 (-2.26, 1.87)
	HDq16 (N=128)	7.71 (0.78)	8.33 (8.88)	61.05	115	HDq16 - 2q8	-1.44 (-3.64, 0.75)
	2q8 (N=112)	9.16 (0.81)	9.26 (8.79)	62.71	103		
Black Or African American (N=62)	HDq12 (N=35)	8.34 (1.78)	8.81 (10.73)	63.37	26	HDq12 - 2q8	-1.62 (-7.97, 4.73)
	HDq16 (N=9)	4.91 (2.32)	4.33 (6.54)	65.56	9	HDq16 - 2q8	-5.05 (-12.20, 2.09)
	2q8 (N=18)	9.96 (2.58)	11.14 (13.18)	59.44	14		
Asian (N=101)	HDq12 (N=48)	5.12 (1.01)	5.91 (6.93)	63.58	46	HDq12 - 2q8	-1.81 (-5.67, 2.05)
	HDq16 (N=23)	6.40 (1.22)	6.64 (6.28)	62.91	22	HDq16 - 2q8	-0.53 (-4.63, 3.56)
	2q8 (N=30)	6.93 (1.63)	7.32 (7.18)	58.33	28		
Not Hispanic Or Latino (N=525)	HDq12 (N=266)	8.23 (0.66)	8.80 (9.11)	63.77	231	HDq12 - 2q8	-0.68 (-2.62, 1.25)
	HDq16 (N=126)	7.34 (0.79)	7.93 (8.37)	62.06	115	HDq16 - 2q8	-1.57 (-3.69, 0.54)
	2q8 (N=133)	8.91 (0.82)	9.41 (9.15)	61.90	119		
Hispanic Or Latino (N=119)	HDq12 (N=54)	7.00 (1.36)	8.28 (8.47)	62.35	40	HDq12 - 2q8	-1.58 (-5.55, 2.38)
	HDq16 (N=34)	7.04 (1.36)	7.58 (8.59)	58.65	31	HDq16 - 2q8	-1.54 (-5.48, 2.39)
	2q8 (N=31)	8.59 (1.43)	8.89 (8.74)	59.65	28		
Japan (N=74)	HDq12 (N=37)	7.07 (1.07)	6.97 (6.58)	63.19	36	HDq12 - 2q8	-0.30 (-4.45, 3.86)
	HDq16 (N=17)	7.54 (1.47)	7.38 (6.79)	62.00	16	HDq16 - 2q8	0.17 (-4.44, 4.78)
	2q8 (N=20)	7.37 (1.72)	7.95 (7.80)	58.20	20		
Rest of the World (N=584)	HDq12 (N=291)	8.41 (0.60)	9.04 (9.23)	63.69	241	HDq12 - 2q8	-0.64 (-2.48, 1.21)
	HDq16 (N=146)	7.29 (0.70)	7.92 (8.57)	61.38	133	HDq16 - 2q8	-1.76 (-3.74, 0.22)
	2q8 (N=147)	9.05 (0.73)	9.41 (9.17)	61.92	130		
BL BCVA: <=73 letters (N=556)	HDq12 (N=269)	8.56 (0.68)	9.46 (8.96)	60.99	225	HDq12 - 2q8	-0.79 (-2.67, 1.09)
	HDq16 (N=140)	7.74 (0.81)	8.40 (8.71)	59.16	126	HDq16 - 2q8	-1.61 (-3.66, 0.44)
	2q8 (N=147)	9.35 (0.80)	9.92 (9.14)	59.53	132		
BL BCVA: >73 letters (N=102)	HDq12 (N=59)	5.22 (1.23)	5.81 (8.33)	75.68	52	HDq12 - 2q8	1.75 (-1.68, 5.17)
	HDq16 (N=23)	4.26 (1.28)	4.87 (5.51)	75.30	23	HDq16 - 2q8	0.79 (-2.84, 4.41)
	2q8 (N=20)	3.47 (1.41)	4.06 (5.68)	75.75	18		
BL CRT: <400 µm (N=271)	HDq12 (N=134)	6.62 (0.92)	7.54 (8.97)	65.86	114	HDq12 - 2q8	-0.17 (-2.38, 2.04)
	HDq16 (N=65)	4.80 (0.83)	5.07 (5.84)	66.08	61	HDq16 - 2q8	-1.99 (-4.08, 0.10)
	2q8 (N=72)	6.79 (0.83)	7.55 (6.82)	63.92	62		
BL CRT: >=400 µm (N=387)	HDq12 (N=194)	9.24 (0.81)	9.63 (8.86)	62.10	163	HDq12 - 2q8	-0.76 (-3.22, 1.69)
	HDq16 (N=98)	8.93 (1.05)	9.80 (9.31)	58.37	88	HDq16 - 2q8	-1.07 (-3.84, 1.70)
	2q8 (N=95)	10.00 (1.10)	10.39 (10.12)	59.62	88		

Prior DME: Y (N=288)	HDq12 (N=143)	8.08 (0.84)	8.24 (8.79)	62.31	124	HDq12 - 2q8	0.87 (-1.71, 3.45)
	HDq16 (N=71)	5.27 (1.08)	5.60 (8.62)	58.58	67	HDq16 - 2q8	-1.94 (-4.86, 0.98)
	2q8 (N=74)	7.21 (1.11)	7.40 (9.15)	62.07	68		
Prior DME: N (N=370)	HDq12 (N=185)	8.12 (0.88)	9.20 (9.08)	64.66	153	HDq12 - 2q8	-1.48 (-3.72, 0.75)
	HDq16 (N=92)	9.05 (0.92)	9.71 (7.76)	63.65	82	HDq16 - 2q8	-0.56 (-2.86, 1.74)
	2q8 (N=93)	9.61 (0.96)	10.72 (8.62)	61.00	82		

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI = Confidence interval. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. LS = Least Square. BL = Baseline.
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. If the subgroup was one of the stratification factors, then it was not included in the statistical model. An unstructured covariance type was used to model the within-subject error for all subgroups.
[a] The contrast also included the interaction term for treatment x visit
[b] Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Tables 14.2.1.9a to 14.2.1.16a Subgroup Analysis of Change from Baseline in BCVA Score at Week 60 (MMRM) (FAS)

Subgroup	Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 60 data	Contrast [a]	Estimate for contrast and 2-sided 95% CI [b]
Male (N=401)	HDq12 (N=210)	7.77 (0.76)	8.38 (9.30)	63.62	162	HDq12 - 2q8	-1.05 (-3.34, 1.24)
	HDq16 (N=99)	8.39 (1.04)	8.92 (10.22)	61.96	84	HDq16 - 2q8	-0.43 (-3.09, 2.23)
	2q8 (N=92)	8.82 (1.00)	8.30 (9.66)	63.08	73		
Female (N=257)	HDq12 (N=118)	9.98 (1.08)	10.27 (9.14)	63.65	90	HDq12 - 2q8	-0.35 (-3.24, 2.55)
	HDq16 (N=64)	6.51 (1.01)	6.48 (6.95)	60.64	54	HDq16 - 2q8	-3.82 (-6.61, -1.02)
	2q8 (N=75)	10.33 (1.22)	11.22 (9.32)	59.51	60		
<55 years (N=144)	HDq12 (N=77)	9.92 (1.19)	10.46 (9.98)	65.04	61	HDq12 - 2q8	-3.20 (-7.24, 0.85)
	HDq16 (N=38)	10.74 (1.51)	11.47 (8.93)	63.16	34	HDq16 - 2q8	-2.38 (-6.75, 1.99)
	2q8 (N=29)	13.12 (1.80)	13.13 (8.90)	62.45	24		
>=55 - <65 years (N=225)	HDq12 (N=108)	7.48 (1.41)	8.35 (10.03)	64.83	84	HDq12 - 2q8	-2.70 (-6.00, 0.61)
	HDq16 (N=54)	8.85 (1.52)	8.75 (10.43)	61.48	48	HDq16 - 2q8	-1.33 (-4.79, 2.12)
	2q8 (N=63)	10.18 (1.30)	9.68 (9.49)	61.70	47		
>=65 - <75 years (N=218)	HDq12 (N=107)	9.23 (0.98)	9.22 (8.67)	61.73	79	HDq12 - 2q8	0.88 (-2.25, 4.00)
	HDq16 (N=57)	6.74 (1.10)	5.98 (6.91)	60.67	44	HDq16 - 2q8	-1.61 (-4.88, 1.67)
	2q8 (N=54)	8.35 (1.44)	8.62 (10.16)	61.91	47		
>=75 years (N=71)	HDq12 (N=36)	7.34 (1.26)	7.64 (6.53)	62.69	28	HDq12 - 2q8	-0.45 (-5.20, 4.29)
	HDq16 (N=14)	2.30 (2.16)	2.17 (7.48)	59.79	12	HDq16 - 2q8	-5.50 (-11.43, 0.43)
	2q8 (N=21)	7.79 (1.97)	6.93 (8.28)	58.33	15		
White (N=471)	HDq12 (N=231)	8.99 (0.73)	9.51 (9.70)	63.45	177	HDq12 - 2q8	-0.99 (-3.22, 1.23)
	HDq16 (N=128)	8.26 (0.83)	8.70 (9.85)	61.05	104	HDq16 - 2q8	-1.72 (-4.09, 0.64)
	2q8 (N=112)	9.98 (0.87)	9.66 (9.66)	62.71	93		
Black Or African American (N=62)	HDq12 (N=35)	8.89 (1.81)	9.09 (10.97)	63.37	22	HDq12 - 2q8	-0.08 (-8.23, 8.06)
	HDq16 (N=9)	4.46 (1.23)	4.56 (4.39)	65.56	9	HDq16 - 2q8	-4.52 (-12.33, 3.29)
	2q8 (N=18)	8.98 (3.53)	13.22 (14.84)	59.44	9		
Asian (N=101)	HDq12 (N=48)	6.72 (0.99)	7.36 (7.19)	63.58	45	HDq12 - 2q8	-1.01 (-4.74, 2.72)
	HDq16 (N=23)	5.61 (1.28)	5.82 (6.86)	62.91	22	HDq16 - 2q8	-2.12 (-6.19, 1.95)
	2q8 (N=30)	7.73 (1.57)	7.77 (7.62)	58.33	26		
Not Hispanic Or Latino (N=525)	HDq12 (N=266)	8.56 (0.68)	9.07 (9.27)	63.77	212	HDq12 - 2q8	-1.28 (-3.28, 0.72)
	HDq16 (N=126)	7.89 (0.82)	8.36 (9.13)	62.06	110	HDq16 - 2q8	-1.95 (-4.14, 0.23)
	2q8 (N=133)	9.84 (0.84)	10.06 (9.71)	61.90	106		
Hispanic Or Latino (N=119)	HDq12 (N=54)	7.71 (1.33)	8.97 (9.79)	62.35	36	HDq12 - 2q8	0.05 (-4.36, 4.47)
	HDq16 (N=34)	5.88 (1.25)	5.80 (9.35)	58.65	25	HDq16 - 2q8	-1.77 (-6.07, 2.52)
	2q8 (N=31)	7.66 (1.76)	8.04 (9.38)	59.65	25		
Japan (N=74)	HDq12 (N=37)	8.66 (0.89)	8.78 (6.32)	63.19	36	HDq12 - 2q8	0.81 (-3.48, 5.10)
	HDq16 (N=17)	6.69 (1.71)	6.38 (7.56)	62.00	16	HDq16 - 2q8	-1.16 (-6.31, 3.99)
	2q8 (N=20)	7.85 (1.88)	8.53 (8.29)	58.20	19		
Rest of the World (N=584)	HDq12 (N=291)	8.41 (0.64)	9.10 (9.69)	63.69	216	HDq12 - 2q8	-1.30 (-3.27, 0.66)
	HDq16 (N=146)	7.73 (0.74)	8.17 (9.33)	61.38	122	HDq16 - 2q8	-1.98 (-4.07, 0.11)
	2q8 (N=147)	9.71 (0.77)	9.80 (9.80)	61.92	114		
BL BCVA: <=73 letters (N=556)	HDq12 (N=269)	8.82 (0.73)	9.54 (9.96)	60.99	203	HDq12 - 2q8	-1.49 (-3.48, 0.50)
	HDq16 (N=140)	8.15 (0.85)	8.38 (9.54)	59.16	120	HDq16 - 2q8	-2.16 (-4.31, -0.01)
	2q8 (N=147)	10.32 (0.82)	10.66 (9.36)	59.53	116		
BL BCVA: >73 letters (N=102)	HDq12 (N=59)	6.53 (1.01)	7.04 (5.21)	75.68	49	HDq12 - 2q8	3.05 (-0.76, 6.85)
	HDq16 (N=23)	4.65 (1.31)	5.17 (5.12)	75.30	18	HDq16 - 2q8	1.16 (-3.06, 5.39)
	2q8 (N=20)	3.48 (1.78)	2.47 (8.09)	75.75	17		

BL CRT: <400 µm (N=271)	HDq12 (N=134)	7.44 (0.89)	7.77 (8.80)	65.86	103	HDq12 - 2q8	-0.20 (-2.70, 2.29)
	HDq16 (N=65)	5.82 (1.08)	5.48 (8.64)	66.08	54	HDq16 - 2q8	-1.83 (-4.61, 0.94)
	2q8 (N=72)	7.65 (1.03)	8.34 (8.70)	63.92	53		
BL CRT: >=400 µm (N=387)	HDq12 (N=194)	9.28 (0.88)	9.94 (9.51)	62.10	149	HDq12 - 2q8	-1.16 (-3.68, 1.36)
	HDq16 (N=98)	9.08 (1.01)	9.56 (9.14)	58.37	84	HDq16 - 2q8	-1.36 (-4.04, 1.32)
	2q8 (N=95)	10.44 (1.08)	10.46 (10.09)	59.62	80		
Prior DME: Y (N=290)	HDq12 (N=145)	8.30 (0.92)	8.36 (9.93)	62.43	115	HDq12 - 2q8	0.14 (-2.54, 2.82)
	HDq16 (N=71)	4.61 (1.01)	4.89 (7.86)	58.58	65	HDq16 - 2q8	-3.55 (-6.35, -0.74)
	2q8 (N=74)	8.16 (1.10)	8.00 (9.48)	62.07	63		
Prior DME: N (N=368)	HDq12 (N=183)	8.67 (0.88)	9.64 (8.67)	64.59	137	HDq12 - 2q8	-1.46 (-3.90, 0.97)
	HDq16 (N=92)	9.99 (1.01)	10.70 (9.37)	63.65	73	HDq16 - 2q8	-0.15 (-2.76, 2.47)
	2q8 (N=93)	10.14 (1.07)	11.07 (9.51)	61.00	70		

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4'week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4'week intervals.
CI = Confidence interval. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. LS = Least Square. BL = Baseline.
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. If the subgroup was one of the stratification factors, then it was not included in the statistical model. An unstructured covariance type was used to model the within-subject error for all subgroups.
[a] The contrast also included the interaction term for treatment x visit
[b] Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

Overall, the primary and key secondary endpoint criteria, to know, the change from baseline in BCVA measured by the ETDRS letter score at Week 48 and 60 (non-inferiority of IVT aflibercept therapy HDq12 and HDq16 dosing regimen to the current authorized IVT aflibercept therapy 2q8 dosing regimen) is considered to be statistically met (95% credible interval for treatment difference with a non-inferiority margin of 4 letters with LS mean change from baseline in BCVA to Week 48) and fruher supported by the sensitivy analysis.

Change from baseline in BCVA measured by ETDRS letter score <u>at Week 96</u>

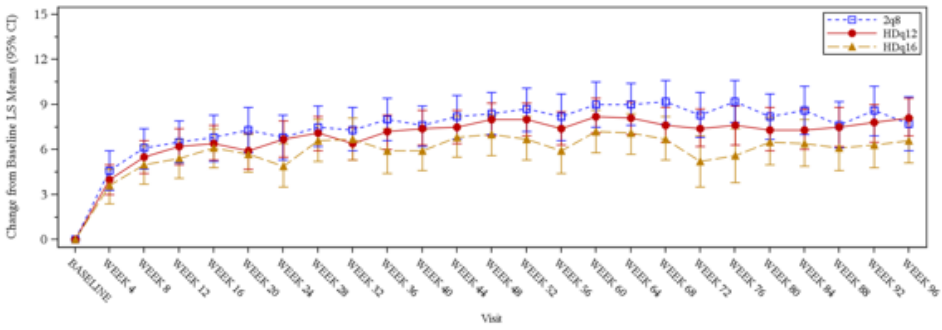
- ***PHOTON study***

Table 8 PHOTON: Change from baseline in BCVA measured by the ETDRS letter score at Week 48, Week 60 and Week 96, MMRM (FAS)

		2q8 N = 167	HDq12 N = 328	HDq16 N = 163
Baseline mean		61.47	63.63	61.44
Week 48	Number of subjects with Week 48 data	150	277	149
Primary	Arithmetic mean (SD) change from baseline	9.21 (8.99)	8.77 (8.95)	7.86 (8.38)
efficacy endpoint	LS mean (SE) change from baseline	8.67 (0.73)	8.10 (0.61)	7.23 (0.71)
	Contrast [a]		HDq12 - 2q8	HDq16 - 2q8
	Estimate for Contrast and two-sided 95% CI [c]		-0.57 (-2.26, 1.13)	-1.44 (-3.27, 0.39)
	p-value of one-sided test for non-inferiority at a margin of 4 letters		<0.0001	0.0031
Week 60	Number of subjects with Week 60 data	133	252	138
Key secondary	Arithmetic mean (SD) change from baseline	9.62 (9.58)	9.05 (9.27)	7.96 (9.14)
efficacy endpoint	LS mean (SE) change from baseline	9.40 (0.77)	8.52 (0.63)	7.64 (0.75)
	DF	/	342.4	315.5
	Contrast [a]	/	HDq12 - 2q8	HDq16 - 2q8
	Estimate for Contrast and two-sided 95% CI [c]	/	-0.88 (-2.67, 0.91)	-1.76 (-3.71, 0.19)
	p-value of one-sided test for non-inferiority at a margin of 4 letters	/	0.0003	0.0122
Week 96	Number of subjects with Week 96 data	124	222	127
Exploratory	Arithmetic mean (SD) change from baseline	8.41 (11.10)	8.82 (9.93)	7.50 (9.86)
efficacy endpoint	LS mean (SE) change from baseline	7.70 (0.89)	8.15 (0.63)	6.59 (0.77)
	DF		386.7	391.5
	Contrast [a]		HDq12 - 2q8	HDq16 - 2q8
	Estimate for Contrast and two-sided 95% CI [c]		0.45 (-1.55, 2.45)	-1.11 (-3.27, 1.05)
	p-value of one-sided test for non-inferiority at a margin of 4 letters [b]		<0.0001	0.0044

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI = Confidence interval. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. LS = Least Square. BL = Baseline.
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CST (from reading center) [<400µm vs. >=400µm], prior treatment for DME [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. Heterogeneous Toeplitz covariance structure was used to model the within-subject error.
Intercurrent events (ICE) were handled according to Table 1 of SAP
[a] The contrast also included the interaction term for treatment x visit.
[b] Nominal p-value.
[c] Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.
Source: Module 5.3.5.1, PHOTON W60 CSR, W48 Table 14.2.1.1 and W60 Table 14.2.1.1a, Module 5.3.5.1, PHOTON TLF EMA CHMP Day-120 W96 CSR_key, Table 14.2.1.1b

Figure 7 PHOTON: LS-mean change from baseline in BCVA measured by the ETDRS letter score by visit through Week 96, MMRM (FAS)



2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP
Least square mean (LSM) was generated from a mixed model for repeated measurements (MMRM), with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400 microns vs. >=400 microns], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.

Source: Module 5.3.5.1, PHOTON TLF EMA CHMP Day-120 W96 CSR_key, Figure 14.2.1.3b

As presented in the initial application, both HDq12 and HDq16 demonstrated non-inferiority to 2q8 with respect to the primary efficacy endpoint (change from baseline in BCVA at Week 48) as well as the key secondary endpoint (change from baseline in BCVA at Week 60) using the non-inferiority margin of 4 letters with LS mean change from baseline in BCVA.

Based on the table and figure above, consistency was shown also for the exploratory efficacy BCVA endpoint at Week 96 with pairwise differences in LS means (95% CI), based on the MMRM model, of 0.45 letters (-1.55, 2.45) for HDq12 vs. 2q8 and -1.11 letters (-3.27, 1.05) for HDq16 vs. 2q8. Indeed, both point estimates are comparable to those observed at Week 48 and Week 60

The LS mean of BCVA gains were stable over time and similar across all groups, with minor numerical differences not being considered as clinically relevant.

Secondary key endpoint analysis

Proportion of Participants With a ≥ 2-Step Improvement in DRSS Score at Week 48

As the statistical tests ranked higher in the EP-SAP testing hierarchy were significant for both HD groups (ie, the statistical tests H10, H20, H30 and H40), the test sequence could be continued with testing the key secondary efficacy endpoint, the proportion of participants with ≥ 2-step improvement in DRSS score (as assessed by the central reading center) at week 48 (ie, H50 and H60).

HDq12 was non-inferior to 2q8 with respect to this endpoint. However, this could not be shown for the HDq16 group. The non-inferiority margin was prespecified at 15%, however HDq12 also met a 10% NI margin. The proportion of participants with ≥ 2-step improvement in DRSS score was 25.7%, 24.7% and 20.7% at week 12 and 26.6%, 29.0%, and 19.6% at week 48 in the 2q8, HDq12, and HDq16 groups respectively. In CMH-weighted estimates, the adjusted difference (95% CI) was 1.98% (-6.61, 10.57) for HDq12 and -7.52% (-16.88, 1.84) for HDq16, respectively versus 2q8 (Table 16).

Table 16: Key Secondary Endpoint – Proportion of Participants with a ≥ 2-Step Improvement from Baseline in DRSS at Week 48 (LOCF) (Full Analysis Set)

Treatment	Patients with a ≥ 2-step Improvement From Baseline in DRSS, n (%)	Adjusted Difference (%) 2-sided (95% CI) [a]
HDq12 (N=328)	90/310 (29.0%)	1.98 (-6.61 , 10.57)
HDq16 (N=163)	30/153 (19.6%)	-7.52 (-16.88 , 1.84)
2q8 (N=167)	42/158 (26.6%)	

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. CI=confidence interval; CRT= central retinal thickness; DRSS=Diabetic Retinopathy Severity Scale; N,n=number of patients; SAP = statistical analysis plan

Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF= the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Patients were considered as non-responders if all post-baseline measurements were missing or non-gradable.

[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). The non-inferiority margin was set at 15%.

Missing or ungradable baseline was not included in the denominator.

Sensitivity analysis using observed cases was performed and are presented in Table 14.2.2.2.

Table 14.2.2.2 Proportion Analysis of Patients with a >=2-Step Improvement from Baseline in DRSS at Week 48 (OC) (Full Analysis Set)

Treatment	Patients with a >= 2-step improvement from baseline in DRSS, n (%)	Adjusted Difference (%) 2-sided (95% CI) [a]
HDq12 (N=328)	77/259 (29.7%)	4.92 (-4.24 , 14.07)
HDq16 (N=163)	26/138 (18.8%)	-5.96 (-15.71 , 3.78)
2q8 (N=167)	33/136 (24.3%)	

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP. OC: observations after an ICE defined for the primary estimand were excluded.
DRSS = Diabetic Retinopathy Severity Scale.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). The non-inferiority margin was set at 15%.
Missing or ungradable baseline was not included in the denominator.

Proportion of Participants With a ≥ 2-Step Improvement in DRSS Score at Week 60 (Exploratory Endpoint)

The proportion of participants with ≥ 2-step improvement in DRSS score was 25.7%, 24.6%, and 20.7% at week 12 and 29.1%, 31.3%, and 22.2% at week 60 in the 2q8, HDq12, and HDq16 groups, respectively. In CMH-weighted estimates, the adjusted difference (95% CI) was 1.87 (-6.88, 10.63) for HDq12 and -7.47 (-17.05, 2.12) for HDq16, respectively, versus 2q8 (Table 17).

Table 17: Exploratory Endpoint – Proportion of Participants with a ≥ 2-Step Improvement from Baseline in DRSS at Week 60 (LOCF) (Full Analysis Set)

Treatment	Patients with a ≥ 2-step Improvement From Baseline in DRSS, n (%)	Adjusted Difference (%) 2-sided (95% CI) [a]
HDq12 (N=328)	97/310 (31.3%)	1.87 (-6.88, 10.63)
HDq16 (N=163)	34/153 (22.2%)	-7.47 (-17.05, 2.12)
2q8 (N=167)	46/158 (29.1%)	

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI=confidence interval; CRT= central retinal thickness; DME=diabetic macular edema; DRSS=Diabetic Retinopathy Severity Scale; LOCF=last observation carried forward; N,n=number of participants; SAP = Statistical analysis plan
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF= the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Participants were considered as non-responders if all post-baseline measurements were missing or non-gradable.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). The non-inferiority margin was set at 15%.
Missing or ungradable baseline was not included in the denominator.

Sensitivity analysis using OC was performed and are presented in Table 14.2.2.2a.

Table 14.2.2.2 Proportion Analysis of Patients with a >=2-Step Improvement from Baseline in DRSS at Week 48 (OC) (Full Analysis Set)

Treatment	Patients with a >= 2-step improvement from baseline in DRSS, n (%)	Adjusted Difference (%) 2-sided (95% CI) [a]
HDq12 (N=328)	77/259 (29.7%)	4.92 (-4.24 , 14.07)
HDq16 (N=163)	26/138 (18.8%)	-5.96 (-15.71 , 3.78)
2q8 (N=167)	33/136 (24.3%)	

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP. OC: observations after an ICE defined for the primary estimand were excluded.
DRSS = Diabetic Retinopathy Severity Scale.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). The non-inferiority margin was set at 15%.
Missing or ungradable baseline was not included in the denominator.

Subgroup Analysis of Participants With a ≥ 2-Step Improvement in DRSS at Week 48 and 60

Subgroup analyses were performed for participants with a ≥ 2-step improvement in DRSS score at week 48 and week 60 by sex, age group, race, ethnicity, baseline BCVA, geographic region, baseline CRT category, and prior DME treatment and are presented in Tables 14.2.2.5 to 14.2.2.12 for week 48 and Tables 14.2.2.5a to 14.2.2.13a for week 60 (LOCF –FAS). Discrepancies in PHOTON study regarding the improvement of ≥2-Step in DRSS Score in the HD groups compared to the 2q8 group were observed for the following subgroups: <50 years, ≥ 55- < 65 years, ≥ 65 to < 75 years, males, females, White, Asian, with a baseline BCVA ≤ 73 letters or ≥ 73 letters, and CRT <400 micron or ≥ 400 micron at baseline subgroups. However, given the smaller size of these subgroups, the validity of these comparisons appeared limited.

Tables 14.2.2.5 to 14.2.2.12 Subgroup Analysis of Patients with a >=2-Step Improvement at Week 48

Subgroup	Treatment	Patients with a >= 2-step improvement from baseline in DRSS, n (%)	Adjusted Difference (%) 2-sided (95% CI) [a]
Sex: Female (N=257)	HDq12 (N=118)	30/113 (26.5%)	11.94 (0.27 , 23.60)
	HDq16 (N=64)	8/63 (12.7%)	-2.11 (-13.44 , 9.22)
	2q8 (N=75)	10/71 (14.1%)	
Sex: Male (N=401)	HDq12 (N=210)	60/197 (30.5%)	-6.62 (-18.59 , 5.34)
	HDq16 (N=99)	22/90 (24.4%)	-12.86 (-26.53 , 0.81)
	2q8 (N=92)	32/87 (36.8%)	
Age: <55 Years (N=144)	HDq12 (N=77)	26/72 (36.1%)	-11.12 (-32.99 , 10.75)
	HDq16 (N=38)	11/38 (28.9%)	-19.11 (-43.16 , 4.95)
	2q8 (N=29)	13/28 (46.4%)	
Age: >=55 - <65 Years (N=225)	HDq12 (N=108)	35/104 (33.7%)	7.71 (-6.52 , 21.95)
	HDq16 (N=54)	7/50 (14.0%)	-12.49 (-27.27 , 2.29)
	2q8 (N=63)	15/61 (24.6%)	
Age: >=65 - <75 Years (N=218)	HDq12 (N=107)	25/102 (24.5%)	-0.99 (-16.55 , 14.58)
	HDq16 (N=57)	11/54 (20.4%)	-4.57 (-21.31 , 12.18)
	2q8 (N=54)	12/48 (25.0%)	
Age: >=75 Years (N=71)	HDq12 (N=36)	4/32 (12.5%)	3.18 (-12.87 , 19.23)
	HDq16 (N=14)	1/11 (9.1%)	0.00 (-19.24 , 19.24)
	2q8 (N=21)	2/21 (9.5%)	
Race: White (N=471)	HDq12 (N=231)	66/219 (30.1%)	5.71 (-4.52 , 15.94)
	HDq16 (N=128)	23/121 (19.0%)	-6.23 (-16.98 , 4.52)
	2q8 (N=112)	26/108 (24.1%)	
Race: Black Or African American (N=62)	HDq12 (N=35)	8/32 (25.0%)	-2.12 (-29.78 , 25.54)
	HDq16 (N=9)	2/8 (25.0%)	12.11 (-24.15 , 48.37)
	2q8 (N=18)	4/15 (26.7%)	
Race: Asian (N=101)	HDq12 (N=48)	12/47 (25.5%)	-2.26 (-24.90 , 20.38)
	HDq16 (N=23)	5/21 (23.8%)	-1.15 (-27.11 , 24.80)
	2q8 (N=30)	9/28 (32.1%)	
Ethnicity: Not Hispanic Or Latino (N=525)	HDq12 (N=266)	78/253 (30.8%)	1.99 (-7.77 , 11.76)
	HDq16 (N=126)	22/118 (18.6%)	-10.10 (-20.73 , 0.52)
	2q8 (N=133)	36/125 (28.8%)	
Ethnicity: Hispanic Or Latino (N=119)	HDq12 (N=54)	11/49 (22.4%)	5.06 (-14.43 , 24.55)
	HDq16 (N=34)	8/32 (25.0%)	10.26 (-10.75 , 31.28)
	2q8 (N=31)	6/30 (20.0%)	
Baseline BCVA: <=73 Letters (N=556)	HDq12 (N=269)	73/252 (29.0%)	2.58 (-6.66 , 11.81)
	HDq16 (N=140)	25/130 (19.2%)	-7.62 (-17.64 , 2.40)
	2q8 (N=147)	36/138 (26.1%)	
Baseline BCVA: >73 Letters (N=102)	HDq12 (N=59)	17/58 (29.3%)	-2.44 (-26.78 , 21.89)
	HDq16 (N=23)	5/23 (21.7%)	-22.95 (-51.32 , 5.42)
	2q8 (N=20)	6/20 (30.0%)	
Region: Japan (N=74)	HDq12 (N=37)	9/36 (25.0%)	-0.60 (-24.74 , 23.54)
	HDq16 (N=17)	4/16 (25.0%)	1.43 (-26.96 , 29.81)
	2q8 (N=20)	5/20 (25.0%)	
Region: Rest Of World (N=584)	HDq12 (N=291)	81/274 (29.6%)	2.34 (-6.85 , 11.53)
	HDq16 (N=146)	26/137 (19.0%)	-8.66 (-18.56 , 1.23)
	2q8 (N=147)	37/138 (26.8%)	
Baseline CRT category: <400 Microns (N=271)	HDq12 (N=134)	35/126 (27.8%)	6.17 (-6.33 , 18.66)
	HDq16 (N=65)	10/59 (16.9%)	-3.99 (-17.56 , 9.58)
	2q8 (N=72)	14/68 (20.6%)	
Baseline CRT category: >=400 Microns (N=387)	HDq12 (N=194)	55/184 (29.9%)	-1.06 (-12.75 , 10.62)
	HDq16 (N=98)	20/94 (21.3%)	-9.93 (-22.67 , 2.80)
	2q8 (N=95)	28/90 (31.1%)	
Prior DME treatment: Y (N=288)	HDq12 (N=143)	29/135 (21.5%)	-3.24 (-15.61 , 9.12)
	HDq16 (N=71)	11/65 (16.9%)	-7.87 (-21.42 , 5.67)
	2q8 (N=74)	17/71 (23.9%)	
Prior DME treatment: N (N=370)	HDq12 (N=185)	61/175 (34.9%)	6.13 (-5.70 , 17.97)
	HDq16 (N=92)	19/88 (21.6%)	-7.25 (-20.11 , 5.61)
	2q8 (N=93)	25/87 (28.7%)	

Intercurrent events (ICE) were handled according to Table 1 of SAP. LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Patients were considered as non-responders if all post-baseline measurements were missing or non-gradable.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). If the subgroup is one of the stratification factors, then it will not be include in the statistical model
DRSS = Diabetic Retinopathy Severity Scale.
Missing or ungradable baseline was not included in the denominator.

Tables 14.2.2.5a to 14.2.2.13a Subgroup Analysis of Patients with a >=2-Step Improvement at Week 60 (LOCF - FAS)

Subgroup	Treatment	Patients with a >= 2-step improvement from baseline in DRSS, n (%)	Adjusted Difference (%) 2-sided (95% CI) [a]
Sex: Female (N=257)	HDq12 (N=118)	36/113 (31.9%)	15.78 (3.44 , 28.12)
	HDq16 (N=64)	9/63 (14.3%)	-2.15 (-14.24 , 9.95)
	2q8 (N=75)	12/71 (16.9%)	
Sex: Male (N=401)	HDq12 (N=210)	61/197 (31.0%)	-8.41 (-20.40 , 3.57)
	HDq16 (N=99)	25/90 (27.8%)	-11.88 (-25.71 , 1.96)
	2q8 (N=92)	34/87 (39.1%)	
Age: <55 Years (N=144)	HDq12 (N=77)	30/72 (41.7%)	-4.09 (-25.97 , 17.79)
	HDq16 (N=38)	12/38 (31.6%)	-17.89 (-42.05 , 6.26)
	2q8 (N=29)	13/28 (46.4%)	
Age: >=55 - <65 Years (N=225)	HDq12 (N=108)	37/104 (35.6%)	6.92 (-7.53 , 21.36)
	HDq16 (N=54)	8/50 (16.0%)	-12.59 (-27.47 , 2.30)
	2q8 (N=63)	17/61 (27.9%)	
Age: >=65 - <75 Years (N=218)	HDq12 (N=107)	26/102 (25.5%)	-1.87 (-17.86 , 14.12)
	HDq16 (N=57)	13/54 (24.1%)	-2.25 (-19.60 , 15.10)
	2q8 (N=54)	13/48 (27.1%)	
Age: >=75 Years (N=71)	HDq12 (N=36)	4/32 (12.5%)	-0.07 (-17.91 , 17.77)
	HDq16 (N=14)	1/11 (9.1%)	0.00 (-19.24 , 19.24)
	2q8 (N=21)	3/21 (14.3%)	
Race: White (N=471)	HDq12 (N=231)	72/219 (32.9%)	5.79 (-4.62 , 16.20)
	HDq16 (N=128)	26/121 (21.5%)	-6.78 (-17.82 , 4.26)
	2q8 (N=112)	29/108 (26.9%)	
Race: Black Or African American (N=62)	HDq12 (N=35)	8/32 (25.0%)	4.98 (-20.37 , 30.32)
	HDq16 (N=9)	2/8 (25.0%)	16.38 (-21.80 , 54.56)
	2q8 (N=18)	3/15 (20.0%)	
Race: Asian (N=101)	HDq12 (N=48)	13/47 (27.7%)	-10.04 (-33.66 , 13.59)
	HDq16 (N=23)	5/21 (23.8%)	-9.23 (-36.20 , 17.74)
	2q8 (N=30)	11/28 (39.3%)	
Ethnicity: Not Hispanic Or Latino (N=525)	HDq12 (N=266)	83/253 (32.8%)	1.65 (-8.29 , 11.59)
	HDq16 (N=126)	26/118 (22.0%)	-9.34 (-20.31 , 1.63)
	2q8 (N=133)	39/125 (31.2%)	
Ethnicity: Hispanic Or Latino (N=119)	HDq12 (N=54)	13/49 (26.5%)	4.76 (-15.25 , 24.77)
	HDq16 (N=34)	8/32 (25.0%)	9.04 (-11.59 , 29.68)
	2q8 (N=31)	7/30 (23.3%)	
Baseline BCVA: <=73 Letters (N=556)	HDq12 (N=269)	78/252 (31.0%)	1.74 (-7.66 , 11.14)
	HDq16 (N=140)	28/130 (21.5%)	-8.34 (-18.62 , 1.93)
	2q8 (N=147)	40/138 (29.0%)	
Baseline BCVA: >73 Letters (N=102)	HDq12 (N=59)	19/58 (32.8%)	2.52 (-22.47 , 27.51)
	HDq16 (N=23)	6/23 (26.1%)	-13.64 (-44.75 , 17.47)
	2q8 (N=20)	6/20 (30.0%)	
Region: Japan (N=74)	HDq12 (N=37)	9/36 (25.0%)	-10.33 (-36.01 , 15.35)
	HDq16 (N=17)	4/16 (25.0%)	-8.57 (-38.54 , 21.40)
	2q8 (N=20)	7/20 (35.0%)	
Region: Rest Of World (N=584)	HDq12 (N=291)	88/274 (32.1%)	3.58 (-5.71 , 12.86)
	HDq16 (N=146)	30/137 (21.9%)	-7.32 (-17.43 , 2.78)
	2q8 (N=147)	39/138 (28.3%)	
Baseline CRT category: <400 Microns (N=271)	HDq12 (N=134)	38/126 (30.2%)	6.96 (-5.85 , 19.76)
	HDq16 (N=65)	9/59 (15.3%)	-7.18 (-20.75 , 6.39)
	2q8 (N=72)	15/68 (22.1%)	
Baseline CRT category: >=400 Microns (N=387)	HDq12 (N=194)	59/184 (32.1%)	-1.83 (-13.70 , 10.03)
	HDq16 (N=98)	25/94 (26.6%)	-7.66 (-20.87 , 5.55)
	2q8 (N=95)	31/90 (34.4%)	
Prior DME treatment: Y (N=290)	HDq12 (N=145)	31/137 (22.6%)	-0.52 (-12.79 , 11.76)
	HDq16 (N=71)	11/65 (16.9%)	-6.25 (-19.63 , 7.13)
	2q8 (N=74)	16/71 (22.5%)	
Prior DME treatment: N (N=368)	HDq12 (N=183)	66/173 (38.2%)	3.79 (-8.55 , 16.13)
	HDq16 (N=92)	23/88 (26.1%)	-8.40 (-21.88 , 5.08)
	2q8 (N=93)	30/87 (34.5%)	

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4'week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4'week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP. LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Patients were considered as non-responders if all post-baseline measurements were missing or non-gradable.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). If the subgroup is one of the stratification factors, then it will not be include in the statistical model
[b] P-value is calculated using 2-sided Cochran-Mantel-Haenszel (CMH) superiority test adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). If the subgroup is one of the stratification factors, then it will not be include in the statistical model
DRSS = Diabetic Retinopathy Severity Scale.

The key secondary endpoint appears to be statistically met in the HDq12 arm but not in the HDq16 and the sensitivity analyses supported the results at week 48 and 60 (PHOTON study). Additionally, results tend to differ in the HDq12 and HDq16 groups and some secondary and exploratory endpoints results tend to stand out more than others between groups. The MAH was asked to discuss the impact of those data and their clinical relevance on the dosing regimen (HDq16) proposed in the SmPC in DME patients.

In response, The Applicant concluded that all treatment arms achieved similar functional benefits. Differences in structural endpoints were mostly associated with injection timing and did not translate into clinically meaningful differences in quality of life or visual acuity.

The eligibility criteria of the PHOTON study aimed to include an informative population in terms of DME assessment, which does not equate the one selected for DRSS assessment. In PHOTON, despite the limitations in study design, the evaluation of DRSS was included in the context of the fact that aflibercept 2 mg is in the US approved not only for the treatment of DME, but also for the treatment of DR. Therefore, evaluating the effects of aflibercept 8 mg was considered relevant for that territory. The key secondary endpoint of the proportion of participants with a ≥ 2-step improvement in DRSS score at Week 48 was pre-specified to potentially support an indication of aflibercept 8 mg for treatment of DR in the US. This endpoint was tested with a non-inferiority margin of 15% which was met by the HDq12 arm (adjusted difference 1.98%, 95% CI -6.61, 10.57) but not by the HDq16 arm (adjusted difference -7.52%, 95% CI -16.88, 1.84). however, considering that the primary endpoint showed that BCVA improvement as a direct effect of DME treatment was non-inferior for HDq12 and HDq16 compared to 2q8, the Applicant concluded that the effect on DRSS stage improvement does not correlate with the effect on DME, and improvements in DRSS are not a prerequisite for vision improvements in DME.

Other secondary and exploratory efficacy endpoints analysis

Proportion of Participants Gaining ≥ 15 Letters in BCVA from Baseline

Week 48

The proportion of participants who gained ≥ 15 letters in BCVA from baseline to week 48 was 18.7% and 16.6% in the HDq12 and HDq16 groups, respectively, compared with 23.0% in the 2q8 group (Table 19).

Table 19: Proportion of Participants who Gained ≥ 15 Letters in BCVA from Baseline at Week 48 (LOCF) (Full Analysis Set)

Treatment	Patients with ≥ 15 Letters gain in BCVA from baseline to Week 48, n (%)	Adjusted Difference (%) (95% CI)[a]	CMH test[b] p-value
HDq12 (N=328)	61/326 (18.7%)	-4.64 (-12.30 , 3.02)	0.2231
HDq16 (N=163)	27/163 (16.6%)	-7.14 (-15.45 , 1.17)	0.0960
2q8 (N=167)	38/165 (23.0%)		

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12=High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16=High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
BCVA=best corrected visual acuity; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CRT= central retinal thickness (or, central subfield retinal thickness); DME= diabetic macular edema; ICE=intercurrent events; LOCF=last observation carried forward; N,n=number of patients; SAP= statistical analysis plan.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Missing data were not included in the denominator.
[a] Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
[b] Nominal p-value for the 2-sided CMH superiority test.

Sensitivity analysis for the proportion of participants who gained ≥ 15 letters in BCVA from baseline at week 48 using OC was consistent with the LOCF analysis (Tables 14.2.3.1.2 and 14.2.3.1.4).

Table 14.2.3.1.2 Proportion Analysis of Patients who Gained >= 15 Letters in BCVA from Baseline at Week 48 (OC)
(Full Analysis Set)

Treatment	Patients with >= 15 Letters gain in BCVA from baseline to Week 48, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test [b] p-value
HDq12 (N=328)	55/277 (19.9%)	-4.19 (-12.44 , 4.06)	0.3094
HDq16 (N=163)	26/149 (17.4%)	-6.84 (-15.64 , 1.96)	0.1304
2q8 (N=167)	36/150 (24.0%)		

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP. OC: observations after an ICE defined for the primary estimand were excluded.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan])
[b] p-value for the two-sided Cochran-Mantel-Haenszel (CMH) superiority test.
Missing data were not included in the denominator.

Table 14.2.3.1.4 Proportion of Patients who Gained >= 15 Letters in BCVA from Baseline by Visit through Week 48 (OC)
(Full Analysis Set)

Visit	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)
Week 4	14/163 (8.6%)	20/326 (6.1%)	8/163 (4.9%)
Week 8	24/163 (14.7%)	39/317 (12.3%)	16/161 (9.9%)
Week 12	27/165 (16.4%)	44/314 (14.0%)	20/160 (12.5%)
Week 16	33/163 (20.2%)	42/299 (14.0%)	22/159 (13.8%)
Week 20	30/147 (20.4%)	40/304 (13.2%)	19/152 (12.5%)
Week 24	38/160 (23.8%)	48/272 (17.6%)	15/155 (9.7%)
Week 28	36/150 (24.0%)	48/285 (16.8%)	28/144 (19.4%)
Week 32	38/159 (23.9%)	40/287 (13.9%)	25/149 (16.8%)
Week 36	38/142 (26.8%)	52/271 (19.2%)	24/146 (16.4%)
Week 40	28/152 (18.4%)	55/267 (20.6%)	22/151 (14.6%)
Week 44	34/141 (24.1%)	62/280 (22.1%)	24/145 (16.6%)
Week 48	36/150 (24.0%)	55/277 (19.9%)	26/149 (17.4%)

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP. OC: observations after an ICE defined for the primary estimand were excluded.
Missing data were not included in the denominator.

Week 60

The proportion of participants who gained ≥ 15 letters in BCVA from baseline to week 60 was 21.5% and 16.0% in the HDq12 and HDq16 groups, respectively, compared with 26.1% in the 2q8 group (Table 20).

Table 20: Proportion of Participants who Gained ≥ 15 Letters in BCVA from Baseline at Week 60 (LOCF) (Full Analysis Set)

Treatment	Patients with ≥ 15 Letters gained in BCVA from baseline to Week 60, n (%)	Adjusted Difference (%) (95% CI)[a]	CMH test p-value[b]
HDq12 (N=328)	70/326 (21.5%)	-5.01 (-13.04 , 3.02)	0.2112
HDq16 (N=163)	26/163 (16.0%)	-10.78 (-19.27 , -2.29)	0.0143
2q8 (N=167)	43/165 (26.1%)		

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12=High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16=High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
BCVA=best corrected visual acuity; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CRT= central retinal thickness (or, central subfield retinal thickness); DME= diabetic macular edema; ICE=intercurrent events; LOCF=last observation carried forward; N,n=number of participants; SAP= statistical analysis plan.
Intercurrent events were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data.
Missing data were not included in the denominator.
[a] Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
[b] Nominal p-value for the 2-sided CMH superiority test.

Sensitivity analysis for the proportion of participants who gained ≥ 15 letters in BCVA from baseline at week 60 using OC was consistent with the LOCF analysis (Tables 14.2.3.1.2a and 14.2.3.1.4a).

Table 14.2.3.1.2a Proportion Analysis of Patients who Gained >= 15 Letters in BCVA from Baseline at Week 60 (OC)
(Full Analysis Set)

Treatment	Patients with >= 15 Letters gain in BCVA from baseline to Week 60, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test [b] p-value
HDq12 (N=328)	56/252 (22.2%)	-5.85 (-14.96 , 3.27)	0.2002
HDq16 (N=163)	23/138 (16.7%)	-11.53 (-21.00 , -2.05)	0.0183
2q8 (N=167)	37/133 (27.8%)		

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4'week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4'week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP. OC: observations after an ICE defined for the primary estimand were excluded.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan])
[b] p-value for the two-sided Cochran-Mantel-Haenszel (CMH) superiority test.
Missing data were not included in the denominator.

Table 14.2.3.1.4a Proportion of Patients who Gained >= 15 Letters in BCVA from Baseline by Visit through Week 60 (OC)
(Full Analysis Set)

Visit	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)
Week 4	14/163 (8.6%)	20/326 (6.1%)	8/163 (4.9%)
Week 8	24/163 (14.7%)	39/317 (12.3%)	16/161 (9.9%)
Week 12	27/165 (16.4%)	44/314 (14.0%)	20/160 (12.5%)
Week 16	33/163 (20.2%)	42/299 (14.0%)	22/159 (13.8%)
Week 20	30/147 (20.4%)	40/304 (13.2%)	19/152 (12.5%)
Week 24	38/160 (23.8%)	48/272 (17.6%)	15/155 (9.7%)
Week 28	36/150 (24.0%)	48/285 (16.8%)	28/144 (19.4%)
Week 32	38/159 (23.9%)	40/287 (13.9%)	25/149 (16.8%)
Week 36	38/142 (26.8%)	52/271 (19.2%)	24/146 (16.4%)
Week 40	28/152 (18.4%)	55/267 (20.6%)	22/151 (14.6%)
Week 44	34/141 (24.1%)	62/280 (22.1%)	24/145 (16.6%)
Week 48	36/150 (24.0%)	55/277 (19.9%)	26/149 (17.4%)
Week 52	44/144 (30.6%)	56/255 (22.0%)	19/137 (13.9%)
Week 56	37/144 (25.7%)	60/266 (22.6%)	21/142 (14.8%)
Week 60	37/133 (27.8%)	56/252 (22.2%)	23/138 (16.7%)

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4'week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4'week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP. OC: observations after an ICE defined for the primary estimand were excluded.

Proportion of Participants with BCVA ≥ 69 Letters

Week 48

The proportion of participants who achieved ≥ 69 letters in BCVA (≥ 20/40 Snellen equivalent) at week 48 was similar across treatment groups (63.0 to 65.3% participants) as shown in Table 21.

Table 21: Proportion of Participants with BCVA ≥ 69 letters at Week 48 (LOCF) (FAS)

Treatment	Patients with BCVA >= 69 letters at Week 48, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test [b] p-value
HDq12 (N=328)	213/326 (65.3%)	2.45 (-6.47 , 11.36)	0.5917
HDq16 (N=163)	102/163 (62.6%)	-0.67 (-11.16 , 9.82)	0.8998
2q8 (N=167)	104/165 (63.0%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). BCVA: best corrected visual acuity; CMH=Cochran-Mantel-Haenszel; CRT= central retinal thickness (or, central subfield retinal thickness); DME= diabetic macular edema; FAS= Full analysis set; LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data; N,n=number of patients.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan])
[b] Nominal p-value for the 2-sided Cochran-Mantel-Haenszel (CMH) superiority test.
Missing data were not included in the denominator.

Week 60

The proportion of participants who achieved ≥ 69 letters in BCVA (≥ 20/40 Snellen equivalent) at week 60 was similar across treatment groups (60.6% to 64.7% participants) as presented in Table 22.

Table 22: Proportion of Patients with BCVA ≥ 69 letters at Week 60 (LOCF) (FAS)

Treatment	Patients with BCVA >= 69 letters at Week 60, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test p-value [b]
HDq12 (N=328)	211/326 (64.7%)	4.34 (-4.72, 13.40)	0.3479
HDq16 (N=163)	101/163 (62.0%)	1.63 (-8.91, 12.17)	0.7620
2q8 (N=167)	100/165 (60.6%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). BCVA: best corrected visual acuity; CMH=Cochran-Mantel-Haenszel ;CRT= central retinal thickness (or, central subfield retinal thickness); DME= diabetic macular edema; FAS= Full analysis set; LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data; N,n=number of participants.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan])
[b] Nominal p-value for the 2-sided Cochran-Mantel-Haenszel (CMH) superiority test.
Missing data were not included in the denominator.

Proportion of Participants Without Fluid at Foveal Center

Week 48

The proportion of participants without fluid (no IRF and no SRF) at the foveal center (as assessed by the central reading center) at week 48 was 58.5% and 43.8% in the HDq12 and HDq16 groups, respectively, compared with 54.5% in the 2q8 group (Table 23).

Table 23: Proportion of Participants without Fluid (no IRF and no SRF) at the Foveal Center at Week 48 (LOCF) (Full Analysis Set)

Treatment	Patients without fluid, n(%)	Adjusted Difference (%) (95% CI)[a]	CMH test[b] p-value
HDq12 (N=328)	190/325 (58.5%)	4.32 (-4.72 , 13.36)	0.3491
HDq16 (N=163)	71/162 (43.8%)	-9.73 (-20.34 , 0.87)	0.0757
2q8 (N=167)	90/165 (54.5%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CRT= central retinal thickness (or, central subfield retinal thickness); DME= diabetic macular edema; ICE=intercurrent events; IRF=intraretinal fluid; LOCF=last observation carried forward; N,n=number of participants; SAP=-statistical analysis plan;SRF=subretinal fluid.
Intercurrent events were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF= the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data.
Missing or undetermined data were not included in the denominator.

[a] Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
[b] Nominal p-value for the 2-sided CMH superiority test.

Week 60

The proportion of participants without fluid (no IRF and no SRF) at the foveal center (as assessed by the central reading center) at week 60 was 61.8% and 58.0% in the HDq12 and HDq16 groups, respectively, compared with 68.5% in the 2q8 group (Table 24).

Table 24: Proportion of Participants Without Fluid (no IRF and no SRF) at the Foveal Center at Week 60 (LOCF) (Full Analysis Set)

Treatment	Patients without fluid, n(%)	Adjusted Difference (%) (95% CI)[a]	CMH test p-value[b]
HDq12 (N=328)	201/325 (61.8%)	-5.98 (-14.71 , 2.75)	0.1878
HDq16 (N=163)	94/162 (58.0%)	-9.88 (-20.31 , 0.56)	0.0647
2q8 (N=167)	113/165 (68.5%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CRT=central retinal thickness (or, central subfield retinal thickness); DME= diabetic macular edema; ICE=intercurrent events; IRF=intraretinal fluid; LOCF=last observation carried forward; N,n=number of participants; SRF=subretinal fluid.
Intercurrent events were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF= the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data.
Missing or undetermined data were not included in the denominator.
[a] Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
[b] Nominal p-value for the 2-sided CMH superiority test.

Change from Baseline in Central Retinal Thickness

Week 48

Overall, the LS mean (SE) change from baseline in CRT (as assessed by the central reading center) at week 48 was -176.77 (5.73) and -148.84 (9.45) in the HDq12 and HDq16 groups, respectively, compared with -164.85 (8.79) in the 2q8 group (Table 27).

Table 27: Statistical Analysis of Change from Baseline in Central Retinal Thickness (microns) at Week 48 (MMRM)(FAS)

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 48 data	DF	Contrast [a]	t-value	p-value [b]	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=328)	-176.77 (5.73)	-171.65 (141.52)	449.15	276	254.9	HDq12 – 2q8	-1.2768	0.2028	-11.92 (-30.30, 6.47)
HDq16 (N=163)	-148.84 (9.45)	-148.30 (133.20)	460.32	149	295.3	HDq16 – 2q8	1.3386	0.1817	16.01 (-7.53, 39.54)
2q8 (N=167)	-164.85 (8.79)	-165.31 (140.22)	457.25	148					

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI = Confidence interval. CRT = Central retinal thickness. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. FAS = Full analysis set. LS = Least Square. BL = Baseline. MMRM = mixed model for repeated measurements. SAP = statistical analysis plan; DME=Diabetic macular edema; EDC=electronic data capture. A mixed model for repeated measurements (MMRM) was used with baseline CRT measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1).
[a] The contrast also included the interaction term for treatment x visit.
[b] Nominal p-value for the 2-sided superiority test
[c] Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with 2-sided 95% CIs.

Week 60

Overall, the LS mean (SE) change from baseline in CRT (as assessed by the central reading center) at week 60 was -181.95 (6.09) and -166.26 (8.56) in the HDq12 and HDq16 groups, respectively, compared with -194.16 (7.15) in the 2q8 group (Table 28).

The mean changes from baseline in CRT using OC are graphically displayed in Figure 5; the corresponding LS mean changes from baseline in CRT using MMRM in the FAS are displayed in Figure 6.

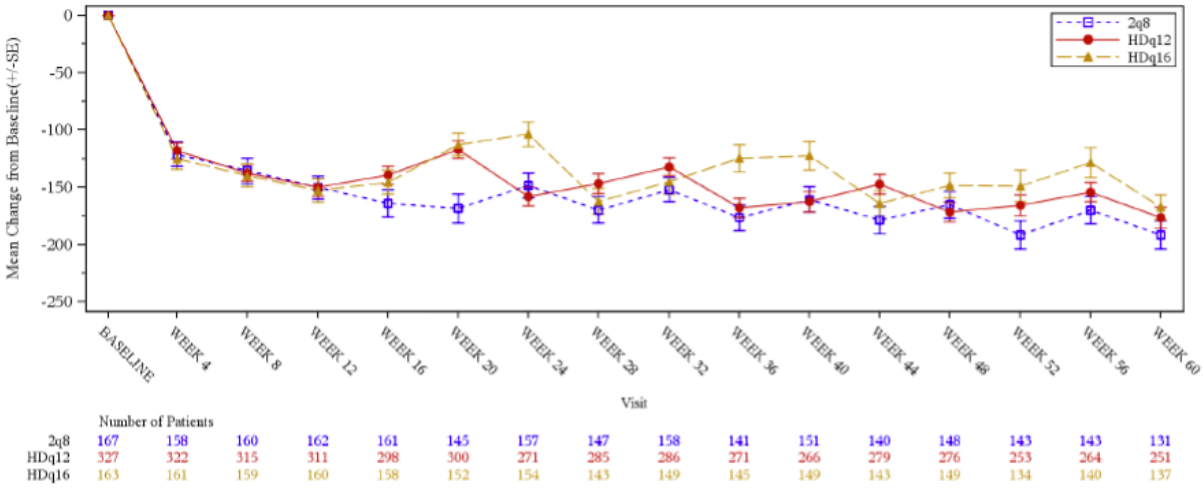
Although reductions from baseline in CRT were consistently observed at all timepoints, some fluctuation in mean CRT was seen by the MAH in all treatment groups with attenuation in magnitude over the course of 60 weeks. The small fluctuations that are observed in all treatment groups over time are not considered to be clinically relevant by the MAH given the demonstration of the non-inferiority in visual acuity.

Table 28: Statistical Analysis of Change from Baseline in Central Retinal Thickness (microns) at Week 60 (MMRM)(FAS)

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 60 data	DF	Contrast [a]	t-value	p-value [b]	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=328)	-181.95 (6.09)	-176.24 (144.71)	449.15	251	346.8	HDq12 - 2q8	1.5051	0.1332	12.21 (-3.74, 28.16)
HDq16 (N=163)	-166.26 (8.56)	-167.18 (127.18)	460.32	137	283.4	HDq16 - 2q8	2.7685	0.0060	27.90 (8.06, 47.74)
2q8 (N=167)	-194.16 (7.15)	-191.31 (142.00)	457.25	131					

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI = Confidence interval. CRT = Central retinal thickness. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. FAS = Full analysis set. LS = Least Square. BL = Baseline. MMRM = mixed model for repeated measurements. SAP = statistical analysis plan
A mixed model for repeated measurements (MMRM) was used with baseline CRT measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1).
[a] The contrast also included the interaction term for treatment x visit.
[b] Nominal p-value for the 2-sided superiority test
[c] Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with 2-sided 95% CIs.

Figure 5: Mean Change from Baseline in Central Retinal Thickness (microns) by Visit Through Week 60, OC (Full Analysis Set)

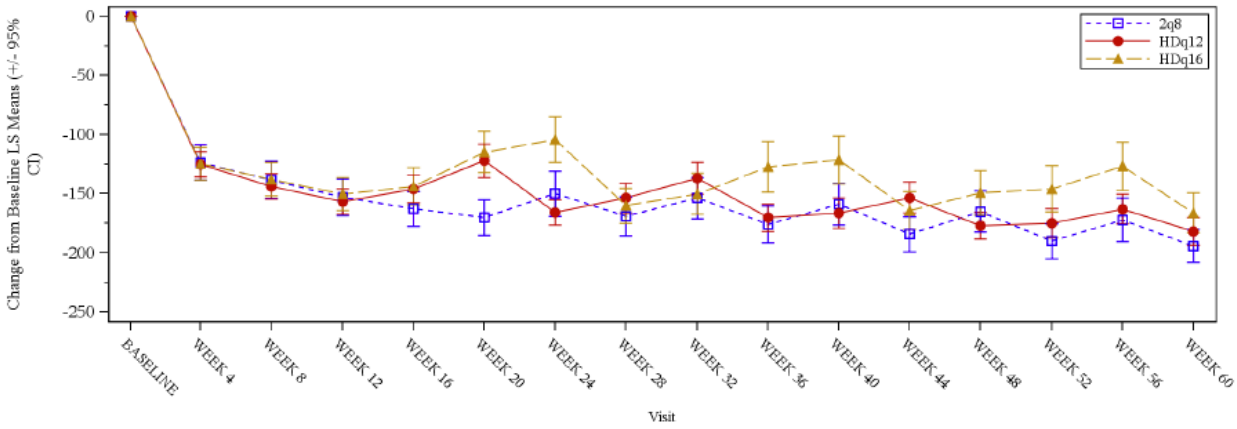


Number of Patients

	BASELINE	WEEK 4	WEEK 8	WEEK 12	WEEK 16	WEEK 20	WEEK 24	WEEK 28	WEEK 32	WEEK 36	WEEK 40	WEEK 44	WEEK 48	WEEK 52	WEEK 56	WEEK 60
2q8	167	158	160	162	161	145	157	147	158	141	151	140	148	143	143	131
HDq12	327	322	315	311	298	300	271	285	286	271	266	279	276	253	264	251
HDq16	163	161	159	160	158	152	154	143	149	145	149	143	149	134	140	137

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
ICE=intercurrent events; OC=observed case; SE=standard error.
Intercurrent events were handled according to Table 1 of SAP (Appendix 16.1.9.1). OC= observations after an ICE defined for the primary estimand were excluded.

Figure 6: Least Square Mean Change from Baseline in Central Retinal Thickness (microns) by Visit Through Week 60, OC (Full Analysis Set)



Abbreviations: 2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
BCVA=best corrected visual activity; CI=confidence interval; CRT=central retinal thickness; DME=diabetic macular edema; HD=high dose; LS=least square; OC=observed cases.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1).
Least square mean (LSM) was generated from a mixed model for repeated measurements (MMRM) with baseline CRT measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT from reading center [<400µm vs. >=400µm], prior treatment for DME per EDC [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.

Leakage on Fluorescein Angiography

Week 48

Overall, the proportion of participants without leakage on fluorescein angiography (as assessed by the central reading center) at week 48 (LOCF) was very low in all 3 treatment groups: 7.6% and 0.7% in the HDq12 and HDq16 groups, respectively, compared with 2.5% in the 2q8 group (Table 14.2.3.5.3a).

Table 14.2.3.5.3a Proportion of Patients without Leakage on Fluorescein Angiography by Visit through Week 60 (LOCF) (Full Analysis Set)

Visit	Leakage status	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)
Baseline	Without leakage	0/164	0/319	0/153
	With leakage	164/164 (100%)	319/319 (100%)	153/153 (100%)
	Undetermined	3	8	10
Week 12	Without leakage	3/153 (2.0%)	7/280 (2.5%)	5/145 (3.4%)
	With leakage	150/153 (98.0%)	273/280 (97.5%)	140/145 (96.6%)
	Undetermined	5	20	13
Week 24	Without leakage	3/162 (1.9%)	13/300 (4.3%)	3/149 (2.0%)
	With leakage	159/162 (98.1%)	287/300 (95.7%)	146/149 (98.0%)
	Undetermined	1	6	10
Week 36	Without leakage	6/162 (3.7%)	25/302 (8.3%)	3/152 (2.0%)
	With leakage	156/162 (96.3%)	277/302 (91.7%)	149/152 (98.0%)
	Undetermined	1	7	7
Week 48	Without leakage	3/162 (1.9%)	23/303 (7.6%)	1/152 (0.7%)
	With leakage	159/162 (98.1%)	280/303 (92.4%)	151/152 (99.3%)
	Undetermined	1	6	8
Week 60	Without leakage	7/162 (4.3%)	24/303 (7.9%)	3/153 (2.0%)
	With leakage	155/162 (95.7%)	279/303 (92.1%)	150/153 (98.0%)
	Undetermined	1	5	7

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP. LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data.
Missing or undetermined data were not included in the denominator.

A summary of the change from baseline in total area of fluorescein leakage within the ETDRS grid at week 48 is shown in Table 29.

Table 29: Summary of the Change from Baseline in Total Area of Fluorescein Leakage within ETDRS Grid (mm2) at Week 48 (OC) (Full Analysis Set)

Statistic	2q8 N=167	HDq12 N=328	HDq16 N=163
Baseline n	164	319	153
Baseline mean (SD)	24.6 (13.20)	24.4 (13.22)	24.6 (11.73)
Week 48 n	131	224	129
Mean (SD) change from baseline at week 48	-9.2 (12.11)	-13.9 (13.91)	-9.4 (11.50)
Median change from baseline at week 48	-6.8	-13.3	-7.7
Min, Max	-85, 18	-88, 52	-39, 55

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; SAP=statistical analysis plan.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). ETDRS: Early Treatment Diabetic Retinopathy Study; OC: observations after an ICE defined for the primary estimand were excluded; SD; standard deviation.

Week 60

Overall, the proportion of participants without leakage on fluorescein angiography (as assessed by the central reading center) at week 60 (LOCF) was very low in all 3 treatment groups: 7.9% and 2.0% in the HDq12 and HDq16 groups, respectively, compared with 4.3% in the 2q8 group (Table 14.2.3.5.3a below).

A summary of the change from baseline in total area of fluorescein leakage within the ETDRS grid at week 60 is shown in Table 30.

Table 30: Summary of the Change from Baseline in Total Area of Fluorescein Leakage within ETDRS Grid (mm2) at Week 60 (OC) (Full Analysis Set)

Statistic	2q8 N=167	HDq12 N=328	HDq16 N=163
Baseline n	164	319	153
Baseline mean (SD)	24.6 (13.20)	24.4 (13.22)	24.6 (11.73)
Week 60 n	112	202	110
Mean (SD) change from baseline at week 60	-14.4 (12.89)	-13.9 (13.54)	-12.0 (13.26)
Median change from baseline at week 60	-12.3	-13.6	-12.6
Min, Max	-86, 4	-80, 57	-37, 68

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; ETDRS=Early Treatment Diabetic Retinopathy Study; OC=observed case; SD=standard deviation.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1).; OC: observations after an ICE defined for the primary estimand were excluded..

Change from Baseline in National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) Total Score

Week 48

Overall, the LS mean change from baseline in NEI-VFQ-25 total score at week 48 was 4.06 and 2.94 in the HDq12, and HDq16 groups, respectively, compared with 2.82 in the 2q8 group (Table 31).

Table 31: Change from Baseline in NEI-VFQ-25 Total Score at Week 48 (MMRM) (Full Analysis Set)

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 48 data	DF	Contrast [a]	t-value	p-value [b]	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=328)	4.06 (0.80)	5.64 (12.56)	76.79	276	251.4	HDq12 - 2q8	1.0515	0.2941	1.25 (-1.09, 3.58)
HDq16 (N=163)	2.94 (0.93)	4.16 (10.94)	77.86	149	261.8	HDq16 - 2q8	0.0995	0.9208	0.13 (-2.37, 2.62)
2q8 (N=167)	2.82 (1.10)	4.41 (13.84)	76.65	150					

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; CI = Confidence interval. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. LS = Least Square. BL = Baseline. MMRM = mixed model for repeated measurements. SAP = statistical analysis plan; DME = diabetic macular edema; EDC = electronic data capture

A mixed model for repeated measurements (MMRM) was used with baseline NEI-VFQ-25 total score measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.

Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1)

[a] The contrast also included the interaction term for treatment x visit

[b] Nominal p-value for the 2-sided superiority test

[c] Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with 2-sided 95% CIs.

Week 60

Summaries of NEI-VFQ-25 total scores by visit through week 60 are provided in Table 14.2.3.6.3a for the OC, and in Table 14.2.3.6.4a for the LOCF of the r-14238 report section.

Globally, results tend to differ in the HDq12 and HDq16 groups and are supported by the sensitivity analysis. Furthermore, some secondary endpoints results tend to stand out more than others in the HD groups rather than in 2q8 treatment group. Therefore the MAH was asked to discuss the clinical relevance and the interpretation of those results with regards to the HD regimen (HDq12 and HDq16) proposed.

Based on the provided responses, the Applicant concluded that all treatment arms achieved similar functional benefits. Differences in structural endpoints were mostly associated with injection timing and did not translate into clinically meaningful differences in quality of life or visual acuity.

The eligibility criteria of the PHOTON study aimed to include an informative population in terms of DME assessment, which does not equate the one selected for DRSS assessment. In PHOTON, despite the limitations in study design, the evaluation of DRSS was included in the context of the fact that aflibercept 2 mg is in the US approved not only for the treatment of DME, but also for the treatment of DR. Therefore, evaluating the effects of aflibercept 8 mg was considered relevant for that territory. The key secondary endpoint of the proportion of participants with a ≥ 2-step improvement in DRSS score at Week 48 was pre-specified to potentially support an indication of aflibercept 8 mg for treatment of DR in the US. This endpoint was tested with a non-inferiority margin of 15% which was met by the HDq12 arm (adjusted difference 1.98%, 95% CI -6.61, 10.57) but not by the HDq16 arm (adjusted difference -7.52%, 95% CI -16.88, 1.84). however, considering that the primary endpoint showed that BCVA improvement as a direct effect of DME treatment was non-inferior for HDq12 and HDq16 compared to 2q8, the Applicant concluded that the effect on DRSS stage improvement does not correlate with the effect on DME, and improvements in DRSS are not a prerequisite for vision improvements in DME

Exploratory efficacy endpoints analysis

Proportion of participants without Retinal Fluid in Center Subfield

Week 48

The proportion of participants without fluid (no IRF and no SRF) in the center subfield at week 48 was 27.4% and 14.8% in the HDq12 and HDq16 groups, respectively, compared with 21.8% in the 2q8 group (Table 25).

Table 25: Proportion of Participants Without Fluid (no IRF and no SRF) at the Central Subfield at Week 48 (LOCF) (Full Analysis Set)

Treatment	Patients without fluid, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test [b] p-value
HDq12 (N=328)	89/325 (27.4%)	5.84 (-2.02 , 13.71)	0.1610
HDq16 (N=163)	24/162 (14.8%)	-6.75 (-14.94 , 1.44)	0.1110
2q8 (N=167)	36/165 (21.8%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CRT = central retinal thickness; DME = diabetic macular edema; ICE= intercurrent events; IRF=intraretinal fluid; LOCF=last observation carried forward; N,n=number of patients; SAP = Statistical analysis plan; SRF=subretinal fluid.
Intercurrent events were handled according to Table 1 of SAP (Appendix 16.1.9.1).
LOCF: the last observation prior to an ICE defined for the primary estimand was to be used to impute subsequent and/or missing data
Missing or undetermined data were not included in the denominator.
[a] Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
[b] Nominal p-value for the 2-sided CMH superiority test.

Additional analyses regarding fluid at the foveal center and the center subfield can be found in tables from the r-14238 report section:

• Intraretinal fluid at the foveal center and center subfield (Tables 14.2.4.1.1 to 14.2.4.1.4 and 14.2.4.1.13 to 14.2.4.1.16)

• Subretinal fluid at the foveal center and center subfield (Tables 14.2.4.1.5 to 14.2.4.1.8 and 14.2.4.1.17 to 14.2.4.1.20)

• Time to fluid-free retina at foveal center and center subfield over 48 weeks (Tables 14.2.4.1.21 and 14.2.4.1.24 and Figures 14.2.4.1.1 and 14.2.4.1.4)

• Time to IRF and SRF-free retina at the foveal center and center subfield (Tables 14.2.4.1.22, 14.2.4.1.23, 14.2.4.1.25, and 14.2.4.1.26)

• Proportion of participants sustained fluid-free retina over 48 weeks at the foveal center and in the center subfield (Tables 14.2.4.1.27 to 14.2.4.1.32)

• Time to sustained fluid-free retina (no IRF and no SRF) in the foveal center and in the center subfield through week 48 (Tables 14.2.4.1.33 to 14.2.4.1.38)

Week 60

The proportion of participants without fluid (no IRF and no SRF) in the center subfield at week 60 was 23.1% and 15.4% in the HDq12 and HDq16 groups, respectively, compared with 29.7% in the 2q8 group (Table 26).

Table 26: Proportion of Participants Without Fluid (no IRF and no SRF) at the Central Subfield at Week 60 (LOCF) (Full Analysis Set)

Treatment	Patients without fluid, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test p-value[b]
HDq12 (N=328)	75/325 (23.1%)	-6.45 (-14.78 , 1.87)	0.1217
HDq16 (N=163)	25/162 (15.4%)	-14.19 (-23.03 , -5.36)	0.0021
2q8 (N=167)	49/165 (29.7%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CRT = central retinal thickness; DME = diabetic macular edema; ICE= intercurrent events; IRF=intraretinal fluid; LOCF=last observation carried forward; N,n=number of participants; SAP = Statistical analysis plan; SRF=subretinal fluid.
Intercurrent events were handled according to Table 1 of SAP (Appendix 16.1.9.1).
LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data.
Missing or undetermined data were not included in the denominator.
[a] Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
[b] Nominal p-value for the 2-sided CMH superiority test.

Additional analyses regarding fluid at the foveal center and the center subfield can be found in tables from the r-14238 report section:

• Intraretinal fluid at the foveal center and center subfield (Tables 14.2.4.1.1a to 14.2.4.1.4a and Tables 14.2.4.1.13a to 14.2.4.1.16a)

• Subretinal fluid at the foveal center and center subfield (Tables 14.2.4.1.5a to 14.2.4.1.8a and Tables 14.2.4.1.17a to 14.2.4.1.20a)

• Time to fluid-free retina at foveal center and center subfield over 60 weeks (Tables 14.2.4.1.21a and 14.2.4.1.24a and Figures 14.2.4.1.1a and 14.2.4.1.4a)

• Time to IRF and SRF-free retina at the foveal center and center subfield (Tables 14.2.4.1.22a, 14.2.4.1.23a, 14.2.4.1.25a and 14.2.4.1.26a)

• Proportion of participants sustained fluid-free retina over 60 weeks at the foveal center and in the center subfield (Tables 14.2.4.1.27a to 14.2.4.1.32a)

• Time to sustained fluid-free retina (no IRF and no SRF) in the foveal center and in the center subfield through week 60 (Tables 14.2.4.1.33a to 14.2.4.1.38a)

Proportion of Participants with a ≥ 3-Step Improvement in DRSS Score

Week 48

The proportion of participants with a ≥ 3-step improvement in DRSS at week 48 was 11.9% and 9.2% in the HDq12 and HDq16 groups, respectively, compared with 14.6% in the 2q8 group (Table 32).

Table 32: Proportion Analysis of Participants with a ≥ 3-Step Improvement from Baseline in DRSS at Week 48 (LOCF) (Full Analysis Set)

Treatment	Patients with a ≥ 3-step improvement from baseline in DRSS at Week 48, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test p-value[b]
HDq12 (N=328)	37/310 (11.9%)	-2.79 (-9.50, 3.91)	0.3920
HDq16 (N=163)	14/153 (9.2%)	-5.59 (-12.88, 1.70)	0.1310
2q8 (N=167)	23/158 (14.6%)		

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12=High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16=High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; DRSS=Diabetic Retinopathy Severity Scale; CRT=Central retinal thickness; DME=Diabetic macular edema; SAP=statistical analysis plan.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Patients were considered as non-responders if all post-baseline measurements were missing or non-gradable.
Missing or ungradable baseline was not included in the denominator.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan])
[b] Nominal p-value for the 2-sided Cochran-Mantel-Haenszel (CMH) superiority test

Week 60

The proportion of participants with a ≥ 3-step improvement in DRSS at week 60 was 15.2% and 10.5% in the HDq12 and HDq16 groups, respectively, compared with 17.7% in the 2q8 group (Table 33).

Table 33: Proportion Analysis of Participants with a ≥ 3-Step Improvement from Baseline in DRSS at Week 60 (LOCF) (Full Analysis Set)

Treatment	Patients with a ≥ 3-step improvement from baseline in DRSS at Week 60, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test p-value[b]
HDq12 (N=328)	47/310 (15.2%)	-2.73 (-9.90, 4.44)	0.4412
HDq16 (N=163)	16/153 (10.5%)	-7.34 (-15.16, 0.47)	0.0660
2q8 (N=167)	28/158 (17.7%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; CRT= central retinal thickness (or, central subfield retinal thickness); DME=diabetic macular edema; DRSS = Diabetic Retinopathy Severity Scale.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Patients were considered as non-responders if all post-baseline measurements were missing or non-gradable.
Missing or ungradable baseline was not included in the denominator.
[a]Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan])
[b] Nominal p-value for the 2-sided Cochran-Mantel-Haenszel (CMH) superiority test

Change from Baseline in BCVA Averaged Over the Period from Week 36 to Week 48

The mean values of BCVA score averaged from week 36 to week 48 were similar across treatment groups, and the change from baseline was similar across treatment groups (Table 34).

Table 34: Summary of Averaged BCVA Score: Week 36 to Week 48 (OC) (Full Analysis Set)

		Value at Visit								Change from Baseline							
Treatment	Visit	n	Mean	SD	SE	Q1	Median	Q3	Min, Max	n	Mean	SD	SE	Q1	Median	Q3	Min, Max
2q8 (N=167)	BASELINE	167	61.5	11.22	0.87	54.0	63.0	70.0	24, 78								
	WEEK 36 TO 48	155	70.5	11.75	0.94	64.0	73.0	79.0	23, 90	155	8.8	8.60	0.69	4.0	9.3	13.5	-26, 48
HDq12 (N=328)	BASELINE	328	63.6	10.10	0.56	57.0	65.0	72.0	27, 79								
	WEEK 36 TO 48	286	71.8	11.35	0.67	65.3	73.9	80.0	22, 92	286	8.1	8.93	0.53	3.0	7.9	12.5	-50, 38
HDq16 (N=163)	BASELINE	163	61.4	11.76	0.92	55.0	64.0	71.0	29, 78								
	WEEK 36 TO 48	154	69.1	12.77	1.03	62.5	72.6	78.3	21, 92	154	7.2	7.95	0.64	2.8	6.3	10.3	-12, 38

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals, HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals, ICE= intercurrent events; n= number; Q= quartile; SAP= statistical analysis plan; SD= standard deviation; SE= standard error
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). OC: observations after an intercurrent event (ICE) defined for the primary estimand were excluded.

Change from Baseline in BCVA Averaged Over the Period from Week 48 to Week 60

The mean values of BCVA score averaged from week 48 to week 60 are presented in Table 35.

Table 35: Summary of Averaged BCVA Score: Week 48 to Week 60 (OC) (Full Analysis Set)

		Value at Visit								Change from Baseline							
Treatment	Visit	n	Mean	SD	SE	Q1	Median	Q3	Min, Max	n	Mean	SD	SE	Q1	Median	Q3	Min, Max
2q8 (N=167)	BASELINE	167	61.5	11.22	0.87	54.0	63.0	70.0	24, 78								
	WEEK 48 TO 60	150	71.2	11.71	0.96	65.0	72.0	79.8	20, 88	150	9.3	8.81	0.72	4.3	9.3	14.8	-30, 45
HDq12 (N=328)	BASELINE	328	63.6	10.10	0.56	57.0	65.0	72.0	27, 79								
	WEEK 48 TO 60	277	72.5	10.72	0.64	66.0	74.3	81.0	30, 94	277	8.7	8.61	0.52	3.8	8.0	13.0	-22, 40
HDq16 (N=163)	BASELINE	163	61.4	11.76	0.92	55.0	64.0	71.0	29, 78								
	WEEK 48 TO 60	149	69.5	12.95	1.06	62.5	73.3	79.3	20, 89	149	7.6	8.35	0.68	3.0	7.5	11.3	-14, 40

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals, HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals, ICE= intercurrent events; max= maximum; min= minimum; N,n= number of participants; Q1= quartile 1; Q3= quartile 3; SAP= statistical analysis plan; SD= standard deviation; SE= standard error
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). OC: observations after an intercurrent event (ICE) defined for the primary estimand were excluded.

Proportions of Participants Gaining or Losing ≥ 5, ≥ 10, or ≥ 15 Letters

Week 48

The proportion of participants who gained or lost ≥ 5, ≥ 10, or ≥ 15 letters from baseline through week 48 is presented in Table 36. Across all treatment groups, more participants gained letters, with the greatest proportion gaining ≥ 5 letters (approximately 65 to 71% across all treatment groups). A numerically lower proportion of participants in the HDq12 and HDq16 groups gained ≥ 10 letters or ≥ 15 letters compared to the 2q8 group. Few participants (approximately 1 to 6%) lost 5 or more letters through week 48 regardless of treatment group.

Table 36: Proportion of Participants who Gained or Lost ≥ 5, ≥ 10, or ≥ 15 Letters in BCVA from Baseline by Visit Through Week 48 (LOCF) (Full Analysis Set)

Endpoint	Visit	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)
Gained >= 5 letters	Week 48	113/165 (68.5%)	231/326 (70.9%)	107/163 (65.6%)
Gained >= 10 letters	Week 48	81/165 (49.1%)	132/326 (40.5%)	57/163 (35.0%)
Gained >= 15 letters	Week 48	38/165 (23.0%)	61/326 (18.7%)	27/163 (16.6%)
Lost >= 5 letters	Week 48	5/165 (3.0%)	21/326 (6.4%)	10/163 (6.1%)
Lost >= 10 letters	Week 48	2/165 (1.2%)	11/326 (3.4%)	2/163 (1.2%)
Lost >= 15 letters	Week 48	2/165 (1.2%)	7/326 (2.1%)	1/163 (0.6%)

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; BCVA= best corrected visual acuity; ICE=intercurrent events; LOCF=last observation carried forward; SAP=statistical analysis plan.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data.
Missing data were not included in the denominator.

Week 60

The proportion of participants who gained or lost ≥ 5, ≥ 10, or ≥ 15 letters from baseline through week 60 is presented in Table 37. Across all treatment groups, more participants gained letters, with the greatest proportion gaining ≥ 5 letters (approximately 64% to 72% across all treatment groups). A numerically lower proportion of participants in the HDq12 and HDq16 groups gained ≥ 10 letters or ≥ 15 letters compared to the 2q8 group. Few participants (approximately 3% to 6%) lost 5 or more letters through week 60 regardless of treatment group.

Table 37: Proportion of Participants who Gained or Lost ≥ 5, ≥ 10, or ≥ 15 Letters in BCVA from Baseline by Visit Through Week 60 (LOCF) (Full Analysis Set)

Endpoint	Visit	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)
Gained >= 5 letters	Week 60	119/165 (72.1%)	227/326 (69.6%)	105/163 (64.4%)
Gained >= 10 letters	Week 60	82/165 (49.7%)	133/326 (40.8%)	56/163 (34.4%)
Gained >= 15 letters	Week 60	43/165 (26.1%)	70/326 (21.5%)	26/163 (16.0%)
Lost >= 5 letters	Week 60	10/165 (6.1%)	21/326 (6.4%)	5/163 (3.1%)
Lost >= 10 letters	Week 60	4/165 (2.4%)	11/326 (3.4%)	2/163 (1.2%)
Lost >= 15 letters	Week 60	1/165 (0.6%)	7/326 (2.1%)	1/163 (0.6%)

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; BCVA= best corrected visual acuity; ICE= intercurrent events; LOCF= last observation carried forward; SAP= statistical analysis plan.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data.
Missing data were not included in the denominator.

Proportions of patients gaining and losing ≥ 5, ≥ 10 or ≥ 15 letters in BCVA from baseline at Week 96

- ***PHOTON study***

Table 9 PHOTON: Proportion of patients who gained or lost ≥ 5, 10, or 15 letters in BCVA from baseline through Week 48, Week 60 and Week 96, LOCF (FAS)

		Subjects with response category, Num/Den (%)		
Response category	**Treatment**	**Week 48**	**Week 60**	**Week 96**
Gained ≥ 15 letters	2q8 (N = 167)	38/165 (23.0%)	43/165 (26.1%)	43/165 (26.1%)
	HDq12 (N = 328)	61/326 (18.7%)	70/326 (21.5%)	80/326 (24.5%)
	HDq16 (N = 163)	27/163 (16.6%)	26/163 (16.0%)	32/163 (19.6%)
Gained ≥ 10 letters	2q8 (N = 167)	81/165 (49.1%)	82/165 (49.7%)	86/165 (52.1%)
	HDq12 (N = 328)	132/326 (40.5%)	133/326 (40.8%)	139/326 (42.6%)
	HDq16 (N = 163)	57/163 (35.0%)	56/163 (34.4%)	54/163 (33.1%)
Gained ≥ 5 letters	2q8 (N = 167)	113/165 (68.5%)	119/165 (72.1%)	116/165 (70.3%)
	HDq12 (N = 328)	231/326 (70.9%)	227/326 (69.6%)	222/326 (68.1%)
	HDq16 (N = 163)	107/163 (65.6%)	105/163 (64.4%)	101/163 (62.0%)
Lost ≥ 5 letters	2q8 (N = 167)	5/165 (3.0%)	10/165 (6.1%)	15/165 (9.1%)
	HDq12 (N = 328)	21/326 (6.4%)	21/326 (6.4%)	26/326 (8.0%)
	HDq16 (N = 163)	10/163 (6.1%)	5/163 (3.1%)	16/163 (9.8%)
Lost ≥ 10 letters	2q8 (N = 167)	2/165 (1.2%)	4/165 (2.4%)	9/165 (5.5%)
	HDq12 (N = 328)	11/326 (3.4%)	11/326 (3.4%)	16/326 (4.9%)
	HDq16 (N = 163)	2/163 (1.2%)	2/163 (1.2%)	4/163 (2.5%)
Lost ≥ 15 letters	2q8 (N = 167)	2/165 (1.2%)	1/165 (0.6%)	6/165 (3.6%)
	HDq12 (N = 328)	7/326 (2.1%)	7/326 (2.1%)	11/326 (3.4%)
	HDq16 (N = 163)	1/163 (0.6%)	1/163 (0.6%)	2/163 (1.2%)

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; BCVA= best corrected visual acuity; ICE=intercurrent events; LOCF=last observation carried forward; SAP=statistical analysis plan.

Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data.

Missing data were not included in the denominator.

Source: Module 5.3.5.1, PHOTON W60 CSR, W48 Table 14.2.4.4.1 and W60 Table 14.2.4.4.1a; Module 5.3.5.1, PHOTON TLF EMA CHMP Day-120 W96 CSR_key, Table 14.2.4.4.1b (Week 96)

Like for Week 48 and Week 60, across all treatment groups, more patients gained letters in BCVA at Week 96, compared to those losing letters in BCVA. A similar proportion of patients in the HDq12 and 2q8 groups gained ≥ 5, ≥ 10 or ≥ 15 letters through Week 96 compared to slightly lower proportions reported for the HDq16 group. Indeed, the HDq16 group failed to reach values > 20% for patients who gained ≥ 15 letters through Week 96. The proportions of patients gaining ≥ 15 letters was 24.5% and 19.6% at Week 96. More globally, the proportions of patients who gained ≥ 15 letters in BCVA from baseline increased fastest in the 2q8 group, followed by HDq12 and HDq16

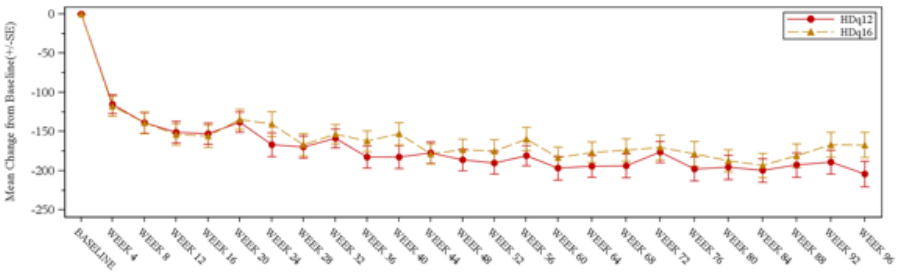
Additional exploratory efficacy results for PHOTON study at Week 96

Change from baseline in CST

The arithmetic mean decreases from baseline in CST over time were similar in both HD treatment groups with minor numerical differences over time. At Week 96, the mean changes from baseline CST (µm) were -194.8 and -157.2 for HDq12 and HDq16, respectively. This is consistent with the results reported for the2q8 group at Week 96.

For the subset of patients who completed two q20 intervals and had q20 or longer as the last intended dosing interval, main CST (µm) decreases over time were consistent with the results seen in HDq16 patients who completed at least one q20 interval.

Figure 11 PHOTON: Mean change from baseline in CST (µm) by visit, OC prior to ICE (FAS, patients who completed at least one q20 interval)



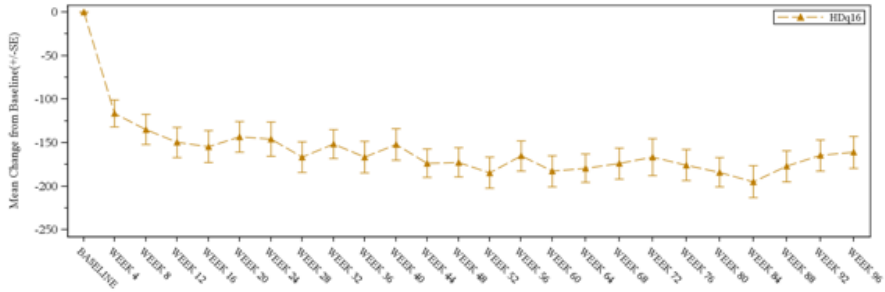
Number of Patients

HDq12	119	118	117	118	113	118	106	116	117	113	109	115	115	108	111	105	101	103	106	99	101	104	103	101	96
HDq16	72	71	70	72	71	70	71	67	69	65	68	65	70	65	68	63	58	58	58	51	57	50	56	57	57

HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CRT = Central Retinal Thickness
SE = Standard error

Source: Module 5.3.5.1, PHOTON TLF EMA CHMP Day-120 W96 posthoc, Figure 2.2.1-3

Figure 12 PHOTON: Mean change from baseline in CRT (µm) by visit through Week 96 (OC) - (FAS, patients who completed two q20 dosing intervals and had q20 or longer as the last intended dosing interval)



Number of Patients

HDq16	48	48	47	48	47	48	47	45	46	43	45	43	47	43	46	44	44	42	41	43	45	40	45	45	45

HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CRT = Central Retinal Thickness
SE = Standard error

Source: Module 5.3.5.1, PHOTON TLF EMA CHMP Day-120 W96 posthoc, Figure 2.2.1-4

Overall, the provided additional long-term data are globally reassuring both on a quantitative (number of exposed patients) and qualitative aspects (results on efficacy endpoints). Indeed, based on data from PULSAR (approx. 80% completed Week 96 data collection) and on the data from all patients in PHOTON, HD aflibercept dosed every 12 weeks or every 16 weeks showed nearly similar maintained efficacy through Week 96 compared to 2 mg aflibercept, consistent with the non-inferiority demonstrated at Week 48 and Week 60 with respect to improvement in BCVA in patients with nAMD or DME.

Proportion of Participants Randomized to High Dose Maintaining ≥ q12 Dosing Intervals

Week 48

Data on the proportion of participants randomized to HDq12 and HDq16, respectively, maintaining q12 or longer and q16 dosing interval through week 48, as well as the proportion of participants with an assigned injection interval of ≥ 12 or ≥ 16 weeks based on assessment at the last injection visit are presented in Table 11 and Table 13.

Table 11: Summary of Treatment Exposure in Study Eye Through Week 48 (Safety Analysis Set)

	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Total number of active injections	1292	1875	806	2681
Total number of sham injections	580	1720	1054	2774
Number of active injections per patient, n (%)				
1	2 (1.2%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
2	0	7 (2.1%)	1 (0.6%)	8 (1.6%)
3	0	11 (3.4%)	3 (1.8%)	14 (2.9%)
4	2 (1.2%)	11 (3.4%)	6 (3.7%)	17 (3.5%)
5	2 (1.2%)	12 (3.7%)	146 (89.6%)	158 (32.2%)
6	3 (1.8%)	273 (83.2%)	2 (1.2%)	275 (56%)
7	10 (6.0%)	12 (3.7%)	4 (2.5%)	16 (3.3%)
8	148 (88.6%)	0	0	0
Summary of active injections				
N	167	328	163	491
Mean (SD)	7.7 (0.98)	5.7 (0.96)	4.9 (0.61)	5.5 (0.93)
Median	8.0	6.0	5.0	6.0
Q1 : Q3	8.0 : 8.0	6.0 : 6.0	5.0 : 5.0	5.0 : 6.0
Min : Max	1 : 8	1 : 7	1 : 7	1 : 7
Treatment duration (weeks) [a]				
N	167	328	163	491
Mean (SD)	46.71 (6.893)	45.67 (9.036)	47.10 (6.002)	46.14 (8.177)
Median	48.00	48.00	48.00	48.00
Q1 : Q3	47.90 : 48.70	47.70 : 48.65	48.00 : 48.60	47.90 : 48.60
Min : Max	4.0 : 52.1	4.0 : 64.4	4.0 : 54.9	4.0 : 64.4

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; All HD= Pooled HDq12 and HDq16 groups; Q1= quartile 1; Q3= quartile 3; min=minimum; max=maximum; N,n=number; SD=standard deviation.

[a] Treatment Duration = (Last study treatment [active or sham] date - First study treatment [active or sham] date + 28 days)/7.

The percentage was based on the number of patients in each treatment group as a denominator.

Study drugs given at week 48 or beyond were not included in this table.

Patients in the HD groups could have had their interval shortened if protocol-specified criteria were met.

Source: PTT 14.1.4.1

Table 13: Summary of Treatment Exposure in the Study Eye (Safety Analysis Set Completing Week 48 and Week 60, respectively)

		HD		
Through Week 48 [a]	**2q8 (N=157)**	**HDq12 (N=300)**	**HDq16 (N=156)**	**All HD (N=456)**
Patients maintained with q12 or longer dosing interval, n (%)	-	273 (91.0%)	150 (96.2%)	423 (92.8%)
Patients maintained with q16 dosing interval, n (%)	-	-	139 (89.1%)	-
Patients with q12 or longer dosing interval as the last [b] intended dosing interval, n (%)	-	262 (87.3%)	146 (93.6%)	408 (89.5%)
Patients with q16 dosing interval as the last [b] intended dosing interval, n (%)	-	-	136 (87.2%)	-
Patients shortened to q8 dosing interval at week 16, n (%)	-	3 (1.0%)	1 (0.6%)	4 (0.9%)
Patients shortened to q8 dosing interval at week 20, n (%)	-	12 (4.0%)	3 (1.9%)	15 (3.3%)
Patients with a shortened dosing interval anytime, n (%)	-	27 (9.0%)	17 (10.9%)	44 (9.6%)
Patients with a shortened dosing interval to q8 anytime, n (%)	-	27 (9.0%)	6 (3.8%)	33 (7.2%)
Patients with a shortened dosing interval to q12 anytime, n (%) [c]	-	-	13 (8.3%)	-
Through Week 60 [d]	**2q8 (N=155)**	**HDq12 (N=289)**	**HDq16 (N=152)**	**All HD (N=441)**
Patients maintained with q12 or longer dosing interval, n (%)	-	261 (90.3%)	142 (93.4%)	403 (91.4%)
Patients maintained with q16 or longer dosing interval, n (%)	-	-	130 (85.5%)	-
Patients with q12 or longer dosing interval as the last [e] intended dosing interval, n (%)	-	248 (85.8%)	136 (89.5%)	384 (87.1%)
Patients with q16 or longer dosing interval as the last [e] intended dosing interval, n (%)	-	123 (42.6%)	124 (81.6%)	247 (56.0%)
Patients with q20 dosing interval as the last c intended dosing interval, n (%)	-	0	52 (34.2%)	52 (11.8%)
Patients shortened to q8 dosing interval at week 16, n (%)	-	3 (1.0%)	1 (0.7%)	4 (0.9%)
Patients shortened to q8 dosing interval at week 20, n (%)	-	12 (4.2%)	3 (2.0%)	15 (3.4%)
Patients with a shortened dosing interval anytime, n (%)	-	28 (9.7%)	22 (14.5%)	50 (11.3%)
Patients with a shortened dosing interval to q8 anytime, n (%)	-	28 (9.7%)	10 (6.6%)	38 (8.6%)
Patients with a shortened dosing interval to q12 anytime (without shortening to q8), n (%)	-	-	12 (7.9%)	20 (4.5%)
Patients never extended dosing interval, n (%)	155 (100%)	156 (54.0%)	93 (61.2%)	249 (56.5%)
Patients extended dosing interval anytime, n (%)	0	133 (46.0%)	59 (38.8%)	192 (43.5%)

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; All HD= Pooled HDq12 and HDq16 groups; n = number; q8= every 8 weeks; q12= every 12 weeks; q16= every 16 weeks.
Hyphen indicates categories that do not apply.
[a] Study drugs given at week 48 or beyond were not included in this table.
[b] Refers to the patient's assigned interval at week 48.
[c] Includes participants who were only shortened to q12 as well as participants who were shortened to q12 and further shortened to q8.
[d] Study drugs given at week 60 or beyond were not included in this table.
[e] Refers to the patient's assigned interval at week 60.

Week 60

Data on the proportion of participants randomized to HDq12 and HDq16 maintaining q12 and q16 dosing interval or longer, respectively, through week 60, as well as the proportion of participants with an assigned injection interval of ≥ 12 or ≥ 16 weeks based on assessment at the last injection visit, are presented in Table 12 and Table 13.

Table 12: Summary of Treatment Exposure in Study Eye Through Week 60 (Safety Analysis Set)

	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Total number of active injections	1592	2167	957	3124
Total number of sham injections	727	2264	1342	3606
Number of active injections per patient, n (%)				
1	2 (1.2%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
2	0	7 (2.1%)	1 (0.6%)	8 (1.6%)
3	0	11 (3.4%)	3 (1.8%)	14 (2.9%)
4	2 (1.2%)	10 (3.0%)	2 (1.2%)	12 (2.4%)
5	2 (1.2%)	5 (1.5%)	11 (6.7%)	16 (3.3%)
6	1 (0.6%)	18 (5.5%)	138 (84.7%)	156 (31.8%)
7	4 (2.4%)	256 (78.0%)	3 (1.8%)	259 (52.7%)
8	6 (3.6%)	18 (5.5%)	3 (1.8%)	21 (4.3%)
9	10 (6.0%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
10	140 (83.8%)	0	0	0
Summary of active injections				
N	167	328	163	491
Mean (SD)	9.5 (1.42)	6.6 (1.26)	5.9 (0.82)	6.4 (1.19)
Median	10.0	7.0	6.0	7.0
Q1 : Q3	10.0 : 10.0	7.0 : 7.0	6.0 : 6.0	6.0 : 7.0
Min : Max	1 : 10	1 : 9	1 : 9	1 : 9
Treatment duration (weeks) [a]				
N	167	328	163	491
Mean (SD)	57.79 (9.727)	56.48 (12.524)	58.45 (8.471)	57.13 (11.369)
Median	60.00	60.00	60.10	60.00
Q1 : Q3	59.90 : 60.60	59.90 : 60.70	60.00 : 60.60	59.90 : 60.70
Min : Max	4.0 : 67.0	4.0 : 75.0	4.0 : 69.0	4.0 : 75.0

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; All HD= Pooled HDq12 and HDq16 groups; Q1=quartile 1; Q3= quartile 3; min=minimum; max=maximum; N,n=number; SD=standard deviation.

[a] Treatment Duration = (Last study treatment [active or sham] date - First study treatment [active or sham] date + 28 days)/7.

The percentage was based on the number of patients in each treatment group as a denominator.

Study drugs given at week 60 or beyond were not included in this table.

Patients in the HD groups could have had their interval shortened if protocol-specified criteria were met.

Overall, the exploratory results stand out more in the 2q8 treatment group compared to the HD groups. Moreover, identically to PULSAR study, in addition to the shortening of the intervals of IVT injections, some patients were eligible starting week 52 to extend up by 4 week the interval based on DRM criteria assessed in HD groups and at 60 weeks (patients in HDq12 group could be injected with a q16 interval and patients in HDq16 group could be injected with a q20 interval).

Common MO was raised with the PULSAR study regarding the wording in the section 4.2 in the SmPC and an OC regarding the clarity of the table presenting the different dosing intervals adopted during the studies by the patients.

In addition to the clarification discussed above and related to the provided new additional data regarding the claimed 5 month/20q interval, the following information have been provided.

As a remainder, all participants in HD groups were eligible for dose interval shortening (to a minimum of q8) as of Week 16 or extension (by 4-week increments) as of Week 52 according to the pre-specified DRM criteria. Due to this option for treatment individualization, by the end of Year 2, the HDq12 and HDq16 groups were allocated into a range of treatment intervals from 8 to 24 weeks. No patient had yet completed a 24-week interval by Week 96, but patients could have completed one or two q20 intervals. As for the requested 2-year data, the Applicant provided exposure details for patients who extended their treatment interval to q20 or longer. Through Week 96, up to 47% and 44.3% of HD patients extended their treatment interval to q20 or longer intervals in the PULSAR and PHOTON study respectively. Numerically, this corresponds to a total of 185 patients completed at least one q20 interval before Week 96 in PULSAR and 133 patients in PHOTON study.

At Week 96, the proportion of patients with q20 or longer as the last intended dosing interval in the PULSAR was 36.8% in the HDq12 group and 54.9% in the HDq16 group. Of 216 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24 (i.e. 53 and 127 HD patients, respectively); only a few patients were shortened back to q16 (i.e. 3 HD patients).

For the PHOTON study, at Week 96 the proportion of patients with q20 or longer as the last intended dosing interval was 42.2% in the HDq12 group and 45.3% in the HDq16 group. Of 177 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24

2.5.4.2. 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 1 Summary of efficacy for trial PULSAR

Title: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration		
Study identifier	Study no.: 20968 EudraCT no.: 2019-003851-12 IND no.: 12462 (Regeneron Pharmaceuticals, Inc.)	
Design	Multi-center, 1:1:1 randomized, double masked, active controlled, comparative clinical study to evaluate the efficacy and safety between high-dose aflibercept (8 mg) and licensed Eylea 2mg in subjects with nAMD treated up to 96 weeks.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	17 OCT 2022 not applicable not applicable
Hypothesis	Non-inferiority	
Treatments groups	HDq12 aflibercept 8 mg	8 mg aflibercept IVT injection every 4 weeks for a total of 3 injections, and then every 12 weeks up to Week 48 (6 doses in total at the minimum, with optional doses to continue at every 8 weeks), n = 336
	HDq16 aflibercept 8 mg	8 mg aflibercept IVT injection every 4 weeks for a total of 3 injections, and then every 8 weeks up to Week 48 (5 doses in total, with optional doses to continue at every 8 or 12 weeks), n = 335

Title: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration			
Study identifier	Study no.: 20968 EudraCT no.: 2019-003851-12 IND no.: 12462 (Regeneron Pharmaceuticals, Inc.)		
	Eylea		2 mg aflibercept IVT injection every 4 weeks for a total of 3 injections, and then every 8 weeks up to Week 48 (9 doses in total, with optional doses to continue at every 4 weeks), n = 338
Endpoints and definitions	Primary endpoint	Mean change from baseline in BCVA (ETDRS letter score) at Week 48	Clinical equivalence is demonstrated if the 95% CI of the LS mean change from baseline in BCVA at Week 48 is contained within a 4 letters margin
	Key secondary endpoint	Mean change from baseline in BCVA (ETDRS letter score) at Week 60	Clinical equivalence is demonstrated if the 95% CI of the LS mean change from baseline in BCVA at Week 48 is contained within a 4 letters margin
	Key secondary endpoint	Proportion of patients without IRF and SRF in central subfield at week 16	Clinical equivalence is demonstrated if the 95% CI of the LS mean change from baseline in BCVA at Week 48 is contained within a 4 letters margin
	Other secondary efficacy endpoints	Mean change in BCVA over time	
		Proportion of subjects who gained ≥5, 10 or 15 letters over time	
		Proportion of patients without IRF and SRF in central subfield over time	
		Number of injections of study drug administered during the study period	
Database lock	04 NOV 2022		

Results and Analysis

Analysis description	**Primary Analysis: Mean change from baseline in BCVA (ETDRS letter score)**			
Analysis population and time point description	MMRM			
Descriptive statistics and estimate variability	Treatment group	2q8	HDq12	HDq16
	Number of subject at Week 48	309	316	312
	Mean change from baseline in BCVA (ETDRS letter score) LS mean (SE) at Week 48	7.03 (0.74)	6.06 (0.77)	5.89 (0.72)

Title: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration				
Study identifier	Study no.: 20968 EudraCT no.: 2019-003851-12 IND no.: 12462 (Regeneron Pharmaceuticals, Inc.)			
	Number of subject at Week 60	305	311	309
	Mean change from baseline in BCVA (ETDRS letter score) LS mean (SE) at Week 60	7.23 (0.68)	6.37 (0.74)	6.31 (0.66)
Effect estimate per comparison	Primary endpoint: **Change from baseline in BCVA at Week 48**	Comparison groups	HDq12 vs 2q8	
		95% confidence interval for difference	-0.97 (-2.87,0.92)	
		P-value	0.0009	
		Comparison groups	HDq16 vs 2q8	
		95% confidence interval for difference	-1.14 (-2.97,0.69)	
		P-value	0.0011	
	Secondary Key endpoint: **Change from baseline in BCVA at Week 60**	Comparison groups	HDq12 vs 2q8	
		95% confidence interval for difference	-0.86 (-2.57,0.84)	
		P-value	0.0002	
		Comparison groups	HDq16 vs 2q8	
		95% confidence interval for difference	-0.92 (-2.51,0.66)	
		P-value	<0.0001	
Notes	Primary and key secondary endpoint is statistically met in both HD groups with the two-sided 95% CI of the adjusted mean difference mean change from baseline in BCVA at Week 48 within a 4 letters margin			
Analysis description	**Key Secondary Analysis: Proportion of patients without IRF and SRF in central subfield at week 16**			
Analysis population and time point description	LOCF			
Descriptive statistics and estimate variability	Treatment group	2q8	HDq12	HDq16
	Number of subject	336	335	338
	Proportion of patients without IRF and SRF in central subfield LS mean (SE) at Week 16	51.6%	61.6%	65.0%
	Number of subject at Week 48	336	335	338

Title: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration				
Study identifier	Study no.: 20968 EudraCT no.: 2019-003851-12 IND no.: 12462 (Regeneron Pharmaceuticals, Inc.)			
	Proportion of patients without IRF and SRF in central subfield LS mean (SE) at Week 48	59.4%	71.1%	66.8%
	Number of subject at Week 60	30 5	311	309
	Proportion of patients without IRF and SRF in central subfield LS mean (SE) at Week 60	74.6%	74.6%	72.2%
Effect estimate per comparison	Key secondary endpoint: **Proportion of patients without IRF and SRF in central subfield at Week 16**	Comparison groups	HD (HDq12+HDq16) vs 2q8	
		95% confidence interval for difference	11.733 (5.263, 18.204)	
		P-value	0.0002	
	Key secondary endpoint: **Proportion of patients without IRF and SRF in central subfield at Week 48**	Comparison groups	HDq12 vs 2q8	
		95% confidence interval for difference	11.725 (4.527, 18.923)	
		P-value	0.0015	
		Comparison groups	HDq16 vs 2q8	
		95% confidence interval for difference	7.451 (0.142, 14.760)	
		P-value	0.0458	
	Key secondary endpoint: **Proportion of patients without IRF and SRF in central subfield at Week Week 60**	Not applicable.		
Notes	Key secondary endpoint is statistically met in both HD groups with the two-sided 95% CI of the adjusted mean difference mean change from baseline in BCVA at Week 48 within a 4 letters margin			

Table 2 Summary of efficacy for trial PHOTON

Title: A randomized, double-masked, active-controlled Phase 2/3 study of the efficacy and safety of high-dose aflibercept in patients with diabetic macular edema			
Study identifier	EudraCT No.: 2019-003643-30 IND Number: 12462		
Design	Multi-center, 1:2:1 randomized, double masked, active controlled, comparative clinical study to evaluate the efficacy and safety between high-dose aflibercept (8 mg) and licensed Eylea 2mg in subjects with diabetic macular edema (DME) treated up to 96 weeks.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		29 JUN 2020 – 30 MAY 2022 not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	HDq12 aflibercept 8 mg		8 mg aflibercept IVT injection every 4 weeks for a total of 3 injections, and then every 12 weeks up to Week 48 (6 doses in total at the minimum, with optional doses to continue at every 8 weeks), n = 328
	HDq16 aflibercept 8 mg		8 mg aflibercept IVT injection every 4 weeks for a total of 3 injections, and then every 8 weeks up to Week 48 (5 doses in total, with optional doses to continue at every 8 or 12 weeks), n = 163
	Eylea		2 mg aflibercept IVT injection every 4 weeks for a total of 5 injections, and then every 8 weeks up to Week 48 (9 doses in total, with optional doses to continue at every 4 weeks), n = 167
Endpoints and definitions	Primary endpoint	Mean change from baseline in BCVA (ETDRS letter score) at Week 48	Clinical equivalence is demonstrated if the 95% CI of the LS mean change from baseline in BCVA at Week 48 is contained within a 4 letters margin
	Key secondary endpoint	Mean change from baseline in BCVA (ETDRS letter score) at Week 60	Clinical equivalence is demonstrated if the 95% CI of the LS mean change from baseline in BCVA at Week 48 is contained within a 4 letters margin
	Key secondary endpoint	Proportion of patients with a ≥ 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) at week 48	Clinical equivalence is demonstrated if the 95% CI of the LS mean change from baseline in BCVA at Week 48 is contained within a 4 letters margin

Title: A randomized, double-masked, active-controlled Phase 2/3 study of the efficacy and safety of high-dose aflibercept in patients with diabetic macular edema					
Study identifier	EudraCT No.: 2019-003643-30 IND Number: 12462				
	Other secondary efficacy endpoints	Mean change in BCVA over time			
		Proportion of subjects who gained ≥5, 10 or 15 letters over time			
		Number of injections of study drug administered during the study period			
Database lock	7 OCT 2022				
Results and Analysis					
Analysis description	**Primary Analysis : Primary Analysis: Change from baseline in BCVA at Week 48**				
Analysis population and time point description	MMRM				
Descriptive statistics and estimate variability	Treatment group	2q8	HDq12	HDq16	
	Number of subject at week 48	167	328	163	
	Mean change from baseline in BCVA (ETDRS letter score) LS mean (SE) at Week 48	8.67 (0.73)	8.10 (0.61)	7.23 (0.71)	
	Number of subject at week 60	167	328	163	
	Mean change from baseline in BCVA (ETDRS letter score) LS mean (SE) at Week 60	9.40 (0.77)	8.52 (0.63)	7.64 (0.75)	
Effect estimate per comparison	Primary endpoint: **Change from baseline in BCVA at Week 48**	Comparison groups	HDq12 vs 2q8		
		95% confidence interval for difference	-0.57 (-2.26, 1.13)		
		P-value	<0.0001		
		Comparison groups	HDq16 vs 2q8		
		95% confidence interval for difference	-1.44 (-3.27, 0.39)		
		P-value	0.0031		
	Secondary Key endpoint: **Change from baseline in BCVA at Week 60**	Comparison groups	HDq12 vs 2q8		
		95% confidence interval for difference	-0.88 (-2.67, 0.91)		
		P-value	0.0003		
		Comparison groups	HDq16 vs 2q8		

Title: A randomized, double-masked, active-controlled Phase 2/3 study of the efficacy and safety of high-dose aflibercept in patients with diabetic macular edema				
Study identifier	EudraCT No.: 2019-003643-30 IND Number: 12462			
		95% confidence interval for difference	-1.76 (-3.71, 0.19)	
		P-value	0.0122	
Notes	Primary and key secondary endpoint is statistically met in both HD groups with the two-sided 95% CI of the adjusted mean difference mean change from baseline in BCVA at Week 48 within a 4 letters margin			
Analysis description	**Key Secondary Analysis: Proportion of patients with a ≥ 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS)**			
Analysis population and time point description	EP-SAP			
Descriptive statistics and estimate variability	Treatment group	2q8	HDq12	HDq16
	Number of subject at week 48	163	328	167
	Proportion of patients with a ≥ 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) mean (SE) at Week 48	26.6%	29.0%	19.6%
	Number of subject at week 60	163	328	167
	Proportion of patients with a ≥ 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) mean (SE) at Week 60	29.1%	31.3%	22.2%
Effect estimate per comparison	Key secondary endpoint: **Proportion of patients with a ≥ 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) at Week 48**	Comparison groups	HDq12 vs 2q8	
		95% confidence interval for difference	1.98 (-6.61 , 10.57)	
		P-value	Not specified	
		Comparison groups	HDq16 vs 2q8	
		95% confidence interval for difference	-7.52 (-16.88 , 1.84)	
		P-value	Not specified	
		Comparison groups	HDq12 vs 2q8	

Title: A randomized, double-masked, active-controlled Phase 2/3 study of the efficacy and safety of high-dose aflibercept in patients with diabetic macular edema			
Study identifier	EudraCT No.: 2019-003643-30 IND Number: 12462		
	Exploratory endpoint: **Proportion of patients with a ⩾ 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) at Week 60**	95% confidence interval for difference	1.87 (-6.88, 10.63)
		P-value	Not specified
		Comparison groups	HDq16 vs 2q8
		95% confidence interval for difference	-7.47 (-17.05, 2.12)
		P-value	Not specified
Notes	Key secondary endpoint is considered by the MAH to be statistically met in HDq12 group with the two-sided 95% CI of the adjusted mean difference change from baseline in patients with a ≥ 2-step improvement in DRSS score at Week 48.		

2.5.4.3. Clinical studies in special populations

Not applicable.

2.5.4.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.5.4.6. Supportive study

Design and conduct of clinical study

A supportive study named CANDELA (21086, VGFTe (HD)-AMD-1905; completed) was planned in the MAH's clinical development program. CANDELA study was a multi-center (US sites only), randomized, single-masked, active-controlled Phase 2 study in participants with nAMD that investigated the efficacy, safety, and tolerability of HD (high-dose aflibcercept 8 mg) versus IAI (aflibcercept 2 mg).

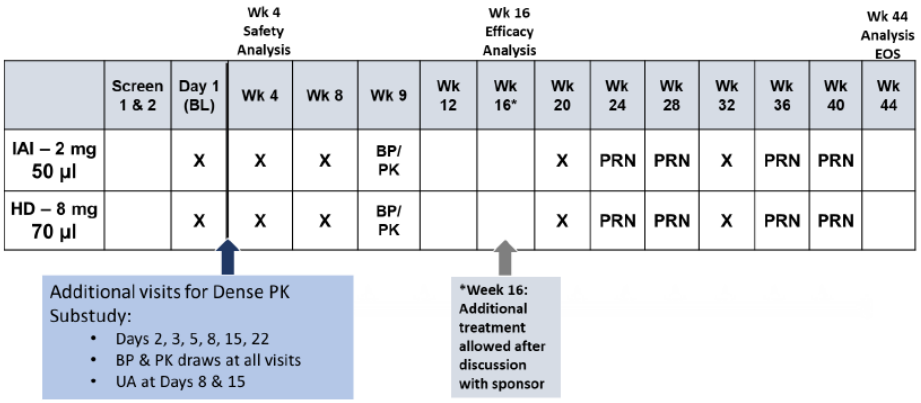
A total of approximately 100 eligible participants were planned to be randomized into 2 groups (IAI and HD) in a 1:1 ratio and within each treatment group, 15 participants (total of 30) were also included in the dense PK substudy. The study duration (44 weeks) is considered long enough to investigate the efficacy and safety profile of the product.

Three consecutive monthly intravitreal injections (baseline, week 4, and week 8), followed by additional doses at weeks 20 and 32 in both groups. At week 16, additional treatment ("rescue") could be given after consultation with the Sponsor, if in the investigator's judgement, a patient could not adhere to the protocol-specified dosing interval due to persistent or worsening disease and required an interim injection. Moreover, at

weeks 24, 28, 36, and 40, participants were evaluated and given a dose (at their randomized dose level) if EITHER of the following criteria were met (pro re nata [PRN] criteria):

- Loss of ≥ 5 letters from week 20 Best Corrected Visual Acuity (BCVA) due to disease progression OR

- Anatomical findings that were considered vision-threatening, such as worsening or persistent retinal fluid, new or worsening retinal pigment epithelial detachment (PED), new or persistent hemorrhage, etc



Abbreviations: BL=baseline; BP=blood pressure; EOS=end of study; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; PK=pharmacokinetics; PRN=pro re nata; wk=week.

Figure 3.6.1 – Dosing schedule

CANDELA study enrolled men or women ≥ 50 years of age subjects with active subfoveal CNV secondary to nAMD, including juxtafoveal lesions that affect the fovea in the study eye as assessed by an independent reading center, and BCVA at 4 m from 78 to 24 letters (ETDRS chart) equivalent to Snellen visual acuity of of 20/32 to 20/320 in the study eye. Subject's selection are considered and similar to the PULSAR study.

The primary efficacy endpoint aimed to determine if HD provides greater intraocular PD effect and/or longer duration of action compared with 2 mg IAI by assessing the proportion of participants without retinal fluid in the center subfield at week 16.

No secondary endpoints were planned. Exploratory efficacy endpoints aim generate additional data to determine the effect of HD vs IAI on anatomical measures of response and on visual acuity.

It is to note that the study enrolment was paused for approximately 3 months during the COVID-19 pandemic and did not have any significant impact on the conduct of the study or the study participants who were already enrolled as only one participant discontinue the study.

In total, 106 participants were randomized: 53 to the IAI group and 53 to the HD group and 92.5% and 96.2% completed the study in IAI and HD groups respectively.

Overall, demographics, baseline disease characteristics and medical history were generally well balanced between the treatment groups, with the exception of sex (there was a higher proportion of male participants in the HD group compared with the IAI group).

Efficacy data and additional analyses

Overall, all efficacy endpoints were analyzed using the FAS and additional OC, aLOCF, and aOC sensitivity analyses were performed. All exploratory efficacy endpoints were analyzed descriptively, with nominal p-values.

Through week 44, the mean (SD) duration of treatment in the study eye was 36.9 (7.77) weeks in the IAI group and 37.7 (4.52) weeks in the HD group with a majority of 5 IVT injections in both groups.

The primary endpoint related to efficacy was the proportion of participants without fluid in the center subfield of the study eye at Week 16 with an exploratory endpoint at week 44 (Table 3.6.1.). The decreasing tendency in the proportion of patients without fluid at week 16 (50.9% in HD group and 34% in IAI group) was further observed at week 44 (39.6% in HD group and 28.3% in IAI group) in both groups with a numerically superiority in the HD groups (without statistical differences).

Treatment	Participants Without Fluid	Difference (%) (95% CI)[a]	p-value[b]
Week 16			
HD (N=53)	27/53 (50.9%)	17.0 (-1.6, 35.5)	0.0770
IAI (N=53)	18/53 (34.0%)		
Week 44			
HD (N=53)	21/53 (39.6%)	11.3 (-6.6, 29.2)	0.2185
IAI (N=53)	15/53 (28.3%)		

Abbreviations: CI=confidence interval; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; IRF=intraretinal fluid; LOCF=last observation carried forward; SRF=subretinal fluid.
No fluid=absence of IRF and/SRF in the center subfield. Center subfield=the circular area in 1 mm diameter centered around the center point of the fovea.
Baseline: the latest available valid measurement taken on Study day 1 prior to administration of study drug.
The percentage is based on the number of participants with available measurements in each treatment group as denominator.
LOCF=Missing observations were imputed by the last non-missing post-baseline observation. Participants were considered as non-responders if all post-baseline observations were missing. For participants receiving additional treatment at week 16, measurements past week 16 were imputed using the last observation prior to additional treatment.
[a] The 95% CI is based on normal approximation.
[b] p-value is calculated using chi-square test at the 2-sided 5% significance level.

Table 3.6.1 - Proportion of Participants without Fluid in the Center Subfield of the Study Eye, LOCF at Week 16 and Week 44 (Full Analysis Set)

Additional precision on IRF/SRF fluid were indicated by the MAH:

- The proportion of participants without IRF in the center subfield of study eye which were numerically similar at week 16 (HD: 69.8%; IAI: 67.9%; treatment difference: 1.9%; 95% CI: -15.7, 19.5;p=0.8339) and at week 44 (HD: 60.4%; IAI: 64.2%; treatment difference: -3.8%; 95% CI: -22.2, 14.7; p=0.6886) in both groups
- The proportion of participants without SRF in the center subfield of study eye at week 16 was numerically higher in the HD group (69.8%) compared with the IAI group (50.9%; treatment difference: 18.9%; 95% CI: 0.6, 37.1; p=0.0471) and at week 44 (HD: 69.8%; IAI: 50.9%)

Other endpoints were also analysis by the MAH, including:

- The proportion of participants without macular fluid in the study eye at week 16 (HD: 43.4%; IAI: 26.4%; treatment difference: 17.0%; 95% CI: -0.9, 34.8; p=0.0667) and at week 44 (HD: 32.1%; IAI: 15.1%; treatment difference: 17.0%; 95% CI: 1.1, 32.8; p=0.0395). With the precision in the:
    - proportion of participants without intraretinal macular fluid in the study eye at week 16 (HD: 58.5%; IAI: 58.5%; treatment difference: 0.0%; 95% CI: -18.8, 18.8; p=1.0000) and at week 44 (HD: 47.2%; IAI: 45.3%; treatment difference: 1.9%; 95% CI: -17.1, 20.9; p=0.8455)
    - proportion of participants without subretinal macular fluid in the study eye at week 16 (HD: 67.9%; IAI: 43.4%; treatment difference: 24.5%; 95% CI: 6.2, 42.9; p=0.0110) and at week 44 (HD: 66.0%; IAI: 43.4%; treatment difference: 22.6%; 95% CI: 4.2, 41.1; p=0.0192). The treatment difference between the 2 groups was nominally statistically significant at both time points.
- The proportion of participants able to maintain a 12-week dosing interval from week 8 through week 44 (ie, participants receiving only protocol required treatments) was numerically higher in the HD group (54.7%) compared with the IAI group (45.3%). Of those participants completing the week 16 visit, a numerically higher proportion of participants in the HD group (81.1%) compared with the IAI group (72.9%) did not require an additional dose of treatment at week 16. Of those participants completing the week 44 visit, a numerically higher proportion of participants in the HD group (56.9%) compared with the IAI group (49.0%) did not require an additional dose of treatment at week 16 or PRN doses at weeks 24, 28, 36, or 40
- The proportion of participants receiving only protocol required treatments and completing Week 44, with and without fluid in the center subfield of the study eye (aLOCF) were similar between HD and IAI groups at weeks 16, 24, 28, 36, and 40.

Additional endpoints as the proportion of participants able to maintain no retinal fluid in the center subfield of study eye through week 16 and week 44, the time to maintaining no retinal fluid in the center subfield of study eye through week 44 and proportion of participants without subretinal pigment epithelium fluid in the macula of study eye, were considered numerically higher in the HD group.

Regarding the change observed from baseline in BCVA score (ETDRS Score) in the study eye, the mean (SE) change from baseline in BCVA was numerically higher in the HD group compared with the IAI group both at week 16 (HD: 8.4 [1.31] ETDRS letters; IAI: 6.5 [1.38] ETDRS letters) and week 44 (HD: 7.9 [1.47] ETDRS letters; IAI: 5.1 [1.52] ETDRS letters). Also, the least squares (LS) mean (standard error [SE]) change in BCVA from baseline was numerically higher in the HD group compared with the IAI group at week 16 and 44 (Table 3.6.2.).

Treatment	IAI (N=53)	HD (N=53)
Week 16		
Number of Patients	51	53
Baseline Means (SD)	58.3 (10.69)	57.9 (13.58)
Means (SD)	64.8 (13.62)	66.2 (15.02)
Mean Change (SD)	6.5 (9.89)	8.4 (9.55)
LS Mean Change (SE)[a]	6.6 (1.35)	8.3 (1.32)
p-value[a]		0.3541
Estimate for Contrast and 95% CI (LS Mean)[a]		1.76 (-1.99, 5.51)
Week 44		
Number of Patients	51	53
Baseline Means (SD)	58.3 (10.69)	57.9 (13.58)
Means (SD)	63.4 (14.82)	65.8 (16.22)
Mean Change (SD)	5.1 (10.83)	7.9 (10.73)
LS Mean Change (SE)[a]	5.2 (1.51)	7.9 (1.48)
p-value[a]		0.1957
Estimate for Contrast and 95% CI (LS Mean)[a]		2.76 (-1.44, 6.95)

Abbreviations: ANCOVA=Analysis of covariance; BCVA=Best Corrected Visual Acuity; CI=confidence interval; ETDRS=early treatment of diabetic retinopathy study; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; LOCF=last observation carried forward; SD=standard deviation; SE=standard error; LS=least squares.
LOCF=missing observations were imputed by the last non-missing post-baseline observation. For patients receiving additional treatment at week 16, measurements past week 16 were imputed using the last observation prior to additional treatment.
Baseline: the latest available valid measurement taken on Study day 1 prior to administration of study drug. If time is not collected, it is assumed the available day 1 measurement is done before dosing.
[a] ANCOVA model with treatment as the main effect and baseline measurement as covariates.

Table 3.6.2 - ANCOVA of Change from Baseline in BCVA Score (ETDRS Letters) in the Study Eye, LOCF (Full Analysis Set)

Moreover, the proportion of participants with no vision change or any loss, or who lost ≥ 5, 10, and 15 ETDRS Letters from Baseline in Study Eye were numerically higher in the IAI group (Table 3.6.3). However, the proportion of participants who gained ≥ 1, 5, 10, and 15 ETDRS Letters from Baseline in Study Eye were numerically higher in the HD group (except for ≥5 letter gain) see Table 3.6.4.

Treatment	IAI (N=53)	HD (N=53)
Proportion of Patients with Any Letter Loss or No Vision Change		
Week 16	11/51 (21.6%)	11/53 (20.8%)
Week 44	14/51 (27.5%)	12/53 (22.6%)
Proportion of Patients Losing ≥ 5 Letters		
Week 16	8/51 (15.7%)	3/53 (5.7%)
Week 44	11/51 (21.6%)	6/53 (11.3%)
Proportion of Patients Losing ≥ 10 Letters		
Week 16	3/51 (5.9%)	1/53 (1.9%)
Week 44	5/51 (9.8%)	3/53 (5.7%)
Proportion of Patients Losing ≥ 15 Letters		
Week 16	1/51 (2.0%)	1/53 (1.9%)
Week 44	3/51 (5.9%)	2/53 (3.8%)

Abbreviations: ETDRS=early treatment of diabetic retinopathy study; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; LOCF=last observation carried forward.
LOCF=missing observations were imputed by the last non-missing post-baseline observation. For patients receiving additional treatment at week 16, measurements past week 16 were imputed using the last observation prior to additional treatment.
Baseline: the latest available valid measurement taken on Study day 1 prior to administration of study drug. If time is not collected, it is assumed the available day 1 measurement is done before dosing.

Table 3.6.3 - Proportion of Patients With No Vision Change or any Loss, or Who Lost ≥ 5,10 and 15 ETDRS Letters from Baseline in Study Eye by Visit, LOCF (FAS)

Treatment	IAI (N=53)	HD (N=53)
Proportion of Patients Gaining ≥ 1 Letters		
Week 16	40/51 (78.4%)	42/53 (79.2%)
Week 44	37/51 (72.5%)	41/53 (77.4%)
Proportion of Patients Gaining ≥ 5 Letters		
Week 16	32/51 (62.7%)	33/53 (62.3%)
Week 44	30/51 (58.8%)	30/53 (56.6%)
Proportion of Patients Gaining ≥ 10 Letters		
Week 16	17/51 (33.3%)	22/53 (41.5%)
Week 44	18/51 (35.3%)	25/53 (47.2%)
Proportion of Patients Gaining ≥ 15 Letters		
Week 16	11/51 (21.6%)	10/53 (18.9%)
Week 44	9/51 (17.6%)	15/53 (28.3%)

Abbreviations: ETDRS=early treatment of diabetic retinopathy study; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; LOCF=last observation carried forward.
LOCF=missing observations were imputed by the last non-missing post-baseline observation. For patients receiving additional treatment at week 16, measurements past week 16 were imputed using the last observation prior to additional treatment.
Baseline: the latest available valid measurement taken on Study day 1 prior to administration of study drug. If time is not collected, it is assumed the available day 1 measurement is done before dosing.

Table 3.6.4 - Proportion of Patients Who Gained ≥ 1, 5, 10 and 15 ETDRS Letters from Baseline in Study Eye by Visit, LOCF (FAS)

Additionally, the change from baseline in CRT, total lesion size and Choroidal Neovascularization Size in the Study Eye were numerically favour of the HD group compared with the IAI group both at week 16 and at week 44.

Overall, the superiority of the HD treatment compared to the IAI group was no met for the primary efficacy endpoint. However, the efficacy results were numerically in favour of the HD group and were further confirmed by the sensitivity analysis performed by the MAH. Moreover, the efficacy results CANDELA study support the initiation dosing regimen in the nAMD patients.

2.5.5. Discussion on clinical efficacy

Design of main studies

This variation include clinical efficacy data of 2 pivotal studies in patients with nAMD (ongoing phase 3 PULSAR, submitted data at 48 and 60 week) and DME (ongoing phase 2/3 PHOTON, submitted data at 48 and 60 week) as well as one supportive study in nAMD patients (CANDELA, completed) for the new high-dose strength of aflibercept 8 mg (114.3 mg/mL). Both pivotal studies were multi-center, randomized, double-masked, active-controlled and composed of 3 arms (2q8, HDq12 and HDq16) and were randomized to receive IVT injections in the study eye of either aflibercept high-dosed (HD) or aflibercept 2 mg in 3 parallel treatment groups. Patient were treated with 3 (in PULSAR) or 5 (in PHOTON) initial IVT injections at 4-week intervals, followed by IVT injection every 8 weeks in the 2q8 group (comparator), or with 3 initial injections at 4-week intervals, followed by IVT injection 12 or 16 weeks in HDq12 and HDq16 groups respectively, with possible interval modification starting week 16.

A CHMP scientific advice (EMA/CHMP/SAWP/277944/2019) included discussion about both pivotal studies in term of comparator choice, overall design of the study (non-inferiority, double-masked, randomised, active-controlled, three-arm), endpoints.

Approximately, 1395 patients had been enrolled in PULSAR (1:1:1 ratio, with 337 patients in 2q8 arm, 336 in HDq12 and 338 in HDq16 arm respectively) and 660 in PHOTON (1:2:1 ratio, with 167 patients in 2q8 arm, 329 in HDq12 and 164 in HDq16). The patients included were adequately selected with regard to the disease. Furthermore, patients were stratified on the geographical region (Japan vs Rest of the World) and the BCVA baseline (<60 vs ≥60) in PULSAR or CRT baseline (<400µm vs ≥400 µm) and prior DME treatment (yes/no) in PHOTON. As in PULSAR trial, the granularity of the geographical stratification could seem a bit wide. The country level could have been an option but no per country patient disposition was found in the trial's CSR to document this point. This per country disposition are of great importance (see comments below) and the Applicant was requested to provide them with the following 2 regions disposition: Europe, including Czech Rep, Germany, Hungary and UK, North America including Canada and USA, Japan is already described in the file. The requested information for the Pulsar trial was provided. The EU population constituted the largest cohort of subjects included in the trial (39%), followed mainly by cohorts from North America (30%) and Asia (23%), representing a total of 92% of the study population. Based on these results, homogeneous treatment responses in these 3 major subgroups should be expected**.**

Additionally, the efficacy populations of analysis in PULSAR study are acceptable, except for PPS which was planned to be analysed "as treated" while an error of treatment allocation should be considered as a major deviation to the protocol. Moreover, if the wrong treatment allocation occurred only at some specific time-points of the 48/60 weeks of exposure (this case is defined as an ICE), the rational for deciding which arm to assign to patient in the "as treated" strategy is unclear and should be explained. As a response, clarifications have been brought by the Applicant regarding the "as treated" terminology used in the trial. Only 6 patients were concerned with the qualification of "as treated", whom only one subject underwent an error of treatment allocation. The other subjects were affected by deviations in the amount of volume injected or in the modalities of administration. The issue could be considered as solved though the PP set do not reflect per-se the definition of such a population where patients presenting deviations in planned regimens potentially affecting the primary efficacy endpoint should be excluded.

Results of main studies

PULSAR - nAMD

1395 enrolled participants in PULSAR study but 383 participants did not complete screening, therefore, the Week 48 and Week 60 datasets analysis provided are based on 1011 participants. For these participants, proportion of male and female were well balanced between the 3 arms, even if slightly more female patients were included in total (54,5%). Data were mostly well balanced across the treatment groups for the demographics and disease characteristics at baseline (BCVA, IOP, CST, CNV size, type and classification, total lesion area and NEI-VFQ-25 total score). The ocular medical and surgical history in the study eye mostly reported (> 10%) were AMD, Cataract and Cataract operation and the non-ocular medical and surgical history in the study eye, most commonly reported SOC (> 30%) were Vascular disorders, Metabolism and nutrition disorders, Surgical and medical procedures, and Musculoskeletal and connective tissue disorders. However, the MAH was requested to further discuss the clinical relevance of baseline disease characteristics of the following observed discrepancies in PULSAR study (in patients of certain categories of age (<65, ≥ 65 to < 75 and ≥ 75 to < 80 years), with history of ischaemic heart disease and hepatic impairment (mild, severe, moderate), cataract, CST). The Applicant provides further discussion on clinical relevance of baseline disease characteristics of the observed discrepancies in PULSAR study. According to the Applicant, the differences are to be considered as minor numerical differences at baseline without clinical significance relevance.

Moreover, among those participants, it is to note that COVID-19 crisis and Ukraine/Russia conflict had a low impact on the discontinuation of the participants, however considering that 35.1% of patients across the groups in PULSAR study reported important protocol deviations, The MAH was requested to further discuss the impact of each protocol deviation of them on the efficacy analysis. As a response, the Applicant has clarified what was meant by "important" protocol deviations in Pulsar study and described extensively the corresponding deviations as well as the decision rules that led to rule out from the primary analysis or the PPS analysis, all or part of data of patients presenting these deviations, depending on the way the might affect efficacy outcome and when they occurred. "Important" deviations to protocol were segmented in 3 categories: 1/ the ones not impacting the efficacy endpoints led to no exclusion from main efficacy analyses; 2/ deviations that might affect the efficacy endpoints and identified at screening led to excluding affected patients from the per-protocol set; 3/ deviations that might impact the efficacy and occurring after baselines measurements led to excluding from the main efficacy analyses partial data of affected patients. These last deviations were considered as intercurrent events and handled according to estimand strategies (mainly, hypothetical and treatment policy strategies, depending of the strength of the impact on efficacy data). Tables illustrating and justifying the updated definition and all concerned cases were provided and even though other approaches could have been considered, the proposed approach is reasonable.

However, in non-inferiority trials, it is well known that heterogeneity of data is a factor artificially favoring the non-inferiority, therefore, it would have been relevant to perform a per-protocol analysis excluding all patients presenting with "important" deviations impacting the primary endpoint within the 48 weeks treatment window, whatever the reason and the time of occurrence. This analysis, repeated on EU population would have been interesting too.

Additionally, to be noticed that there were 47 cases of wrong treatment allocation. It was requested to briefly describe these cases in a table presenting the randomized and actual allocated treatment, the time point(s) concerned and the "as-treated" arm assigned in the PPS analysis. Thus, all the data requested have been provided and it is confirmed that except for one patient, all patients had their treatment allocated according to the randomization. However, it is still questionable to keep in the PPS, patients having received the wrong dose (as described by the Applicant).

For the analysis of the primary endpoint, a mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate and treatment group, visit, the stratification variables (geographic region [Japan vs. Rest of World], and baseline BCVA [< 60 vs. ≥ 60]) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit.

The primary endpoint was the change from baseline in BCVA (ETDRS letter score) at Week 48, completed with a key secondary endpoint of that measure at week 60. The mean BCVA at baseline was 58.9, 59.9 and 60.0 letters for 2q8 (n=336 patients), HDq12 (n=335 patients) and HDq16 (n=338 patients) groups respectively.

The LS mean (SE) change of BCVA from baseline to week 48 observed were: 7.03 (0.74), 6.06 (0.77) and 5.89 (0.72) letters in 2q8 (n=285 patients), HDq12 (n=299 patients) and HDq16 (n=289 patients) groups respectively with an estimated difference in LS means from baseline to Week 48 in BCVA (with corresponding 95% CI) changes and the p-values for the non-inferiority test at a margin of 4 letters of HDq12 vs. 2q8 -0.97 (-2.87, 0.92; p-value 0.0009) letters and of HDq16 vs. 2q8 was -1.14 (-2.97, 0.69; p-value 0.0011) letters. At week 60, 7.23 (0.68), 6.37 (0.74) and 6.31 (0.66) letters in 2q8 (n=268 patients), HDq12 (n=283 patients) and HDq16 (n=282 patients) groups were observed for the LS mean (SE), respectively and the estimated difference of HDq12 vs. 2q8 was -0.86 (-2.57, 0.84; p-value 0.0002) letters and of HDq16 vs. 2q8 was -0.92 (-2.51, 0.66; p-value < 0.0001) letters.

The MAH also performed subgroup analysis in change from baseline in BCVA measured by the ETDRS letter score at Week 48 and Week 60 and the results presented were similar with the overall population. Tendency for higher mean increases in the HD groups compared to the 2q8 group were noted for the Asian and Japanese subgroups. However, given the smaller size of these subgroups, the validity of these comparisons is limited.

Additionally, two sensitivity analyses were performed regarding the change from baseline in BCVA measured by the ETDRS letter score at Week 48 and 60, using ANCOVA method. The results were consistent with the primary analysis.

Overall, the primary and key secondary endpoint criteria, to know, the change from baseline in BCVA measured by the ETDRS letter score at Week 48 and 60 (non-inferiority of IVT aflibercept therapy HDq12 and HDq16 dosing regimen to the current authorized IVT aflibercept therapy 2q8 dosing regimen) is considered to be statistically met (95% credible interval for treatment difference with a non-inferiority margin of 4 letters with LS mean change from baseline in BCVA to Week 48 and 60), at Week 48 and 60. However, even if the non-inferiority appear to be statistically met, given the longer intervals in the new proposed dosing regimen (HDq12 and HDq16), more long-term efficacy and safety results are awaited for both PHOTON and PULSAR studies. Therefore, and as discussed in the previous scientific advice dated from 2019, in order to straighten the efficacy

and safety results, the Applicant was requested to provide the 2 years data. All the data requested have been provided.

Consequently, to respond to the requested 2-year data, a snapshot of PULSAR data up to Week 96 was performed in May 2023. This dataset comprises all patients (100%) enrolled in PULSAR. Of ongoing patients, approximately 80% (689 out of 875) had already completed the Week 96 visit and almost all had completed visits up to Week 88. More precisely, of the 1009 randomized patients included in the FAS and the SAF, 689 patients had completed the study through Week 96. 137 patients had discontinued prematurely. For 186 patients (18.4%), according to the Applicant, these patients constitute the ongoing patients at the time of the data snapshot

The mean number of active injections in the Week 96 completers of the PULSAR SAF population was 12.8, 9.8 and 8.2 in the 2q8, HDq12 and HDq16 treatment groups, respectively, over the first 96 weeks of the study.

Of note, the proportions of Week 96 completers in the European subgroups were even higher than in the non-European subgroups given that the recruitment in Europe was completed earlier than in other regions

For the PHOTON study, this later reached Week 96 LPLV in May 2023. Therefore, complete Week 96 key results for the DME indication are available in full for all study participants. Of the 660 randomized patients included in the FAS and the SAF, 534 patients completed the study through Week 96. However, 126 patients did not complete the study, with a higher proportion of patients in the HDq12 group (22.2% vs. 15.2% and 16.8%), mainly attributable to withdrawal of consent by subject, lost to follow-up and death. Of note, 31 (4.7%) patients were reported as lost to follow-up through Week 96. As for PULSAR study, the mean number of active injections in the PHOTON SAF population of Week-96 completers was proportional to allocated interval dosing with a number of injection of 13.8, 9.5 and 7.8 in the 2q8, HDq12 and HDq16 treatment groups, respectively over the first 96 weeks of the study

Overall, the provided additional long-term data are globally reassuring both on a quantitative (number of exposed patients) and qualitative aspects (results on efficacy endpoints). Indeed, based on data from PULSAR (approx. 80% completed Week 96 data collection) and on the data from all patients in PHOTON, HD aflibercept dosed every 12 weeks or every 16 weeks showed nearly similar maintained efficacy through Week 96 compared to 2 mg aflibercept, consistent with the non-inferiority demonstrated at Week 48 and Week 60 with respect to improvement in BCVA in patients with nAMD or DME.

The MAH was requested to further discuss clinical relevance of the chosen 4 letters margin rather than a smaller one as advised in the previous scientific advice in both PULSAR and PHOTON studies. The justification of the non-inferiority margin provided by the Applicant has been consistent and clinically relevant. This margin ensures that any difference in visual acuity within one line of the ETDRS chart is not clinically meaningful. This 4-letters margin has been used in many non-inferiority trials investigating visual acuity.

Moreover, the MAH was requested to discuss and justify the initiation dosing regimen of 3 monthly IVT injections that appears to be 4 times higher exposure than the current regimen authorized and provide efficacy and safety results regarding that period for both PULSAR and PHOTON studies. Furthermore, for PHOTON study, the MAH was also requested to discuss the difference in term of number of injections in HD group during that period compared to the current authorized dosing regimen. It appears that during the loading phase (up to Week 12), in PULSAR (3 monthly injections in all study arms) and PHOTON studies (5 monthly injections for 2q8 and 3 monthly injections for all HD) all treatment arms received active monthly injection with either 2 mg or 8 mg aflibercept at day 1, week 4 and week 8.

In PULSAR, comparable proportions of ocular TEAE were reported (17,3% for 2q8 vs 18,1% for all HD) and proportions of TEAE reported in more than 2 patients and with a difference ≥ 0.5% to the 2 mg arm (retinal haemorrhage, conjunctivitis, IOP increase and vitreous floaters) were low and comparable. Additionally, comparable proportions were reported for ocular safety topics (cataract, retinal detachment/tear, RPE tear, and intraocular inflammation) other than IOP increase for which event were all non-serious and without sustained IOP elevations. Non-ocular TEAE were reported in higher proportions for HD group (22.1% vs 16.7% in 2q8 arm). For SOC in which a difference of > 1% was observed and higher incidence in the HD arms (Infections and infestations and Vascular disorders), PT reported in more than 1 patient were Pulpitis dental, Upper respiratory and Urinary tract infection and Hypertension. Incidence for non-ocular safety topics were low and comparable between treatment arms.

In PHOTON, incidences of ocular TEAEs were higher in the HD group (2q8: 9.6%, all HD: 17.1%) however when compared to PULSAR studies a lower proportion of ocular TEAE was reported in 2q8 arm (PULSAR - 2q8: 17.3%, PHOTON – 2q8: 9.6%) and incidences for ocular TEAE in the HD group were nevertheless similar to PULSAR. Events reported in more than 2 patients and with a difference ≥ 0.5% to the 2 mg arm consisted of cataract/cataract cortical, conjunctival hemorrhage, photopsia, punctate keratitis, and vitreous detachment for which no consistent trend were observed across studies. Proportions of ocular safety topics were low and comparable between treatment arms. Non-ocular event were reported in comparable proportions between treatment arms. For the SOC with a difference of > 1% and higher incidence in the HD arms (Gastrointestinal disorders, Infections and infestations, Nervous system disorders, Psychiatric disorders, Renal and urinary disorders and Respiratory, thoracic and mediastinal disorders), majority of PTs were reported in single patient with no consistent trend were observed across studies. Incidences for non-ocular safety topics were low and comparable.

Overall, although exposures to aflibercept in the HD treatment arms in both PULSAR and PHOTON studies were higher during the loading phase and that the incidence of ocular TEAE in the 2q8 arms in both groups were disparate, safety data are still reassuring and in favour of a comparable safety profile with ocular and non-ocular TEAE being reported in similar range between both studies. No consistent trend could be observed in both studies**.**

The second key secondary endpoint concerned the proportion of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in Central Subfield at Week 16 with a comparison between the 2q8 group versus pooled HD groups (HDq12 and HDq16). At week 16, 51.6% in the 2q8 treatment group compared to 63.3% of participants in the pooled HD groups (61.6% in HDq12 and 65% in HDq16arm) had no retinal fluid (no IRF and no SRF) with a difference (95% CI) between pooled HD groups vs. 2q8 treatment of 11.733% points (5.263%, 18.204%) superiority and a p-value of the 1-sided CMH test for superiority of 0.0002. The key secondary endpoint appears to be statistically met for both HD groups at week 16. More long-term data were provided for this endpoint (week 48 and 60) and same tendency was observed with an absence of IRF and SRF more pronounce in the HD groups and more particularly in the HDq12 group.

Subgroups regarding the proportions of participants with no IRF and no SRF in central subfield at Week 16 were analysed by subgroups of age, sex, geographic region, ethnicity, race, baseline BCVA, and baseline PCV and discrepancies are noted in the following subgroups of patients: < 65 years, ≥ 65 to < 75 years, ≥ 80 to < 85 years, females, from Rest of the world, not Hispanic or Latino, White, with a baseline BCVA ≤ 73 letters, and no PCV at baseline.

A sensitivity analyses was performed regarding the presence/absence of IRF/SRF in Central Subfield at Week 16 using LOCF in FAS and the results were consistent with the primary analysis.

Additionally, other secondary endpoints were analysed at week 48 and 60, such as: proportions of participants gaining at least 15 letters in BCVA, proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent), mean change in CNV size, mean change in total lesion area, mean change in CST and the mean change in NEI-VQF-25 total score. Overall, secondary efficacy endpoints results for HD groups (HDq12 and HDq16) in PULSAR study appears to be following the same tendency as for the 2q8 group with a slight numerical superiority in favour to the HDq12 regimen compared to the HDq16. Therefore, the MAH was invited to further discuss the clinical relevance of the secondary endpoint results with regards to the two new proposed dosing regimen. As requested, the applicant provides a comprehensive discussion regarding the clinical relevance of the Secondary efficacy endpoints results for HD groups (HDq12 and HDq16) in PULSAR study (functional and anatomical response based on Change from baseline in BCVA measured by the ETDRS letter, Proportion of participants with no IRF and no SRF in central subfield, Proportion of participants gaining ≥ 15 letters in BCVA, Change from baseline in CST...).

Overall, the functional measures show similar outcomes across the 3 treatment groups, with non-inferiority demonstrated in the key secondary endpoint of change from baseline in BCVA at Week 60, in line with the primary endpoint results at Week 48. Between the two HD groups, numerical differences in other secondary endpoints are small, and not always in favour of HDq12 (e.g. proportion of patients gaining at least 15 letters in BCVA from baseline to Week 48). In conclusion, the results of the secondary efficacy endpoints in PULSAR are in line with the primary analysis and seem clinically relevant for demonstrating the value of aflibercept for the treatment of nAMD.

To note, results of exploratory endpoints were similar between groups, except for the presented proportion of patients with different dosing intervals that appear to be unclear for which the MAH was asked to provide a Table clearly identifying the patient's dosing interval of treatment in each arms at Week 48 and 60 (q8, q12, q16 and q20). As requested, the Applicant provides details identifying the patient's dosing interval of treatment in each arms at Week 48 and 60 (q8, q12, q16 and q20) in both PULSAR and PHOTON studies

Table 51 Actual dosing intervals at Week 48 and 60 by assigned treatment arm - PULSAR and PHOTON

Figures denote number (%) of subjects

		PULSAR			PHOTON		
		2q8	HDq12	HDq16	2q8	HDq12	HDq16
Week 48 completers		N=309 (100%)	N=316 (100%)	N=312 (100%)	N=157 (100%)	N=300 (100%)	N=156 (100%)
Interval at Week 48	q8	309 (100%)	65 (20.6%)	40 (12.8%)	157 (100%)	27 (9.0%)	6 (3.8%)
	q12	NA	251 (79.4%)	33 (10.6%)	NA	273 (91.0%)	11 (7.1%)
	q16	NA	NA	239 (76.6%)	NA	NA	139 (89.1%)
Week 60 completers		N=305 (100%)	N=311 (100%)	N=309 (100%)	N=155 (100%)	N=289 (100%)	N=152 (100%)
Interval at Week 60	q8	305 (100%)	51 (16.4%)	33 (10.7%)	155 (100%)	23 (8.0%)	8 (5.3%)
	q12	NA	126 (40.5%)	42 (13.6%)	NA	138 (47.8%)	12 (7.9%)
	q16	NA	134 (43.1%)	116 (37.5%)	NA	128 (44.3%)	77 (50.7%)
	Q20	NA	NA	118 (38.2%)	NA	NA	55 (36.2%)

Manually calculated from swimmer plots shown in Figure 18 to Figure 25.

For PULSAR study, it appears that the majority of patients were rather maintained on their originally assigned interval or extended to a greater interval (eg, from q12 to q16 interval) both on W48 and W60 completers. However, even low, it should be noted that a certain proportion of patients were shortened their treatment interval (less than 20% in both HDq12 and HDq16 arm at W48 and W60). In the meantime, and as discussed

above, a proportion of patients were extended from their original assignment (43.1% of HDq12 arm were extended to a q16 dosing interval and 38.2% of HDq16 arm were extended to a q20 dosing interval)

For PHOTON study, the proportion of patients who maintained their original interval was greater with around 90% of patients maintained their originally assigned q12 or q16 dosing at W48 and W60 and around 10% who shortened the originally assigned interval. In parallel, 43.3% and 36.2% of patients were extended to a q16 and q20 dosing interval for HDq12 and HDq16 arm respectively.

This exploratory endpoint appears critical in order to better assess the HD groups given the posology proposed is also based on the following results:

- No dose modification permitted in 2Q8, (85.7% of participant received 7 IVT injections at week 48 and 77.4% received 9 IVT injections at Week 60).

- In the HDq12 group: at week 48 with a total of 316 patient, 79.4% of patients stayed with the HDq12 dosing regimen and 20.6% shortened to q8; at week 60 with a total of 311 patients, 77.8% of patients stayed with the HDq12 dosing regimen and 22.2% shortened to q8. In total, 77.6% of participant received 6 IVT injections at week 48 and 71.3% received 7 IVT injections at Week 60.

- In the HDq16 group: at week 48 with a total of 312 patient, 76.6% of patients stayed with the HDq16 dosing regimen and 23.4% shortened (12.8% to q8 and 10.6% to HDq12 regimen); at week 60 with a total of 309 patients, 86.9% of patients stayed with the HDq16 dosing regimen and 23.4% shortened (14.6% to q8 and 11.3% to HDq12 regimen). In total, 77.8% of participant received 5 IVT injections at week 48 and 75.4% received 6 IVT injections at Week 60.

Overall, the efficacy results issued from PULSAR study are very limited to support the 5 months injection interval during the maintenance phase. More long-term results are awaited by the sponsor. As a response, the applicant provides additional new data that could support the claimed q20 (or longer) intervals. Through Week 96, up to 47% and 44.3% of HD patients extended their treatment interval to q20 or longer intervals in the PULSAR and PHOTON study respectively. Numerically, this corresponds to a total of 185 patients completed at least one q20 interval before Week 96 in PULSAR and 133 patients in PHOTON study.

At Week 96, the proportion of patients with q20 or longer as the last intended dosing interval in the PULSAR was 36.8% in the HDq12 group and 54.9% in the HDq16 group. Of 216 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24 (i.e. 53 and 127 HD patients, respectively); only a few patients were shortened back to q16 (i.e. 3 HD patients).

For the PHOTON study, at Week 96 the proportion of patients with q20 or longer as the last intended dosing interval was 42.2% in the HDq12 group and 45.3% in the HDq16 group. Of 177 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24.

In addition, further discussion was requested to be carried by the MAH on the absence of visits between two injections during the maintenance phase. In response, the Applicant provides some clarifications regarding the relevance of absence of visits between two injections during the maintenance phase for patients allocated to HD intervals.

As discussed in the MO above, considering that the HDq12 and HDq16 treatment regimens have overall demonstrated BCVA gains non-inferior compared to 2q8, it is supported that modification of treatment intervals is not needed between doses and therefore monitoring visits are not a requirement for these regimens.

Nevertheless, in line with the current practice regarding aflibercept 2 mg and the information included in the SmPC for aflibercept 2 mg, the Applicant proposes that event for the HD intervals, the frequency of monitoring visits may be higher than the dosing frequency, based on the discretion of the treating physician. As for validated regimen, the applicant proposal to leave need for monitoring visits to the physician´s discretion seems to be acceptable.

PHOTON – DME

Data were mostly balanced across the treatment groups for the demographics and disease characteristics at baseline for the following assessed criteria: BCVA, IOP, CRT, prior DME treatment. The ocular medical and surgical history in the study eye mostly reported (> 10%) were AMD, Cataract, cataract nuclear, cataract operation and retinal laser coagulation. Given that a lot of baseline characteristics appears to be unbalanced between the 3 groups, the MAH was requested to further discuss the clinical relevance of the following discrepancies in PHOTON study : patients of different age category (<55, ≥ 55 to < 65), ethnicity (Black or African American, White), percentage of Hemoglobin A1c at baseline category (≤8% and ≥ 8%), patients with history of cerebrovascular disease, history of ischaemic heart disease and diabetes type II (Non/insulin dependent), BCVA category (≤73 and ≥ 73 letters) CRT, DRSS, cataract history, vitreous detachment, intraocular lens implant, metabolism and nutrition disorders (Hyperlipidaemia, Hypercholesterolaemia, diabetes mellitus), gastrointestinal disorders (gastroesophageal reflux disease), immune system disorders (seasonal allergy and drug hypersensitivity) and endocrine disorders (hypothyroidism). Based on the Applicant responses, regarding the age, in the age group < 55 there were 17.4%, 23.5% and 23.3% subjects and in the ≥ 55 to < 65 group there were 37.7%, 32.9% and 33.1% subjects in the 2q8, HDq12 and HDq16 group respectively. Based on the mean and median age including the standard deviation, the Applicant concluded that there was a similar distribution of age for the treatment groups and thus the minor numerical differences at baseline with regards to age groups are not considered clinically relevant. Due to the lower sample size per subgroup these did show some minor variability but did not reveal clinically meaningful differences between the subgroup populations and the total population.

For the ethnicity and Hemoglobin A1c differences, the observed imbalance among these subgroups is due to their relatively small sample sizes and is therefore not considered clinically relevant. Indeed, the Applicant considers that the primary and secondary endpoints are calculated based on the entire population (and not subgroups), such differences are judged as not clinically relevant.

Regarding the Medical history, the numerical imbalance in the distribution is also explained by the small number of patients and are not considered clinically relevant.

The primary endpoint analysis assessed the change from baseline in BCVA (ETDRS letter score) at Week 48, completed with a key secondary endpoint of that measure at week 60. The mean BCVA (SD) from baseline to week 48 were: +9.21 (8.99), 8.77 (8.95) and 7.86 (8.38) letters for 2q8 (n=167 patients), HDq12 (n=328 patients) and HDq16 (n=163 patients) treatment groups respectively.

The LS mean (SE) change of BCVA from baseline to week 48 were: +8.67 (0.73), 8.10 (0.61) and 7.23 (0.71) letters in 2q8, HDq12 and HDq16 groups respectively with an estimated difference in LS means from baseline to Week 48 in BCVA (with corresponding 95% CI) changes and the p-values for the non-inferiority test at a margin of 4 letters of HDq12 vs. 2q8 was -0.57 (-2.26, 1.13; p-value <0.0001) letters and of HDq16 vs. 2q8 was -1.44 (-3.27, 0.39; p-value 0.0031). At week 60, 9.4 (0.77), 8.52 (0.63) and 7.64 (0.75) letters in 2q8 (n=167 patients), HDq12 (n=328 patients) and HDq16 (n=163 patients) treatment were observed, respectively

and differences between HDq12 vs. 2q8 was -0.88 (-2.67, 0.91; p-value 0.0003) letters and of HDq16 vs. 2q8 was -1.76 (-3.71, 0.19; p-value 0.0122) letters.

Subgroup analysis regarding the change from baseline in BCVA at Week 48 and Week 60 were performed and stratified by age, sex, geographic region, ethnicity, race, baseline BCVA letters, and baseline PCV in PHOTON study and discrepancies were noted in patients of ≥65 - <75 years, Black or African American and with a BCVA ≥73 letters across the 3 treatment arms. However, given the smaller size of these subgroups, the validity of these comparisons appears limited.

Overall, the primary and key secondary endpoint criteria, to know, the change from baseline in BCVA measured by the ETDRS letter score at Week 48 and 60 (non-inferiority of IVT aflibercept therapy HDq12 and HDq16 dosing regimen to the current authorized IVT aflibercept therapy 2q8 dosing regimen) is considered to be statistically met (95% credible interval for treatment difference with a non-inferiority margin of 4 letters with LS mean change from baseline in BCVA to Week 48) and were confirmed by sensitivity analysis.

The other key secondary endpoint concerned the proportion of participants with a ≥2-Step improvement in DRSS Score at Week 48. At week 48, 26.6% participants in the 2q8 treatment group compared to 29% in HDq12 and 19.6% in HDq16arm had ≥2-Step improvement in DRSS Score with a difference (95% CI) between HDq12 vs. 2q8 treatment of 1.98% (-6.61, 10.57) and -7.52% (- 16.88, 1.84) for HDq16 vs. 2q8 treatment. Results at Week 60 followed the same tendency, with a proportion of participants with ≥ 2-step improvement in DRSS score of 29.1%, 31.3%, and 22.2% at week 60 in the 2q8, HDq12, and HDq16 groups, and an adjusted difference (95% CI) versus 2q8 of 1.87 (-6.88, 10.63) for HDq12 and -7.47 (-17.05, 2.12) for HDq16, respectively. The key secondary endpoint appears to be statistically met in the HDq12 arm but not in the HDq16 and the sensitivity analyses supported the results at week 48 and 60. The MAH was requested to further discuss this point and the impact on the dosing regimen proposed in the SmPC. As a response, The Applicant concluded that all treatment arms achieved similar functional benefits. Differences in structural endpoints were mostly associated with injection timing and did not translate into clinically meaningful differences in quality of life or visual acuity.

The eligibility criteria of the PHOTON study aimed to include an informative population in terms of DME assessment, which does not equate the one selected for DRSS assessment. In PHOTON, despite the limitations in study design, the evaluation of DRSS was included in the context of the fact that aflibercept 2 mg is in the US approved not only for the treatment of DME, but also for the treatment of DR. Therefore, evaluating the effects of aflibercept 8 mg was considered relevant for that territory. The key secondary endpoint of the proportion of participants with a ≥ 2-step improvement in DRSS score at Week 48 was pre-specified to potentially support an indication of aflibercept 8 mg for treatment of DR in the US. This endpoint was tested with a non-inferiority margin of 15% which was met by the HDq12 arm (adjusted difference 1.98%, 95% CI -6.61, 10.57) but not by the HDq16 arm (adjusted difference -7.52%, 95% CI -16.88, 1.84). however, considering that the primary endpoint showed that BCVA improvement as a direct effect of DME treatment was non-inferior for HDq12 and HDq16 compared to 2q8, the Applicant concluded that the effect on DRSS stage improvement does not correlate with the effect on DME, and improvements in DRSS are not a prerequisite for vision improvements in DME.

Additionally, subgroups analysis by sex, age group, race, ethnicity, baseline BCVA, geographic region, baseline CRT category, and prior DME treatment were performed at 48 and 60 week and discrepancies in the HD groups compared to the 2q8 group were observed for the following subgroups: <50 years, ≥ 55- < 65 years, ≥ 65 to < 75 years, males, females, White, Asian, with a baseline BCVA ≤ 73 letters or ≥ 73 letters, and CRT <400 micron or ≥ 400 micron at baseline .

Additionally, other secondary endpoints were analysed at week 48 and 60, such as: proportions of participants gaining at least 15 letters in BCVA, proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent), proportion of participants without retinal fluid (total fluid, IRF, and/or SRF) at the foveal center, proportion of participants without leakage, mean change in CRT and the mean change in NEI-VQF-25 total score. Globally, results tend to differ in the HDq12 and HDq16 groups and some secondary and exploratory endpoints results tend to stand out more than others between groups with a worrying tendency not in favor of the HD regiment. In its response, the Applicant concluded that all treatment arms achieved similar functional benefits. Differences in structural endpoints were mostly associated with injection timing and did not translate into clinically meaningful differences in quality of life or visual acuity.

The eligibility criteria of the PHOTON study aimed to include an informative population in terms of DME assessment, which does not equate the one selected for DRSS assessment. In PHOTON, despite the limitations in study design, the evaluation of DRSS was included in the context of the fact that aflibercept 2 mg is in the US approved not only for the treatment of DME, but also for the treatment of DR. Therefore, evaluating the effects of aflibercept 8 mg was considered relevant for that territory. The key secondary endpoint of the proportion of participants with a $\geq$ 2-step improvement in DRSS score at Week 48 was pre-specified to potentially support an indication of aflibercept 8 mg for treatment of DR in the US. This endpoint was tested with a non-inferiority margin of 15% which was met by the HDq12 arm (adjusted difference 1.98%, 95% CI -6.61, 10.57) but not by the HDq16 arm (adjusted difference -7.52%, 95% CI -16.88, 1.84). however, considering that the primary endpoint showed that BCVA improvement as a direct effect of DME treatment was non-inferior for HDq12 and HDq16 compared to 2q8, the Applicant concluded that the effect on DRSS stage improvement does not correlate with the effect on DME, and improvements in DRSS are not a prerequisite for vision improvements in DME.

2.5.6. Conclusions on the clinical efficacy

The development plan and more specific points of aflibercept 8 mg for the treatment of nAMD and DME subjects was discussed in the Scientific Advice EMA/CHMP/SAWP/277944/2019. The MAH present 2 pivotal studies, one regarding each of the indication: PULSAR in patients with nAMD (phase 3 study) and PHOTON in patients with DME (phase 2/3 study). Both studies assessed the change of BCVA (ETDRS score) change from baseline to week 48 as a primary endpoint and at week 60 as a key secondary endpoint. Those endpoints were considered statistically met for both the new proposed formula with the new dosing regimen (HDq12 and HDq16). However, given the large IVT injections intervals of the new dosing regimen at this point further long-term results were considered as mandatory in order to straighten the efficacy results for both HDq12 and HDq16 treatment regimen in patients with nAMD and DME.

As a remainder, the PHOTON and PULSAR studies met their primary efficacy endpoint of non-inferiority to 2 mg Eylea at the dosing intervals of HDq12 and HDq16 after 48 weeks in both indications DME and nAMD. Moreover, the maintenance of efficacy were also confirmed after 60 weeks on the basis of the corresponding key secondary endpoint which also met non-inferiority

Regarding this long-term 2 years efficacy results requested in order to ensure the maintenance of treatment efficacy, the Applicant provides long-term data from PULSAR study where around 80% of patients completed

Week 96 and PHOTON study where 100% completed Week 96. Overall and based on the provided long-term data, it appears that the product dosed every 12 weeks (HDq12) or every 16 weeks (HDq16) showed maintained non-inferior efficacy through Week 96 compared to 2 mg aflibercept, consistent with the results demonstrated at Week 48 and Week 60 with respect to improvement in BCVA and CST in patients with nAMD or DME. Indeed, a snapshot of PULSAR data up to Week 96 was performed in May 2023. This dataset comprises all patients (100%) enrolled in PULSAR. Of ongoing patients, approximately 80% (689 out of 875) had already completed the Week 96 visit and almost all had completed visits up to Week 88. More precisely, of the 1009 randomized patients included in the FAS and the SAF, 689 patients had completed the study through Week 96. 137 patients had discontinued prematurely. For 186 patients (18.4%), according to the Applicant, these patients constitute the ongoing patients at the time of the data snapshot.

Moreover, regarding the second part of the MO related to the lack of sufficient data that could support the claimed q20 (or longer) intervals, it should be noted that through Week 96, up to 47% and 44.3% of HD patients extended their treatment interval to q20 or longer intervals in the PULSAR and PHOTON study respectively. Numerically, this corresponds to a total of 185 patients completed at least one q20 interval before Week 96 in PULSAR and 133 patients in PHOTON study.

At Week 96, the proportion of patients with q20 or longer as the last intended dosing interval in the PULSAR was 36.8% in the HDq12 group and 54.9% in the HDq16 group. Of 216 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24 (i.e. 53 and 127 HD patients, respectively); only a few patients were shortened back to q16 (i.e. 3 HD patients).

For the PHOTON study, at Week 96 the proportion of patients with q20 or longer as the last intended dosing interval was 42.2% in the HDq12 group and 45.3% in the HDq16 group. Of 177 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24.

2.5.7. Clinical safety

This submission summarizes the safety data for aflibercept 8 mg (114.3 mg/mL) in two indications: nAMD (phase 3 PULSAR ongoing and phase 2 CANDELA completed) and DME (phase 2/3 PHOTON ongoing). The objective was to demonstrate the non-inferiority of aflibercept 8 mg (70µL of 114.3 mg/mL), every 12 or 16 weeks compared to aflibercept 2 mg (50 µL of 40 mg/mL), every 8 weeks. In this submission, the safety data up to week 44 for the completed CANDELA study and up to week 48 and week 60 for the ongoing PULSAR and PHOTON studies were provided. The Applicant also provided as requested in the LoQ efficacy and safety data up to 96 weeks all patients in PHOTON and approximately 80% in PULSAR.

Table 1: Studies conducted in the HD aflibercept program for nAMD and DME

Study / CSR / location	Study design	Study objectives	No. of participants in SAF/FAS per treatment arm and total
PULSAR (nAMD) Study 20968 Module 5.3.5.1, PULSAR W48 CSR	Phase 3, multi-center, randomized, double-masked, active-controlled Treatment duration 96 weeks **	**Primary:** To determine if treatment with HD aflibercept at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to aflibercept 2 mg every 8 weeks in participants with nAMD **Secondary:** • To determine the effect of HD versus 2 mg aflibercept on other visual and anatomic measures of response • To assess the efficacy of HD compared to 2 mg aflibercept on vision-related quality of life • To evaluate the safety of aflibercept • To evaluate the PK and immunogenicity of aflibercept	2q8*: N=336 HDq12*: N =335 HDq16*: N =338 Total: N =1009
CANDELA (nAMD) Study 21086 VGFTe (HD)-AMD-1905 Module 5.3.5.1, CANDELA CSR	Phase 2, multi-center, randomized, single-masked, active-controlled Treatment duration 44 weeks	**Primary**: • To determine the safety of aflibercept 8 mg • To determine if aflibercept 8 mg provides greater intraocular pharmacodynamic effect and/ or longer duration of action compared to aflibercept 2 mg **Secondary**: There were no secondary objectives in this study	IAI 2 mg*: N = 53 HD*: N = 53 Total: N = 106
PHOTON (DME) Study 21091 VGFTe-HD-DME-1934 Module 5.3.5.1, PHOTON W48 CSR	Phase 2/3, multi-center, randomized, double-masked, active-controlled Treatment duration 96 weeks **	**Primary**: To determine if treatment with HD aflibercept at intervals of 12 or 16 weeks provides non-inferior BCVA compared to aflibercept 2 mg dosed every 8 weeks **Secondary**: • To determine the effect of HD versus 2 mg aflibercept on anatomic and other visual measures of response • To evaluate the safety, immunogenicity, and PK of aflibercept	2q8*: N=167 HDq12*: N=328 HDq16*: N=163 Total: N=658

BCVA = best corrected visual acuity, IAI = intravitreal aflibercept injection, CSR = clinical study report, DME = diabetic macular edema, FAS = full analysis set, HD = high dose, IVT = intravitreal, N = number of participants, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetics, SAF = safety analysis set
FAS and SAF are identical.
* See for treatment arms description.
** Studies are planned to be extended beyond Week 96 by approximately 1 year (60 weeks).

The SAF included all randomized patients who received at least one dose of study treatment (n=1115 patients for nAMD and n=658 patients for DME). Safety variables consisted of ocular and non-ocular AEs (including AESI), ocular examination including IOP measurement, vital signs, clinical laboratory testing and ECG. The Applicant also assessed safety topics of interest (ocular and non-ocular). For both PHOTON and PULSAR, the 2 HD groups (i.e. HDq12 and HDq16) were pooled into the Pooled HD group and were also presented for the 2 HD groups separately. For CANDELA study, only the Pooled HD group was presented which is acceptable considering the size of the population (n=106).

For description on dosing regimen modification, study design, demographic characteristics and medical history at baseline, see *Efficacy* section and clinical AR. Overall, for both PULSAR and PHOTON, the Applicant was requested to further discuss the clinical relevance of the observed differences regarding demographic characteristics and reported medical history for nAMD and DME population in *Efficacy* section (see OC). In both AMD and DME studies, prior and concomitant treatments were reported in similar proportions and the most reported ATC in both indications were consistent with medical history.

2.5.7.1. Patient exposure

In PULSAR (nAMD), at week 60, the mean number of injections in the study eye were 8.5, 6.9 and 6.0 in the 2q8, HDq12 and HDq16 treatment groups respectively. In PHOTON (DME), patients received in 2q8, HDq12 and HDq16 respectively 10.0, 7.0 and 6.0 injections. Overall, this is coherent with the protocol's dosing schedule.

Up to week 96, the mean number of injections were respectively in the 2q8, HDq12 and HDq16 treatment groups 12.8, 9.8 and 8.2 for PULSAR and 13.8, 9.5 and 7.8 for PHOTON.

Table 5 AMD: Exposure to study eye treatment through Week 48 (PULSAR, safety analysis set)

	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Total number of active injections, n	2267	1986	1703	3689
Total number of sham injections, n	1212	1515	1793	3308
Number of active injections, n (%)				
1	1 (0.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
2	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
3	4 (1.2%)	3 (0.9%)	9 (2.7%)	12 (1.8%)
4	6 (1.8%)	7 (2.1%)	22 (6.5%)	29 (4.3%)
5	6 (1.8%)	22 (6.6%)	263 (77.8%)	285 (42.3%)
6	29 (8.6%)	260 (77.6%)	11 (3.3%)	271 (40.3%)
7	288 (85.7%)	39 (11.6%)	29 (8.6%)	68 (10.1%)
8	1 (0.3%)	0	0	0
Summary of active injections				
n	336	335	337 *	672
Mean (SD)	6.7 (0.8)	5.9 (0.8)	5.1 (0.8)	5.5 (0.9)
Median	7.0	6.0	5.0	6.0
Min, Max	1,8	1,7	1,7	1,7
Summary of sham injections				
n	327	328	330	658
Mean (SD)	3.7 (0.7)	4.6 (0.7)	5.4 (1.0)	5.0 (1.0)
Median	4.0	5.0	6.0	5.0
Min, Max	1,5	1,5	1,6	1,6
Total amount (mg)				
n	336	335	337	672
Mean (SD)	13.4845 (1.5942)	47.3671 (6.2219)	40.4324 (6.5479)	43.8894 (7.2650)
Median	14.0000	48.0060	40.0050	46.8630
Min, Max	2,16	8.001,56.007	8.001,56.007	8.001,56.007
Duration of treatment (weeks)				
n	336	335	337	672
Mean (SD)	46.28 (6.62)	46.54 (6.56)	46.18 (6.97)	46.36 (6.77)
Median	48.00	48.00	48.00	48.00
Min, Max	4,50.9	4,52	4,53.3	4,53.3

Max = maximum, Min = minimum, n = number of participants, SD = standard deviation
* Exposure information is missing for one participant.
See Definition of terms for treatment arms description.
Duration (weeks) = [(date of last study treatment) – (date of first study treatment) +28]/7; 28 days were added because of the minimum 4-week dosing interval in the study.
Study treatment given at Week 48 visit or beyond is not included in this table. Week 48 visit could occur later than the actual Week 48.

Table 2 DME: Summary of treatment exposure in study eye through Week 48 (PHOTON, safety analysis set)

	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Total number of active injections	1292	1875	806	2681
Total number of sham injections	580	1720	1054	2774
Number of active injections per participant, n (%)				
1	2 (1.2%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
2	0	7 (2.1%)	1 (0.6%)	8 (1.6%)
3	0	11 (3.4%)	3 (1.8%)	14 (2.9%)
4	2 (1.2%)	11 (3.4%)	6 (3.7%)	17 (3.5%)
5	2 (1.2%)	12 (3.7%)	146 (89.6%)	158 (32.2%)
6	3 (1.8%)	273 (83.2%)	2 (1.2%)	275 (56.0%)
7	10 (6.0%)	12 (3.7%)	4 (2.5%)	16 (3.3%)
8	148 (88.6%)	0	0	0
Summary of active injections				
N	167	328	163	491
Mean (SD)	7.7 (0.98)	5.7 (0.96)	4.9 (0.61)	5.5 (0.94)
Median	8.0	6.0	5.0	6.0
Q1 : Q3	8.0 : 8.0	6.0 : 6.0	5.0 : 5.0	5.0 : 6.0
Min : Max	1 : 8	1 : 7	1 : 7	1 : 7
Treatment duration (weeks) [a]				
N	167	328	163	491
Mean (SD)	46.71 (6.893)	45.67 (9.036)	47.10 (6.002)	46.14 (8.177)
Median	48.00	48.00	48.00	48.00
Q1 : Q3	47.90 : 48.70	47.70 : 48.65	48.00 : 48.60	47.90 : 48.60
Min : Max	4.0 : 52.1	4.0 : 64.4	4.0 : 54.9	4.0 : 64.4

See Definition of terms for treatment arms description.
HD=high dose , Q=quartile; Min=minimum; Max=maximum; n=number; PRN=pro re nata; SD=standard deviation.
[a] Treatment Duration = (Last study treatment [active or sham] –date - First study treatment [active or sham] date + 28 days)/7
Study interventions given at Week 48 visit or beyond were not included in this table. Week 48 visit could occur later than the actual Week 48.
Source: Module 5.3.5.1, PHOTON W48 CSR, Table 14.1.4.1

Patients in both phase 2/3 studies (PULSAR and PHOTON) were exposed to at least three times the dose of aflibercept in HD group compared to 2q8 group during the initiation phase. The Applicant provided safety data for the initiation phase in which all treatment arms received active monthly injection with either 2 mg or 8 mg aflibercept at day 1, week 4 and week 8. Although exposures to aflibercept in the HD treatment arms in both PULSAR and PHOTON studies were higher during the loading phase and that the incidence of ocular TEAE in the 2q8 arms in both groups were disparate, safety data are still reassuring and in favour of a comparable safety profile with ocular and non-ocular TEAE being reported in similar range between both studies. No consistent trend could be observed in both studies.

Participants in PULSAR and PHOTON were eligible for dose interval shortening (to a minimum of q8) starting from week 16 or 20 or extension (by 4-week increments) starting from week 52. In PULSAR, the majority (more than >75%) of the patients at week 48 and week 60 in HD group maintained their dosing regimen (q12 or q16). Less than 10% of the HDq12 participants shortened to HDq8 and 38.5% of the patients in HDq16 extended to HDq20 at week 60. In PHOTON, a large majority of the patients (more than 90%) maintained their assigned dosing regimen (HDq12 or HDq16) at week 48 and week 60. A total of 34.2% in HDq16 extended to HDq20 and 14.5% shortened to HDq12 or HDq8. In the fellow eye, slightly less patients received treatment in HD group (18.5% vs 20.2 % at week 60) in PULSAR while similar proportions were observed between groups in CANDELA and PHOTON.

The Applicant provided safety data for the patients shortened to HDq8 and extended to HDq20 up to week 60. As the patient with an HDq20 interval regimen are less exposed, no worsening of the safety profile is expected. Safety data for HDq8 were submitted and compared to not modified HDq12/Hdq16 and 2q8. No consistent trend could be observed for higher reported ocular and non-ocular TEAE and the safety profile seems similar to the known safety profile of aflibercept 2 mg. In PHOTON in particular, lower ocular TEAE rates were reported. Up to week 96, the majority of the patient had a treatment interval of ≥ 12 weeks (all HD 87.1% PULSAR and

92.9% in PHOTON) and ≥ 16 weeks (all HD 69.2% PULSAR and 72.4% in PHOTON) and more than 40% of the patient in both studies had extended to q20 (46.6% in PULSAR and 44.8% in PHOTON). Proportion of patient shortened to HDq8 were higher for PULSAR (21.3% in all HD group) compared to PHOTON (10.6% in all HD group) and with a similar trend for proportions of patients in HDq8 regimen which were low in both studies and higher in nAMD population (13.1% in PULSAR and 7.3% in PHOTON).

2.5.7.2. Adverse events

2.5.7.2.1. nAMD indication (CANDELA and PULSAR)

In CANDELA, for the study eye, a higher proportion of TEAE were reported in the HD group due to non-ocular TEAE being more reported (52.8% HD vs 45.3% IAI) while ocular TEAE were reported with similar frequencies (37.7% in both group). The most reported PT were vitreous detachment (higher in HD group) and nAMD (higher in IAI 2 mg group). Regarding non-ocular TEAE in CANDELA, while a higher frequency was reported in the HD group, the majority of the TEAE were mild or moderate and the proportion of severe non-ocular TEAE was similar between the two groups.

Table 14 AMD: Overall summary of adverse events through Week 48 (PULSAR, safety analysis set)

Number (%) of participants with	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Any TEAE*	235 (69.9%)	239 (71.3%)	249 (73.7%)	488 (72.5%)
Ocular in study eye	130 (38.7%)	129 (38.5%)	127 (37.6%)	256 (38.0%)
Non-ocular	178 (53.0%)	175 (52.2%)	182 (53.8%)	357 (53.0%)
Any study drug related TEAE*	13 (3.9%)	22 (6.6%)	13 (3.8%)	35 (5.2%)
Ocular in study eye	9 (2.7%)	20 (6.0%)	11 (3.3%)	31 (4.6%)
Non-ocular	3 (0.9%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Any TEAE related to IVT injection procedure*	37 (11.0%)	38 (11.3%)	33 (9.8%)	71 (10.5%)
Ocular in study eye	35 (10.4%)	32 (9.6%)	32 (9.5%)	64 (9.5%)
Non-ocular	0	4 (1.2%)	1 (0.3%)	5 (0.7%)
Any TEAE related to protocol procedure*	19 (5.7%)	13 (3.9%)	15 (4.4%)	28 (4.2%)
Ocular in study eye	11 (3.3%)	7 (2.1%)	9 (2.7%)	16 (2.4%)
Non-ocular	7 (2.1%)	6 (1.8%)	6 (1.8%)	12 (1.8%)
Any TEAE leading to study drug discontinuation*	5 (1.5%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Ocular in study eye	1 (0.3%)	3 (0.9%)	3 (0.9%)	6 (0.9%)
Non-ocular	4 (1.2%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Any serious TEAE*	49 (14.6%)	41 (12.2%)	37 (10.9%)	78 (11.6%)
Ocular in study eye	2 (0.6%)	6 (1.8%)	5 (1.5%)	11 (1.6%)
Non-ocular	46 (13.7%)	34 (10.1%)	32 (9.5%)	66 (9.8%)
Any study drug related serious TEAE*	2 (0.6%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Ocular in study eye	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Non-ocular	2 (0.6%)	0	2 (0.6%)	2 (0.3%)
Any serious TEAE related to IVT injection procedure	0	3 (0.9%)	2 (0.6%)	5 (0.7%)
Ocular in study eye	0	2 (0.6%)	2 (0.6%)	4 (0.6%)
Non-ocular	0	1 (0.3%)	0	1 (0.1%)
Any serious TEAE related to protocol procedure*	0	1 (0.3%)	0	1 (0.1%)
Ocular in study eye	0	0	0	0
Non-ocular	0	1 (0.3%)	0	1 (0.1%)
Any AE with outcome death	5 (1.5%)	3 (0.9%)	1 (0.3%)	4 (0.6%)

AE = adverse event, HD = high dose, IVT = intravitreal, N = number of participants in a group, TEAE = treatment-emergent adverse event
* This includes events in the fellow eye.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PULSAR W48 CSR, Table 14.3.1/1

In PULSAR, at week 48 and 60, for the study eye, comparable proportion of TEAE (any TEAE, ocular TEAE and non-ocular TEAE) were reported between groups. While the SOC "Eye disorders" was reported in slightly higher

proportion in the HDq12 at week 48, proportions were comparable at week 60 (38.1% in 2q8 vs 37.1% in all HD group). The most reported ocular TEAEs consisted of "Visual acuity reduced", "Cataract" (slightly higher in HDq12) and "Retinal haemorrhage". Ocular events were for the majority mild or moderate in severity. Severe TEAE were reported in low and similar proportions with retinal haemorrhage, solely, being reported in more than one patient (n=2). Slight ddifferences can be observed up to week 60 between all HD group and 2q8 but also between HDq12 and HDq16 regarding the PT "Visual acuity reduced" (higher in HDq16 5.3% than in HDq12 3.6%), "Vitreous floaters" (higher in HDq16 4.1% than HDq12 1.2%), "Vitreous detachment" (1.5% in 2q8 vs 2.5% in HD group (3.0% in HDq16)), "nAMD" (0.6% vs 2.1% vs 2.1%), and "Macular oedema" (2.4% vs 0.3% vs 2.1%). However, incidences in the HDq12 arm were comparable to 2q8 or lowest although exposure is the highest except for the PT "nAMD" however this seems to reflect underlying conditions with similar proportions between HDq16 and 2q8 at week 96 which is not in favour of a dose related effect. For known PT, observed incidences remains below or in the same range as compared to the frequency listed for EYLEA 2 mg.

Table 16 AMD: Ocular TEAEs in the study eye occurring in ≥1% of the participants in any treatment group through Week 48 (PULSAR, safety analysis set)

Primary system organ class Preferred term MedDRA version 25.0	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Number (%) of participants with at least one such adverse event	130 (38.7%)	129 (38.5%)	127 (37.6%)	256 (38.0%)
Eye disorders	110 (32.7%)	114 (34.0%)	111 (32.8%)	225 (33.4%)
Visual acuity reduced	20 (6.0%)	12 (3.6%)	18 (5.3%)	30 (4.5%)
Cataract	10 (3.0%)	12 (3.6%)	12 (3.6%)	24 (3.6%)
Retinal haemorrhage	14 (4.2%)	11 (3.3%)	10 (3.0%)	21 (3.1%)
Vitreous floaters	11 (3.3%)	4 (1.2%)	12 (3.6%)	16 (2.4%)
Subretinal fluid	11 (3.3%)	10 (3.0%)	5 (1.5%)	15 (2.2%)
Vitreous detachment	5 (1.5%)	6 (1.8%)	9 (2.7%)	15 (2.2%)
Neovascular age-related macular degeneration	2 (0.6%)	7 (2.1%)	7 (2.1%)	14 (2.1%)
Conjunctival haemorrhage	5 (1.5%)	8 (2.4%)	5 (1.5%)	13 (1.9%)
Macular thickening	3 (0.9%)	7 (2.1%)	6 (1.8%)	13 (1.9%)
Dry eye	4 (1.2%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Eye pain	2 (0.6%)	5 (1.5%)	4 (1.2%)	9 (1.3%)
Retinal pigment epithelial tear	3 (0.9%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
Age-related macular degeneration	1 (0.3%)	5 (1.5%)	3 (0.9%)	8 (1.2%)
Macular oedema	8 (2.4%)	1 (0.3%)	7 (2.1%)	8 (1.2%)
Macular fibrosis	4 (1.2%)	3 (0.9%)	3 (0.9%)	6 (0.9%)
Ocular hypertension	1 (0.3%)	2 (0.6%)	4 (1.2%)	6 (0.9%)
Eye irritation	0	1 (0.3%)	4 (1.2%)	5 (0.7%)
Punctate keratitis	4 (1.2%)	1 (0.3%)	4 (1.2%)	5 (0.7%)
Retinal oedema	2 (0.6%)	1 (0.3%)	4 (1.2%)	5 (0.7%)
Retinal pigment epitheliopathy	4 (1.2%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Dry age-related macular degeneration	4 (1.2%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Detachment of macular retinal pigment epithelium	4 (1.2%)	0	1 (0.3%)	1 (0.1%)
Investigations	7 (2.1%)	14 (4.2%)	12 (3.6%)	26 (3.9%)
Intraocular pressure increased	7 (2.1%)	11 (3.3%)	9 (2.7%)	20 (3.0%)
General disorders and administration site conditions	12 (3.6%)	9 (2.7%)	9 (2.7%)	18 (2.7%)
Sensation of foreign body	7 (2.1%)	3 (0.9%)	4 (1.2%)	7 (1.0%)
Infections and infestations	5 (1.5%)	9 (2.7%)	3 (0.9%)	12 (1.8%)
Conjunctivitis	4 (1.2%)	5 (1.5%)	3 (0.9%)	8 (1.2%)
Injury, poisoning and procedural complications	6 (1.8%)	6 (1.8%)	4 (1.2%)	10 (1.5%)
Corneal abrasion	4 (1.2%)	2 (0.6%)	2 (0.6%)	4 (0.6%)

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group, TEAE = treatment-emergent adverse event
The threshold of > 1% was applied to any system organ class and any preferred term in any treatment group. System organ classes and preferred terms that met the threshold are sorted by decreasing order of frequency in the Pooled HD group. System organ classes that met the threshold but none of the underlying preferred terms are not displayed. The number (%) of participants with at least one TEAE overall and in each system organ class are without consideration for the threshold.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PULSAR W48 CSR, Table 14.3.1/2

Up to week 96, similar tendencies could be observed for ocular TEAE with slightly lower incidence in the HD group (53.6% in 2q8 vs 50.5§ in all HD). Most reported ocular PT were consistent with the known safety

profile of aflibercept and incidences were comparable except for cataract (listed ADR and important identified safety concern for aflibercept) however this could be explained by the reported medical history of cataract being higher in the HD group and comparable proportions were reported when looking at all PT related to cataract.

Regarding non-ocular TEAE in PULSAR, more than half of the patient in all group reported at least one non-ocular TEAE up to week 60 and with comparable proportions. The most reported SOC were "Infections and Infestations" (most reported PT being "COVID-19"), "Gastrointestinal disorders" (slightly higher in HDq12, the most reported PT was" Nausea") "Musculoskeletal and connective tissues disorders" (most reported PT was" Back pain") and "Vascular disorders" (higher in HDq12 8.7% vs 5.4% with the most reported PT being 'Hypertension"). A higher incidence was reported for HDq16 compared to HDq12 at week 60 in the SOC Cardiac disorders (5.9% vs 3.0%), Metabolism and nutrition disorders (5.0% vs 2.7%) and Psychiatric disorders (2.7% vs 1.2%). However, this is not in favour of a dose related effects as lower incidences were reported in the HDq12 arm in which exposure is the highest. Additionally, these differences could be explained by the higher incidences of medical history of hypertension and psychiatric disorders. When looking per TEAE (SOC gastrointestinal disorders), events were low or reported in single patients. Up to week 96, similar tendencies could be observed.

Non-ocular TEAE were mostly mild to moderate in severity and severe non-ocular TEAE were more reported in the 2q8 group (8.3% vs 5.1% in HDq12 and 3.6% in HDq16). At week 60, similar tendencies were observed.

Table 17 AMD: Non-ocular TEAEs occurring in >1% of the participants in any treatment group through Week 48 (PULSAR, safety analysis set)

Primary system organ class Preferred term MedDRA version 25.0	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Number (%) of participants with at least one such event	178 (53.0%)	175 (52.2%)	182 (53.8%)	357 (53.0%)
Infections and infestations	73 (21.7%)	73 (21.8%)	77 (22.8%)	150 (22.3%)
COVID-19	11 (3.3%)	10 (3.0%)	21 (6.2%)	31 (4.6%)
Nasopharyngitis	15 (4.5%)	12 (3.6%)	14 (4.1%)	26 (3.9%)
Urinary tract infection	9 (2.7%)	7 (2.1%)	10 (3.0%)	17 (2.5%)
Asymptomatic COVID-19	4 (1.2%)	7 (2.1%)	8 (2.4%)	15 (2.2%)
Cystitis	3 (0.9%)	5 (1.5%)	1 (0.3%)	6 (0.9%)
Pneumonia	4 (1.2%)	4 (1.2%)	2 (0.6%)	6 (0.9%)
Upper respiratory tract infection	1 (0.3%)	4 (1.2%)	0	4 (0.6%)
Sinusitis	4 (1.2%)	0	2 (0.6%)	2 (0.3%)
Gastrointestinal disorders	30 (8.9%)	34 (10.1%)	29 (8.6%)	63 (9.4%)
Nausea	4 (1.2%)	3 (0.9%)	4 (1.2%)	7 (1.0%)
Vomiting	2 (0.6%)	1 (0.3%)	6 (1.8%)	7 (1.0%)
Diarrhoea	4 (1.2%)	5 (1.5%)	1 (0.3%)	6 (0.9%)
Gastrooesophageal reflux disease	1 (0.3%)	2 (0.6%)	4 (1.2%)	6 (0.9%)
Dental caries	3 (0.9%)	4 (1.2%)	0	4 (0.6%)
Musculoskeletal and connective tissue disorders	37 (11.0%)	32 (9.6%)	30 (8.9%)	62 (9.2%)
Back pain	15 (4.5%)	12 (3.6%)	13 (3.8%)	25 (3.7%)
Arthralgia	5 (1.5%)	7 (2.1%)	7 (2.1%)	14 (2.1%)
Osteoarthritis	2 (0.6%)	1 (0.3%)	4 (1.2%)	5 (0.7%)
Nervous system disorders	21 (6.3%)	23 (6.9%)	21 (6.2%)	44 (6.5%)
Headache	6 (1.8%)	6 (1.8%)	7 (2.1%)	13 (1.9%)
Dizziness	6 (1.8%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Vascular disorders	12 (3.6%)	22 (6.6%)	19 (5.6%)	41 (6.1%)
Hypertension	8 (2.4%)	14 (4.2%)	13 (3.8%)	27 (4.0%)
Injury, poisoning and procedural complications	25 (7.4%)	19 (5.7%)	17 (5.0%)	36 (5.3%)
Contusion	3 (0.9%)	4 (1.2%)	2 (0.6%)	6 (0.9%)
Fall	5 (1.5%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Upper limb fracture	3 (0.9%)	0	4 (1.2%)	4 (0.6%)
Respiratory, thoracic and mediastinal disorders	16 (4.8%)	14 (4.2%)	17 (5.0%)	31 (4.6%)
Cough	4 (1.2%)	4 (1.2%)	8 (2.4%)	12 (1.8%)
Oropharyngeal pain	4 (1.2%)	1 (0.3%)	0	1 (0.1%)
Cardiac disorders	15 (4.5%)	8 (2.4%)	16 (4.7%)	24 (3.6%)
Atrial fibrillation	7 (2.1%)	2 (0.6%)	3 (0.9%)	5 (0.7%)
General disorders and administration site conditions	13 (3.9%)	12 (3.6%)	11 (3.3%)	23 (3.4%)
Pyrexia	5 (1.5%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Fatigue	4 (1.2%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Skin and subcutaneous tissue disorders	10 (3.0%)	12 (3.6%)	10 (3.0%)	22 (3.3%)
Dermatitis	0	4 (1.2%)	2 (0.6%)	6 (0.9%)
Psychiatric disorders	2 (0.6%)	4 (1.2%)	8 (2.4%)	12 (1.8%)
Anxiety	0	0	4 (1.2%)	4 (0.6%)
Reproductive system and breast disorders	5 (1.5%)	2 (0.6%)	4 (1.2%)	6 (0.9%)
Benign prostatic hyperplasia	3 (0.9%)	1 (0.3%)	4 (1.2%)	5 (0.7%)
Blood and lymphatic system disorders	6 (1.8%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Anaemia	5 (1.5%)	1 (0.3%)	1 (0.3%)	2 (0.3%)

In CANDELA, for the study eye, one ocular TEAE (iritis, mild, non-serious) and one non-ocular TEAE (Transient ischemic attack, mild, serious) in the HD group were assessed as drug study related. Proportion of injection related ocular TEAE were similar between groups (7.5%) with the most reported PT being Conjunctival haemorrhage (2 patients in IAI 2 mg and 3 in HD group) and one non-ocular TEAE (Facial pain) was assessed as injection related in IAI while none in the HD group. No TEAEs were assessed as protocol–specified procedure related. In the fellow eye, ocular TEAE were reported in similar proportion in both groups (24.5%) with the most reported ocular TEAE being Conjunctival haemorrhage (higher in HD group) and nAMD (higher in HD). No severe ocular TEAE were reported. No ocular TEAE were assessed as study drug related and one event of "Conjunctival haemorrhage" in both groups were assessed as injection procedure related. No serious ocular TEAE were reported.

Table 20 AMD: Ocular TEAEs in the study eye related to the study drug through Week 48 (PULSAR, safety analysis set)

Primary system organ class Preferred term MedDRA version 25.0	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Number (%) of subjects with at least one such adverse event	9 (2.7%)	20 (6.0%)	11 (3.3%)	31 (4.6%)
Eye disorders	6 (1.8%)	17 (5.1%)	9 (2.7%)	26 (3.9%)
Visual acuity reduced	0	4 (1.2%)	1 (0.3%)	5 (0.7%)
Retinal pigment epithelial tear	1 (0.3%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Age-related macular degeneration	1 (0.3%)	2 (0.6%)	0	2 (0.3%)
Retinal haemorrhage	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Angle closure glaucoma	0	0	1 (0.3%)	1 (0.1%)
Cataract	0	0	1 (0.3%)	1 (0.1%)
Choroidal detachment	0	1 (0.3%)	0	1 (0.1%)
Eye pain	0	1 (0.3%)	0	1 (0.1%)
Glaucoma	0	1 (0.3%)	0	1 (0.1%)
Iridocyclitis	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Maculopathy	0	0	1 (0.3%)	1 (0.1%)
Neovascular age-related macular degeneration	0	0	1 (0.3%)	1 (0.1%)
Ocular hypertension	0	0	1 (0.3%)	1 (0.1%)
Retinal detachment	0	1 (0.3%)	0	1 (0.1%)
Rhegmatogenous retinal detachment	0	1 (0.3%)	0	1 (0.1%)
Subretinal fibrosis	0	1 (0.3%)	0	1 (0.1%)
Subretinal fluid	0	0	1 (0.3%)	1 (0.1%)
Vitreous floaters	2 (0.6%)	1 (0.3%)	0	1 (0.1%)
Vitreous haemorrhage	0	1 (0.3%)	0	1 (0.1%)
Vitritis	0	1 (0.3%)	0	1 (0.1%)
Macular degeneration	1 (0.3%)	0	0	0
Metamorphopsia	1 (0.3%)	0	0	0
Vision blurred	1 (0.3%)	0	0	0
Vitreal cells	1 (0.3%)	0	0	0
Investigations	2 (0.6%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Intraocular pressure increased	2 (0.6%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
General disorders and administration site conditions	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Atrophy	0	1 (0.3%)	0	1 (0.1%)
Injection site pain	0	0	1 (0.3%)	1 (0.1%)
Injury, poisoning and procedural complications	0	1 (0.3%)	0	1 (0.1%)
Intra-ocular injection complication	0	1 (0.3%)	0	1 (0.1%)
Nervous system disorders	0	1 (0.3%)	0	1 (0.1%)
Headache	0	1 (0.3%)	0	1 (0.1%)
Skin and subcutaneous tissue disorders	1 (0.3%)	0	0	0
Pigmentation disorder	1 (0.3%)	0	0	0

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group, TEAE = treatment-emergent adverse event.
See Definition of terms for treatment arms description.
Source: Module 5.3.2.1, PULSAR W48 CSR, Table 14.3.1/5

In PULSAR, ocular study drug related TEAE in the study eye were reported in higher proportion in the HD group (higher in HDq12: 6.0%) compared to 2q8 group (3.6%) at week 48. All reported PT occurred with low incidence (<1%). PT reported in more than one patient (all PT were reported in less than 1%) at week 48 and 60 were "Visual Acuity Reduced" (in HD groups only and higher in HDq12), "Retinal pigment epithelial tear" (higher in HDq12), "Age-related macular degeneration" (higher in HDq12) and "Intraocular pressure increased" (higher in 2q8 group). Non-ocular study drug related TEAEs were reported in similar proportions between groups and PT reported in more than one patient were "Myocardial infarction" (in HDq16, n=2 at week 96) and "Cerebrovascular accident" for non-ocular TEAE (in 2q8 group, both serious). Up to week 96, similar tendencies were observed.

Table 21 AMD: Ocular TEAEs in the study eye related to injection procedure through Week 48 (PULSAR, safety analysis set)

Primary system organ class Preferred term MedDRA version 25.0	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Number (%) of subjects with at least one such adverse event	35 (10.4%)	32 (9.6%)	32 (9.5%)	64 (9.5%)
Eye disorders	21 (6.3%)	24 (7.2%)	23 (6.8%)	47 (7.0%)
Conjunctival haemorrhage	3 (0.9%)	6 (1.8%)	2 (0.6%)	8 (1.2%)
Vitreous floaters	7 (2.1%)	1 (0.3%)	5 (1.5%)	6 (0.9%)
Ocular hypertension	1 (0.3%)	2 (0.6%)	3 (0.9%)	5 (0.7%)
Eye irritation	0	1 (0.3%)	3 (0.9%)	4 (0.6%)
Eye pain	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Vitreous detachment	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Corneal erosion	0	0	2 (0.6%)	2 (0.3%)
Amaurosis fugax	0	1 (0.3%)	0	1 (0.1%)
Angle closure glaucoma	0	0	1 (0.3%)	1 (0.1%)
Blindness transient	0	1 (0.3%)	0	1 (0.1%)
Cataract	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Choroidal detachment	0	1 (0.3%)	0	1 (0.1%)
Conjunctival irritation	0	1 (0.3%)	0	1 (0.1%)
Conjunctival suffusion	0	0	1 (0.3%)	1 (0.1%)
Episcleritis	0	1 (0.3%)	0	1 (0.1%)
Eye pruritus	0	1 (0.3%)	0	1 (0.1%)
Foreign body sensation in eyes	0	1 (0.3%)	0	1 (0.1%)
Neovascular age-related macular degeneration	0	0	1 (0.3%)	1 (0.1%)
Ocular discomfort	1 (0.3%)	1 (0.3%)	0	1 (0.1%)
Ocular surface disease	0	0	1 (0.3%)	1 (0.1%)
Punctate keratitis	0	0	1 (0.3%)	1 (0.1%)
Retinal detachment	0	1 (0.3%)	0	1 (0.1%)
Retinal microangiopathy	0	1 (0.3%)	0	1 (0.1%)
Retinal pigment epithelial tear	0	0	1 (0.3%)	1 (0.1%)
Ulcerative keratitis	0	1 (0.3%)	0	1 (0.1%)
Vitreous opacities	0	0	1 (0.3%)	1 (0.1%)
Vitritis	0	1 (0.3%)	0	1 (0.1%)
Xerophthalmia	0	1 (0.3%)	0	1 (0.1%)
Ocular hyperaemia	1 (0.3%)	0	0	0
Photopsia	1 (0.3%)	0	0	0
Swelling of eyelid	1 (0.3%)	0	0	0
Vitreal cells	1 (0.3%)	0	0	0
Vitreous degeneration	1 (0.3%)	0	0	0
Vitreous haemorrhage	1 (0.3%)	0	0	0
General disorders and administration site conditions	9 (2.7%)	5 (1.5%)	6 (1.8%)	11 (1.6%)
Sensation of foreign body	6 (1.8%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Injection site pain	3 (0.9%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Injection site haemorrhage	0	0	2 (0.6%)	2 (0.3%)
Pain	0	1 (0.3%)	0	1 (0.1%)
Investigations	4 (1.2%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Intraocular pressure increased	4 (1.2%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Injury, poisoning and procedural complications	3 (0.9%)	0	2 (0.6%)	2 (0.3%)
Corneal abrasion	3 (0.9%)	0	1 (0.3%)	1 (0.1%)
Skin laceration	0	0	1 (0.3%)	1 (0.1%)
Immune system disorders	0	0	1 (0.3%)	1 (0.1%)
Iodine allergy	0	0	1 (0.3%)	1 (0.1%)
Infections and infestations	0	1 (0.3%)	0	1 (0.1%)
Conjunctivitis	0	1 (0.3%)	0	1 (0.1%)
Nervous system disorders	0	1 (0.3%)	0	1 (0.1%)
Headache [a]	0	1 (0.3%)	0	1 (0.1%)
Surgical and medical procedures	0	1 (0.3%)	0	1 (0.1%)
Ophthalmic fluid-air exchange procedure	0	1 (0.3%)	0	1 (0.1%)

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group, TEAE = treatment-emergent adverse event

[a] Reported as an ocular TEAE by the study site

See Definition of terms for treatment arms description.

Source: Module 5.3.5.1, PULSAR W48 CSR, Table 14.3.1/8

At week 48 and 60, proportions of ocular TEAE related to IVT were slightly higher in 2q8 group and slight differences could be observed between HD group and 2q8 and HDq12 and HDq16 (7.1% in 2q8 vs 6.9% in HDq12 vs 8.9% in HDq16 at week 60)**.** At week 96, similar proportions were observed (9.2% in 2q8, 8.7% in HDq12 and 9.5% HDq16). The most reported PT for ocular TEAE assessed as related to IVT were "Conjunctival haemorrhage", "Vitreous floaters» and "Sensation of foreign body". Incidences in HDq12 (highest exposure) were lower or comparable to observed incidences in 2q8. The majority of the events were reported in single patients. Non-ocular TEAE assessed as related to IVT injection were reported in the HD group only (in solely one patient in each HD group) and consisted of chest pain, cerebral ischemia, head discomfort, headache, trigeminal neuralgia and hypertension. The Applicant provided the narratives of the cases and all event were

majorly non serious, resolved, mild to moderate in intensity and with no drug change. Ocular and non-ocular TEAE assessed as protocol-specified procedure related were low and comparable between groups. The most reported PT consisted of "Corneal abrasion" (0.6% at week 60 in HD group) for ocular TEAE and "Nausea" and "Vomiting" for non-ocular TEAE.

In the fellow eye at week 48, ocular TEAE were reported in similar proportions with the most reported PT being nAMD. One event of Cataract (HDq16) and one event of nAMD (2q8) were assessed as drug related. Similar proportions of injection and protocol required procedure related ocular TEAE were reported and the most reported PT was "Conjunctival haemorrhage". Ocular TEAE were mostly mild to moderate and severe TEAE were reported in low proportions and in single participants only. At week 60, similar tendencies were observed. Additional events of "Iridocyclitis" (HDq16) and "Endophthalmitis" (2q8) were assessed as drug related. Up to week 96, similar tendencies were overall observed.

2.5.7.2.2. DME indication (PHOTON)

At week 48, TEAE were more reported in all HD group (70.3%) than in the 2q8 (63.5%) and proportions were slightly higher in the HDq16 (72.4%) than in the HDq12 (69.2%).

Table 8 DME: Summary of adverse events through Week 48 (PHOTON, safety analysis set)

Number of participants, n (%), with	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Any TEAE*	106 (63.5%)	227 (69.2%)	118 (72.4%)	345 (70.3%)
Ocular in study eye	46 (27.5%)	104 (31.7%)	48 (29.4%)	152 (31.0%)
Non-ocular TEAE	79 (47.3%)	174 (53.0%)	95 (58.3%)	269 (54.8%)
Any study drug related TEAE*	3 (1.8%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
Ocular in study eye	3 (1.8%)	5 (1.5%)	0	5 (1.0%)
Non-ocular	0	0	1 (0.6%)	1 (0.2%)
Any injection procedure related TEAE*	18 (10.8%)	43 (13.1%)	13 (8.0%)	56 (11.4%)
Ocular in the study eye	15 (9.0%)	40 (12.2%)	13 (8.0%)	53 (10.8%)
Non-ocular	0	2 (0.6%)	1 (0.6%)	3 (0.6%)
Any TEAE related to protocol procedure*	2 (1.2%)	6 (1.8%)	0	6 (1.2%)
Ocular in study eye	0	2 (0.6%)	0	2 (0.4%)
Non-ocular	2 (1.2%)	4 (1.2%)	0	4 (0.8%)
Any serious TEAE*	31 (18.6%)	55 (16.8%)	24 (14.7%)	79 (16.1%)
Ocular in study eye	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Non-ocular	26 (15.6%)	52 (15.9%)	22 (13.5%)	74 (15.1%)
Any study drug related serious TEAE*	0	0	0	0
Any serious TEAE related to IVT injection procedure*	0	1 (0.3%)	0	1 (0.2%)
Ocular in study eye	0	1 (0.3%)	0	1 (0.2%)
Non-ocular	0	0	0	0
Any serious TEAE related to protocol procedure*	0	0	0	0
Any TEAE leading to discontinuation of study drug*	2 (1.2%)	8 (2.4%)	2 (1.2%)	10 (2.0%)
Ocular in study eye	0	2 (0.6%)	0	2 (0.4%)
Non-ocular	2 (1.2%)	6 (1.8%)	2 (1.2%)	8 (1.6%)
Any death*	4 (2.4%)	9 (2.7%)	3 (1.8%)	12 (2.4%)
Any TEAE	4 (2.4%)	8 (2.4%)	2 (1.2%)	10 (2.0%)
Any post-treatment AE	0	1 (0.3%)	1 (0.6%)	2 (0.4%)

AE=adverse event; IVT = intravitreal; N=number of participants; TEAE = treatment-emergent adverse event
* This includes events in the fellow eye.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PHOTON W48 CSR, Table 14.3.1.1

Ocular TEAE in study eye were reported in slightly higher incidences (31.0% in all HD group vs 27.5% in 2q8). Non-ocular TEAE were reported in higher proportion in HDq16 group (58.3%) than in the 2q8 group (47.3%) and the HDq12 group (53.0%). Similar tendencies were observed at week 96.

The most reported PT for ocular TEAE in the study eye were IOP (in higher proportions with 3.6% in 2q8 group), vitreous floaters (in higher proportions with 4.9% in HDq12 group), retinal haemorrhage (in higher proportions with 4.9% in HDq16 group), Conjunctival haemorrhage (comparable proportions) and Cataract (in higher proportions with 4.9% in HDq16 group). Ocular TEAE in the study eye were for the majority mild in severity and in higher proportions in the HDq16 group (28.2% in HDq16 vs 26.2 % in HDq12 vs 22.8% in 2q8 at week 60) although exposure was highest in the HDq12 and this could be explained due to higher reported medical history in HDq16. Comparable proportions were observed between the 2q8 and HDq12 arms, comparable or higher proportion were reported in the fellow eye which is not in favour of a drug-related treatment effect. Reported ocular TEAEs were consistent with the known safety profile of aflibercept and underlying conditions.

Table 9 DME: Ocular TEAEs in the study eye occurring in > 1.0% of participants in any treatment group through Week 48 (PHOTON, safety analysis set)

Primary System Organ Class Preferred Term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	46 (27.5%)	104 (31.7%)	48 (29.4%)	152 (31.0%)
Eye disorders	41 (24.6%)	94 (28.7%)	46 (28.2%)	140 (28.5%)
Cataract	2 (1.2%)	5 (1.5%)	8 (4.9%)	13 (2.6%)
Cataract nuclear	2 (1.2%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Conjunctival haemorrhage	6 (3.6%)	14 (4.3%)	6 (3.7%)	20 (4.1%)
Corneal erosion	0	0	2 (1.2%)	2 (0.4%)
Diabetic retinal oedema	3 (1.8%)	9 (2.7%)	3 (1.8%)	12 (2.4%)
Dry eye	1 (0.6%)	2 (0.6%)	2 (1.2%)	4 (0.8%)
Epiretinal membrane	2 (1.2%)	1 (0.3%)	0	1 (0.2%)
Eye irritation	1 (0.6%)	2 (0.6%)	2 (1.2%)	4 (0.8%)
Eye pain	4 (2.4%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
Keratitis	0	0	2 (1.2%)	2 (0.4%)
Macular oedema	2 (1.2%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
Ocular hypertension	1 (0.6%)	4 (1.2%)	0	4 (0.8%)
Posterior capsule opacification	2 (1.2%)	0	2 (1.2%)	2 (0.4%)
Punctate keratitis	1 (0.6%)	5 (1.5%)	6 (3.7%)	11 (2.2%)
Retinal aneurysm	2 (1.2%)	0	1 (0.6%)	1 (0.2%)
Retinal exudates	2 (1.2%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Retinal haemorrhage	1 (0.6%)	0	6 (3.7%)	6 (1.2%)
Vision blurred	3 (1.8%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
Visual acuity reduced	3 (1.8%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
Visual impairment	1 (0.6%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
Vitreous detachment	2 (1.2%)	11 (3.4%)	3 (1.8%)	14 (2.9%)
Vitreous floaters	4 (2.4%)	16 (4.9%)	3 (1.8%)	19 (3.9%)
Vitreous haemorrhage	1 (0.6%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
Infections and infestations	1 (0.6%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
Conjunctivitis	0	0	2 (1.2%)	2 (0.4%)
Injury, poisoning and procedural complications	2 (1.2%)	4 (1.2%)	1 (0.6%)	5 (1.0%)
Corneal abrasion	2 (1.2%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
Investigations	7 (4.2%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
Intraocular pressure increased	6 (3.6%)	7 (2.1%)	1 (0.6%)	8 (1.6%)

HD = high dose, MedDRA=medical dictionary for regulatory activities, N=number of participants; TEAE=Treatment-emergent adverse event
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PHOTON W48 CSR, Table 14.3.1.2.1

Incidence of ocular TEAE in the fellow eye were comparable with the study eye and between the HDq16 group (27.6%) and the 2q8 group (26.3%) but reported in less proportion in the HDq12 group (31.7% in the study eye vs 23.8% in the fellow eye). Higher incidences of injection related TEAE were reported for the study eye compared to the fellow eye in all groups. Ocular TEAE in the fellow eye were for the majority mild and in comparable proportions between all groups. The most reported PT in the fellow eye were Cataract, vitreous floaters and diabetic retinopathy. At week 60, similar tendencies were observed.

The most reported non-ocular TEAE (more than 10%) were the SOC Infections and infestations, Vascular disorders (with the PT Hypertension reported in similar proportions between all HD group and 2q8 group: 9.6% and slightly higher in HDq16 12.3%), Gastrointestinal disorders (Higher in HD group) and Metabolism and nutrition disorders. Events were either reported majorly in single patients or could be due to a higher medical history for these SOCs being reported in HDq16 arm. Non-ocular TEAE were for the majority mild (in higher proportion 30.7% in HDq16 vs 25.0 % in HDq12 vs 25.7% in 2q8 at week 60) or moderate in severity.

Table 10 DME: Non-ocular TEAEs occurring in ≥ 2.0% of the participants in any treatment group through Week 48 (PHOTON, safety analysis set)

Primary System Organ Class Preferred Term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	79 (47.3%)	174 (53.0%)	95 (58.3%)	269 (54.8%)
Blood and lymphatic system disorders	6 (3.6%)	8 (2.4%)	9 (5.5%)	17 (3.5%)
Anaemia	3 (1.8%)	6 (1.8%)	7 (4.3%)	13 (2.6%)
Cardiac disorders	13 (7.8%)	19 (5.8%)	8 (4.9%)	27 (5.5%)
Atrial fibrillation	4 (2.4%)	1 (0.3%)	0	1 (0.2%)
Gastrointestinal disorders	12 (7.2%)	28 (8.5%)	23 (14.1%)	51 (10.4%)
Diarrhoea	1 (0.6%)	5 (1.5%)	6 (3.7%)	11 (2.2%)
Gastrooesophageal reflux disease	1 (0.6%)	7 (2.1%)	4 (2.5%)	11 (2.2%)
Infections and infestations	36 (21.6%)	63 (19.2%)	37 (22.7%)	100 (20.4%)
COVID-19	5 (3.0%)	19 (5.8%)	17 (10.4%)	36 (7.3%)
Nasopharyngitis	6 (3.6%)	10 (3.0%)	7 (4.3%)	17 (3.5%)
Urinary tract infection	5 (3.0%)	4 (1.2%)	5 (3.1%)	9 (1.8%)
Investigations	11 (6.6%)	23 (7.0%)	15 (9.2%)	38 (7.7%)
Blood pressure increased	3 (1.8%)	8 (2.4%)	4 (2.5%)	12 (2.4%)
Metabolism and nutrition disorders	20 (12.0%)	26 (7.9%)	18 (11.0%)	44 (9.0%)
Diabetes mellitus	5 (3.0%)	6 (1.8%)	5 (3.1%)	11 (2.2%)
Hyperkalaemia	0	2 (0.6%)	4 (2.5%)	6 (1.2%)
Hyponatraemia	4 (2.4%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Musculoskeletal and connective tissue disorders	15 (9.0%)	28 (8.5%)	12 (7.4%)	40 (8.1%)
Arthralgia	3 (1.8%)	2 (0.6%)	4 (2.5%)	6 (1.2%)
Back pain	1 (0.6%)	7 (2.1%)	2 (1.2%)	9 (1.8%)
Nervous system disorders	15 (9.0%)	21 (6.4%)	16 (9.8%)	37 (7.5%)
Headache	4 (2.4%)	10 (3.0%)	4 (2.5%)	14 (2.9%)
Cerebrovascular accident	0	2 (0.6%)	4 (2.5%)	6 (1.2%)
Renal and urinary disorders	11 (6.6%)	20 (6.1%)	12 (7.4%)	32 (6.5%)
Acute kidney injury	4 (2.4%)	5 (1.5%)	3 (1.8%)	8 (1.6%)
Respiratory, thoracic and mediastinal disorders	7 (4.2%)	14 (4.3%)	9 (5.5%)	23 (4.7%)
Acute respiratory failure	4 (2.4%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
Skin and subcutaneous tissue disorders	7 (4.2%)	13 (4.0%)	10 (6.1%)	23 (4.7%)
Skin ulcer	4 (2.4%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
Vascular disorders	19 (11.4%)	37 (11.3%)	24 (14.7%)	61 (12.4%)
Hypertension	16 (9.6%)	27 (8.2%)	20 (12.3%)	47 (9.6%)

AE=adverse event; COVID-19=Coronavirus Disease 2019; MedDRA=Medical Dictionary for Regulatory Activities, N=number of participants; TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PHOTON W48 CSR, Table 14.3.1.2.3

Study drug related TEAE were ocular TEAE for the majority and reported in less than 2% of the patients and proportions were similar between all HD group and 2q8 group. The only TEAE reported in more than one patient up to week 48 and 60 was IOP increase (3 patient 0.9% in the HDq12 group only). One non-ocular study drug related TEAE was reported in the HDq16 group (Lacunar infarction) through week 48 and 60. The Applicant provided the case narrative as requested. The event occurred in a bilaterally treated patients with confounding factors (hypertension, hypercholesterolemia) and resolved with no treatment and no recurrence were observed. Up to week 96, similar tendencies were observed. One additional event of cerebrovascular accident was reported at week 96 (HDq16).

Table 11 DME: Ocular TEAEs related to study drug in the study eye through Week 48 (PHOTON, safety analysis set)

Primary System Organ Class Preferred Term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	3 (1.8%)	5 (1.5%)	0	5 (1.0%)
Eye disorders	3 (1.8%)	3 (0.9%)	0	3 (0.6%)
Iritis	0	1 (0.3%)	0	1 (0.2%)
Ocular hypertension	0	1 (0.3%)	0	1 (0.2%)
Retinal artery stenosis	1 (0.6%)	0	0	0
Vision blurred	1 (0.6%)	0	0	0
Vitreous floaters	1 (0.6%)	0	0	0
Vitreous opacities	1 (0.6%)	0	0	0
Vitritis	0	1 (0.3%)	0	1 (0.2%)
Investigations	1 (0.6%)	3 (0.9%)	0	3 (0.6%)
Intraocular pressure decreased	1 (0.6%)	0	0	0
Intraocular pressure increased	0	3 (0.9%)	0	3 (0.6%)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event; N=number of participants.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PHOTON W48 CSR, Table 14.3.1.3.1

Injection related TEAE were ocular TEAE for the majority and slightly more reported in the HDq12 group (13.1%) than HDq16 (8.0%) but in similar proportions between 2q8 group (10.8%) and all HD group (11.4%). Ocular IVT-injection-related TEAEs were reported in more than 2 patients in all groups up to week 48 for Conjunctival haemorrhage, Eye pain (comparable proportions between all HD group and 2q8 for all three PT), Intraocular eye pressure increased (slightly higher in 2q8 group 2.4% vs 1.2% in all HD group) and Vitreous floaters (slightly higher in HDq12 2.1% vs 0.6% in other groups). Ocular IVT-injection-related TEAEs in the fellow eye were reported in similar proportions between all groups.

Non-ocular IVT-injection-related TEAEs in the HD group only (3 patients 0.6% in all HD group) and consisted of Nausea, Vomiting and Headache.

Table 12 DME: Ocular TEAEs in the study eye related to injection procedure through Week 48 (PHOTON, safety analysis set)

Primary System Organ Class Preferred Term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	15 (9.0%)	40 (12.2%)	13 (8.0%)	53 (10.8%)
Eye disorders	10 (6.0%)	32 (9.8%)	12 (7.4%)	44 (9.0%)
Conjunctival haemorrhage	6 (3.6%)	10 (3.0%)	5 (3.1%)	15 (3.1%)
Eye irritation	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Eye pain	1 (0.6%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
Foreign body sensation in eyes	0	1 (0.3%)	0	1 (0.2%)
Keratopathy	0	1 (0.3%)	0	1 (0.2%)
Lacrimation increased	0	1 (0.3%)	0	1 (0.2%)
Ocular discomfort	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Ocular hypertension	0	1 (0.3%)	0	1 (0.2%)
Punctate keratitis	0	0	1 (0.6%)	1 (0.2%)
Retinal artery occlusion	0	1 (0.3%)	0	1 (0.2%)
Retinal vascular disorder	0	1 (0.3%)	0	1 (0.2%)
Vision blurred	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Visual impairment	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Vitreous detachment	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Vitreous floaters	1 (0.6%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
Vitreous haemorrhage	0	2 (0.6%)	0	2 (0.4%)
Vitritis	0	1 (0.3%)	0	1 (0.2%)
General disorders and administration site conditions	0	3 (0.9%)	0	3 (0.6%)
Injection site irritation	0	1 (0.3%)	0	1 (0.2%)
Injection site pain	0	2 (0.6%)	0	2 (0.4%)
Injury, poisoning and procedural complications	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Corneal abrasion	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Intra-ocular injection complication	0	1 (0.3%)	0	1 (0.2%)
Investigations	4 (2.4%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
Intraocular pressure increased	4 (2.4%)	5 (1.5%)	1 (0.6%)	6 (1.2%)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event; N=number of participants.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PHOTON W48 CSR, Table 14.3.1.4.1

Incidence of protocol procedure related TEAE were low (none in the HDq16), consisted for the majority of non-ocular TEAE and were comparable between HDq12 group and 2q8 group. Ocular TEAEs related to other protocol-specified procedures in the study eye were reported in low proportions and in the HDq12 group only (Conjunctival haemorrhage and Injection site irritation). No ocular study-conduct-related TEAEs in the fellow eye were reported.

Non-ocular TEAEs related to other protocol-specified procedures were reported in low proportions and included Nausea, Vessel puncture site haematoma, Contrast media allergy, Post procedural pruritus, Rash, and Vein rupture. Overall, similar tendencies were observed up to week 96.

2.5.7.3. Serious adverse event/deaths/other significant events

2.5.7.3.1. nAMD indication (CANDELA and PULSAR)

In CANDELA study, one patient died of glioblastoma in HD group after study discontinuation and was not assessed as related to study drug.

Table 22 AMD: Number of participants with AEs with fatal outcome through Week 48 (PULSAR, safety analysis set)

Primary system organ class Preferred term MedDRA version 25.0	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Number (%) of subjects with at least one such adverse event	5 (1.5%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (0.6%)	0	2 (0.3%)
Metastatic neoplasm	0	1 (0.3%)	0	1 (0.1%)
Non-small cell lung cancer	0	1 (0.3%)	0	1 (0.1%)
General disorders and administration site conditions	0	0	1 (0.3%)	1 (0.1%)
Death	0	0	1 (0.3%)	1 (0.1%)
Infections and infestations	1 (0.3%)	1 (0.3%)	0	1 (0.1%)
COVID-19 pneumonia	0	1 (0.3%)	0	1 (0.1%)
Pneumonia aspiration	1 (0.3%)	0	0	0
Cardiac disorders	1 (0.3%)	0	0	0
Cardiac arrest	1 (0.3%)	0	0	0
Gastrointestinal disorders	1 (0.3%)	0	0	0
Abdominal strangulated hernia	1 (0.3%)	0	0	0
Injury, poisoning and procedural complications	1 (0.3%)	0	0	0
Skull fracture	1 (0.3%)	0	0	0
Nervous system disorders	1 (0.3%)	0	0	0
Cerebral infarction	1 (0.3%)	0	0	0

AE = adverse events, MedDRA=medical dictionary for regulatory activities, N = number of participants in a group
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PULSAR W48 CSR, Table 14.3.1/80

In PULSAR, a total of 9 deaths occurred at week 48 (1.5% in 2q8, 0.9% in HDq12 and 0.3% in HDq16) and one additional death (PT sepsis) was recorded at week 60. None were assessed as related to study drug. Up to week 96, incidences of deaths were lower in the HD group (2.1% and 3.6% in PULSAR).

In CANDELA, ocular serious TEAE occurred in three patients (1 event of "Visual acuity reduced "in IAI 2 mg and 2 events of "Retinal tear" and "Visual impairment" in HD group). None were assessed as drug related and no action with drug were taken. One severe event of "Retinal tear" was assessed as injection related. Non ocular serious TEAE were reported in similar proportions. One mild event of "Transient ischemic attack" was assessed as study related and occurred with a TTO of 2 months after last dose in a patient with risk factors.

Table 23 AMD: Ocular serious TEAEs in the study eye through Week 48 (PULSAR, safety analysis set)

Primary system organ class Preferred term MedDRA version 25.0	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Number (%) of subjects with at least one such adverse event	2 (0.6%)	6 (1.8%)	5 (1.5%)	11 (1.6%)
Eye disorders	2 (0.6%)	4 (1.2%)	4 (1.2%)	8 (1.2%)
Retinal detachment	0	3 (0.9%)	1 (0.3%)	4 (0.6%)
Retinal haemorrhage	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Angle closure glaucoma	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Cataract	0	1 (0.3%)	0	1 (0.1%)
Choroidal detachment	0	1 (0.3%)	0	1 (0.1%)
Vitreous haemorrhage	0	0	1 (0.3%)	1 (0.1%)
Investigations	0	2 (0.6%)	0	2 (0.3%)
Intraocular pressure increased	0	2 (0.6%)	0	2 (0.3%)
Injury, poisoning and procedural complications	0	0	1 (0.3%)	1 (0.1%)
Skin laceration	0	0	1 (0.3%)	1 (0.1%)

HD = high dose, MedDRA=medical dictionary for regulatory activities, N = number of participants in a group, TEAE = treatment-emergent adverse event
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PULSAR W48 CSR, Table 14.3.1/48

In PULSAR, ocular serious TEAE were reported in low proportions (<2%) with a slightly higher frequency in the HD group at both week 48 and 60. Reported ocular SAE at week 48 and 60 occurring in n≥2 were "Retinal haemorrhage" (in both HD groups) and "IOP increased" (in HDq12). The majority of serious ocular TEAE in the

study eye were moderate in intensity. Ocular serious TEAE assessed as drug study related at week 60 was "Angle closure glaucoma" (1 in HDq16). Ocular serious TEAEs assessed as IVT injection procedure related were "Angle closure glaucoma" (HDq16) "Skin laceration" (HDq16) "Endophthalmitis" (2q8) and "IOP increased" (HDq12). For the fellow eye, ocular serious TEAE were reported in similar proportion and none were assessed as related. The majority of serious ocular TEAE in the fellow eye were moderate in intensity. Up to week 96, serious ocular TEAE were low in rate and proportions were slightly higher in all HD group (2.8% vs 1.2% in 2q8) in PULSAR. In both PHOTON and PULSAR, most serious TEAE were reported in single patients (except for cataract (n=2 HDq16), retinal detachment (n=5 all HD group), retinal hemorrhage (n=4 all HD group) and IOP increase (n=2 HDq12) for PULSAR and vitreous detachment (n=2 HDq16) for PHOTON)).

Table 24 AMD: Non-ocular serious TEAEs occurring in ≥ 2 participants in any treatment group through Week 48 (PULSAR, safety analysis set)

Primary system organ class Preferred term MedDRA version 25.0	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Number (%) of subjects with at least one such adverse event	46 (13.7%)	34 (10.1%)	32 (9.5%)	66 (9.8%)
Infections and infestations	6 (1.8%)	8 (2.4%)	7 (2.1%)	15 (2.2%)
Pneumonia	1 (0.3%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Cellulitis	0	2 (0.6%)	0	2 (0.3%)
Pyelonephritis acute	0	0	2 (0.6%)	2 (0.3%)
Urinary tract infection	4 (1.2%)	1 (0.3%)	0	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (2.4%)	9 (2.7%)	6 (1.8%)	15 (2.2%)
Bladder neoplasm	3 (0.9%)	0	0	0
Cardiac disorders	6 (1.8%)	3 (0.9%)	6 (1.8%)	9 (1.3%)
Angina pectoris	0	0	3 (0.9%)	3 (0.4%)
Musculoskeletal and connective tissue disorders	8 (2.4%)	3 (0.9%)	5 (1.5%)	8 (1.2%)
Osteoarthritis	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Nervous system disorders	4 (1.2%)	4 (1.2%)	3 (0.9%)	7 (1.0%)
Syncope	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Cerebrovascular accident	2 (0.6%)	1 (0.3%)	0	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	3 (0.9%)	4 (1.2%)	3 (0.9%)	7 (1.0%)
Chronic obstructive pulmonary disease	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
General disorders and administration site conditions	0	2 (0.6%)	2 (0.6%)	4 (0.6%)
Chest pain	0	2 (0.6%)	0	2 (0.3%)
Injury, poisoning and procedural complications	9 (2.7%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Upper limb fracture	2 (0.6%)	0	0	0
Metabolism and nutrition disorders	3 (0.9%)	0	2 (0.6%)	2 (0.3%)
Hyponatraemia	2 (0.6%)	0	2 (0.6%)	2 (0.3%)

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group, TEAE = treatment-emergent adverse event
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1. PULSAR W48 CSR. Table 14.3.1/50

Non-ocular serious TEAE were observed in similar proportions with comparable frequency between groups for each reported SOCs at week 48 and 60. Non-ocular serious TEAE assessed as drug related occurred in 6 patients (2 in HDq16 and 4 in 2q8). The most reported serious TEAE assessed as study related was "Cerebrovascular accident" (n=2) observed in 2q8. Additionally, one event of "Chest pain" in HDq12 occurred on the day of the first injection in a 91 years old patient with history of hypertension and was attributed to anxiety. The event was assessed as injection and procedure related and resolved on the same day. The majority of serious non-ocular TEAE were moderate in intensity. Most reported serious non-ocular PT were consistent with underlying conditions and no similar trends were seen between both studies.

AESI

AESI were presented by the Applicant for each study and consisted of intraocular inflammation, IOP increase, retinal pigment epithelium tear, retinal tear/detachment, cataract, hypersensitivity, arterial thromboembolic events and adjudicated Anti-platelet Trialists' Collaboration (APTC) events, venous thromboembolic events, hypertension, non-ocular bleedings, and nasal mucosal findings.

- Intraocular inflammation (IOI)

Table 27 AMD: TEAEs of intraocular inflammation of study eye through Week 48: number of participants (PULSAR, safety analysis set)

Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of participants with at least one such adverse event	2 (0.6%)	4 (1.2%)	1 (0.3%)	5 (0.7%)
Chorioretinitis	0	1 (0.3%)	0	1 (0.3%)
Iridocyclitis	1 (0.3%)	0	1 (0.3%)	1 (0.3%)
Iritis	0	1 (0.3%)	0	1 (0.3%)
Vitreal cells	1 (0.3%)	1 (0.3%)	0	1 (0.3%)
Vitritis	0	1 (0.3%)	0	1 (0.3%)

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3/12

For CANDELA, one mild, non-serious, resolved event of Iritis and assessed as related to study drug was reported in the HD group. Low and comparable proportions of TEAE of intraocular inflammation were reported for PULSAR in HD group and 2q8 at week 48 and 60. Events were non-serious, mild for the majority and resolved or resolving. 2 cases of Endophthalmitis were reported in the 2q8 groups at week 60. No cases of Occlusive retinal vasculitis were reported. In the 2q8 group and in the HDq16, one event (each) of Iridocyclitis were assessed as related to study drug.

Up to week 96, no cases of Endophthalmitis, ocular vasculitis and occlusive retinitis were reported for the all HD group.

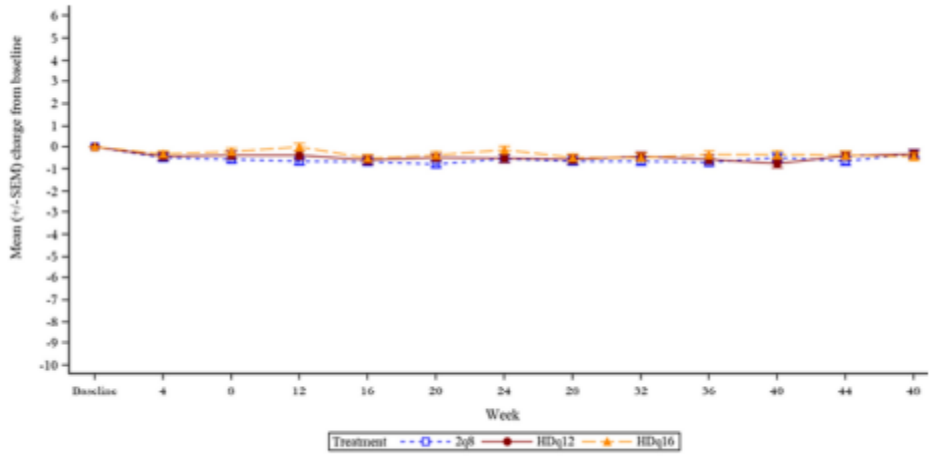
- Intraocular pressure (IOP) increased

Table 28 AMD: TEAEs of intraocular pressure increase in study eye through Week 48: number of participants (PULSAR, safety analysis set)

Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of participants with at least one such adverse event	8 (2.4%)	12 (3.6%)	12 (3.6%)	24 (3.6%)
Intraocular pressure increased	7 (2.1%)	11 (3.3%)	9 (2.7%)	20 (3.0%)
Ocular hypertension	1 (0.3%)	2 (0.6%)	4 (1.2%)	6 (0.9%)

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3/3

Figure 1 AMD: Mean change in pre-injection intraocular pressure (mmHg) through Week 48 – study eye (PULSAR, safety analysis set)



SEM = standard error of mean
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PULSAR W48 CSR, Figure 14.3.7/1

In CANDELA, no TEAEs of Intraocular pressure increased or Ocular hypertension were reported. In PULSAR, comparable proportion of IOP increase were observed. Majority of the events were mild and non-serious. The frequencies of pre- and post-injection IOP increase from baseline at all values (≥ 10 mmHg through ≥ 35 mmHg) were comparable across groups at week 48 and 60. In both studies, pre-dose intraocular pressure > 21 mmHg at any visit was numerically higher in the HD group however there were no clinically meaningful trends in mean or median changes from baseline in pre-dose intraocular pressure in the study eye in either treatment group. Similar tendencies were observed up to week 96.

- Retinal pigment epithelial tear

Table 30 AMD: TEAEs of retinal pigment epithelial tear in study eye through Week 48: number of participants (PULSAR, safety analysis set)

Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of participants with at least one such adverse event	3 (0.9%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
Retinal pigment epithelial tear	3 (0.9%)	6 (1.8%)	3 (0.9%)	9 (1.3%)

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group, ...
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PULSAR W48 CSR, Table 14.3.1/2

In CANDELA, one non-serious, mild and unrelated event of Retinal pigment epithelial tear was reported. In PULSAR, frequencies of Retinal pigment epithelial tear were higher in HDq12 at week 48 and 60. Events were mild or moderate, non-serious and not resolved for the majority of the patients. Five were assessed as drug related (4 in the pooled HD) and one event was assessed as related to IVT procedure.

RPE tear is a known and listed ADR for Eylea 2 mg/8 mg. Although a higher proportion was reported at week 48 and 60 for HDq12 compared to HDq16 and 2q8; the rate of 1.8% is in line with the pooled incidence found in previous studies in AMD (VIEW 1/VIEW 2) which was 1.6%. Furthermore, all events of RPE tears occurred up to 12 weeks (loading phase) in which exposure to Eylea was similar between HDq12 and HDq16 groups and similar proportions were reported for HDq16 and 2q8 (0,9%). Thus occurrence of RPE tears does not seems to be dose-dependent or injection frequency related.

- Retinal tear/detachment

Table 31 AMD: TEAEs of retinal tear / detachment in study eye through Week 48: number of participants (PULSAR, safety analysis set)

Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of participants with at least one such adverse event	0	3 (0.9%)	3 (0.9%)	6 (0.9%)
Retinal detachment	0	3 (0.9%)	1 (0.3%)	4 (0.6%)
Retinal tear	0	0	2 (0.6%)	2 (0.3%)

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3/13

In CANDELA, no events of retinal detachment were reported and retinal tear occurred in 2 patients in HD group. Events were assessed as unrelated, one serious retinal tear was resolved and treated by laser while the other was non-serious, mild and not resolved. At week 48 and 60, 6 patients presented "Retinal detachment/retinal tear" in the study eye (3 in the HDq12 group). One patient in the HDq16 group discontinued the study drug and events of retinal detachment and retinal tear were serious in one patient in HDq12 and one patient in 2q8. Events were for the majority moderate, assessed as unrelated to study drug or IVT and resolved or resolved with sequelae.

- Cataract

Table 32 AMD: TEAEs of cataract in study eye through Week 48: number of participants (PULSAR, safety analysis set)

Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of participants with at least one such adverse event	13 (3.9%)	14 (4.2%)	15 (4.4%)	29 (4.3%)
Cataract	10 (3.0%)	12 (3.6%)	12 (3.6%)	24 (3.6%)
Cataract cortical	1 (0.3%)	0	0	0
Cataract subcapsular	1 (0.3%)	0	1 (0.3%)	1 (0.1%)

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3/1

In CANDELA, two non-serious, non-related events of cataract (1 Cataract subcapsular in IAI 2mg and 1 Posterior capsule opacification) occurred in the study eye. In PULSAR patients in the HDq16 group had more reported medical history of cataract (60.9% vs 50.4% in the HDq12 and 53.9 in the 2q8 group) while proportions were similar between the pooled HD group and the 2q8 group. At week 48 and 60, events of cataract were reported in comparable proportions between all groups and all events were for the majority non-serious, mild or moderate and assessed as unrelated (in HDq16 one event was related to study drug and one to IVT, in 2q8 one event was related to IVT). No events lead to discontinuation of study drug. However, considering the imbalance of incidence of cataract as medical history for the study eye at baseline, the Applicant was requested to provide further discussion on the clinical relevance (discussed in Efficacy section). Similar tendencies were observed up to week 96, incidences were 9.1% in all HD group vs 6.5% 2q8 for PULSAR. Higher proportions of TEAE were also seen for subtypes of cataract (cataract cortical, cataract nuclear and cataract subcapsular) but when looking at pooled data slightly lower or comparable proportions were reported

between all HD and 2q8 groups (frequency uncommon for all in SmPc Eylea 8 mg). Cataract is listed in the SmPc of Eylea 2 mg (common: 8%) and Eylea 8 mg (common: 4%) and is an important identified safety concern in the RMP of Eylea.

- Hypersensitivity

Table 33 AMD: TEAEs of hypersensitivity through Week 48: number of participants (PULSAR, safety analysis set)

Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of participants with at least one such adverse event	3 (0.9%)	4 (1.2%)	5 (1.5%)	9 (1.3%)
Corneal oedema	0	1 (0.3%)	0	1 (0.1%)
Eye swelling	0	0	1 (0.3%)	1 (0.1%)
Eyelid oedema	0	0	1 (0.3%)	1 (0.1%)
Pruritus	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Rash	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Swelling of eyelid	1 (0.3%)	0	0	0
Urticaria	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group
See Definition of terms for treatment arms description.
All ocular TEAEs, including TEAEs in the fellow eye, are included in the table.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3/8

No events of Hypersensitivity were reported in CANDELA. In PULSAR, incidences were low and comparable. Events were mild or moderate, non-serious and not assessed as related to study drug.

- Arterial thromboembolic events/APTC

Table 34 AMD: TEAEs of arterial thromboembolic events through Week 48 adjudicated by APTC: number of participants (PULSAR, safety analysis set)

Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of participants with at least one such adverse event	5 (1.5%)	1 (0.3%)	2 (0.6%)	3 (0.4%)*
Acute coronary syndrome	1 (0.3%)	0	0	0
Cardiac arrest	1 (0.3%)	0	0	0
Cerebral infarction	1 (0.3%)	0	0	0
Cerebrovascular accident	1 (0.3%)	1 (0.3%)	0	1 (0.1%)
Death	0	0	1 (0.3%)	1 (0.1%)
Myocardial infarction	1 (0.3%)	0	1 (0.3%)	1 (0.1%)

APTC = Antiplatelet Trialists' Collaboration, MedDRA=medical dictionary for regulatory activities, N = number of participants in a group, TEAEs = treatment-emergent adverse events
* One APTC event in HDq16 group was not displayed in the source table, because it was not correctly displayed in the database but is shown in this table. For more details, see Module 5.3.5.1, PULSAR W48 CSR, Sections 10.3.3.4.2 and 16.4.2 (Database errata).
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3/11

In CANDELA, one serious, mild in intensity, assessed as related to study drug and resolved event of Transient ischaemic attack occurred in HD group. Incidences for APTC events were low and events were less reported in the HD group compared to 2q8 group.

Table 35 AMD: TEAEs of arterial thromboembolic events through Week 48: number of participants (PULSAR, safety analysis set)

Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of participants with at least one such adverse event	7 (2.1%)	11 (3.3%)	7 (2.1%)	18 (2.7%)
Acute coronary syndrome	1 (0.3%)	0	0	0
Acute myocardial infarction	1 (0.3%)	0	0	0
Amaurosis fugax	0	1 (0.3%)	0	1 (0.1%)
Angina pectoris	0	2 (0.6%)	3 (0.9%)	5 (0.7%)
Angina unstable	0	1 (0.3%)	0	1 (0.1%)
Arteriosclerosis coronary artery	1 (0.3%)	0	0	0
Carotid arteriosclerosis	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Cerebral infarction	1 (0.3%)	0	0	0
Cerebral ischaemia	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Cerebrovascular accident	2 (0.6%)	1 (0.3%)	0	1 (0.1%)
Cerebrovascular disorder	0	0	1 (0.3%)	1 (0.1%)
Myocardial infarction	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Myocardial ischaemia	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Precerebral arteriosclerosis	0	1 (0.3%)	0	1 (0.1%)
Stroke in evolution	0	1 (0.3%)	0	1 (0.1%)
Transient ischaemic attack	0	2 (0.6%)	0	2 (0.3%)
Vertebrobasilar insufficiency	0	0	1 (0.3%)	1 (0.1%)

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group, …
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3/10

Arterial thromboembolic events were reported in slightly higher proportion in HDq12 (3.3% vs 1.1%) but events were overall mild or moderate in severity and resolved. Events of Angina pectoris, Cerebrovascular accident and Transient ischaemic attack were reported in more than 1 patient. Frequencies in SOC Cardiac disorders and Nervous system disorders were low and comparable. No dose dependency was observed. At week 96, for ATE events, incidences were low and similar proportions were reported in both studies (ATEs 4.8% 2q8 and 5.3% all HD group for PULSAR).

- Venous thromboembolic events

Table 36 AMD: TEAEs of venous thromboembolic events through Week 48: number of participants (PULSAR, safety analysis set)

Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of participants with at least one such adverse event	1 (0.3%)	4 (1.2%)	1 (0.3%)	5 (0.7%)
Deep vein thrombosis	0	2 (0.6%)	0	2 (0.3%)
Pulmonary embolism	0	0	1 (0.3%)	1 (0.1%)
Retinal vein thrombosis	1 (0.3%)	0	0	0
Superficial vein thrombosis	0	1 (0.3%)	0	1 (0.1%)
Venous thrombosis limb	0	1 (0.3%)	0	1 (0.1%)

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3/7

No venous thromboembolic events were reported in CANDELA. In PULSAR, at week 48 and 60, incidences were low and comparable. Two serious events were reported Pulmonary embolism (resolved, in patient treated by bilateral therapy, in HDq16 group) assessed as related to study drug and Venous thrombosis limb (resolved, in HDq12 group) not assessed as related. Both events were severe in severity.

- Hypertension

Table 37 AMD: TEAEs of hypertension through Week 48: number of participants (PULSAR, safety analysis set)

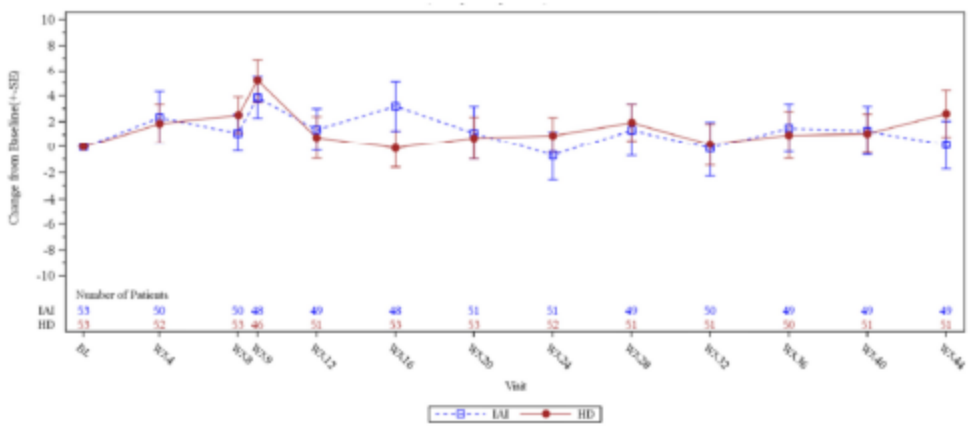
Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of participants with at least one such adverse event	12 (3.6%)	16 (4.8%)	16 (4.7%)	32 (4.8%)
Blood pressure diastolic increased	1 (0.3%)	0	0	0
Blood pressure increased	2 (0.6%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Blood pressure systolic increased	1 (0.3%)	2 (0.6%)	0	2 (0.3%)
Diastolic hypertension	0	0	1 (0.3%)	1 (0.1%)
Hypertension	8 (2.4%)	14 (4.2%)	13 (3.8%)	27 (4.0%)
Systolic hypertension	0	1 (0.3%)	0	1 (0.1%)
White coat hypertension	1 (0.3%)	0	0	0

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group, TEAE = treatment-emergent adverse event
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3/4

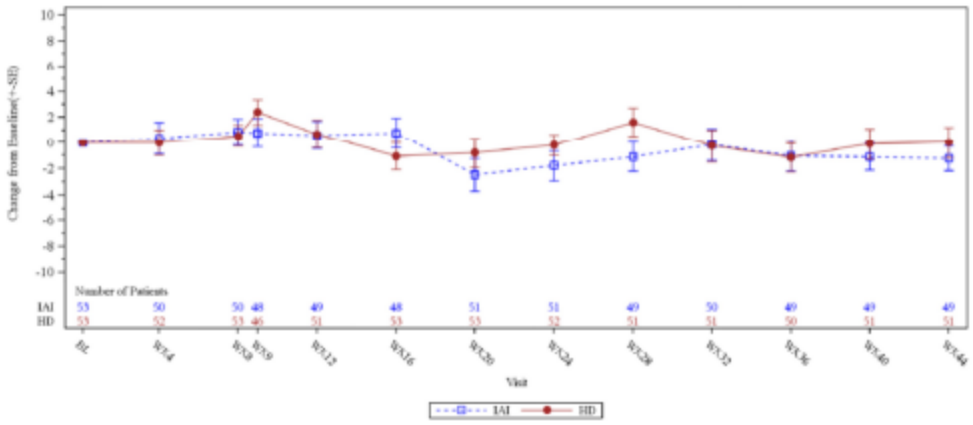
In CANDELA, one non-serious, mild event of hypertension was reported. Medical history of hypertension was reported in 2/3 of the patients (60.7% in 2q8 and 65.5 in pooled HD group). Incidence of hypertension in PULSAR was slightly higher in the pooled HD group and similar between HDq12 and HDq16. One mild in severity, serious, non-related event of hypertension was reported in HDq12.

Figure 3 AMD: Mean change from baseline in systolic and diastolic blood pressure (mmHg) through Week 44 (CANDELA, safety analysis set)

Systolic blood pressure



Diastolic blood pressure



BL = baseline, SE = standard error, WK = week
See Definition of terms for treatment arms description.
Baseline for blood pressure was defined as the average of all 3 valid measurements taken prior to administration of study drug.
Source: Module 5.3.5.1, CANDELA CSR, Figure 14.03.03/1.a and Figure 14.03.03/2.a

No increase from baseline in mean systolic and diastolic blood pressure were observed. As hypertension is a listed event for aflibercept administered by IV although at a much higher posology, the topic is actually followed through the PSUR and that a difference could be observed up to week 60, the Applicant further discussed on the topic of Hypertension with the newly proposed regimen. At week 96, incidences were similar in PULSAR (2q8: 7.4%, all HD 8.0%). Proportion of patient with medical history of hypertension was similar with and without hypertension event although higher blood pressures at baseline were higher in HD group (PULSAR: 141 mmHg (SBP)/77.3 mmHg (DBP) vs 133.3 mmHg (SBP)/76.4 mmHg (DBP)). In PULSAR, the lowest incidence (15,5%) was reported in HDq12 group in which the exposure is the highest. Onset of hypertension TEAEs over time (up to week 60) were well distributed and is not in favour of a correlated aflibercept induced hypertension. Pooled mean changes in blood pressure (CANDELA/PULSAR/PHOTON) for 8 mg were lower than the baseline through week 60. Pre-defined treatment-emergent potentially clinically significant values of systolic blood pressure related to elevations and decrease were comparable or slightly higher in the all HD group for both PULSAR and PHOTON. Compared to previous experience with Eylea 2 mg, similar or higher incidence were observed at 1 and 2 year in the 2 mg group compared to week 60 and 96 with 8 mg (for DME

25.8 % 2 mg at 2 years vs 17.3% at week 96 for all HD and for AMD 14.7% 2 mg at 2 years vs 8.0% at week 96 for all HD). Furthermore, the risk of hypertension is currently monitored through the PSUR.

- Non-ocular haemorrhages and Nasal mucosal findings

Table 38 AMD: TEAEs of non-ocular hemorrhages through Week 48: number of participants (PULSAR, safety analysis set)

Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of participants with at least one such adverse event	10 (3.0%)	8 (2.4%)	5 (1.5%)	13 (1.9%)
Blood loss anaemia	1 (0.3%)	0	0	0
Contusion	3 (0.9%)	4 (1.2%)	2 (0.6%)	6 (0.9%)
Cystitis haemorrhagic	1 (0.3%)	0	0	0
Epistaxis	0	0	2 (0.6%)	2 (0.3%)
Haematoma	1 (0.3%)	0	0	0
Haematuria	2 (0.6%)	0	0	0
Haemorrhage	1 (0.3%)	2 (0.6%)	0	2 (0.3%)
Post procedural haemorrhage	0	1 (0.3%)	0	1 (0.1%)
Rectal haemorrhage	0	0	1 (0.3%)	1 (0.1%)
Upper gastrointestinal haemorrhage	1 (0.3%)	0	0	0
Vaginal haemorrhage	0	1 (0.3%)	0	1 (0.1%)
Vein rupture	1 (0.3%)	0	0	0

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3/6

In CANDELA, no events of non-ocular haemorrhages were reported. In PULSAR, at week 48 and 60, incidences were comparable and events were for the majority non-serious, mild in intensity and resolved. Four serious non-ocular haemorrhage events were reported (one event of Epistaxis in HDq16 and events of blood loss anaemia, upper gastrointestinal haemorrhage and cystitis haemorrhagic).

In CANDELA, no TEAE of nasal mucosal findings were reported. In PULSAR, at week 48 and 60, 2 events (one serious, moderate, unrelated and resolved) of Epistaxis in HDq16 were reported.

2.5.7.3.2. DME indication (PHOTON)

A total of 16 deaths occurred up to week 48 and 2 additional deaths were recorded up to week 60. All deaths were associated to an SAE and none were considered as related to study drug or study procedure. The most reported SOC was Cardiac disorders (3 deaths in each group at week 60). The cause of death was unknown for 2 patients in HDq12 group and for one patient in HDq12. All three patients had cardiovascular risk factors (cardiac stent, hypertension,) and the chronology did not evocate a causal relationship with aflibercept. Up to week 96, incidences of deaths were lower in the HD group (4.7% vs 5.4% 2q8 in PHOTON).

Table 13 DME: Number of participants with AEs with fatal outcome through Week 48 (PHOTON, safety analysis set)

Primary System Organ Class Preferred Term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	4 (2.4%)	9 (2.7%)	3 (1.8%)	12 (2.4%)
Cardiac disorders	3 (1.8%)	3 (0.9%)	2 (1.2%)	5 (1.0%)
Cardiac arrest	2 (1.2%)	2 (0.6%)	0	2 (0.4%)
Cardio-respiratory arrest	0	0	1 (0.6%)	1 (0.2%)
Left ventricular failure	0	0	1 (0.6%)	1 (0.2%)
Myocardial infarction	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
General disorders and administration site conditions	0	2 (0.6%)	1 (0.6%)	3 (0.6%)
Death	0	2 (0.6%)	0	2 (0.4%)
Sudden Death	0	0	1 (0.6%)	1 (0.2%)
Infections and infestations	0	2 (0.6%)	0	2 (0.4%)
COVID-19	0	1 (0.3%)	0	1 (0.2%)
Pneumonia	0	1 (0.3%)	0	1 (0.2%)
Metabolism and nutrition disorders	1 (0.6%)	0	0	0
Diabetic metabolic decompensation	1 (0.6%)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.3%)	0	1 (0.2%)
Endometrial cancer	0	1 (0.3%)	0	1 (0.2%)
Renal and urinary disorders	0	1 (0.3%)	0	1 (0.2%)
Acute kidney injury	0	1 (0.3%)	0	1 (0.2%)

AE=adverse event; COVID-19=Coronavirus Disease 2019; MedDRA=Medical Dictionary for Regulatory Activities
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PHOTON W48 CSR, Table 14.3.1.17

Up to week 48 and 60, 5 ocular serious TEAE occurred in 4 participants and consisted of Ulcerative keratitis (moderate in intensity) in 2q8, Cataract subcapsular (severe in intensity), and Intraocular pressure increased in HDq12 (moderate in severity, assessed as related to injection procedure) and Retinal detachment (severe in intensity) and Vitreous haemorrhage (severe in intensity) in HDq16. All events, except for Vitreous haemorrhage, resolved. In the fellow eye, 11 ocular serious TEAE occurred and none were assessed as related to study drug. Up to week 96, serious ocular TEAE were low in rate and proportions were similar in PHOTON (1.2%). In both PHOTON and PULSAR, most serious TEAE were reported in single patients (except for cataract (n=2 HDq16), retinal detachment (n=5 all HD group), retinal hemorrhage (n=4 all HD group) and IOP increase (n=2 HDq12) for PULSAR and vitreous detachment (n=2 HDq16) for PHOTON)).

Table 14 DME: Non-ocular serious TEAEs events in ≥ 2 participants in any treatment group through Week 48 (PHOTON, safety analysis set)

Primary System Organ Class Preferred Term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	26 (15.6%)	52 (15.9%)	22 (13.5%)	74 (15.1%)
Blood and lymphatic system disorders	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Anaemia	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Cardiac disorders	9 (5.4%)	13 (4.0%)	4 (2.5%)	17 (3.5%)
Acute left ventricular failure	3 (1.8%)	1 (0.3%)	0	1 (0.2%)
Acute myocardial infarction	2 (1.2%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Cardiac arrest	2 (1.2%)	2 (0.6%)	0	2 (0.4%)
Cardiac failure	1 (0.6%)	2 (0.6%)	0	2 (0.4%)
Coronary artery disease	1 (0.6%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
Coronary artery occlusion	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Myocardial infarction	2 (1.2%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
General disorders and administration site conditions	2 (1.2%)	2 (0.6%)	2 (1.2%)	4 (0.8%)
Chest pain	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Infections and infestations	8 (4.8%)	13 (4.0%)	2 (1.2%)	15 (3.1%)
COVID-19	0	3 (0.9%)	1 (0.6%)	4 (0.8%)
COVID-19 pneumonia	2 (1.2%)	2 (0.6%)	0	2 (0.4%)
Gangrene	2 (1.2%)	0	0	0
Pneumonia	1 (0.6%)	4 (1.2%)	0	4 (0.8%)
Metabolism and nutrition disorders	5 (3.0%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
Hyponatraemia	2 (1.2%)	0	0	0
Musculoskeletal and connective tissue disorders	0	3 (0.9%)	2 (1.2%)	5 (1.0%)
Neuropathic arthropathy	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Nervous system disorders	2 (1.2%)	5 (1.5%)	6 (3.7%)	11 (2.2%)
Cerebrovascular accident	0	2 (0.6%)	4 (2.5%)	6 (1.2%)
Renal and urinary disorders	0	8 (2.4%)	1 (0.6%)	9 (1.8%)
Acute kidney injury	0	4 (1.2%)	0	4 (0.8%)
Respiratory, thoracic and mediastinal disorders	3 (1.8%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
Acute respiratory failure	2 (1.2%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
Pulmonary embolism	0	2 (0.6%)	0	2 (0.4%)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PHOTON W48 CSR, Table 14.3.1.9.3

Regarding non-ocular serious TEAE, similar proportions were reported between treatment arms and none were assessed as related to study drug. The most reported SOC was Cardiac disorders reported in slightly higher proportion in the 2q8 group at week 48 but in similar proportion between 2q8 group (5.4%) and all HD group (5.5%) at week 60. The SOC Nervous system disorders was reported in higher proportion in the HDq16 group (3.7%) and the PT Cerebrovascular accident was reported with higher incidence in HDq16 (4 in the HDq16, 2 in the HD12 and none in the 2q8) of which none were assessed as drug related. Furthermore, HDq16 arm had higher reported medical history of hypertension, insulin dependent diabetes mellitus and obesity and incidences in the HDq12 arm and 2q8 arm were similar.

Up to week 96, lower proportions were observed in PHOTON (2q8: 25.1, all HD: 23.2%) with PT majorly reported in single patients. Most reported serious non-ocular PT were consistent with underlying conditions and no similar trends were seen between both studies.

AESI

- Intraocular inflammation

Table 15 DME: TEAEs of intraocular inflammation in the study eye through Week 48: number of participants (PHOTON, safety analysis set)

Preferred Term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	1 (0.6%)	4 (1.2%)	0	4 (0.8%)
Iridocyclitis	1 (0.6%)	0	0	0
Iritis	0	1 (0.3%)	0	1 (0.2%)
Uveitis	0	1 (0.3%)	0	1 (0.2%)
Vitreal cells	0	1 (0.3%)	0	1 (0.2%)
Vitritis	0	1 (0.3%)	0	1 (0.2%)

MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3 / 40

Ocular TEAE of intraocular inflammation in the study eye occurred for the majority in the HDq12 group with comparable proportions between all HD group and 2q8 (none in the HDq16 group). No events of Endophthalmitis and no Occlusive retinal vasculitis were reported. All events were mild or moderate, non-serious and all resolved apart from one event of iritis in the HDq12 assessed as study drug related which lead to study discontinuation.

Up to week 96, no cases of Endophthalmitis, ocular vasculitis and occlusive retinitis were reported for the all HD group in PHOTON and overall incidence of IOI events are low and comparable between arms.

- Intraocular pressure (IOP) increase

Table 16 DME: TEAEs of intraocular pressure increase in the study eye through Week 48: number of participants (PHOTON, safety analysis set)

Preferred Term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	7 (4.2%)	11 (3.4%)	1 (0.6%)	12 (2.4%)
Intraocular pressure increased, study eye	7 (4.2%)	11 (3.4%)	1 (0.6%)	12 (2.4%)
Intraocular pressure increased	6 (3.6%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
Ocular hypertension	1 (0.6%)	4 (1.2%)	0	4 (0.8%)

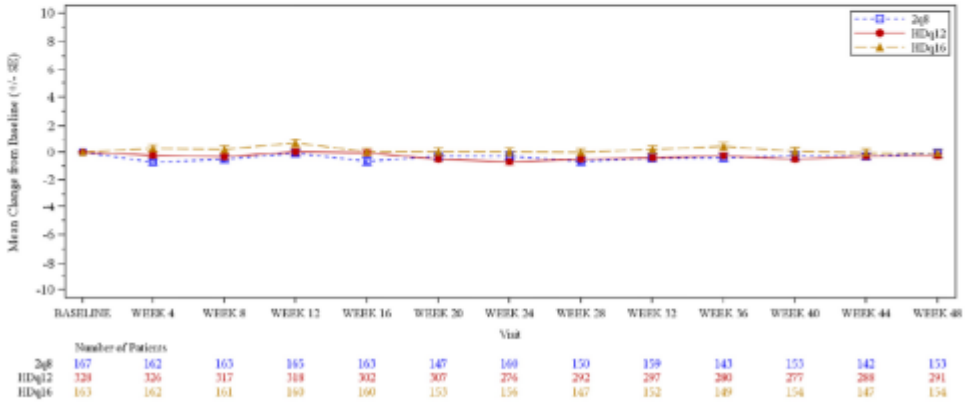
MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3 / 31

Table 17 DME: Number of participants meeting intraocular pressure increase criteria in study eye at any visit through Week 48 (PHOTON, safety analysis set)

Analysis category (number of participants)	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Increase ≥ 10 mmHg in pre-dose intraocular pressure from baseline	4 (2.4%)	12 (3.7%)	6 (3.7%)	18 (3.7%)
> 21 mmHg pre-dose measurement	30 (18.0%)	54 (16.5%)	26 (16.0%)	80 (16.3%)
≥ 25 mmHg pre-dose measurement	2 (1.2%)	12 (3.7%)	3 (1.8%)	15 (3.1%)
≥ 35 mmHg pre-dose or post-dose measurement	2 (1.2%)	1 (0.3%)	0	1 (0.2%)

HD=high dose; MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PHOTON W48 CSR, Table 14.3.5.3.12

Figure 4 DME: Mean change in pre-injection intraocular pressure (mmHg) through Week 48 – study eye (PHOTON, safety analysis set)



SE = standard error
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PHOTON W48 CSR, Figure 14.3.5.3.1

TEAE of IOP increase and Ocular hypertension were slightly more reported in the 2q8 group than in the HDq12 and the HDq16 groups. Furthermore, more events were reported in the HDq12 than the HDq16 (3.4% vs 0.6%). All events were mild or moderate and non-serious apart from one TEAE of IOP increase in the HDq12 group (moderate, resolved on the same day and related to injection procedure).

Number of patients with pre-dose IOP ≥25 mmHg was higher in HDq12 (3.7% vs 1.2% in 2q8 and 1.8% in HDq16) however no relevant clinical differences could be observed regarding mean change in pre-injection IOP. IOP incidence was highest in the 2q8 arm (4.2% vs 3.4% in HDq12 and 0.6% in HDq16) in which there was the lowest aflibercept exposure in the compared to HDq12 and HDq16.

- Retinal pigment epithelial tear

No events of Retinal pigment epithelial tear were reported in PHOTON.

- Retinal tear/detachment

One serious and severe in severity event of Retinal detachment assessed as unrelated to study drug or injection procedure occurred in the HDq16 group after 2 injections (TTO 58 days after first dose). The patient also experienced vitreous haemorrhage which was severe in severity. The patient was treated for the event of Retinal detachment. Both events resolved (on day 124) after drug interruption and study drug was resumed on day 134.

- Cataract

Table 18 DME: TEAEs of cataract in the study eye through Week 48: number of participants (PHOTON, safety analysis set)

Preferred Term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	7 (4.2%)	11 (3.4%)	12 (7.4%)	23 (4.7%)
Cataract	2 (1.2%)	5 (1.5%)	8 (4.9%)	13 (2.6%)
Cataract cortical	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Cataract nuclear	2 (1.2%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Cataract subcapsular	1 (0.6%)	3 (0.9%)	0	3 (0.6%)
Posterior capsule opacification	2 (1.2%)	0	2 (1.2%)	2 (0.4%)

MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3 / 29

Medical history of cataract in the study eye were more reported in the HDq16 group (39.3% vs 34.5% in the HDq12 and 33.5% in the 2q8 group). Events of cataract were slightly more reported in the HDq16 group (4.9%) than in the HDq12 group (1.5%) and 2q8 group (1.2%). All events were non-serious, mild or moderate except one event of Cataract Subcapsular (serious and severe in intensity in the HDq12 group) which occurred after 2 injections and was associated with visual acuity loss. The event was resolved after cataract surgery. The dose of study drug was unchanged. The event was assessed as unrelated to study drug and injection procedure. Similar tendencies were observed up to week 96, incidence of cataract were 7.5% in all HD vs 3.6% for 2q8 for PHOTON. Higher proportions of TEAE were also seen for subtypes of cataract (cataract cortical, cataract nuclear and cataract subcapsular) but when looking at pooled data slightly lower or comparable proportions were reported between all HD and 2q8 groups (frequency uncommon for all in SmPc Eylea 8 mg). Cataract is listed in the SmPc of Eylea 2 mg (common: 8%) and Eylea 8 mg (common: 4%) and is an important identified safety concern in the RMP of Eylea.

- Hypersensitivity

Table 19 DME: TEAEs of Hypersensitivity through Week 48: number of participants (PHOTON, safety analysis set)

Preferred Term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	2 (1.2%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
Conjunctival oedema*	0	1 (0.3%)	0	1 (0.2%)
Corneal oedema*	1 (0.6%)	0	0	0
Pruritus*	0	0	1 (0.6%)	1 (0.2%)
Rash	0	1 (0.3%)	0	1 (0.2%)
Swelling face	0	1 (0.3%)	0	1 (0.2%)
Swelling of eyelid*	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Swollen tongue*	0	1 (0.3%)	0	1 (0.2%)

MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
* All ocular TEAEs, including TEAEs in the fellow eye, are included in the table.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3 / 36

TEAE events of Hypersensitivity were reported in less than 2% of the participants in all groups and reported in similar proportions between all HD group and 2q8 group. All events were non-serious, mild in intensity and unrelated to study drug.

- Arterial thromboembolic events/APTC

Table 21 DME: TEAEs of arterial thromboembolic events through Week 48: number of participants (PHOTON, safety analysis set)

Preferred term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	10 (6.0%)	11 (3.4%)	11 (6.7%)	22 (4.5%)
Acute coronary syndrome	1 (0.6%)	0	0	0
Acute myocardial infarction	2 (1.2%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Angina pectoris	1 (0.6%)	0	1 (0.6%)	1 (0.2%)
Angina unstable	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Arteriosclerosis coronary artery	1 (0.6%)	0	0	0
Blood creatine phosphokinase increased	2 (1.2%)	0	0	0
Carotid artery disease	1 (0.6%)	0	0	0
Cerebrovascular accident	0	2 (0.6%)	4 (2.5%)	6 (1.2%)
Coronary artery disease	3 (1.8%)	2 (0.6%)	2 (1.2%)	4 (0.8%)
Coronary artery occlusion	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Coronary artery stenosis	0	1 (0.3%)	0	1 (0.2%)
Electrocardiogram ST segment elevation	0	0	1 (0.6%)	1 (0.2%)
Lacunar infarction	0	0	1 (0.6%)	1 (0.2%)
Myocardial infarction	2 (1.2%)	4 (1.2%)	1 (0.6%)	5 (1.0%)
Myocardial ischaemia	1 (0.6%)	0	2 (1.2%)	2 (0.4%)
Transient ischaemic attack	0	2 (0.6%)	0	2 (0.4%)
Troponin increased	0	1 (0.3%)	0	1 (0.2%)

MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3 / 38

Medical history of myocardial infarction was reported in higher proportions in the HDq16 (7.4% vs 6.1% in HDq12 and 4.8% in the 2q8 group). Incidences of APTC events were low and slightly higher in the HDq16 group (4.3% vs 3.6% in the 2q8 group and 2.4% in the HDq12 group at week 48) with similar observed tendencies at week 60.

Arterial thromboembolic events were more reported in the HDq16 group and 2q8 group than in the HDq12 group (6.7% vs 6.0% vs 3.4% respectively). The majority of the patient had no medical history of cerebrovascular disease and the incidence of patient with such medical history were reported in higher proportion in the 2q8 group (11.4% vs 7.6% in all HD group). The PT of Cerebrovascular incidents was reported in higher incidence in the HDq16 group (2.5%) and none occurred in the 2q8 group. No events were assessed as related to study drug. Although ATE events were more reported in the HDq16 group and 2q8 group than in the HDq12 group (6.7% vs 6.0% vs 3.4% respectively), the cumulative exposure was the highest in the HDq12 which showed the lowest incidence (3.4%).

- Venous thromboembolic events

Table 22 DME: TEAEs of venous thromboembolic events through Week 48: number of participants (PHOTON, safety analysis set)

Preferred term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	0	3 (0.9%)	0	3 (0.6%)
Deep vein thrombosis	0	1 (0.3%)	0	1 (0.2%)
Pulmonary embolism	0	2 (0.6%)	0	2 (0.4%)

MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3 / 35

TEAE of venous thrombosis were reported in less than 1% of the participants at week 48 and 60. One non-serious and moderate in severity event of Deep vein thrombosis and two serious and severe in intensity event of pulmonary embolism were reported in the HDq12 group. None were assessed as related to study drug.

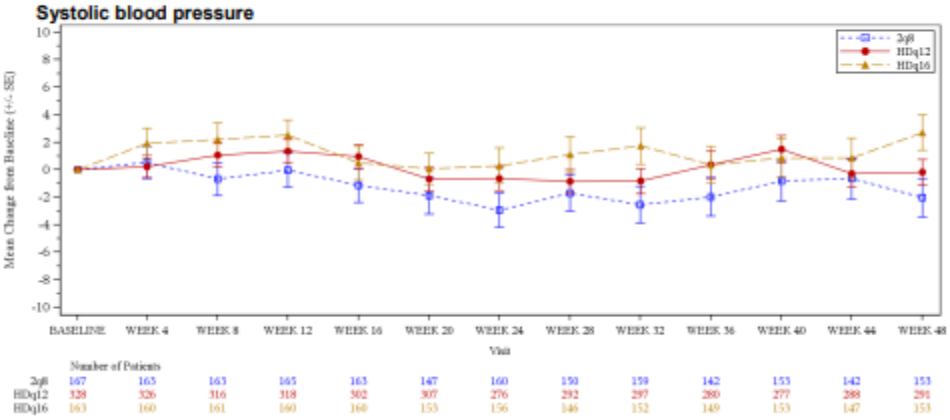
- Hypertension

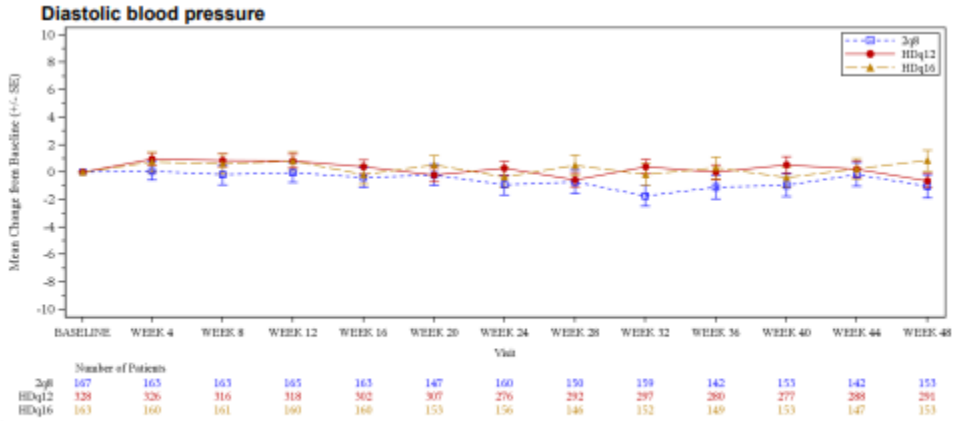
Table 23 DME: TEAEs of hypertension through Week 48: number of participants (PHOTON, safety analysis set)

Preferred term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	20 (12.0%)	36 (11.0%)	23 (14.1%)	59 (12.0%)
Blood pressure increased	3 (1.8%)	8 (2.4%)	4 (2.5%)	12 (2.4%)
Hypertension	16 (9.6%)	27 (8.2%)	20 (12.3%)	47 (9.6%)
Hypertensive crisis	1 (0.6%)	0	0	0
Hypertensive emergency	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Hypertensive urgency	1 (0.6%)	0	1 (0.6%)	1 (0.2%)
Labile hypertension	0	1 (0.3%)	0	1 (0.2%)
White coat hypertension	0	0	1 (0.6%)	1 (0.2%)

MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.3 / 32

Figure 5 DME: Mean change from baseline in systolic and diastolic blood pressure (mmHg) by visit through Week 48 (PHOTON, safety analysis set)





SE = standard error
See Definition of terms for treatment arms description.
Source: Module 5.3.5.1, PHOTON W48 CSR, Figures 14.3.5.1.1 and 14.3.5.1.2

More than 75% of the patient had medical history of hypertension. In the SOC "Vascular disorders" the most reported PT was "Hypertension" with a higher incidence in the group HDq16 (12.3% vs 8.2% in the HDq12 group and 9.6% in the 2q8 group at week 48 and with similar tendencies at week 60). The majority of the events were non-serious and mild or moderate in severity. At week 48 and 60, the majority of the patient who reported a TEAE of hypertension had reported medical history of hypertension and similar proportions were reported between all groups. Variation in mean change from baseline in systolic and diastolic blood pressure through week 48 and week 60 were clinically not significant.

As hypertension is a listed event for aflibercept administered by IV although at a much higher posology, the topic is actually followed through the PSUR and that a difference could be observed up to week 60, the Applicant further discussed on the topic of Hypertension with the newly proposed regimen. At week 96, incidences were comparable in PHOTON (2q8: 16.2 %, all HD 17.3 %). Proportion of patients with medical history of hypertension was similar with and without hypertension event although higher blood pressures at baseline were higher in HD group (PHOTON: 138.3 mmHg (SBP)/78.8 mmHg (DBP) vs 133.1 mmHg (SBP)/74.6 mmHg (DBP)). Onset of hypertension TEAEs over time (up to week 60) were well distributed and is not in favour of a correlated aflibercept induced hypertension. Pooled mean changes in blood pressure (CANDELA/PULSAR/PHOTON) for 8 mg were lower than the baseline through week 60. Pre-defined treatment-emergent potentially clinically significant values of systolic blood pressure related to elevations and decrease were comparable or slightly higher in the all HD group for both PULSAR and PHOTON. Furthermore, the risk of hypertension is currently monitored through the PSUR.

- Non-ocular haemorrhage and Nasal mucosal findings

Table 24 DME: TEAEs of non-ocular hemorrhage through Week 48: number of participants (PHOTON, safety analysis set)

Preferred term MedDRA Version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of participants with at least one such adverse event	6 (3.6%)	5 (1.5%)	2 (1.2%)	7 (1.4%)
Blood loss anaemia	1 (0.6%)	0	0	0
Contusion	3 (1.8%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Gastrointestinal haemorrhage	0	0	1 (0.6%)	1 (0.2%)
Haematoma	0	1 (0.3%)	0	1 (0.2%)
Haematoma muscle	0	1 (0.3%)	0	1 (0.2%)
Incision site haemorrhage	0	1 (0.3%)	0	1 (0.2%)
Retroperitoneal haematoma	0	1 (0.3%)	0	1 (0.2%)
Shock haemorrhagic	0	0	1 (0.6%)	1 (0.2%)
Subarachnoid haemorrhage	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Vein rupture	0	1 (0.3%)	0	1 (0.2%)
Vessel puncture site haematoma	1 (0.6%)	0	0	0

MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
Source Module 5.3.5.3, PH-42761, Table 3.3.1.3 / 34

At week 48, higher proportions of non-ocular haemorrhage were reported in the 2q8 group with the most reported PT being "Contusion" (1.8% in the 2q8 group, all event were mild or moderate). Events were for the majority non serious, mild or moderate and none were assessed as related to study drug. Serious TEAE were reported in low and similar proportions (less than 1% of the participants) in 2q8 group and HDq12 group.

One event of non-serious and moderate blood loss anaemia was reported in a patient in the 2q8 group. The patient was discontinued of the study due to serious TEAE all assessed as not related to aflibercept 2 mg (malnutrition, Post procedural infection, Multiple organ dysfunction syndrome, Cholecystitis acute). No participants reported nasal mucosal events.

2.5.7.4. Laboratory findings

No clinically relevant findings in the mean or median changes from baseline in PULSAR and PHOTON were observed. Furthermore, no significant trend in vital signs or ECG in any of the two studies were observed.

2.5.7.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.5.7.6. Safety in special populations

2.5.7.6.1. Subgroup analysis

The Applicant provided ocular and non-ocular by age, sex, ethnicity, geographic region and medical history (hypertension, cardiovascular disease, and ischemic heart disease, renal and hepatic impairment) for PULSAR and PHOTON. For both studies, at week 48 and 60, differences could be observed for ocular adverse events and non-ocular TEAE with higher proportions for HDq12 by categories of age and for the Japan subgroups

(10% in PULSAR and 20% in PHOTON of included patients were Asian). However, taking into account the low number of participants included in the subgroups, these results should be interpreted with caution. For other analysed subgroups, no safety concerns can be raised regarding the submitted data for both studies.

2.5.7.6.2. Bilateral therapy

In CANDELA, a small proportion of patients received bilateral treatment which consisted of a population in HD group with higher proportion of history of nAMD in the fellow eye (54.5%), medical history of hypertension (81.8% vs 40.5%), medical history of CVA stroke (compared to IAI bilateral 9.1% vs 0%) and moderate renal impairment (18.2% vs 4.8%). In PULSAR and PHOTON, ≤20% and ≥50% of the patients received bilateral therapy with aflibercept 2 mg in the fellow eye.

In PULSAR, less than 20% of the patient received bilateral treatment in the pooled HD group. The population consisted of patient with higher proportion of patient aged ≥75 years old and with a medical history of nAMD in the fellow eye (46.5% in bilateral all HD group). The bilateral population also had slightly higher proportion of medical history hypertension (70% vs 65.5 % in HDq12), medical history of CVA stroke (11.6% vs 8.1% in all HD group) and renal impairment (20% vs 15.3% in HDq12). Furthermore, a higher proportion of vitreous detachment (16.3% vs 6.6%) and cataract operation (36.4% vs 21.5%) were observed in all HD group. Regarding non-ocular medical history, comparable proportions were reported between unilateral and bilateral treated patients. Higher proportions were reported for the bilateral treatment for the SOC Musculoskeletal and connective tissue disorders (higher in all HD 39.5% vs 31.6%) and Nervous system disorders (28.7% vs 18.8%).

While frequencies of ocular TEAEs were similar between groups, a higher frequency of non-ocular TEAE was reported (62.0%% for bilateral vs 50.9% for unilateral) in the HD group. The most reported ocular TEAE in bilateral group (more than 5%) consisted of Cataract (higher in 2q8), Punctate keratitis (HDq16 only), Retinal pigment epithelial tear (higher in HDq12), subretinal fluid (higher in HDq12), Vitreous floaters (higher in 2q8) and IOP increased (higher in HDq12).

Table 39 AMD: Ocular TEAEs in the study eye by uni- vs bilateral treatment through Week 48: number of participants (PULSAR, safety analysis set)*

	Unilateral treatment				Bilateral treatment			
Primary system organ class Preferred term MedDRA version 25.0	2q8 N=258 (100%)	HDq12 N=275 (100%)	HDq16 N=269 (100%)	All HD N=544 (100%)	2q8 N=78 (100%)	HDq12 N=60 (100%)	HDq16 N=69 (100%)	All HD N=129 (100%)
Number (%) of subjects with a least one such adverse event	96 (37.2%)	107 (38.9%)	100 (37.2%)	207 (38.1%)	34 (43.6%)	22 (36.7%)	27 (39.1%)	49 (38.0%)
Eye disorders	80 (31.0%)	95 (34.5%)	87 (32.3%)	182 (33.5%)	30 (38.5%)	19 (31.7%)	24 (34.8%)	43 (33.3%)
Age-related macular degeneration	0	4 (1.5%)	2 (0.7%)	6 (1.1%)	1 (1.3%)	1 (1.7%)	1 (1.4%)	2 (1.6%)
Cataract	6 (2.3%)	11 (4.0%)	9 (3.3%)	20 (3.7%)	4 (5.1%)	1 (1.7%)	3 (4.3%)	4 (3.1%)
Dry eye	4 (1.6%)	4 (1.5%)	2 (0.7%)	6 (1.1%)	0	1 (1.7%)	3 (4.3%)	4 (3.1%)
Eye irritation	0	1 (0.4%)	2 (0.7%)	3 (0.6%)	0	0	2 (2.9%)	2 (1.6%)
Macular oedema	6 (2.3%)	1 (0.4%)	7 (2.6%)	8 (1.5%)	2 (2.6%)	0	0	0
Macular thickening	3 (1.2%)	5 (1.8%)	5 (1.9%)	10 (1.8%)	0	2 (3.3%)	1 (1.4%)	3 (2.3%)
Neovascular age-related macular degeneration	2 (0.8%)	6 (2.2%)	6 (2.2%)	12 (2.2%)	0	1 (1.7%)	1 (1.4%)	2 (1.6%)
Ocular hypertension	0	2 (0.7%)	2 (0.7%)	4 (0.7%)	1 (1.3%)	0	2 (2.9%)	2 (1.6%)
Photopsia	1 (0.4%)	2 (0.7%)	1 (0.4%)	3 (0.6%)	2 (2.6%)	0	1 (1.4%)	1 (0.8%)
Posterior capsule opacification	1 (0.4%)	0	2 (0.7%)	2 (0.4%)	0	2 (3.3%)	0	2 (1.6%)
Punctate keratitis	4 (1.6%)	1 (0.4%)	0	1 (0.2%)	0	0	4 (5.8%)	4 (3.1%)

For non-ocular TEAEs the most reported SOC (more than 10%) in bilateral group consisted of Vascular disorders (10.9% in all HD group vs 5.0%), Musculoskeletal and connective tissue disorders, injury poisoning and procedural complication (10% vs 4.0% in HDq12) and Infection and Infestations.

Table 40 AMD: Non-ocular TEAEs by uni- vs bilateral treatment through Week 48: number of participants (PULSAR, safety analysis set)*

	Unilateral treatment				Bilateral treatment			
Primary system organ class Preferred term MedDRA version 25.0	2q8 N=258 (100%)	HDq12 N=275 (100%)	HDq16 N=269 (100%)	All HD N=544 (100%)	2q8 N=78 (100%)	HDq12 N=60 (100%)	HDq16 N=69 (100%)	All HD N=129 (100%)
Number (%) of subjects with at least one such event	137 (53.1%)	139 (50.5%)	138 (51.3%)	277 (50.9%)	41 (52.6%)	36 (60.0%)	44 (63.8%)	80 (62.0%)
Blood and lymphatic system disorders	4 (1.6%)	1 (0.4%)	1 (0.4%)	2 (0.4%)	2 (2.6%)	0	0	0
Anaemia	3 (1.2%)	1 (0.4%)	1 (0.4%)	2 (0.4%)	2 (2.6%)	0	0	0
Cardiac disorders	13 (5.0%)	5 (1.8%)	13 (4.8%)	18 (3.3%)	2 (2.6%)	3 (5.0%)	3 (4.3%)	6 (4.7%)
Arrhythmia	2 (0.8%)	0	1 (0.4%)	1 (0.2%)	0	1 (1.7%)	1 (1.4%)	2 (1.6%)
Endocrine disorders	0	0	0	0	0	1 (1.7%)	2 (2.9%)	3 (2.3%)
Hypothyroidism	0	0	0	0	0	1 (1.7%)	1 (1.4%)	2 (1.6%)
Gastrointestinal disorders	24 (9.3%)	30 (10.9%)	24 (8.9%)	54 (9.9%)	6 (7.7%)	4 (6.7%)	5 (7.2%)	9 (7.0%)
Gastrooesophageal reflux disease	0	1 (0.4%)	3 (1.1%)	4 (0.7%)	1 (1.3%)	1 (1.7%)	1 (1.4%)	2 (1.6%)
Vomiting	1 (0.4%)	1 (0.4%)	4 (1.5%)	5 (0.9%)	1 (1.3%)	0	2 (2.9%)	2 (1.6%)
General disorders and administration site conditions	13 (5.0%)	9 (3.3%)	6 (2.2%)	15 (2.8%)	0	3 (5.0%)	5 (7.2%)	8 (6.2%)
Fatigue	4 (1.6%)	1 (0.4%)	0	1 (0.2%)	0	0	2 (2.9%)	2 (1.6%)
Oedema peripheral	1 (0.4%)	1 (0.4%)	0	1 (0.2%)	0	1 (1.7%)	1 (1.4%)	2 (1.6%)
Immune system disorders	1 (0.4%)	2 (0.7%)	2 (0.7%)	4 (0.7%)	0	0	2 (2.9%)	2 (1.6%)
Seasonal allergy	1 (0.4%)	0	0	0	0	0	2 (2.9%)	2 (1.6%)
Infections and infestations	52 (20.2%)	63 (22.9%)	61 (22.7%)	124 (22.8%)	21 (26.9%)	10 (16.7%)	16 (23.2%)	26 (20.2%)
Asymptomatic COVID-19	3 (1.2%)	5 (1.8%)	6 (2.2%)	11 (2.0%)	1 (1.3%)	2 (3.3%)	2 (2.9%)	4 (3.1%)
COVID-19	6 (2.3%)	8 (2.9%)	16 (5.9%)	24 (4.4%)	5 (6.4%)	2 (3.3%)	5 (7.2%)	7 (5.4%)
Nasopharyngitis	13 (5.0%)	10 (3.6%)	14 (5.2%)	24 (4.4%)	2 (2.6%)	2 (3.3%)	0	2 (1.6%)
Urinary tract infection	5 (1.9%)	7 (2.5%)	9 (3.3%)	16 (2.9%)	4 (5.1%)	0	1 (1.4%)	1 (0.8%)
Injury, poisoning and procedural complications	22 (8.5%)	13 (4.7%)	15 (5.6%)	28 (5.1%)	3 (3.8%)	6 (10.0%)	2 (2.9%)	8 (6.2%)
Contusion	2 (0.8%)	2 (0.7%)	2 (0.7%)	4 (0.7%)	1 (1.3%)	2 (3.3%)	0	2 (1.6%)
Fall	4 (1.6%)	0	2 (0.7%)	2 (0.4%)	1 (1.3%)	2 (3.3%)	0	2 (1.6%)
Metabolism and nutrition disorders	14 (5.4%)	5 (1.8%)	10 (3.7%)	15 (2.8%)	4 (5.1%)	3 (5.0%)	4 (5.8%)	7 (5.4%)
Hyponatraemia	0	0	2 (0.7%)	2 (0.4%)	2 (2.6%)	0	0	0
Musculoskeletal and connective tissue disorders	30 (11.6%)	25 (9.1%)	23 (8.6%)	48 (8.8%)	7 (9.0%)	7 (11.7%)	7 (10.1%)	14 (10.9%)
Arthralgia	4 (1.6%)	5 (1.8%)	5 (1.9%)	10 (1.8%)	1 (1.3%)	2 (3.3%)	2 (2.9%)	4 (3.1%)
Back pain	12 (4.7%)	10 (3.6%)	11 (4.1%)	21 (3.9%)	3 (3.8%)	2 (3.3%)	2 (2.9%)	4 (3.1%)
Osteoarthritis	2 (0.8%)	1 (0.4%)	2 (0.7%)	3 (0.6%)	0	0	2 (2.9%)	2 (1.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (4.3%)	10 (3.6%)	11 (4.1%)	21 (3.9%)	5 (6.4%)	3 (5.0%)	3 (4.3%)	6 (4.7%)
Basal cell carcinoma	1 (0.4%)	1 (0.4%)	2 (0.7%)	3 (0.6%)	1 (1.3%)	1 (1.7%)	1 (1.4%)	2 (1.6%)
Nervous system disorders	17 (6.6%)	17 (6.2%)	17 (6.3%)	34 (6.3%)	4 (5.1%)	6 (10.0%)	4 (5.8%)	10 (7.8%)
Headache	6 (2.3%)	4 (1.5%)	6 (2.2%)	10 (1.8%)	0	2 (3.3%)	1 (1.4%)	3 (2.3%)
Psychiatric disorders	2 (0.8%)	3 (1.1%)	3 (1.1%)	6 (1.1%)	0	1 (1.7%)	5 (7.2%)	6 (4.7%)
Anxiety	0	0	1 (0.4%)	1 (0.2%)	0	0	3 (4.3%)	3 (2.3%)
Skin and subcutaneous tissue disorders	9 (3.5%)	9 (3.3%)	6 (2.2%)	15 (2.8%)	1 (1.3%)	3 (5.0%)	4 (5.8%)	7 (5.4%)
Dermatitis	0	2 (0.7%)	1 (0.4%)	3 (0.6%)	0	2 (3.3%)	1 (1.4%)	3 (2.3%)
Vascular disorders	9 (3.5%)	16 (5.8%)	11 (4.1%)	27 (5.0%)	3 (3.8%)	6 (10.0%)	8 (11.6%)	14 (10.9%)
Hypertension	6 (2.3%)	12 (4.4%)	8 (3.0%)	20 (3.7%)	2 (2.6%)	2 (3.3%)	5 (7.2%)	7 (5.4%)
Hypotension	0	0	0	0	0	2 (3.3%)	1 (1.4%)	3 (2.3%)

Footnotes to Table 40 AMD: Non-ocular TEAEs by uni- vs bilateral treatment through Week 48: number of participants (PULSAR, safety analysis set)*

MedDRA=medical dictionary for regulatory activities, N = number of participants in a group, uni = unilateral; SOC = system organ class

*Non-ocular TEAEs where the frequency of a preferred term is >1 participant in the bilaterally treated All HD group

See Definition of terms for treatment arms description.

The bilateral treatment group includes all participants with at least one anti-VEGF treatment in the fellow eye during study. All adverse events are considered, including the ones that occurred before first fellow eye injection

The unilateral treatment group includes all participants without anti-VEGF treatment in the fellow eye during study.

Source: Module 5.3.5.3, PH-42761, Table 3.3.1.1/7

Serious ocular TEAE in bilateral were slightly higher in HDq12 group between groups and compared to unilateral (3.3% vs 1.5%) while proportions for serious non-ocular TEAE were comparable. Higher proportions of ocular TEAE related to study drug were reported in 2q8 (1.6% vs 6.4%) and HDq12 (5.5% vs 8.3%) and one non-ocular study drug related TEAE was reported in 2q8. AESI (Cataract, Hypertension, IOP, non-ocular haemorrhage, APCT) were reported in slightly higher proportion in bilateral therapy for HD group. Other events such as IOI, retinal tear/detachment, nasal mucosal events were reported in low and comparable proportions (all event occurred in one patient).

In PHOTON, more than half of the patients received bilateral treatment (either aflibercept HD or 2q8 in the study eye and aflibercept 2q8 in the fellow eye) in PHOTON (61.7% in the 2q8 group; 61.0% in HDq12 and 62.0% in HDq16 at week 48). The population who received bilateral therapy consisted of patients with a higher proportion of female in the HDq16 group compared to unilateral 42.6% vs 33.9%), aged below 65 years old, a higher Hemoglobin A1c > 8% (Pooled HD group: 41.7% vs 32.8%), baseline DRSS ≥ 53 (Pooled HD group: 25.2% vs. 11.6%) , higher medical history of cataract in HDq12 (37.3% vs 29.9%) and 2q8 (39.8% vs 23.4%) for bilateral therapy but well balanced between groups. Regarding non-ocular medical history, proportions were comparable between unilateral and bilateral treated population or lower for the bilateral in SOC Cardiac disorders (19.2% vs 23.8%) and Vascular disorders (76.8% vs 82.0% in all HD group).

Ocular TEAEs were slightly more reported in the HDq12 and HDq16 groups (33.8% and 30.7% respectively) compared to the unilaterally treated population and the bilaterally treated 2q8 group. PT of "Conjunctival haemorrhage" in 2q8 and HDq16 groups and "Diabetic retinal oedema" and "Vitreous floaters" in the HDq12 group were reported in higher incidence in the bilaterally treated population. Furthermore, PT reported in ≥5% of the patients receiving bilateral treatment were "Cataract" (HDq16 group), "Conjunctival haemorrhage" (2q8 and HDq16 group), "Punctate keratitis" (HDq16 group) and "Vitreous floaters" (HDq12 group).

Table 25 DME: Ocular TEAEs in the study eye by uni- vs bilateral treatment through Week 48: number of participants (PHOTON, safety analysis set)*

Primary system organ class Preferred term MedDRA version 25.0	Unilateral treatment				Bilateral treatment			
	2q8 N=64 (100%)	HDq12 N=127 (100%)	HDq16 N=62 (100%)	All HD N=189 (100%)	2q8 N=103 (100%)	HDq12 N=201** (100%)	HDq16 N=101 (100%)	All HD N=302 (100%)
Number (%) of subjects with at least one such adverse event	20 (31.3%)	36 (28.3%)	17 (27.4%)	53 (28.0%)	26 (25.2%)	68 (33.8%)	31 (30.7%)	99 (32.8%)
Eye disorders	18 (28.1%)	32 (25.2%)	16 (25.8%)	48 (25.4%)	23 (22.3%)	62 (30.8%)	30 (29.7%)	92 (30.5%)
Cataract	1 (1.6%)	2 (1.6%)	3 (4.8%)	5 (2.6%)	1 (1.0%)	3 (1.5%)	5 (5.0%)	8 (2.6%)
Cataract nuclear	0	0	1 (1.6%)	1 (0.5%)	2 (1.9%)	1 (0.5%)	0	1 (0.3%)
Cataract subcapsular	0	0	0	0	1 (1.0%)	3 (1.5%)	0	3 (1.0%)
Conjunctival haemorrhage	1 (1.6%)	5 (3.9%)	1 (1.6%)	6 (3.2%)	5 (4.9%)	9 (4.5%)	5 (5.0%)	14 (4.6%)
Corneal erosion	0	0	0	0	0	0	2 (2.0%)	2 (0.7%)
Diabetic retinal oedema	1 (1.6%)	1 (0.8%)	1 (1.6%)	2 (1.1%)	2 (1.9%)	8 (4.0%)	2 (2.0%)	10 (3.3%)
Eye irritation	0	0	0	0	1 (1.0%)	2 (1.0%)	2 (2.0%)	4 (1.3%)
Eye pain	3 (4.7%)	3 (2.4%)	0	3 (1.6%)	1 (1.0%)	4 (2.0%)	1 (1.0%)	5 (1.7%)
Ocular hypertension	0	0	0	0	1 (1.0%)	4 (2.0%)	0	4 (1.3%)
Macular oedema	1 (1.6%)	1 (0.8%)	1 (1.6%)	2 (1.1%)	1 (1.0%)	2 (1.0%)	0	2 (0.7%)
Photopsia	0	0	0	0	0	2 (1.0%)	1 (1.0%)	3 (1.0%)
Punctate keratitis	0	1 (0.8%)	1 (1.6%)	2 (1.1%)	1 (1.0%)	4 (2.0%)	5 (5.0%)	9 (3.0%)
Retinal exudates	0	0	0	0	2 (1.9%)	1 (0.5%)	1 (1.0%)	2 (0.7%)
Retinal haemorrhage	0	0	2 (3.2%)	2 (1.1%)	1 (1.0%)	0	4 (4.0%)	4 (1.3%)
Visual acuity reduced	1 (1.6%)	1 (0.8%)	1 (1.6%)	2 (1.1%)	2 (1.9%)	2 (1.0%)	0	2 (0.7%)
Visual impairment	0	2 (1.6%)	0	2 (1.1%)	1 (1.0%)	2 (1.0%)	2 (2.0%)	4 (1.3%)
Vitreous detachment	0	3 (2.4%)	1 (1.6%)	4 (2.1%)	2 (1.9%)	8 (4.0%)	2 (2.0%)	10 (3.3%)
Vitreous floaters	3 (4.7%)	5 (3.9%)	1 (1.6%)	6 (3.2%)	1 (1.0%)	11 (5.5%)	2 (2.0%)	13 (4.3%)
Vitreous haemorrhage	0	2 (1.6%)	1 (1.6%)	3 (1.6%)	1 (1.0%)	3 (1.5%)	0	3 (1.0%)
General disorders and administration site conditions	0	0	0	0	0	3 (1.5%)	0	3 (1.0%)
Injection site pain	0	0	0	0	0	2 (1.0%)	0	2 (0.7%)
Injury, poisoning and procedural complications	0	1 (0.8%)	0	1 (0.5%)	2 (1.9%)	3 (1.5%)	1 (1.0%)	4 (1.3%)
Corneal abrasion	0	1 (0.8%)	0	1 (0.5%)	2 (1.9%)	2 (1.0%)	1 (1.0%)	3 (1.0%)
Investigations	4 (6.3%)	3 (2.4%)	1 (1.6%)	4 (2.1%)	3 (2.9%)	4 (2.0%)	0	4 (1.3%)
Intraocular pressure increased	3 (4.7%)	3 (2.4%)	1 (1.6%)	4 (2.1%)	3 (2.9%)	4 (2.0%)	0	4 (1.3%)

MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
* Ocular TEAEs in the study eye where the frequency of a preferred term is >1 participant in any group in the bilaterally treated participants.
** One participant reporting an injection on the Fellow Eye Electronic Data Capture (EDC) page but with missing laterality is included.
The bilateral treatment group includes all participants with at least one anti-VEGF treatment in the fellow eye during study.
All adverse events are considered, including the ones that occurred before first fellow eye injection. The unilateral treatment group includes all participants without anti-VEGF treatment in the fellow eye during study.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.1 / 3

Non ocular TEAEs in the HD group treated bilaterally were reported in comparable proportions (54.0% vs 56.1% in all HD group). Incidence were slightly lower in the all HD bilateral group regarding the SOC Cardiac disorders (4.6% vs 6.9%) and for the HDq12 group (4.0% vs 8.7%) but incidence was slightly higher in the HDq16 bilateral group (5.9% vs 3.2%). In the SOC Vascular disorders, incidences were lower in the all HD bilateral group (11.6% vs 13.9%) and the HDq16 group (9.9% vs 22.6%) and higher for the 2q8 and HDq12 group (14.6% vs 6.3% and 12.4% vs 9.4% respectively). Regarding the PT "Hypertension", differences were observed in the 2q8 group and HDq12 group with higher incidence for the bilateral population (12.6% vs 4.7% and 10.9% vs 3.9%). For the SOC Nervous system disorders, differences were observed with higher incidence in the 2q8 group and HDq16 group bilaterally treated (11.7% vs 4.7% and 11.9 vs 6.5% respectively). Serious ocular TEAE in bilateral treatment arms were low and comparable (none in the HDq16 group). Non ocular serious TEAE were higher in 2q8 in bilateral (19.4% vs 9.4%) but in comparable proportions for HD group. Study drug related TEAE (ocular and non-ocular) were reported with low incidence in the bilateral HD group. One study drug related non ocular related (Lacunar infarction) was reported in HDq16. AESI such as Cataract, IOP, APTC events and Hypertension were reported in slightly higher incidence in HDq12 group in bilateral. No

case of injection related cataract were reported. A difference can be observed for ATE between HDq12 and HDq16 (4.8% vs 3.9 in unilateral and 7.9% vs 3.0% in bilateral).

Table 26 DME: Non-ocular TEAEs by uni- vs bilateral treatment through Week 48: number of subjects (PHOTON, safety analysis set)*

Primary system organ class Preferred term MedDRA version 25.0	Unilateral treatment				Bilateral treatment			
	2q8 N=64 (100%)	HDq12 N=127 (100%)	HDq16 N=62 (100%)	All HD N=189 (100%)	2q8 N=103 (100%)	HDq12 N=201 (100%)	HDq16 N=101 (100%)	All HD N=302 (100%)
Number (%) of subjects with at least one such adverse event	28 (43.8%)	68 (53.5%)	38 (61.3%)	106 (56.1%)	51 (49.5%)	106 (52.7%)	57 (56.4%)	163 (54.0%)
Blood and lymphatic system disorders	3 (4.7%)	5 (3.9%)	4 (6.5%)	9 (4.8%)	3 (2.9%)	3 (1.5%)	5 (5.0%)	8 (2.6%)
Anaemia	2 (3.1%)	4 (3.1%)	4 (6.5%)	8 (4.2%)	1 (1.0%)	2 (1.0%)	3 (3.0%)	5 (1.7%)
Cardiac disorders	5 (7.8%)	11 (8.7%)	2 (3.2%)	13 (6.9%)	8 (7.8%)	8 (4.0%)	6 (5.9%)	14 (4.6%)
Atrial fibrillation	2 (3.1%)	1 (0.8%)	0	1 (0.5%)	2 (1.9%)	0	0	0
Coronary artery disease	1 (1.6%)	1 (0.8%)	1 (1.6%)	2 (1.1%)	2 (1.9%)	1 (0.5%)	1 (1.0%)	2 (0.7%)
Myocardial infarction	1 (1.6%)	1 (0.8%)	1 (1.6%)	2 (1.1%)	1 (1.0%)	3 (1.5%)	0	3 (1.0%)
Ear and labyrinth disorders	1 (1.6%)	1 (0.8%)	0	1 (0.5%)	2 (1.9%)	2 (1.0%)	1 (1.0%)	3 (1.0%)
Vertigo	1 (1.6%)	1 (0.8%)	0	1 (0.5%)	2 (1.9%)	2 (1.0%)	1 (1.0%)	3 (1.0%)
Gastrointestinal disorders	3 (4.7%)	11 (8.7%)	7 (11.3%)	18 (9.5%)	9 (8.7%)	17 (8.5%)	16 (15.8%)	33 (10.9%)
Constipation	0	0	1 (1.6%)	1 (0.5%)	0	3 (1.5%)	1 (1.0%)	4 (1.3%)
Diarrhoea	0	3 (2.4%)	2 (3.2%)	5 (2.6%)	1 (1.0%)	2 (1.0%)	4 (4.0%)	6 (2.0%)
Food poisoning	0	0	0	0	0	2 (1.0%)	2 (2.0%)	4 (1.3%)
Gastrooesophageal reflux disease	1 (1.6%)	1 (0.8%)	2 (3.2%)	3 (1.6%)	0	6 (3.0%)	2 (2.0%)	8 (2.6%)
Nausea	0	2 (1.6%)	0	2 (1.1%)	1 (1.0%)	2 (1.0%)	3 (3.0%)	5 (1.7%)
Vomiting	0	0	0	0	0	1 (0.5%)	2 (2.0%)	3 (1.0%)
General disorders and administration site conditions	3 (4.7%)	4 (3.1%)	4 (6.5%)	8 (4.2%)	5 (4.9%)	7 (3.5%)	6 (5.9%)	13 (4.3%)
Oedema peripheral	1 (1.6%)	0	0	0	1 (1.0%)	1 (0.5%)	2 (2.0%)	3 (1.0%)
Pyrexia	0	1 (0.8%)	0	1 (0.5%)	3 (2.9%)	2 (1.0%)	3 (3.0%)	5 (1.7%)
Hepatobiliary disorders	0	3 (2.4%)	3 (4.8%)	6 (3.2%)	4 (3.9%)	1 (0.5%)	4 (4.0%)	5 (1.7%)
Cholelithiasis	0	1 (0.8%)	0	1 (0.5%)	2 (1.9%)	0	2 (2.0%)	2 (0.7%)
Infections and infestations	9 (14.1%)	23 (18.1%)	15 (24.2%)	38 (20.1%)	27 (26.2%)	40 (19.9%)	22 (21.8%)	62 (20.5%)
COVID-19	2 (3.1%)	10 (7.9%)	8 (12.9%)	18 (9.5%)	3 (2.9%)	9 (4.5%)	9 (8.9%)	18 (6.0%)
COVID-19 pneumonia	0	1 (0.8%)	1 (1.6%)	2 (1.1%)	2 (1.9%)	2 (1.0%)	0	2 (0.7%)
Cellulitis	0	1 (0.8%)	1 (1.6%)	2 (1.1%)	3 (2.9%)	0	1 (1.0%)	1 (0.3%)
Gangrene	0	0	0	0	2 (1.9%)	0	0	0
Influenza	0	1 (0.8%)	0	1 (0.5%)	2 (1.9%)	3 (1.5%)	0	3 (1.0%)
Localised infection	0	1 (0.8%)	0	1 (0.5%)	0	2 (1.0%)	1 (1.0%)	3 (1.0%)
Nasopharyngitis	1 (1.6%)	5 (3.9%)	2 (3.2%)	7 (3.7%)	5 (4.9%)	5 (2.5%)	5 (5.0%)	10 (3.3%)
Pneumonia	2 (3.1%)	2 (1.6%)	1 (1.6%)	3 (1.6%)	1 (1.0%)	3 (1.5%)	0	3 (1.0%)
Sepsis	0	1 (0.8%)	0	1 (0.5%)	2 (1.9%)	0	0	0
Sinusitis	0	0	0	0	0	4 (2.0%)	1 (1.0%)	5 (1.7%)
Tooth infection	0	1 (0.8%)	1 (1.6%)	2 (1.1%)	0	0	2 (2.0%)	2 (0.7%)
Upper respiratory tract infection	0	0	0	0	0	3 (1.5%)	1 (1.0%)	4 (1.3%)
Urinary tract infection	1 (1.6%)	3 (2.4%)	0	3 (1.6%)	4 (3.9%)	1 (0.5%)	5 (5.0%)	6 (2.0%)
Injury, poisoning and procedural complications	6 (9.4%)	9 (7.1%)	6 (9.7%)	15 (7.9%)	6 (5.8%)	12 (6.0%)	7 (6.9%)	19 (6.3%)
Fall	0	0	1 (1.6%)	1 (0.5%)	1 (1.0%)	2 (1.0%)	1 (1.0%)	3 (1.0%)
Humerus fracture	0	0	0	0	2 (1.9%)	1 (0.5%)	0	1 (0.3%)

Muscle strain	0	1 (0.8%)	0	1 (0.5%)	0	2 (1.0%)	0	2 (0.7%)
Rib fracture	0	1 (0.8%)	0	1 (0.5%)	0	2 (1.0%)	0	2 (0.7%)
Investigations	4 (6.3%)	11 (8.7%)	4 (6.5%)	15 (7.9%)	7 (6.8%)	12 (6.0%)	11 (10.9%)	23 (7.6%)
Blood glucose increased	0	0	1 (1.6%)	1 (0.5%)	0	2 (1.0%)	0	2 (0.7%)
Urine protein/creatinine ratio increased	0	0	0	0	0	0	2 (2.0%)	2 (0.7%)
Blood creatine phosphokinase increased	0	0	0	0	2 (1.9%)	0	0	0
Blood pressure increased	1 (1.6%)	4 (3.1%)	1 (1.6%)	5 (2.6%)	2 (1.9%)	4 (2.0%)	3 (3.0%)	7 (2.3%)
Protein urine present	0	1 (0.8%)	0	1 (0.5%)	0	0	3 (3.0%)	3 (1.0%)
SARS-CoV-2 test positive	1 (1.6%)	1 (0.8%)	0	1 (0.5%)	1 (1.0%)	3 (1.5%)	0	3 (1.0%)
Metabolism and nutrition disorders	6 (9.4%)	9 (7.1%)	11 (17.7%)	20 (10.6%)	14 (13.6%)	17 (8.5%)	7 (6.9%)	24 (7.9%)
Dehydration	0	0	0	0	0	2 (1.0%)	1 (1.0%)	3 (1.0%)
Diabetic ketoacidosis	0	0	0	0	2 (1.9%)	0	0	0
Diabetes mellitus	0	3 (2.4%)	5 (8.1%)	8 (4.2%)	5 (4.9%)	3 (1.5%)	0	3 (1.0%)
Hypercholesterolaemia	0	2 (1.6%)	1 (1.6%)	3 (1.6%)	1 (1.0%)	4 (2.0%)	2 (2.0%)	6 (2.0%)
Hyperglycaemia	0	0	0	0	2 (1.9%)	2 (1.0%)	0	2 (0.7%)
Hyperkalaemia	0	1 (0.8%)	2 (3.2%)	3 (1.6%)	0	1 (0.5%)	2 (2.0%)	3 (1.0%)
Hyperlipidaemia	0	0	1 (1.6%)	1 (0.5%)	0	2 (1.0%)	1 (1.0%)	3 (1.0%)
Hyponatraemia	2 (3.1%)	1 (0.8%)	1 (1.6%)	2 (1.1%)	2 (1.9%)	0	0	0
Iron deficiency	0	0	0	0	2 (1.9%)	0	0	0
Musculoskeletal and connective tissue disorders	6 (9.4%)	10 (7.9%)	6 (9.7%)	16 (8.5%)	9 (8.7%)	18 (9.0%)	6 (5.9%)	24 (7.9%)
Arthralgia	1 (1.6%)	1 (0.8%)	2 (3.2%)	3 (1.6%)	2 (1.9%)	1 (0.5%)	2 (2.0%)	3 (1.0%)
Arthritis	0	0	0	0	1 (1.0%)	2 (1.0%)	0	2 (0.7%)
Back pain	0	2 (1.6%)	0	2 (1.1%)	1 (1.0%)	5 (2.5%)	2 (2.0%)	7 (2.3%)
Nervous system disorders	3 (4.7%)	8 (6.3%)	4 (6.5%)	12 (6.3%)	12 (11.7%)	13 (6.5%)	12 (11.9%)	25 (8.3%)
Cerebrovascular accident	0	1 (0.8%)	1 (1.6%)	2 (1.1%)	0	1 (0.5%)	3 (3.0%)	4 (1.3%)
Diabetic neuropathy	0	0	0	0	1 (1.0%)	4 (2.0%)	0	4 (1.3%)
Headache	1 (1.6%)	5 (3.9%)	1 (1.6%)	6 (3.2%)	3 (2.9%)	5 (2.5%)	3 (3.0%)	8 (2.6%)
Neuropathy peripheral	0	0	0	0	2 (1.9%)	1 (0.5%)	2 (2.0%)	3 (1.0%)
Transient ischaemic attack	0	0	0	0	0	2 (1.0%)	0	2 (0.7%)
Renal and urinary disorders	4 (6.3%)	9 (7.1%)	7 (11.3%)	16 (8.5%)	7 (6.8%)	11 (5.5%)	5 (5.0%)	16 (5.3%)
Acute kidney injury	2 (3.1%)	3 (2.4%)	3 (4.8%)	6 (3.2%)	2 (1.9%)	2 (1.0%)	0	2 (0.7%)
Chronic kidney disease	0	0	2 (3.2%)	2 (1.1%)	3 (2.9%)	4 (2.0%)	1 (1.0%)	5 (1.7%)
Renal impairment	0	0	0	0	1 (1.0%)	0	2 (2.0%)	2 (0.7%)
Respiratory, thoracic and mediastinal disorders	4 (6.3%)	6 (4.7%)	5 (8.1%)	11 (5.8%)	3 (2.9%)	8 (4.0%)	4 (4.0%)	12 (4.0%)
Acute respiratory failure	2 (3.1%)	1 (0.8%)	2 (3.2%)	3 (1.6%)	2 (1.9%)	0	0	0
Cough	0	0	0	0	0	2 (1.0%)	2 (2.0%)	4 (1.3%)
Pulmonary embolism	0	0	0	0	0	2 (1.0%)	0	2 (0.7%)
Skin and subcutaneous tissue disorders	4 (6.3%)	6 (4.7%)	5 (8.1%)	11 (5.8%)	3 (2.9%)	7 (3.5%)	5 (5.0%)	12 (4.0%)
Skin ulcer	2 (3.1%)	2 (1.6%)	1 (1.6%)	3 (1.6%)	2 (1.9%)	1 (0.5%)	0	1 (0.3%)
Vascular disorders	4 (6.3%)	12 (9.4%)	14 (22.6%)	26 (13.8%)	15 (14.6%)	25 (12.4%)	10 (9.9%)	35 (11.6%)
Hypertension	3 (4.7%)	5 (3.9%)	12 (19.4%)	17 (9.0%)	13 (12.6%)	22 (10.9%)	8 (7.9%)	30 (9.9%)

MedDRA=Medical Dictionary for Regulatory Activities, TEAE=Treatment-emergent adverse event.
See Definition of terms for treatment arms description.
* Ocular TEAEs in the study eye where the frequency of a preferred term is >1 participant in any group in the bilaterally treated participants
The bilateral treatment group includes all subjects with at least one anti-VEGF treatment in the fellow eye during study. All adverse events are considered, including the ones that occurred before first fellow eye injection.
The unilateral treatment group includes all subjects without anti-VEGF treatment in the fellow eye during study.
Source: Module 5.3.5.3, PH-42761, Table 3.3.1.1 / 9

In particular, results for nAMD bilaterally treated population (PULSAR) must be interpreted with caution considering the low group size compared to DME treated population (PHOTON).

The Applicant also provide data from PK simulation bilateral treatment 8 mg + 2 mg which simulate the worst-case scenario (bilateral 8+2 mg IVT aflibercept administered every 4 weeks (q4) through 56 weeks) although it may not represent bilateral exposure in PULSAR and PHOTON. The simulation shows accumulation of free aflibercept in plasma after three initial monthly dose (AUC 2.60 mg*day/L for nAMD and 2.89 mg*day/L for DME) and with no further dose accumulation beyond week 8-12. Additionally, free aflibercept being slowly absorbed from the eye into the systemic circulation after IVT administration, no increase in blood pressure is expected. However, as discussed in the Pharmacokinetic section it is to be noted that the model tends to overpredictive and may in particular lead to imprecisions in estimation of free aflibercept.

Additionally, data on bilateral therapy with 8 mg are missing. In general practice, the Applicant explain that the most expected regimen of administration while be bilateral exposure with initial treatment and maintenance schedule which consist of 3 initial monthly injection in the active eye followed by a maintenance dose of 12 weeks after the last monthly injection and in the fellow eye (already treated eye) of a maintenance dose with HD aflibercept every 12 weeks. This is justified by the Applicant that the clinical presentation with bilateral newly diagnosed CI-DME or nAMD is relatively uncommon (Mathenge 2014, Adrian et al. 2022, Dhoot et al. 2023).

2.5.7.6.3. Exposure during pregnancy and lactation

Regarding use in pregnancy and lactation, in non-clinical trials, the absence of safety margin with this new formulation in animal study (see non clinical assessment) was observed and available clinical safety data with aflibercept, which are limited, concluded with a potential signal of spontaneous abortion/pregnancy loss that needs to be followed carefully. According to the procedure PSUSA of aflibercept (EMEA/H/C/PSUSA/00010020/202211) which is ongoing, the labelling of paragraph "breastfeeding" in section 4. was updated in line with the EMA conclusions.

2.5.7.7. Immunological events

ADA analysis set and NAb analysis set consisted of n=793 (ADA) and n=786 (NAb) for nAMD (PULSAR study) and 541 (ADA) and 541 (NAb) for DME (PHOTON). In both nAMD and DME indication, more than 90% of the patients were ADA negative and low proportions of patients had pre-existing immunogenicity. No treatment-boosted ADA was observed, and all treatment-emergent responses were low titer (< 1000). Furthermore, no relevant impact of treatment-emergent ADAs on the safety profile were observed.

2.5.7.8. Safety related to drug-drug interactions and other interactions

No drug interaction studies were conducted with HD aflibercept.

2.5.7.9. Discontinuation due to adverse events

In PULSAR, the proportions of ocular and non-ocular TEAE leading to discontinuation were low and similar between treatment groups at week 48 and 60 and in HD group solely "Retinal haemorrhage" occurred in more than one patient. One serious event of "Retinal detachment" was recorded at week 48 but not at week 60, the MAH was requested to explain the difference (see OC in Clinical AR).

In PHOTON, two ocular events lead to study discontinuation, Iritis (moderate in severity, study drug related) and Visual impairment (moderate in severity), both in the HDq12 group. Non ocular TEAE leading to study discontinuation were reported in similar proportion between 2q8 group and all HD group. Most events were reported in single participants.

Up to week 96, in PULSAR and PHOTON, 68.1% (n=689) and 80.9% (n=534) respectively of the randomized patients (n=1009) completed Week 96. The main reasons of withdrawal in both studies were due to withdrawal of consent by the patient (5.1% in PULSAR and 5.2% in PHOTON) and proportions were comparable between arm regarding reasons for not completing the study.

2.5.7.10. Post marketing experience

No post-marketing data are available for HD aflibercept. Most recent post-marketing data on the approved aflibercept 2 mg is available in the latest version of the PSUSA/00010020/202211.

2.5.8. Discussion on clinical safety

This submission for aflibercept HD 8 mg (114.3 mg/mL) summarize the 48 week and 60 week safety data for two phase 3 studies PULSAR (nAMD) and PHOTON (DME) as well as 44 week safety data for the phase 2 study CANDELA (nAMD). The objective was to demonstrate the non-inferiority of aflibercept 8 mg (70µL of 114.3 mg/mL), every 12 or 16 weeks compared to aflibercept 2 mg (50 µL of 40 mg/mL), every 8 weeks. The safety analysis set consisted of 1009 patients in PULSAR and 106 patients in CANDELA for nAMD indication and 658 patients in PHOTON for DME indication. More than 90% of the patients in both nAMD and DME studies completed up to week 60 for PHOTON and PULSAR (both ongoing) and up to week 44 for CANDELA (completed). The Applicant also provided as requested in the LoQ efficacy and safety data up to 96 weeks all patients in PHOTON and approximately 80% in PULSAR.

In PULSAR, at week 60, patients received in 2q8, HDq12 and HDq16 respectively 8.5, 6.9 and 6.0 injections. In CANDELA, the mean number of injections at week 16 in both group (all HD and IAI) was of 5.8. Overall, in PULSAR the mean total amount of aflibercept injected into the study eye up to week 60 was three times higher in the HD group. In PHOTON, up to week 60 patients received in 2q8, HDq12 and HDq16 respectively 10.0, 7.0 and 6.0 injections. Up to week 96, the mean number of injections were respectively in the 2q8, HDq12 and HDq16 treatment groups 12.8, 9.8 and 8.2 for PULSAR and 13.8, 9.5 and 7.8 for PHOTON.

The dosing regimen for HD group in PULSAR and PHOTON was of respectively 3 monthly injections followed by a maintenance phase with 12 or 16 weeks intervals. Considering the higher exposure, the Applicant provided further discussion on the efficacy and on the safety profile of the HDq12 and HDq16 groups in the initiation phase for PULSAR and PHOTON phase in which all treatment arms received active monthly injection with either 2 mg or 8 mg aflibercept at day 1, week 4 and week 8. Although exposures to aflibercept in the HD treatment arms in both PULSAR and PHOTON studies were higher during the loading phase and that the incidence of ocular TEAE in the 2q8 arms in both groups were disparate, safety data are still reassuring and in favour of a comparable safety profile with ocular and non-ocular TEAE being reported in similar range between both studies. No consistent trend could be observed in both studies. In both phase 3 studies, patients in HDq12 and HDq16 were eligible for dose interval shortening (to a minimum of HDq8) starting from week 12 or 16 or extension (by 4-week increments: HDq20) starting from week 52. This is further discussed in the *Efficacy s*ection. The majority of the patients more than >75% in PULSAR and more than 90% in PHOTON maintained their dosing regimen. In PULSAR, less than 10% of the HDq12 participants shortened to HDq8 and 38.5% of the patients in HDq16 extended to HDq20 at week 60. In PHOTON, a total of 34.2% in HDq16 extended to HDq20 and 14.5% shortened to HDq12 or HDq8. In the fellow eye, slightly less patients received treatment in HD group (18.5% vs 20.2 % at week 60) in PULSAR while similar proportions were observed between groups in CANDELA and PHOTON.

As the patient with an HDq20 interval regimen are less exposed, no worsening of the safety profile is expected. Safety data for HDq8 were submitted and compared to not modified HDq12/Hdq16 and 2q8. No consistent trend could be observed for higher reported ocular and non-ocular TEAE and the safety profile seems similar to the known safety profile of aflibercept 2 mg. In PHOTON in particular, lower ocular TEAE rates were reported. Up to week 96, the majority of the patient had a treatment interval of ≥ 12 weeks (all HD 87.1% PULSAR and 92.9% in PHOTON) and ≥ 16 weeks (all HD 69.2% PULSAR and 72.4% in PHOTON) and more than 40% of the patient in both studies had extended to q20 (46.6% in PULSAR and 44.8% in PHOTON). Proportion of

patient shortened to HDq8 were higher for PULSAR (21.3% in all HD group) compared to PHOTON (10.6% in all HD group) and with a similar trend for proportions of patients in HDq8 regimen which were low in both studies and higher in nAMD population (13.1% in PULSAR and 7.3% in PHOTON).

Regarding demographic characteristic and medical history in nAMD and DME, differences could be observed in both populations between HD group and 2q8. This is further discussed in *Efficacy* section. Overall, the Applicant was requested to further discuss the clinical relevance of the observed differences regarding demographic characteristics and reported medical history for nAMD and DME population in Efficacy section.

In both AMD and DME studies, prior and concomitant treatments were reported in similar proportions and the most reported ATC in both indications were consistent with medical history.

Overview of TEAE

- **nAMD**

For nAMD, comparable proportion for ocular and non-ocular TEAE were observed in PULSAR up to week 48 and 60. The most reported ocular TEAEs for the study eye consisted of "Visual acuity reduced", "Cataract", and "Retinal haemorrhage" which are very common/common listed ADR of Eylea 2 mg. Ocular TEAEs were for the majority mild or moderate. Severe TEAE were reported in low and similar proportions with retinal detachment, solely, being reported in more than one patient. Reported ocular TEAEs are consistent with the known safety profile of aflibercept (2mg), slight differences can be observed between all HD and 2q8 groups (for the PT nAMD) but also between HDq16 and HDq12 (for the PT Visual acuity reduced, Vitreous detachment, Vitreous floaters and Macular oedema) however incidences in the HDq12 arm were comparable to 2q8 or lowest although exposure is the highest and observed incidences remains below or in the same range as compared to the frequency listed for EYLEA 2 mg. Up to week 96, similar tendencies could be observed for ocular TEAE with slightly lower incidence in the HD group (53.6% in 2q8 vs 50.5§ in all HD). Most reported ocular PT were consistent with the known safety profile of aflibercept and incidences were comparable except for cataract (listed ADR and important identified safety concern for aflibercept) however this could be explained by the reported medical history of cataract being higher in the HD group and comparable proportions were reported when looking at all PT related to cataract.

Regarding non-ocular TEAE in PULSAR at week 48 and 60, more than half of the patient in all group reported at least one non-ocular TEAE. The most reported PT were "Infection and Infestations", "Gastrointestinal disorders", "Musculoskeletal and connective tissues disorders" and "Vascular disorders" (Hypertension being more reported in HDq12). Incidences between PT were overall comparable although slight differences could be observed. Non-ocular TEAE were mostly mild to moderate in severity and severe non-ocular TEAE were more reported in the 2q8 group. Lower incidences were reported in the HDq12 arm in which exposure is the highest which does not seem in favour of a dose related effect. Additionally, these differences could be explained by the higher incidences of medical history of hypertension and psychiatric disorders. When looking per TEAE (SOC gastrointestinal disorders), events were low or reported in single patients. Up to week 96, similar tendencies could be observed.

Up to week 48 and week 60, comparable proportions for study drug-related TEAE, IVT injection-procedure and protocol-required procedure were reported between 2q8 and all HD groups. However, ocular study drug related TEAE in study eye were reported in slightly higher incidence in HDq12. Incidence of ocular study drug related TEAEs (PT) in the study eye in all HD group were low (<1% at week 60) and consisted of Visual Acuity reduced, IOP increased and Retinal pigment epithelial tear (all reported in more than one patient). Non-ocular study

drug related TEAE were reported in similar proportions between groups and PT reported in more than one patient was "Cerebrovascular accident" for non-ocular TEAE (in 2q8 group). Incidences of ocular TEAE related to IVT procedure were slightly higher in 2q8 group and differences could be observed between HDq12 and HDq16. However, incidences in HDq12 (highest exposure) were lower or comparable to observed incidences in 2q8. The majority of the events were reported in single patients. The most reported PT for ocular TEAE assessed as related to IVT were "Conjunctival haemorrhage", "Vitreous floaters» and "Sensation of foreign body". Non-ocular TEAE assessed as related to IVT injection were reported in the HD group only (in solely one patient in each HD group) and consisted of chest pain, cerebral ischemia, head discomfort, headache, trigeminal neuralgia and hypertension. The Applicant provided the narratives of the cases and all event were majorly non serious, resolved, mild to moderate in intensity and with no drug change. Ocular and non-ocular TEAE assessed as protocol-specified procedure related were low (less than 1%) and comparable between groups. The most reported PT consisted of "Corneal abrasion" for ocular TEAE and "Nausea" and "Vomiting" for non-ocular TEAE. Up to week 96, similar tendencies could be observed.

The proportion of patients presenting serious TEAE were low in rate and slightly higher in the 2q8 than in the HD group and similar tendencies were observed up to week 96 (2.8% in all HD group vs 1.2% in 2q8 group). Proportions of TEAE leading to study discontinuation were similar and low between groups. Ocular serious TEAE were reported in low proportions (<2%) with a slightly higher frequency in the HD group at both week 48 and 60. Reported ocular SAE at week 48 and 60 occurring in n≥2 were "Retinal haemorrhage" (in both HD groups) and "IOP increased" (in HDq12). The majority of serious ocular TEAE in the study eye were moderate in intensity. Ocular serious TEAE assessed as drug study related at week 60 was "Angle closure glaucoma" (1 in HDq16). Ocular serious TEAEs assessed as IVT injection procedure related in HD group were "Angle closure glaucoma", "Skin laceration" and "IOP increased". Non-ocular serious TEAE were observed in similar proportions with comparable frequency between groups for each reported SOCs at week 48 and 60. Non-ocular serious TEAE assessed as drug related occurred in 6 patients (2 in HDq16 and 4 in 2q8). The most reported serious TEAE assessed as study related was "Cerebrovascular accident" (n=2) observed in 2q8. Additionally, one event of "Chest pain" in HDq12 was attributed to anxiety and assessed as injection and procedure related and resolved on the same day. The majority of serious non-ocular TEAE were moderate in severity. The proportions of ocular and non-ocular TEAE leading to discontinuation were low and similar between treatment groups at week 48 and 60 and in HD group solely "Retinal haemorrhage" occurred in more than one patient. Most reported serious non-ocular PT were consistent with underlying conditions and no similar trends were seen between both studies.

Regarding AESI (IOI, IOP, retinal tear/detachment, hypersensitivity, ATE, VTE, non-ocular haemorrhage, nasal mucosal findings), these events were reported in comparable proportions between treatment arms and no concern were raised from the analysis of the submitted data compared to the known profile for Eylea 2 mg. Higher incidence of Cataract were observed up to week 96 (9.1% in all HD group vs 6.5% 2q8 for PULSAR). Cataract is listed in the SmPc of Eylea 2 mg (common: 8%) and Eylea 8 mg (common: 4%) and is an important identified safety concern in the RMP of Eylea. Up to week 96, no cases of Endophthalmitis, ocular vasculitis and occlusive retinitis were reported for all HD group and for retinal pigment epithelial tear which was more reported in the HDq12 group (all events occurred in the initiation phase) the reported rate of 1.8% is in line with the pooled incidence found in previous studies in AMD (VIEW 1/VIEW 2) which was 1.6%. At week 96, for ATE events, incidences were low and similar proportions were reported in both studies (ATEs 4.8% 2q8 and 5.3% all HD group for PULSAR).

In PULSAR, less than 20% of the patient received bilateral treatment in the pooled HD group. Participants receiving bilateral treatment in HD group had slightly higher proportion of medical history hypertension, CVA/stroke, renal impairment vitreous detachment, cataract operation, nervous system disorders and Musculoskeletal and connective tissue disorders. Non-ocular TEAEs were reported in higher proportion for the HD group. The most reported SOC (more than 10%) in bilateral group consisted of Vascular disorders (10.9% in all HD group vs 5.0%), Musculoskeletal and connective tissue disorders, injury poisoning and procedural

complication (10% vs 4.0% in HDq12) and Infection and Infestations. Serious ocular TEAE in bilateral were slightly higher in HDq12 group between groups and compared to unilateral. AESI (Cataract, Hypertension, IOP, non-ocular haemorrhage, APCT) were reported in slightly higher proportion in bilateral therapy for HD group. These results must be interpreted with caution considering the low group size.

- DME

At week 48 and 60, TEAE in PHOTON were more reported in HD group (60.9% in all HD group vs 57.5% in 2q8 at week 60) as ocular TEAE in study eye and non–ocular TEAE were more reported in HD group. Similar tendencies were observed at week 96. The most reported PT for ocular TEAE in the study eye were IOP increased, Conjunctival haemorrhage, vitreous floaters, retinal haemorrhage, and Cataract (all three more reported in HDq16 or HDq12 groups) all known and listed ADR of Eylea 2 mg. Comparable proportions were observed between the 2q8 and HDq12 arms, comparable or higher proportion were reported in the fellow eye. Ocular TEAE in the study eye were for the majority mild in severity and with a higher incidence in the HDq16 group. Reported ocular TEAEs were consistent with the known safety profile of aflibercept and underlying conditions. The most reported non-ocular TEAE (more than 10%) were the SOC Infections and infestations, Vascular disorders (slightly more reported in HDq16), Gastrointestinal disorders and Metabolism and nutrition disorders. Events were either reported majorly in single patients or could be due to a higher medical history for these SOCs being reported in HDq16 arm Non-ocular TEAE were for the majority mild (higher incidence in HDq16) or moderate in severity.

Study drug related TEAE were ocular TEAE for the majority and reported in less than 2% of the patients and proportions were similar between all HD group and 2q8 group. The only TEAE reported in more than one patient up to week 48 and 60 was IOP increase and one non-ocular study drug related 'Lacunar infarction" was reported in HDq16 group (bilateral treatment, resolved, no recurrence observed). IVT injection related TEAE were ocular TEAE and protocol procedure related TEAE (none in HDq16) were non-ocular TEAE for the majority and reported in comparable proportion between HDq12 and 2q8 groups. Ocular IVT-injection-related TEAEs were reported in more than 2 patients in all groups for Conjunctival haemorrhage, Eye pain, IOP increased and Vitreous floaters. Non-ocular IVT-injection-related TEAEs in the HD group only (3 patients 0.6% in all HD group at week 60) and consisted of Nausea, Vomiting and Headache. Ocular TEAEs related to other protocol-specified procedures in the study eye were reported in low proportions and in the HDq12 group only (Conjunctival haemorrhage and Injection site irritation). Non-ocular TEAEs related to other protocol-specified procedures were reported in low proportions included Nausea, Vessel puncture site haematoma, Contrast media allergy, Post procedural pruritus, Rash, and Vein rupture. Up to week 96, similar tendencies could be observed.

Serious TEAE were slightly higher in 2q8 group. Serious ocular TEAE were for the majority mild to moderate in severity while serious non-ocular TEAE were for the majority moderate to severe. Serious ocular TEAE consisted in HD group of Cataract subcapsular, IOP increased, Retinal detachment and vitreous haemorrhage. All were moderate or severe in severity, resolved and one event IOP increased was assessed as IVT injection related. Up to week 96, serious ocular TEAE were low in rate and proportions were similar in PHOTON (1.2%). In both PHOTON and PULSAR, most serious TEAE were reported in single patients (except for cataract (n=2 HDq16), retinal detachment (n=5 all HD group), retinal hemorrhage (n=4 all HD group) and IOP increase (n=2 HDq12) for PULSAR and vitreous detachment (n=2 HDq16) for PHOTON)).

Serious non-ocular TEAE were slightly less reported in the HDq16 group compared to other treatment arms. Serious non-ocular TEAEs were primarily reported in the SOC of Cardiac disorders with comparable incidence between groups at week 60. The SOC Nervous system disorders were reported in higher proportion in the HDq16 group (3.7%) and the PT Cerebrovascular accident was reported with higher incidence in HDq16 of

which none were assessed as drug related and incidences in the HDq12 arm and 2q8 arm were similar. Up to week 96, lower proportions were observed in PHOTON (2q8: 25.1, all HD: 23.2%) with PT majorly reported in single patients. Most reported serious non-ocular PT were consistent with underlying conditions and no similar trends were seen between both studies.

TEAE leading to discontinuation were more reported in the HDq12 group and consisted for the majority of non-ocular TEAE (all reported in single participants in similar proportion between groups). Two events, one case of Iritis (study drug related) and Visual impairment, both moderate in severity. A total of 18 deaths occurred in PHOTON up to week 60. All deaths were associated to an SAE and none were considered as related to study drug or study procedure. The most reported SOC was Cardiac disorders (3 deaths in each group at week 60*).* The cause of death was unknown for 2 patients in HDq12 group and for one patient in HDq12 (patients had cardiovascular risk factors and the chronology was not in favour of a causality). Up to week 96, incidences of deaths were lower in the HD group (4.7% vs 5.4% 2q8 in PHOTON).

AESI (IOI, IOP increased, hypersensitivity, VTE) were reported in comparable proportion between treatment arms and no safety concerns overall were raised from the submitted data. Other events such as Cataract were reported in higher incidence in HDq16. Similar tendencies were observed up to week 96, incidence of cataract was 7.5% in all HD vs 3.6% for 2q8 for PHOTON. Higher proportions of TEAE were also seen for subtypes of cataract (cataract cortical, cataract nuclear and cataract subcapsular) but when looking at pooled data slightly lower or comparable proportions were reported between all HD and 2q8 groups (frequency uncommon for all in SmPc Eylea 8 mg). Cataract is listed in the SmPc of Eylea 2 mg (common: 8%) and Eylea 8 mg (common: 4%) and is an important identified safety concern in the RMP of Eylea. Up to week 96, no cases of Endophthalmitis, ocular vasculitis and occlusive retinitis were reported for all HD group in PHOTON and overall incidence of IOI events are low and comparable between arms. Concerning IOP increase although comparable proportions were reported between all HD and 2q8, pre-dose IOP (≥25 mmHg and ≥10 mmHg) were reported in higher incidence in HD group no relevant clinical differences could be observed regarding mean change in pre-injection IOP. IOP incidence was highest in the 2q8 arm in which there was the lowest aflibercept exposure in the compared to HDq12 and HDq16. For APTC and ATE events, while incidences were low, higher proportions were reported in HDq16 group. Although ATE events were more reported in the HDq16 group and 2q8 group than in the HDq12 group (6.7% vs 6.0% vs 3.4% respectively), the cumulative exposure was the highest in the HDq12 which showed the lowest incidence.

More than half of the patients received bilateral treatment in PHOTON (61.7% in the 2q8 group; 61.0% in HDq12 and 62.0% in HDq16 at week 48). The population who received bilateral therapy consisted of patients with a higher proportion of female in the HDq16 group compared to unilateral, aged below 65 years old, a higher Haemoglobin A1c > 8%, baseline DRSS ≥ 53, higher medical history of cataract in HDq12 for bilateral therapy but well balanced between groups. Regarding non-ocular medical history, proportions were comparable between unilateral and bilateral treated population or lower for the SOC Cardiac disorders and Vascular disorders. Ocular TEAEs were reported in higher incidence in HD group. Most reported PT (≥5%) in HD bilateral arms consisted of Cataract, Conjunctival haemorrhage, Punctate keratitis and vitreous floaters (all higher in HD group). Non ocular TEAEs in the HD group treated bilaterally were reported in comparable proportions. Slight differences could be observed for the SOC Cardiac disorders, Vascular disorders and Nervous system disorders. Serious ocular TEAE in bilateral treatment arms were low and comparable (none in the HDq16 group). Serious non-ocular TEAE were more reported in 2q8 group. Study drug related TEAE (ocular and non-ocular) were reported with low incidence in the bilateral HD group. One study drug related non ocular related (Lacunar infarction) was reported in HDq16. AESI such as Cataract, IOP, APTC events and Hypertension were reported in slightly higher incidence in HDq12 group in bilateral. No cases of injection related cataract were reported. A difference can be observed for ATE between HDq12 and HDq16. The Applicant also provide data from PK simulation bilateral treatment 8 mg + 2 mg which simulate the worst-case scenario (bilateral 8+2 mg IVT aflibercept administered every 4 weeks (q4) through 56 weeks) although it may not represent bilateral exposure in PULSAR and PHOTON. The simulation shows accumulation of free aflibercept in plasma after three

initial monthly dose (AUC 2.60 mg*day/L for nAMD and 2.89 mg*day/L for DME) and with no further dose accumulation beyond week 8-12. Additionally, free aflibercept being slowly absorbed from the eye into the systemic circulation after IVT administration, no increase in blood pressure is expected. However, as discussed in the Pharmacokinetic section it is to be noted that the model tends to overpredictive and may in particular lead to imprecisions in estimation of free aflibercept. In general practice, the Applicant explain that the most expected regimen of administration while be bilateral exposure with initial treatment and maintenance schedule which consist of 3 initial monthly injection in the active eye followed by a maintenance dose of 12 weeks after the last monthly injection and in the fellow eye (already treated eye) of a maintenance dose with HD aflibercept every 12 weeks. This is justified by the Applicant that the clinical presentation with bilateral newly diagnosed CI-DME or nAMD is relatively uncommon (Mathenge 2014, Adrian et al. 2022, Dhoot et al. 2023). The Applicant will assess the safety profile associated to bilateral exposure with aflibercept 114.3 mg/ml through the PSUR. Additionally, the Applicant proposed to conduct a Phase 4 PK study to assess exposure with bilateral treatment with Eylea 114.3 mg/ml as a REC (recommendation) for which results will thus be submitted by the Applicant as a PAM (post-authorization measure) or as a type II variation if appropriate. Depending on the results of the study, the Applicant committed to evaluate the need for a post-approval study.

Hypertension

As hypertension is a listed event for aflibercept administered by IV (although at a much higher posology), that the topic is actually followed through the PSUR and a difference could be observed up to week 60, the Applicant further discussed on the topic of Hypertension with the newly proposed regimen. Proportion of patients with medical history of hypertension was similar with and without hypertension event although higher blood pressures at baseline were higher in HD group (PULSAR: 141 mmHg (SBP)/77.3 mmHg (DBP) vs 133.3 mmHg (SBP)/76.4 mmHg (DBP)). In PULSAR, the lowest incidence (15,5%) was reported in HDq12 group in which the exposure is the highest. Onset of hypertension TEAEs over time (up to week 60) were well distributed and is not in favour of a correlated aflibercept induced hypertension. Pooled mean changes in blood pressure (CANDELA/PULSAR/PHOTON) for 8 mg were lower than the baseline through week 60. Pre-defined treatment-emergent potentially clinically significant values of systolic blood pressure related to elevations and decrease were comparable or slightly higher in all HD group for both PULSAR and PHOTON. Compared to previous experience with Eylea 2 mg, similar or higher incidence were observed at 1 and 2 years in the 2 mg group compared to week 60 and 96 with 8 mg (for DME 25.8 % 2 mg at 2 years vs 17.3% at week 96 for all HD and for AMD 14.7% 2 mg at 2 years vs 8.0% at week 96 for all HD). At week 96, incidences were similar in PULSAR (2q8: 7.4%, all HD 8.0%) and PHOTON (2q8: 16.2%, all HD 15.5%). Furthermore, the risk of hypertension is currently monitored through the PSUR.

Subgroup analysis

For PULSAR and PHOTON, at week 48 and 60, differences could be observed for ocular adverse events and non-ocular TEAE with higher proportions for HDq12 by categories of age and for the Japan subgroups (10% in PULSAR and 20% in PHOTON of included patients were Asian). However, taking into account the low number of participants included in the subgroups, these results should be interpreted with caution. For other analysed subgroups, no safety concerns can be raised regarding the submitted data for both studies.

Immunogenicity

In both nAMD and DME studies, the majority of the patient were ADA negative, No treatment-boosted ADA was observed, and all treatment-emergent responses were low titer (< 1000). No relevant impact of treatment-emergent ADAs on the safety profile were observed.

Use in pregnancy and lactation

In non-clinical trials, the absence of safety margin with this new formulation in animal study (see non clinical assessment and available clinical safety data with aflibercept, which are limited, concluded with a potential signal of spontaneous abortion/pregnancy loss that needs to be followed carefully. The Applicant provided further discussion on recommendation level in pregnancy which is acknowledged.

According to the procedure PSUSA of aflibercept (EMEA/H/C/PSUSA/00010020/202211) which is ongoing, the labelling of paragraph "breastfeeding" in section 4.6 was updated by the Applicant in line with the EMA conclusions.

2.5.9. Conclusions on the clinical safety

In this submission, the Applicant provided data up to 60 week for a new posology Aflibercept 8 mg in vial (114.3 mg/mL), which is 3 times higher than the marketed 2 mg (40 m/mL). The overall submitted data for the safety profile for Aflibercept 8 mg up to week 96 seems (see LoI) to be in line with the already known and established safety profile of Eylea. Some differences could be observed regarding ocular and non-ocular TEAEs in PULSAR and PHOTON which were discussed by the Applicant and no new safety concerns can be raised at this stage.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP version 33.2:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelial tears • Cataract (especially of traumatic origin)
Important potential risks	• Medication errors • Off-label use and misuse • Embryo-fetotoxicity
Missing information	• Long term safety of aflibercept in preterm infants with ROP • Exposure with bilateral 8 mg aflibercept therapy

2.6.1.1. Discussion on safety specification

The Applicant proposed the list of safety concerns presented above. In PULSAR (AMD) and PHOTON (DME), patients were treated in the fellow eye with Aflibercept 2 mg or another anti-VEGF, thus no data are actually available regarding bilateral treatment with 8 mg. The proposal of the addition of the safety concern "Exposure with bilateral 8 mg aflibercept therapy" as missing information is acceptable.

For the safety concern "Medication errors", the Applicant proposed a mock-up for the packaging of Eylea 8 mg to differentiate the two posology. The disparities between the two posology will also be highlighted in the Educational material and in the SmPC (section 4.2 and 6.6). All the proposed changes to minimize the risk of medication error by the Applicant are accepted.

For the safety concern 'off-label use and misuse", the risk of off-label use of Eylea 8mg in the other approved indication of Eylea (2 mg) is expected to be low in both the adult and paediatric population (in particular as the paediatric device is specific to the 2 mg PFS and that no data were published in this indication according to the Applicant). The safety concern is addressed in the Educational material.

No concerns are raised regarding the other safety concerns of Eylea.

2.6.1.2. Conclusions on the safety specification

At this stage, having considered the data in the safety specification it is agreed that the safety concerns listed by the applicant are appropriate.

2.6.2. Pharmacovigilance plan

- ***Routine Pharmacovigilance Activities***

Routine pharmacovigilance activities include two specific follow-up questionnaires one for endophthalmitis/intraocular inflammation, and one concerning IOP increases with the 2 mg Eylea PFS. The questionnaire for Endophthalmitis/Intraocular inflammation was updated to include the 8 mg dosage for wet AMD/DME indications (Annex 4). Furthermore, as the Eylea 8 mg 114.3 mg/ml) is available in vial only, the questionnaire specific to IOP increase with the PFS was not updated. This is acceptable.

- ***Additional Pharmacovigilance Activities***

The Applicant initially proposed a category 3 phase 4 PK study (An open-label, non-randomized, multicenter, Phase 4 Pharmacokinetic (PK) study to evaluate the systemic exposure of bilateral intravitreal administration of high dose (HD) (8 mg) aflibercept in adults with diabetic macular edema (DME) or neovascular age-related macular degeneration (nAMD)) as additional pharmacovigilance activities to assess the safety concern "Exposure with bilateral treatment of Eylea 114.3 mg/ml". However. the proposed PK study sample size is expected to provide limited information on the safety and efficacy of the HD use in patients. The proposed study will be able to inform on the PK profile of aflibercept solution 114.3 mg/mL, which could impact on safety in case of bilateral treatment as reflected in the latest proposed section 4.4 of the SmPC:

The safety and efficacy of bilateral treatment with Eylea 114.3 mg/ml per eye have not been studied (see section 5.1). If bilateral treatment is performed at the same time this could lead to an increased systemic exposure, which could increase the risk of systemic adverse events.

Thus, the proposed PK study was downgraded as a REC (recommendation) for which results will be submitted by the Applicant as a PAM (post-authorization measure) or as a type II variation if appropriate. Depending on the results of the study, the Applicant committed to evaluate the need for a post-approval study.

Overall, the safety associated with the bilateral administration with the 8 mg dosage will be monitored by the Applicant in the PSUR with a particular focus on systemic adverse effects.

In conclusion, there are no new additional pharmacovigilance activities and the ongoing or planned additional PV activities remains as follow:

Table Part III.2: On-going and planned additional PV activities

Study Status	Objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional Pharmacovigilance (PhV) activity (to address specific safety concerns or to measure effectiveness of risk minimization measures).				
Review safety outcomes of FIREFLEYE NEXT study BAY 86-5321/20275: An extension study to evaluate the long-term outcomes of subjects who received treatment for retinopathy of prematurity in Study 20090 Status: Ongoing	• Primary study objective: To evaluate long-term safety outcomes and visual function of subjects included in Study 20090 for treatment for retinopathy of prematurity (ROP) • Secondary study objective: To describe the visual function and overall development of subjects included in Study 20090 for treatment for ROP	• The purpose of the current study is to collect the missing data of the potential long-term effects after treatment with aflibercept and laser. Subjects will be followed up to 5 years of chronological age, which will enable a detailed assessment of visual function and overall development.	Protocol finalized (27 NOV 2019) LPLV: planned for OCT 2025	Interim study report: • 2-year of age data in Q2 2023 • 3-year of age data in 2024, • 4-year of age data in 2025 Final study report 2026

Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations.
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimization measures).

- ***Overall conclusions on the PhV Plan***

The PRAC 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.

2.6.3. Risk minimisation measures

- ***Routine Risk Minimisation Measures***

- ***Summary of additional risk minimisation measures***

The following risk minimisation measure in section V of the RMP version 33.2 were updated:

Medication errors	**Routine risk minimization measures:** SmPC sections 4.2, 4.9 and 6.6 Package Leaflet sections 1 and 3 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections. Packing differentiation Eylea 40 mg/ml versus Eylea 114.3 mg/ml. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video; in addition for adult indications: patient guide "Your guide to Eylea", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable. **Additional pharmacovigilance activities:** None

No other significant changes were made regarding other potential and identified risk as well as missing information in tables V.1. Considering the OC raised on the status of the PK study as a recommended post-authorisation measure (REC), changes were applied to this section and to every other concerned section of the RMP. The Applicant submitted a RMP version 33.4 which is accepted.

The Educational Material will cover all approved dosages (0.4 mg/2 mg/8 mg) and approved formats (2 mg aflibercept PFS, 2/8 mg aflibercept vial) which is similar to the conduct which was taken in procedure EMEA/H/C/002392/II/0077/G (positive approval in end of 2022). This is acceptable as the safety profile seems similar between the 2 and 8 mg and as the Applicant will highlight the differences between the two dosages including injection volume/dose, indications, packaging/labeling, and format PFS/vial.

Furthermore, a common EM will be available in case of favourable issue of this procedure and that, after CHMP opinion, EU PI for the 114.3 mg/ml will be merged to the complete Eylea EU PI. Thus Annex IID of the SmPC and Annex 6 of the RMP will have to apply to the different strengths, presentations (vial and PFS as applicable) and indications of Eylea.

However, the following key elements in bold are not applicable in the 8 mg:

- **Pre-filled syringe**, the vial and **the paediatric dosing device** are for single use only
- **Use of the paediatric dosing device is mandatory**

- **The need to properly prime the paediatric dosing device before injection "**

Therefore, the Applicant updated the Annex VI of the RMP v 33.4 and IID of the SmPC as follow (in red):

Physician information
Intravitreal injection procedure video
Intravitreal injection procedure pictogram
Patient information packs (for adult population only)

The physician information in the educational material contains the following key elements:

Techniques for the intravitreal injection including use of a 30 G needle, and angle of injection
~~Pre-filled syringe, the vial and the paediatric dosing device are for single use only~~
The vial is for single use only
The need to expel excess volume of the syringe before injecting Eylea to avoid overdose (in adult population only)
Patient monitoring after intravitreal injection including monitoring for visual acuity and increase of intraocular pressure post-injection
Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract
Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea (in adult population only)

The following key element is specific to the 40 mg/mL:

- The pre-filled syringe and paediatric dosing device are for single use only

The following key elements are specific to the ROP (retinopathy of prematurity) indication:

- Use of the paediatric dosing device is mandatory
- The need to properly prime the paediatric dosing device before injection

- ***Overall conclusions on risk minimisation measures***

The PRAC having considered the data submitted is of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.6.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 33.4 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication applied for by the MAH is for the treatment of adult patients with nAMD and DME.

The aim of new strength (aflibercept 8 mg) proposed by the MAH is to decrease the patient/healthcare professional's burden (number of visits and IVT injections, adverse events associated with the IVT injections …).

3.1.2. Available therapies and unmet medical need

Treatments of patients with nAMD and DME are initiated as soon as diagnosed by anti-VEGF marketed products in Europe (EYLEA® – aflibercept; LUCENTIS® – ranibizumab and biosimilars; BEOVU® – broculizumab; VABYSMO® – faricimab), laser photocoagulation or vitrectomy in order to stop the disease progression. Despite progress in its current treatment and management, both diseases remains incurable. Patients receiving the anti-VEGH therapy undergo specific dosing regimen with regard to the molecule used for their treatment. However, the actual dosing regimen for the anti-VEGF therapy are limited to 4 month interval in the maintenance phase.

Aflibercept is a known anti-VEGF molecule use as a standard of care in both indications (nAMD and DME).

3.1.3. Main clinical studies

The clinical development program of aflibercept consisted of three studies including two considered as pivotal and one supportive:

- Study PHOTON (21091, VGFTe-HD-DME-1934): an on-going (with data through Week 60), multi-center, randomized, double-masked, active-controlled Phase 2/3 study in participants with DME.
- Study PULSAR (20968): an on-going (with data through Week 60), multi-center, randomized, double-masked, active-controlled Phase 3 study in participants with nAMD.
- Study CANDELA (21086, VGFTe (HD)-AMD-1905): completed (supportive study), multi-centerrandomized, single-masked, active-controlled Phase 2 study in participants with nAMD.

3.2. Favourable effects

PULSAR Study (20968) is an on-going, multi-center, randomized, double-masked, active-controlled Phase 3 study in participants with nAMD (ratio 1:1:1, 2q8, HDq12, HDq16).

PHOTON study (21091, VGFTe-HD-DME-1934) is an on-going, multi-center, randomized, double-masked, active-controlled Phase 2/3 study in participants with DME (ratio 1:2:1, 2q8, HDq12, HDq16).

Both studies intend to demonstrate the non-inferiority of aflibercept 8 mg (70µL of 114.3 mg/mL), every 12 or 16 weeks compared to aflibercept 2 mg (50 µL of 40 mg/mL) and included patients accordingly to their disease.

Treatment success (primary efficacy variable), was defined with the change from baseline in BCVA (ETDRS letter score) at Week 48, completed with a key secondary endpoint of that measure at Week 60. Overall, the primary and key secondary endpoint criteria, to know, the change from baseline in BCVA measured by the ETDRS letter score at Week 48 and 60 (non-inferiority of IVT aflibercept therapy HDq12 and HDq16 dosing regimen to the current authorized IVT aflibercept therapy 2q8 dosing regimen) is considered to be statistically met (95% credible interval for treatment difference with a non-inferiority margin of 4 letters with LS mean change from baseline in BCVA to Week 48 and 60), at Week 48 and 60 for both studies.

Moreover, based on data from PULSAR (snapshot including all patients with approx. 80% completed Week 96 data collection) and on the data from all patients in PHOTON, HD aflibercept dosed every 12 weeks or every 16 weeks showed maintained efficacy through Week 96 compared to 2 mg aflibercept, consistent with the non-inferiority demonstrated at Week 48 and Week 60 with respect to improvement in BCVA in patients with nAMD or DME. Through Week 96, HD aflibercept provided improvements in mean change in CST in both nAMD and DME populations, consistent with the results reported at Week 48 and Week 60. Indeed, the preliminary Week 96 data from the PULSAR study and the full Week 96 data from PHOTON further support the proposed dosing regimens for nAMD and DME of 8 mg aflibercept administered by intravitreal injection

In both studies, a large majority of patients treated with HD aflibercept had treatment intervals of every ≥ 12 weeks and every ≥ 16 weeks which led to a clinically meaningful reduction in the number of injections for Week 96 completers. In PULSAR, the number of injections were reduced from a mean of 12.8 injections in 2q8 down to 9.8 (-23%) and to 8.2 (-36%) in HDq12 and HDq16, respectively; in PHOTON, from a mean of 13.8 in 2q8 down to 9.5 (-31%) and 7.8 (-43%) in HDq12 and HDq16, respectively.

In both studies, a high proportion of patients in the HD groups (48% and 56% respectively in the PHOTON and PULSAR HDq16 groups) extended their treatment intervals to q20 or longer while only a very few patients extended to intervals of q20 required a subsequent shortening of the treatment interval. As for the requested 2-year data, the Applicant provided exposure details for patients who extended their treatment interval to q20 or longer. Through Week 96, up to 47% and 44.3% of HD patients extended their treatment interval to q20 or longer intervals in the PULSAR and PHOTON study respectively. Numerically, this correspond to a total of 185 patients completed at least one q20 interval before Week 96 in PULSAR and 133 patients in PHOTON study

At Week 96, the proportion of patients with q20 or longer as the last intended dosing interval in the PULSAR was 36.8% in the HDq12 group and 54.9% in the HDq16 group. Of 216 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24 (i.e. 53 and 127 HD patients, respectively); only a few patients were shortened back to q16 (i.e. 3 HD patients).

For the PHOTON study, at Week 96 the proportion of patients with q20 or longer as the last intended dosing interval was 42.2% in the HDq12 group and 45.3% in the HDq16 group. Of 177 HD patients that were extended

to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24

The other secondary endpoint differs in both studies:

In PULSAR study, the proportion of participants with no IRF and no SRF in Central Subfield at Week 16 with a comparison between the 2q8 group versus pooled HD groups (HDq12 and HDq16) was assessed and the superiority appears to be statistically met for both HD groups at week 16. More long-term data were provided for this endpoint (week 48 and 60) and same tendency was observed with an absence of IRF and SRF more pronounce in the HD groups and more particularly in the HDq12 group.

In PHOTON study, the proportion of participants with a ≥2-Step improvement in DRSS Score at Week 48 was assessed and the non-inferiority appears to be statistically met only in the HDq12 group at week 48.

3.3. Uncertainties and limitations about favourable effects

The provided long term efficacy data from PULSAR and PHOTON studies are reassuring and it appears that the product dosed every 12 weeks (HDq12) or every 16 weeks (HDq16) showed maintained non-inferior efficacy through Week 96 compared to 2 mg aflibercept, consistent with the results demonstrated at Week 48 and Week 60 with respect to improvement in BCVA and CST in patients with nAMD or DME.

To be noticed also that the per-protocol population which is a key population in non-inferiority trials is somewhat questionable in PULSAR trial for it includes patients presenting with deviations to planned regimens of administration.

Finally, in response to the question about EDTRS reading process in Asian populations, the Applicant described a reading procedure but it is unclear if it was specific to Asian subjects or applied to all geographical regions. As noted above, it is anyway to be noticed that point-estimates of treatment effect go in opposite directions for Asian and Europe.

3.4. Unfavourable effects

The safety profile of Aflibercept 8 mg (114.93 mg/mL) up to week 60 in nAMD and DME indications appears comparable to the already established profile of Eylea in adults.

In nAMD, comparable proportions were reported for ocular, non-ocular TEAEs and serious TEAE. The most reported ocular TEAE consisted of "Visual acuity reduced", "Cataract" and "Retinal haemorrhage" which were mostly mild to moderate in severity. Incidences of ocular and non-ocular TEAE leading to discontinuation were low and comparable, with "Retinal haemorrhage", solely, being reported in n≥ 2 patients.

In DME, higher incidence of ocular and non-ocular TEAE were reported in HD group. Most reported ocular TEAE consisted of "Cataract", Retinal haemorrhage" and "Vitreous floaters". TEAE were mostly mild to moderate in severity. Serious TEAE were reported in comparable proportions.

Incidences were comparable for study drug-related and IVT injection-procedure TEAE in both studies. TEAE assessed as related to study drug and IVT injection were consistent with the known safety profile of Eylea.

In PULSAR, TEAEs leading to discontinuation were low and comparable. In PHOTON slightly more patients discontinued study drug in HD group.

Non-ocular TEAE were reported in comparable proportions with the most reported SOC being Vascular disorders, Infections and infestations and Gastrointestinal disorders.

A total of 14 and 1 patients died in respectively nAMD and DME studies up to week 96. Incidences of deaths were lower in the HD group in both studies (2.1% and 3.6% in PULSAR and 4.7% vs 5.4% 2q8 in PHOTON). None were assessed to aflibercept (study drug, IVT injection and protocol procedure).

AESI were in general comparable between groups in both studies and no clinically relevant laboratory findings in the mean or median changes from baseline in PULSAR and PHOTON were observed. No case of endophthalmitis were reported in both studies for HD group.

Furthermore, non-clinical data did not reveal any difference in the toxicity profile with a higher dose level. The safety margins for unilateral IVT treatment of patients with aflibercept 8 mg and IVT injection are considered significant.

Regarding immunogenicity, in both nAMD and DME studies, the majority of the patients were ADA negative, No treatment-boosted ADA was observed, and all treatment-emergent responses were low titer (< 1000). . No relevant impact of treatment-emergent ADAs on the safety profile were observed.

Additionally, the recommended duration of contraception for females of reproductive potential following the last dose of aflibercept 8 mg is 4 months (vs 3 months for Aflibercept 2 mg).

3.5. Uncertainties and limitations about unfavourable effects

At baseline, discrepancies could be observed in both nAMD and DME populations between HD group and 2q8 regarding demographic characteristics and medical history. Further discussion was provided by the Applicant to assess the clinical relevance of the observed discrepancies on both efficacy and safety data assessment (see Efficacy section).

Considering the exposure being 3 times higher compared to the already recommended dosing regimen of 2 mg every 8 weeks after a 3 monthly initiation phase, uncertainties were raised regarding the safety profile of HD aflibercept during the initiation phase. The Applicant provided discussion and although exposures to aflibercept in the HD treatment arms in both PULSAR and PHOTON studies were higher during the loading phase and that the incidence of ocular TEAE in the 2q8 arms in both groups were disparate (17,3% for 2q8 for nAMD and 2q8: 9.6% in DME), safety data are still reassuring and in favour of a comparable safety profile with ocular and non-ocular TEAE being reported in similar range between both studies. No consistent trend could be observed in both studies.

Up to week 96, the majority of the patients had a treatment interval of ≥ 12 weeks (all HD 87.1% PULSAR and 92.9% in PHOTON) and ≥ 16 weeks (all HD 69.2% PULSAR and 72.4% in PHOTON) and more than 40% of the patients in both studies had extended to q20 (46.6% in PULSAR and 44.8% in PHOTON). Proportion of patients shortened to HDq8 were higher for PULSAR (21.3% in all HD group) compared to PHOTON (10.6% in all HD group) and with a similar trend for proportions of patients in HDq8 regimen which were low in both studies and higher in nAMD population (13.1% in PULSAR and 7.3% in PHOTON). As the patients with an HDq20 interval regimen are less exposed, no worsening of the safety profile is expected. Safety data for HDq8 were submitted and compared to not modified HDq12/Hdq16 and 2q8. No consistent trend could be observed for higher reported ocular and non-ocular TEAE and the safety profile seems similar to the known safety profile of aflibercept 2 mg. In PHOTON in particular, lower ocular TEAE rates were reported. An OC was raised in regards of the PI (section 4.2).

Further discussion was also provided for the topic hypertension, a listed event for aflibercept administered by IV, as a higher proportion was seen in all HD group at week 48 and 60. However, up to week 60, incidences were similar in PULSAR (2q8: 7.4%, all HD 8.0%) and PHOTON (2q8: 16.2%, all HD 15.5%). Compared to previous experience with Eylea 2 mg, similar or higher incidences were observed at 1 and 2 year in the 2 mg group compared to week 60 and 96 with 8 mg (for DME 25.8 % 2 mg at 2 years vs 17.3% at week 96 for all HD and for AMD 14.7% 2 mg at 2 years vs 8.0% at week 96 for all HD). The risk of hypertension is currently monitored through the PSUR.

Furthermore, the Applicant provided as requested safety data up to week 96 which confirms a similar safety profile for aflibercept 8 mg compared to the known profile of 2 mg. No new safety concern can be raised. The Applicant is requested to provide additional safety data regarding relatedness and severity for ocular and non-ocular TEAEs.

Approximately ≤20% of patients in PULSAR (AMD) and ≥ 50% of patients in PHOTON (DME) received bilateral treatment in the fellow eye with aflibercept 2 mg or another anti-VEGF (exclusively in PULSAR) up to week 60. Differences could be observed regarding baseline characteristics and medical history between unilateral and bilateral treated patients and thus further discussion were provided for both studies. For nAMD population, ocular TEAE were reported with comparable incidence and non-ocular TEAE were more reported in HD group (62.0%% for bilateral vs 50.9% for unilateral). For PHOTON (DME), incidences for ocular and non-ocular TEAE were comparable but differences could be observed. AESI (Cataract, Hypertension, IOP, non-ocular haemorrhage, APCT) were reported in slightly higher proportion in bilateral therapy for HD group in both nAMD and DME. It is to be noted, that safety results for nAMD patients must be interpreted with caution considering the low group size of patients receiving bilateral therapy. Bilateral exposure is expected in clinical practice in both nAMD and DME populations, however safety data on exposure with bilateral therapy with 8 mg are currently missing. The Applicant proposed a phase 4 PK study to evaluate bilateral exposure with 8 mg aflibercept (Cmax and AUC) as a REC and the topic will also be monitored through the PSUR.

Additionally, in non-clinical trials, the observed absence of safety margin with HD aflibercept in animal study and available clinical safety data with aflibercept, which are limited, concluded with a potential signal of spontaneous abortion/pregnancy loss that needs to be followed carefully.

3.6. Effects Table

Table 4.6. Effects Table for aflibercept 8 mg (HDq12 and HDq16) versus aflibercept 2 mg (control) at 48 and 60 week.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
BCVA (primary endpoint) at 48 week	PULSAR	LS (mean (SE) from baseline in letters	Hdq12: 6.06 (0.77) HDq16: 5.89 (0.72)	2q8: 7.03 (0.74)	Statistically significant (non-inferiority).	
	PHOTON		Hdq12: 8.10 (0.61) HDq16: 7.23 (0.71)	2q8: 8.67 (0.73)	Statistically significant (non-inferiority).	
BCVA (key secondary endpoint) at 60 week	PULSAR	LS (mean (SE) from baseline in letters	Hdq12: 6.37 (0.74) HDq16: 6.31 (0.66)	2q8: 7.23 (0.68)	Statistically significant (non-inferiority).	
	PHOTON		Hdq12: 8.52 (0.63) HDq16: 7.64 (0.75)	2q8: 9.40 (0.77)	Statistically significant (non-inferiority).	
Proportion of participants with no IRF and no SRF in central subfield (key secondary endpoint)	PULSAR results at week 16	N (%)	Hdq12: 61.6 HDq16: 65	2q8: 51.6	Statistically significance of the pooled HD group (superiority).	
	PULSAR results at week 48		Hdq12: 71.1 HDq16: 66.8	2q8: 59.4	Descriptive	
	PULSAR results at week 60		Hdq12: 74.6 HDq16: 72.2	2q8: 74.6	Descriptive	
Proportion of Participants With a ⩾ 2-Step Improvement in DRSS Score (key secondary endpoint)	PHOTON results at week 48	N (%)	Hdq12: 29 HDq16: 16.6	2q8: 26.6	Statistically significant only for HDq12 (non-inferiority).	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Ocular AE	Cataract	N (%)	3.0%	2.2 %	Most reported known ADR of Eylea related to injection procedure	(1)
	Vitreous detachment		2.7%	1.6%	Most reported known ADR of Eylea related to injection procedure	(1)
	Conjunctival haemorrhage		3.0 %	2.3%	Most reported known ADR of Eylea related to injection procedure	(1)
	Visual acuity reduced		2.9%	4.5%	Most reported known ADR of Eylea	(1)
	Vitreous floaters		3.0	2.7%	Most reported known ADR of Eylea	(1)
Non-ocular AE	Hypertension	N (%)	6.2%	4.5%	Most reported non-ocular TEAE and Uncertainties on systemic exposure	(1)

Abbreviations:
Notes:
(1) Pooled 60 weeks safety data CANDELA/PULSAR/PHOTON

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The development plan of aflibercept 8 mg for the treatment of nAMD and DME subjects is based on 2 pivotal studies (PULSAR and PHOTON) and a supportive study (CANDELA), also discussed in a scientific advice.

PULSAR Study (20968) is an on-going, multi-center, randomized (1:1:1, 2q8, HDq12, HDq16), double-masked, active-controlled Phase 3 study in participants with nAMD and PHOTON study (21091, VGFTe-HD-DME-1934) is an on-going, multi-center, randomized (1:2:1, 2q8, HDq12, HDq16), double-masked, active-controlled Phase 2/3 study in participants with DME. Both studies aimed to assess the efficacy, safety, and tolerability of intravitreal 8 mg aflibercept (HDq12 and HDq16) compared to aflibercept 2 mg. Participants were treated at baseline and rescue treatment (aflibercept 8 mg with a q8 IVT injection interval) could be administrated from Week 16 in HD groups as per the defined criteria.

Treatment success (primary efficacy variable) was defined as the change from baseline in BCVA (ETDRS letter score) at Week 48, completed with a key secondary endpoint of that measure at week 60. Overall, the primary and key secondary endpoint criteria, to know, the change from baseline in BCVA measured by the ETDRS letter score at Week 48 and 60 (non-inferiority of IVT aflibercept therapy HDq12 and HDq16 dosing regimen to the current authorized IVT aflibercept therapy 2q8 dosing regimen) is considered to be statistically met (95% credible interval for treatment difference with a non-inferiority margin of 4 letters with LS mean change from baseline in BCVA to Week 48 and 60), at Week 48 and 60 for both studies.

Moreover, the Applicant provides additional new long-term data from PULSAR study where around 80% of patients completed Week 96 and PHOTON study where 100% completed Week 96. Of ongoing patients, approximately 80% (689 out of 875) had already completed the Week 96 visit and almost all had completed visits up to Week 88. Overall and based on the provided long-term data, it appears that the product dosed every 12 weeks (HDq12) or every 16 weeks (HDq16) showed maintained non-inferior efficacy through Week 96 compared to 2 mg aflibercept, consistent with the results demonstrated at Week 48 and Week 60 with respect to improvement in BCVA and CST in patients with nAMD or DME.

Regarding the need for further data to support the 5 months injection interval during the maintenance phase, the applicant provides additional new data that seems adequate to support the claimed q20 (or longer) intervals. Through Week 96, up to 47% and 44.3% of HD patients extended their treatment interval to q20 or longer intervals in the PULSAR and PHOTON study respectively. Numerically, this corresponds to a total of 185 patients completed at least one q20 interval before Week 96 in PULSAR and 133 patients in PHOTON study

At Week 96, the proportion of patients with q20 or longer as the last intended dosing interval in the PULSAR was 36.8% in the HDq12 group and 54.9% in the HDq16 group. Of 216 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24 (i.e. 53 and 127 HD patients, respectively); only a few patients were shortened back to q16 (i.e. 3 HD patients).

For the PHOTON study, at Week 96 the proportion of patients with q20 or longer as the last intended dosing interval was 42.2% in the HDq12 group and 45.3% in the HDq16 group. Of 177 HD patients that were extended to a q20 treatment interval at any time through Week 96, the majority of patients maintained on q20 or were extended even further to q24.

The other secondary endpoint differs in both studies:

In PULSAR study, the proportion of participants with no IRF and no SRF in Central Subfield at Week 16 with a comparison between the 2q8 group versus pooled HD groups (HDq12 and HDq16) was assessed and the superiority appears to be statistically met for both HD groups at week 16. More long-term data were provided for this endpoint (week 48 and 60) and same tendency was observed with an absence of IRF and SRF more pronounce in the HD groups and more particularly in the HDq12 group.

In PHOTON, despite the limitations in study design, the evaluation of DRSS was included in the study design in view of the fact that aflibercept 2 mg is in the US approved not only for the treatment of DME, but also for the treatment of DR. Therefore, evaluating the effects of aflibercept 8 mg on DRSS was considered relevant for that territory. The key secondary endpoint of the proportion of participants with a ≥ 2-step improvement in DRSS score at Week 48 was pre-specified to potentially support an indication of aflibercept 8 mg for treatment of DR in the US. This endpoint was tested with a non-inferiority margin of 15% which was met by the HDq12 arm (adjusted difference 1.98%, 95% CI -6.61, 10.57) but not by the HDq16 arm (adjusted difference -7.52%, 95% CI -16.88, 1.84). However, considering that the primary endpoint showed that BCVA improvement as a direct effect of DME treatment was non-inferior for HDq12 and HDq16 compared to 2q8, the Applicant concluded that the effect on DRSS stage improvement does not correlate with the with the effect on DME, and improvements in DRSS are not a prerequisite for vision improvements in DME.

The safety profile of Eylea 8 mg (114.93 mg/mL) up to 60 weeks and week 96 in both nAMD and DME indications appears comparable to the already established profile of Eylea. Concerns raised regarding the higher exposure with HD groups during the initiation phase, uncertainties on systemic adverse events (hypertension), need for

long-term data on systemic exposure with HD group up to 96 weeks and also on bilateral exposure were answered by the Applicant and no safety issues were raised.

3.7.2. Balance of benefits and risks

Results available from two pivotal studies (PULSAR and PHOTON) for aflibercept 8 mg showed statistical non-inferiority in treatment success rates of HDq12 and HDq16 (change in BCVA measured by EDTRS score from baseline) compared with aflibercept 2 mg up to 60 weeks after initial treatment.

The lacking and thus requested long-term efficacy data have been provided within the Applicant responses to list of questions. Based on data from PULSAR (snapshot including all patients, with approx. 80% completed Week 96 data collection) and on the data from all patients in PHOTON, HD aflibercept dosed every 12 weeks or every 16 weeks showed maintained efficacy through Week 96 compared to 2 mg aflibercept, consistent with the non-inferiority demonstrated at Week 48 and Week 60 with respect to improvement in BCVA in patients with nAMD or DME. In addition, through Week 96, HD aflibercept provided substantial improvements in mean change in CST in both nAMD and DME populations, consistent with the results reported at Week 48 and Week 60.

Given the longer intervals in the new proposed dosing regimen (HDq12 and HDq16) and limited data to support the claimed 5 months injection interval during the maintenance phase, the Applicant provides additional new data that seems adequate to support the claimed q20 (or longer) intervals. Through Week 96, up to 47% and 44.3% of HD patients extended their treatment interval to q20 or longer intervals in the PULSAR and PHOTON study respectively. Numerically, this corresponds to a total of 185 patients completed at least one q20 interval before Week 96 in PULSAR and 133 patients in PHOTON study. Overall, the results for this cohort of patients are in line with global results.

The safety profile of Eylea 8 mg appears comparable to the known safety profile of Eylea. Long term data up to week 96, safety data during the initiation phase and for patient who had shortened to HDq8 or extended HDq20 were provided by the Applicant and no concerns could be raised.

The benefit/risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall benefit/risk balance of Eylea is considered positive.

4. Recommendations

5. Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Eylea new strength is favourable in the following indication:

Eylea is indicated for the treatment of adult patients with

- neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),

- visual impairment due to diabetic macular oedema (DME) (see section 5.1).

The CHMP therefore recommends the extension of the marketing authorisation for Eylea subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change:

Variation requested		**Type**	**Annexes affected**
B.II.g.2	Introduction of a post approval change management protocol related to the finished product	II	n.a.

Extension application to add a new strength of Aflibercept 114.3 mg/ml solution for injection (in a vial), to be indicated in adults for the (1) treatment of neovascular (wet) age-related macular degeneration (nAMD) and (2) visual impairment due to diabetic macular oedema (DME), grouped with a type II variation (B.II.g.2) to introduce a post-approval change management protocol to add a new presentation for Aflibercept solution 114.3 mg/ml in a single-use pre-filled syringe for intravitreal injection.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information

being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

6. Additional risk minimisation measures

The MAH has agreed to provide EU educational material for Eylea. Prior to launch and during the product's lifecycle in each Member State the MAH will agree to the final educational material with the National Competent Authority.

The MAH ensures that, following discussions and agreement with the National Competent Authorities in each Member State where Eylea is marketed, ophthalmological clinics where Eylea is expected to be used are provided with an updated physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs (for adult population only)

The physician information in the educational material contains the following key elements:

- Techniques for the intravitreal injection including use of a 30 G needle, and angle of injection
- The vial is for single use only
- The need to expel excess volume of the syringe before injecting Eylea to avoid overdose (in adult population only)
- Patient monitoring after intravitreal injection including monitoring for visual acuity and increase of intraocular pressure post-injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea (in adult population only)

The following key element is specific to the 40 mg/ml:

- The pre-filled syringe and the paediatric dosing device are for single use only

The following key elements are specific to the ROP (retinopathy of prematurity) indication:

- Use of the paediatric dosing device is mandatory
- The need to properly prime the paediatric dosing device before injection

The patient information pack of the educational material for the adult population includes a patient information guide and its audio version. The patient information guide contains following key elements:

- Patient information leaflet
- Who should be treated with Eylea
- How to prepare for Eylea treatment
- What are the steps following treatment with Eylea
- Key signs and symptoms of serious adverse events including endophthalmitis, intraocular inflammation, intraocular pressure increased, retinal pigment epithelial tear and cataract
- When to seek urgent attention from their health care provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea