EMA/206018/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Susvimo

International non-proprietary name: ranibizumab

Procedure No. EMEA/H/C/005610/0000

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
BCVA	best corrected visual acuity
B/R	benefit/ risk
CATT	Comparison of Age-Related Macular Degeneration Treatments Trials
CCOD	clinical cut-off date
CE	Conformité Européenne (European Conformity)
CFT	central foveal thickness
CI	confidence interval
Cmax	maximum serum concentration
Cmin	minimum serum concentration
CNV	choroidal neovascularization
COVID-19	Coronavirus Disease 2019
CPT	centre point thickness
CSR	clinical study report
CST	central subfield thickness
CTD	common technical document
ETDRS	Early Treatment Diabetic Retinopathy Study
HR	hazard ratio
iDMC	independent Data Monitoring Committee
IFU	Instructions for Use
IML	inner limiting membrane
IVT	intravitreal
L	Letters
LL	lower limit
MA	macular atrophy
MAA	marketing authorization application
MDR	Medical Device Regulation
MMRM	mixed-effect model with repeated measures
nAb	neutralizing antibody
nAMD	neovascular age-related macular degeneration
NI	non-inferiority
OAT	oral anti-thrombotic
OCT	optical coherence tomography
PD	pharmacodynamics
PDS	Port Delivery System with ranibizumab
PED	pigment epithelial detachment
PK	pharmacokinetics
PopPK	population pharmacokinetics
PP	per protocol
PPPQ	Port Delivery System Patient Preference Questionnaire
PRN	pro re nata (“as needed”)
PT	preferred term
Q4W	every 4 weeks
Q24W	every 24 weeks
RCE	release control element
RPE	retinal pigment epithelium
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy

SCS	Summary of Clinical Safety
SD-OCT	spectral domain optical coherence tomography
TTFR	time to first refill
VA	visual assessor
VAE	visual acuity examiner
VEGF	vascular endothelial growth factor

1. CHMP Recommendations

Based on the review of the data on quality, safety, efficacy and the Applicant´s responses to the CHMP D120 LoQ, the application for Susvimo (PDS with ranibizumab) in the treatment of neovascular (wet) age-related macular degeneration (AMD) in adult patients is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of this major objection are provided in the List of Outstanding Issues.

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Outstanding Issues.

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

Clinical

Indication wording

The wording of the indication as it is currently proposed: "*Susvimo is indicated in adult patients for the treatment of neovascular (wet) age-related macular degeneration (AMD) who have previously responded to at least two intravitreal injections of a vascular endothelial growth factor (VEGF) inhibitor medication*" cannot be accepted.

The indication should be restricted to patients who have demonstrated an adequate response to anti-VEGF therapy and a stabilization of the disease's progression. Thus, it is considered mandatory to define responders based on clinical outcome and to incorporate this in the SmPC. Not the number of injections, but rather clinically stable disease, based on ophthalmological judgement, should be a prerequisite for treatment with the PDS. This needs to be reflected in the indication wording, e.g. as follows:

"*Susvimo is indicated in adult patients for the treatment of neovascular (wet) age related macular degeneration (AMD) who have achieved stable disease (see 4.2) after previously responding to intravitreal treatment with a vascular endothelial growth factor (VEGF) inhibitor medication.*"

In addition, in SmPC Section 4.2, „Patient selection", corresponding criteria for stable disease have to be provided. (**MO**)

Multidisciplinary

A safety memo concerning Susvimo, specifically related to the dislodgment of the septum of the port delivery system observed during clinical trials, was received from the Applicant Roche in order to share this important information with Health Authorities. The reported septum dislodgements of the implant might have a major impact on the benefit/risk of Susvimo in terms of product quality within the implant and/or release of the drug product from the implant, and on clinical efficacy and safety. Namely:

- Patients affected can no longer undergo refill-exchange and must discontinue treatment with Susvimo;
- The long-term risks of retaining vs. removing vs. replacing a PDS implant in this situation are not well characterized at this time;
- Patients concerned would likely have to switch at some stage to existing treatment for a locally approved anti-VEGF agent.

Therefore, the Applicant should:

1. Confirm that the legal manufacturer is liaising with the Notified Body and timely share any updates of this interaction;
2. Provide a risk assessment on the impact of the septum dislodgement on quality, safety and efficacy of the product and a corresponding root cause analysis.

3. Discuss potential risk mitigation measures.
4. Discuss the risk of potential issues such as the need for explantation as Patients affected might discontinue treatment
5. Provide an update to the RMP and to the SmPC.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

No request for a GMP inspection is considered necessary at the moment.

GCP inspection(s)

No request for a GCP inspection is considered necessary at the moment.

New active substance status

Based on the review of the data the active substance ranibizumab contained in the medicinal product Susvimo is not to be qualified as a new active substance in itself. Ranibizumab has previously been authorised in the European Union as Lucentis. No NAS was claimed by the Applicant.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The target indication applied for by the Applicant is for the treatment of adult patients with neovascular (wet) age-related macular degeneration (nAMD).

Age-related macular degeneration (AMD) is a chronic, progressive disease of the macula and a leading cause of central vision loss among people over the age of 50 years. nAMD (also known as choroidal neovascularization [CNV] secondary to AMD and wet AMD) is a form of advanced AMD that, if left untreated, causes rapid and severe visual loss, and remains a leading cause of visual impairment in the elderly.

2.1.2. Epidemiology

The prevalence of any AMD varies by ethnicity and racial group; however, it is greatest among individuals of European descent compared with people with Asian, African or Hispanic ancestry (Wong et al 2014). The nAMD prevalence has been found to be similar across the US (0.06% at 50-54 years to 14.6% ≥90 years) and European regions (0.04% at 50 years to 10.49% at 90 years). nAMD primarily affects the elderly population, and the prevalence increases with age (Rudnicka et al. 2012). In the next 20 years, the global population aged 60 years and older is projected to increase dramatically, resulting in a significant increase in the prevalence of nAMD from 23.47 million in 2010 to 80.44 million by 2050 (Smith 2010).

2.1.3. Aetiology and pathogenesis

nAMD is typically characterized by the development of CNV in the macula. Abnormal capillary vessels and fibrovascular membranes proliferate in regions of Bruch's membrane. The new vessels are abnormally permeable and result in accumulation of exudative fluid and hemorrhage beneath the retinal pigment epithelium and/or neurosensory retina. The fluid and hemorrhage can cause acute vision impairment and may result in permanent loss of central vision. At the end stage, fibrous metaplasia can occur, resulting in a chronic subretinal scar (Jager et al. 2008). The stimuli that result in the development of CNV remain unclear. However, there is significant experimental and clinical evidence implicating vascular endothelial growth factor (VEGF)-A in the pathogenesis of nAMD.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Common consequences of nAMD are an inability to drive, read, watch television, recognize faces, and engage in other valued daily activities. Visual impairment has many serious psychological and physical consequences; it often leads to a negative future outlook, a reduction in cognitive ability, anxiety and depression, limited physical activity, an increased risk of falls and fractures, and a need for greater assistance. Thus, nAMD has a substantial impact on older adults' every day and overall quality of life.

2.1.5. Management

Until the introduction of anti-VEGF therapy, patients with nAMD were at high risk of severe vision loss and blindness. Verteporfin photodynamic therapy (PDT) was approved in 2001 to limit the proportion of nAMD patients losing <15 letters compared to placebo. However, this treatment was not able to prevent progressive visual loss secondary to nAMD, and the availability of anti-VEGF therapy has markedly improved visual outcomes and management of nAMD (Brown et al. 2006; Rosenfeld et al. 2006; Heier et al. 2012). Anti-VEGF agents block the pathophysiological functioning of nAMD by preventing abnormal angiogenesis, and limit fluid build-up in the retina, thereby preserving vision (Rosenfield et al. 2006). Three anti-VEGF agents given via intravitreal route are currently approved for the treatment of nAMD (ranibizumab, aflibercept, and brolucizumab).

- Ranibizumab (Lucentis®): Approved 22 Jan 2007 (Product no.: EMEA/H/C/000715)
- Aflibercept (Eylea®): Approved 21 Nov 2012 (Product no.: EMEA/H/C/002392)
- Brolucizumab (Beovu®): Approved 13 Feb 2020 (Product no.: EMEA/H/C/004913)

As a chronic disease, nAMD requires life-long treatment and assessment. Intravitreal anti-VEGF injection therapy is the globally recognized standard of care treatment for nAMD. Ranibizumab was the first anti-VEGF agent proven to be more efficacious in reducing visual loss and blindness compared to other treatments such as PDT and also to improve and maintain vision when using a monthly regimen as in the FVF2587g ANCHOR study (Brown et al. 2009). After 5 injections and a gain of approximately 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, monthly ranibizumab was able to maintain the gained visual acuity throughout the 24-month duration of the study.

An important challenge for anti-VEGF therapy is the requirement for frequent administration of intravitreal injections and monitoring visits (Heier et al. 2012; CATT Research Group 2016). Indeed, many patients are treated with monthly anti-VEGF injections for nAMD control. Less-than-monthly injection regimens are possible for some patients (i.e. PRN or Treat & Extend); however, they still require frequent eye examinations and office visits to achieve the patient's best visual outcomes.

2.2. About the product

The Port Delivery System with ranibizumab (PDS) is presented as an intraocular drug delivery system that consists of an ocular implant, a customized formulation of ranibizumab (100 mg/mL), and 4 ancillary devices used to fill, insert, refill-exchange, and explant the implant. PDS is designed to continuously release the customized formulation of ranibizumab into the eye over time.

The primary mode of action of the PDS is the pharmacologic activity of the ranibizumab drug product. Ranibizumab is a recombinant humanized IgG1 k isotype monoclonal antibody (mAb) antigen-binding fragment (Fab) targeted against vascular endothelial growth factor A (VEGF-A). The ranibizumab drug substance is produced by an Escherichia coli (E. coli) expression system and purified by standard protein purification methods. It consists of a 214-residue light chain linked by a disulfide bond at its C-terminus to the 231-residue N-terminal segment of the heavy chain. Ranibizumab is not glycosylated and has a molecular mass of 48,380 Da.

The PDS devices will not be marketed separately from the ranibizumab drug product, as the drug product and devices are specifically designed to be used together to achieve the desired therapeutic result.

Ranibizumab binds to the receptor-binding site of active forms of VEGF-A, including all three biologically active isoforms (VEGF110, VEGF121, and VEGF165). VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and is thought to contribute to the progression of neovascular age-related macular degeneration (nAMD). The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

The PDS implant is intended to be permanent and is designed to continuously deliver ranibizumab (100 mg/mL) drug product to the eye and maintain the vitreous concentration of ranibizumab at therapeutic levels. The implant is intended for surgical placement through the pars plana of the eye and is designed to be refillable in situ, via an injection through the conjunctiva and through the device septum using the PDS refill needle. Prior to implantation, the implant is filled with customized ranibizumab drug product (approximately 20 µL) using the PDS initial fill needle. After placement of the implant, subsequent implant refills are performed with the PDS refill needle that allows for the simultaneous exchange of the contents of the implant (residual ranibizumab, vitreal components) with the fresh ranibizumab drug product. The mechanism of drug product release from the implant is passive, concentration gradient-driven diffusion. The porous release control element (RCE) at the distal end of the implant acts as a barrier between the implant reservoir and the vitreous humor to control the diffusion rate of ranibizumab from the implant.

According to the Applicant, the PDS was designed to address the high treatment burden and frequent monitoring visits associated with currently available intravitreal anti-VEGF agents for chronic ocular conditions requiring lifelong treatment. With 2 treatments per year (Q24W refill-exchange procedure), the PDS is presented to enable continuous delivery of ranibizumab via the implant.

The initially proposed indication for the Susvimo PDS was:

Susvimo is indicated in adult patients for the treatment of neovascular (wet) age-related macular degeneration (AMD).

The indication proposed for Susvimo does, however, not reflect the study population of the clinical development program and is thus not acceptable. In the pivotal Phase III efficacy and safety study (as well as in the two other clinical trials) only patients who had been shown to be responsive to anti-VEGF treatment were included. This needs to be reflected in the indication wording.

The Applicant agreed with the Rapporteur's request of including the requisite of being responder to intravitreal anti-VEGF inhibition for the PDS ranibizumab administration, and the labelling of the product has been changed as follows:

Susvimo is indicated in adult patients for the treatment of neovascular (wet) age-related macular degeneration (AMD) who have previously responded to at least two intravitreal injections of a vascular endothelial growth factor (VEGF) inhibitor medication.

The indication should be restricted to patients who have demonstrated an adequate response to anti-VEGF therapy and a stabilization of the disease's progression. Thus, it is considered mandatory to define responders based on clinical outcome and to incorporate this in the SmPC. Not the number of injections, but rather clinically stable disease, based on ophthalmological judgement, should be a prerequisite for treatment with the PDS. This needs to be reflected in the indication wording, e.g. as follows:

"Susvimo is indicated in adult patients for the treatment of neovascular (wet) age related macular degeneration (AMD) *who have achieved stable disease (see 4.2) after previously responding to intravitreal treatment with a vascular endothelial growth factor (VEGF) inhibitor medication*."

In addition, in SmPC Section 4.2, „Patient selection", corresponding criteria for stable disease have to be provided. **(MO)**

The recommended dose of ranibizumab is 2 mg (0.02 mL of solution) continuously delivered via the implant with refills administered every 24 weeks (approximately 6 months).

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

During the development of Susvimo, the Applicant sought Scientific Advice (SA) from the EMA SAWP/ CHMP:

In September 2019, the Applicant received SA with regard to quality development, pre-clinical development and clinical development for their Port Delivery System (PDS) with ranibizumab, a drug-device combination product which includes a customized formulation of ranibizumab (100 mg/mL), an ocular implant and four ancillary devices (insertion tool assembly, initial fill needle, refill needle, explant tool) (EMA/CHMP/SAWP/493964/2019). The PDS is designed to continuously release the customized formulation of ranibizumab into the eye over time.

The Applicant suggested obtaining the Notified Body opinion for the integral device and the CE mark certificates for the non-integral devices in parallel to the MAA review and to provide these only prior to final CHMP opinion. The CHMP recommended submitting the declaration of conformity/ notified body opinion already as part of the MAA to facilitate a smooth running of the procedure. In case the Applicant could not provide the required documentation at the time of MAA submission, the Applicant was recommended to discuss at the EMA/NCA pre-submission meeting their plans to provide the required documentation as the documentation is necessary for the adoption of a favourable CHMP opinion.

With regard to the pivotal trial GR40548 Archway, it was agreed by the CHMP that subjects enrolled should have received and been found responsive to prior treatment with anti-VEGFs. The requirement of 3 or more previous IVT injections plus a mandatory boost injection at the screening visit was supported. Furthermore, it was anticipated that this should be reflected in the label. In addition, a non-inferiority margin below 4 letters was advised. It was stressed that the overall PDS safety profile was expected to reflect the combined effects of ranibizumab, the surgical implantation procedure, the implant as such, the refill procedure, and a potential explantation procedure. Furthermore, the Applicant was advised to detail not only severity, but also durability of these SAEs and their impact on BCVA.

Overall, it was recognized that a potential advantage of the PDS is a less frequent dosing regimen. However, a superior safety profile of the PDS would have to be demonstrated before this argument could be accepted.

Furthermore, pre-submission meetings were held with the EMA, with both the Rapporteur's and the Co-Rapporteur's team.

In the meeting held with EMA in Dec 2022, the Roche proposal to follow parallel review of the MAA dossier by EMA and of the devices dossier by the Notified Body was accepted and EMA highlighted that Roche will need to provide sufficient data in the MAA regarding the performance, safety and quality aspects of the device in combination with the drug. In the meeting with the Rapporteur's team from DE-PEI held in February 2021, the Rapporteur's team acknowledged promising efficacy data, however, pointed out that the PDS safety data seem to be different from those seen with IVT injections, the differences being primarily due to the implant-/ surgical procedure-related risks. Within this context, it would be necessary to understand whether the safety profile would become more similar to IVT injections over time and to get more clarity on the safety profile of refill-exchange procedures. It was concluded that B/R has to be carefully weighted, and that it might be a critical point to decide which indication might be ideal for Susvimo.

In the meeting with the Co-Rapporteur's team from AEMPS, the Co-Rapporteur indicated that in principle the currently available data could be acceptable for the provision of a favorable B/R profile for Susvimo. However, the potential risk of overdosing for those patients who would not need a refill after 24 weeks should be addressed in the MAA submission, as well as the applicability of the PDS in comparison to the so-called Treat and Extend regimen practiced in Europe. Furthermore, the Co-Rapporteur's team stated that guidance should be given to physicians with regard to the management of patients with bilateral disease.

In both meetings, Rapporteur and Co-Rapporteur stated that the proposed indication for Susvimo might be too broad and would need to reflect the patient population in the pivotal study GR40548 (i.e. patients who responded to prior anti-VEGF treatment).

Further scientific advice meetings were held with other European agencies (AGES, FAMHP) during development of Susvimo.

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

GMP

GMP compliance has been demonstrated for all manufacturing and testing sites.

GLP

The PDS toxicology studies (with the exception of pilot rabbit Study 13-1963 and investigative surgical Study 16-0261), as well as pivotal legacy toxicology studies ranibizumab administered via intravitreal injection, were conducted in accordance with Organisation for Economic Cooperation and Development (OECD) Principles of GLP [C(97)186/Final], and were conducted in a country that is a member of the OECD Mutual Acceptance of Data program.

GCP

The Applicant declares that all studies were conducted in accordance with the principles of Good Clinical Practice (GCP) (the ICH guidelines on good clinical practice [ICH E6], the US FDA regulations, the Declaration of Helsinki [October 1996], and applicable local, state, and federal laws, as well as other applicable national legal requirements). The studies were approved by the appropriate Ethics Committees and Institutional Review Boards, were audited for GCP and were source document verified.

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

Legal basis

The legal basis for this application refers to:

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

New active substance status

Based on the review of the data the active substance ranibizumab contained in the medicinal product Susvimo is not to be qualified as a new active substance in itself. Ranibizumab has previously been authorised in the European Union as Lucentis. No NAS was claimed by the Applicant.

Orphan designation

Not Applicable.

Information on paediatric requirements

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

Neovascular age-related macular degeneration (nAMD) falls under the scope of Agency Decision CW/0001/2015 and are therefore eligible for class waivers in the context of the Port Delivery System with ranibizumab (PDS).

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

Ranibizumab is a humanised monoclonal antibody fragment produced in Escherichia coli cells by standard recombinant DNA technology and is targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to VEGF-A isoforms generated by alternative mRNA splicing (VEGF121, VEGF165, VEGF110). The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors VEGFR-1 and VEGFR-2 on the surface of endothelial cells. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, which contribute to the progression of wet age-related macular degeneration.

To differentiate between the already approved ranibizumab and the ranibizumab PDS for administration via the port delivery system, the following terms are used throughout Module 3: ranibizumab intravitreal for the commercial product and ranibizumab PDS for administration via the port delivery system (PDS).

Ranibizumab PDS has the same active pharmaceutical ingredient, ranibizumab, as commercial ranibizumab intravitreal, only differing in one formulation excipient and protein concentration (here: 100 mg/mL). The ranibizumab PDS drug substance manufacturing process was developed from the commercial ranibizumab intravitreal process and uses the same fermentation and chromatography-purification process as ranibizumab intravitreal.

The drug product is provided as a sterile liquid solution for injection in a single-use 2 mL vial (USP/Ph. Eur./JP Type I glass). It is a clear to slightly brown aqueous solution. The drug product is composed of

100 mg/mL ranibizumab in histidine HCl, ucrose, polysorbate Ranibizumab PDS drug product is available as two different presentations: (i) co-packaged with the non-integral, single-use initial fill needle or (ii) the refill needle. Additionally, specific non-integral devices (an intraocular implant, insertion tool, and explant tool) are also required for administration of ranibizumab PDS drug product. These will be available separately.

The PDS implant is a refillable, permanent intraocular device uniquely designed for the continuous delivery of ranibizumab (100 mg/mL). The PDS is designed to maintain therapeutic drug concentrations in the vitreous for longer durations than the available anti-VEGF treatments administered by intravitreal injection.

3.1.2. Active Substance

General Information

Ranibizumab PDS is the antigen-binding fragment (Fab) of a humanized monoclonal antibody based on a human IgG1 framework. The recombinant antibody fragment is produced in E. coli and consists of one heavy chain (231 amino acid residues) and one light chain (214 amino acid residues). Ranibizumab does not have the typical N-linked glycosylation site (Asn297) since it does not contain the Fc region. The calculated molecular mass of intact ranibizumab is 48,379 Da (peptide chains only). The expected intrachain and interchain disulfide linkages were confirmed (five cysteine residues per light chain, five cysteine residues per heavy chain).

The antibody has an extinction coefficient of 1.9 mL mg^{-1} cm^{-1} and an isoelectric point of 8.1.

The biological activity of ranibizumab PDS is binding to all known biologically active forms of VEGF and, thereby, preventing binding to their receptors VEGFR-1 and VEGFR-2. As an antibody fragment, ranibizumab does not have antibody-mediated effector functions.

Manufacture, process controls and characterisation

Manufacture, process controls

Confirmation of the GMP status for the drug substance manufacturing and testing sites has been provided. A GMP certificate has been provided. Ranibizumab drug substance manufacture was in the scope of the inspection. FDA establishment inspection reports have been provided with the outcome NAI (no action indicated).

Manufacturing process and process controls

Manufacture of ranibizumab PDS drug substance consists of thaw, fermentation, harvest, and purification. Process Parameter target and acceptable ranges are defined and critical process parameters are identified. In-process testing is performed and limits are identified as action limits or acceptance criteria, respectively. Control measures are in place throughout the manufacturing process.

Raw materials, cell substrate, cell banking system

Process control and validation

Reports from process validation studies have been provided. The drug substance manufacturing process was validated. The PPQ campaign consisted of eleven runs; the first three consecutive runs were

designated as the PPQ batches. The data from the PPQ campaign showed that all quality attributes met their acceptance criteria, all key performance indicators and IPCs met their process performance acceptance criteria. Process parameters (CPPs and non-CPPs) were maintained within their acceptabl. Overall, process performance was consistent among the PPQ batches.

Process consistency was assessed

Process hold-times were validated by physicochemical stability studies and microbial validation studies.

Process-related impurities and product variants have been demonstrated to be removed to an acceptable level. Shipping qualification studies demonstrate that the shipping process is capable of maintaining frozen drug substance inside the storage container at the recommended storage temperature of – 20°C.

Manufacturing process development

Overall, the development process material is representative for the intended commercial process material, as supported by the comparability exercise. The comparability acceptance criteria were derived using two-sided 95/99 TIs from the manufacturing ranges of the comparator batches. Results demonstrate that all quality attributes are highly similar between the processes.

Characterization

Critical quality attribute (CQA) assessment:

A risk ranking filtering (RRF) approach was used to identify and classify product quality attributes (QAs) as CQAs or non-CQAs – whereby a CQA is a quality attribute having a (potential) impact on product safety or efficacy, and a non-CQA is a quality attribute that is not expected to have an impact on safety or efficacy.

The RRF tool assesses the impact and uncertainty score of each product quality attributes in the following categories: Bioactivity, pharmacokinetics, immunogenicity and safety. Risk ranking is performed by considering the impact and the uncertainty of that impact. Each is ranked on a low, medium, high scale.

Given the design of the PDS implant, the release rate is driven by the diffusion of ranibizumab PDS down the concentration gradient into the vitreous. Studies with ranibizumab variants, as well as other antibodies and antibody fragments, support that the diffusive properties of a molecule within the vitreous, play a major role in vitreal elimination, with little influence from molecular charge, hydrophobicity, or oxidation. Therefore, among the identified product variants, only size-related variants have the potential to impact the pharmacokinetic.

Characterization:

The primary structure, higher order structures, and the biological activity of ranibizumab PDS were sufficiently evaluated using a series of biochemical, biophysical, and functional characterization techniques.

- Other properties:

Minor protein impurities were determined.

- Biological activity:

Functional analysis of ranibizumab PDS was performed Stress materials exhibited a slightly reduced potency. All process-relevant stress samples retained potency with respect to corresponding controls and the ranibizumab PDS reference standard.

In addition, the impact of size variants on bioactivity was assessed for ranibizumab PDS

Impurities:

Potential product-related substances, and potential product-related impurities have been sufficiently characterized and are controlled at release.

ECP, bioburden and endotoxins are controlled. Removal of other process-related impurities has been demonstrated during process validation.

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

Specification, analytical procedures, batch analysis

Ranibizumab PDS drug substance specifications are in general adequate. The release specifications include tests for appearance (physical state, colour, clarity/opalescence), identity (peptide mapping and protein content), purity and impurities (SE-HPLC, non-reduced CE-SDS, IE-HPLC, ECP-ELISA), quantity (protein concentration by UV), potency (bioassay; inhibition of proliferation assay by HUVEC), microbial safety (bacterial endotoxins, bioburden), and general attributes (pH, osmolality). Ranibizumab PDS drug substance (and drug product) is formulated with polysorbate 20 as a stabilizer. The polysorbate 20 concentration is tested at drug substance release.

The stability specification for ranibizumab PDS drug substance comprises a reduced set of parameters: physical state, pH, osmolality, identity, ECP, protein content, biobureden, bacterial endotoxins and polysorbate 20 are not monitored. Since no change in most of these parameters is expected, this is acceptable.SE-HPLC, non-reduced CE-SDS, IE-HPLC and potency by bioassay have been demonstrated to be stability-indicating. Overall, the set of release parameters tested complies with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008.

For the compendial methods (colour, clarity/opalescence, pH, bacterial endotoxins, bioburden) reference has been made to the respective Ph. Eur monographs. For both the compendial and the internal methods, a reference to the respective in-house SOP and a brief description of the method has been provided. For methods used for both drug substance and drug product, reference has been made to section P.5.2.

Original method validation and transfer reports have been provided.

Non-compendial analytical procedures have been validated according to ICH Q2 (R1). All results have passed the acceptance criteria specified in the method validation protocol. Compendial methods have been verified. Batch release data are presented for PPQ campaign drug substance batches manufactured according to the intended commercial manufacturing process. In addition, release data is presented for drug substance batches. Data for five drug substance batches manufactured is also presented.

Overall, the batch release data shows consistent and comparable quality of ranibizumab PDS drug substance manufactured across all batches. All the drug substance batches comply with the pre-established specifications valid at the time of testing.

For justification of specifications reference has been made to the ranibizumab PDS drug product section P.5.6. The acceptance criteria were established taking the following considerations into account: clinical experience, stability and process effects, product-specific knowledge, prior knowledge, current compendia or regulatory guidelines, and formulation development studies. However, the acceptance criteria for some of the parameters are considered too wide and should be tightened **(OC)**.

Reference standard

A two-tiered reference standard system, consisting of a primary and a secondary reference standard, was established for ranibizumab PDS drug substance and drug product. The primary reference standard will be used to qualify subsequent secondary reference standards. The secondary reference standard is used for testing in all assays requiring a reference standard.

Both the primary reference standard and secondary reference standard were produced from ranibizumab intravitreal drug substance batches, which were manufactured from the ranibizumab intravitreal commercial process and are representative of ranibizumab intravitreal pivotal batches. The ranibizumab intravitreal reference standards have been used throughout ranibizumab PDS development. Since ranibizumab PDS development is based on ranibizumab intravitreal, this can be accepted.

The primary and secondary reference standards were qualified by release and extended characterization testing. All specifications were met. The primary reference standard is currently assessed biannually for stability.

Container closure system

Ranibizumab PDS drug substance is stored in bags.

The specifications of the bag along with the technical drawings are provided in compliance with Ph. Eur. 3.2.2.1. To assess leachables and extractables for the drug substance storage container, extractables data provided by the vendor were reviewed. Based on the results of this study, a leachables study was conducted. The bags were characterized for volatile, semi-volatile, non-volatile, acetate, formate and elemental leachables. To date, leachables determined from drug substance storage container are available. Ongoing leachables studies will continue until the end of shelf life. The study is still ongoing and updated results should be provided – as applicable (**REC**).

Stability

The proposed long term storage condition for ranibizumab PDS drug substance is -20°C. A shelf-life of 36 months is proposed, based on long-term primary stability data (real-time recommended storage conditions). A Long-term stability data for two clinical drug substance batches are available. Stability data at accelerated conditions are available.

Long-term and accelerated stability data for 3 PPQ drug substance batches are available. Furthermore, stability data at accelerated conditions are available Supportive stability data is provided. 60 months real time data obtained for the three primary stability drug substance manufactured at commercial scale should be presented once available. **(REC)**

Stability protocols, analytical procedures and stability specifications are provided. In addition, stress stability studies were performed. The available stability data for samples stored at the recommended storage conditions (-20°C) show good stability. The presented data for ranibizumab PDS drug substance support the claimed shelf-life.

A post-approval stability commitment has been provided. The Applicant commits to add at least one commercial drug substance batch to the stability program annually at the recommended storage condition of -20°C if commercial production occurs during the calendar year. It is noted that there is a difference in the commercial acceptance criteria for shelf-life setting and the specifications mentioned in the post-approval stability protocol. Stability specifications in the post-approval stability protocol are tighter for purity by SE-HPLC, purity by IE-HPLC and potency. Certain parameters are omitted from the stability protocol. pH, "Main Peak" as measured by non-reduced CE-SDS, protein content and polysorbate 20 content are no longer measured post-approval. This approach is considered acceptable. Stability-indicating parameters are still covered.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the drug product

The drug product is provided in single-dose 2 mL vials as a sterile solution. It is intended for intravitreal use with the Port Delivery System (PDS). The excipients for the formulation are compliant with the requirements of the Ph. Eur. and are commonly used in parenteral medicinal products. Ranibizumab PDS drug product is formulated as 100 mg/mL ranibizumab in sucrose, histidine HCl, polysorbate 20,. Sucrose is used as tonicity agent and cryoprotectant. Since the route of administration is parenteral, no extra information in the SmPC and PL is required.

Ranibizumab PDS drug product is available as two different presentations: (i) co-packaged with the non-integral, single-use initial fill needle or (ii) the refill needle. Additionally, specific non-integral devices (an intraocular implant, insertion tool, and explant tool) are also required for administration of ranibizumab PDS drug product. These will be available separately.

Although the intraocular implant is a non-integral device which is not co-packaged with ranibizumab PDS drug product, relevant information for the use of the device should be included in the appropriate sections of the medicinal product package leaflet and SmPC.

Pharmaceutical development

The drug product is provided as a sterile liquid solution for injection in a single-use 2 mL vial (USP/Ph. Eur./JP Type I glass). It is a clear to slightly brown aqueous solution. The drug product is composed of 100 mg/mL ranibizumab in histidine HCl, ucrose, polysorbate 20 at pH 5.5. Histidine is used as buffer to maintain solution, sucrose is used as tonicity agent and cryoprotectant, and polysorbate 20 is used to prevent aggregate formation.

Formulation development

Selection of initial formulation was based on prior development knowledge and commercial experience from ranibizumab intravitreal drug product A formulation screening study was conducted at stress conditions.

The commercial drug product is provided in a 2 mL Type I clear glass vial with a 13 mm fluororesin, laminated butyl rubber stopper and an aluminium seal with plastic flip-off cap. The target fill volume for ranibizumab PDS drug product vials is 0.395 mL. The label claim (nominal volume) is 0.1 mL (10 mg), which is the amount required to ensure the complete 2 mg initial dose for implant refill-exchange. The fill volume was confirmed by an extractable study.

To evaluate the robustness of the drug product formulation, a multi-parameter formulation design of experiment (DOE) study was conducted.

Manufacturing process development

During development of ranibizumab for Port Delivery System (ranibizumab PDS) drug product, three different manufacturing process versions were used. All processes were based on the intravitreal ranibizumab commercial process. Comparability was assessed for the 100 mg/mL commercial drug product and the phase III pivotal clinical drug product . The exercise demonstrates that the drug products are considered comparable in terms of quality, safety, and efficacy.

The primary packaging components (vial and stopper) for ranibizumab PDS drug product are standard, pharmaceutical-grade components. The 2 mL glass vial and 13 mm fluororesin-laminated rubber stopper

meet pharmacopeial requirements for container closure. Compatibility of the drug product solution with the components of the primary packaging is verified by stability studies at the recommended storage condition of 2-8°C. Extractables studies were conducted for the rubber stopper and the glass vial. Leachables that were identified in the extractable studies were defined as target leachables and assessed in the leachables testing. To date, leachables data from drug product vials are available. None of the leachables associated with the drug product container closure system is considered to be of toxicological concern from a local or systemic perspective at the doses associated with ranibizumab PDS. Ongoing leachables studies to further characterize potential patient exposures to leachables will be continued until end of shelf life. Updated results of the ongoing leachables study should be provided, as available. **(REC)**

Compatibility of ranibizumab PDS drug product with the initial fill needle and the refill needle has been shown. The results demonstrate that ranibizumab PDS drug product is physically and chemically stable under the tested conditions. No impact to product quality was observed when comparing control samples and the in-use stability test samples. From a microbiological point of view, the ranibizumab drug product solution should be used immediately.

For clinical practice, ranibizumab PDS is used together with several medical devices: initial fill needle, refill needle, and implant. Currently, no information concerning extractables/leachables from the initial fill needle, the refill needle or the implant is available. Although the implant is not considered an integral drug-device combination, the ranibizumab-filled implant remains in patients´ eyes for several months and is refilled with ranibizumab every 6 months. A drug-product-specific extractables/leachables study has been conducted for the device parts coming into contact with the ranibizumab PDS drug product and supports the use of ranibizumab together with the device parts.

Manufacture of the product and process controls

Drug product manufacturing process:

The manufacturing process comprises thawing of drug substance at ambient temperature, homogenization, optional pooling and mixing, bioburden reduction filtration, in-line sterile filtration, aseptic filling into depyrogenated 2 R glass vials, stoppering, capping and crimping.

The ranibizumab PDS drug product manufacturing process is a standard manufacturing process (fill-and-finish) for monoclonal antibodies and has been adequately described.

The quality of ranibizumab PDS drug product is controlled by in-process controls (IPC) during critical steps of manufacture. Validation of the drug product manufacturing process included the manufacture of three consecutive PPQ batches Data from the PPQ batches and the GMP batches confirm that the process is validated and capable of producing consistent product quality at scale in the commercial manufacturing site. All CQAs met their acceptance criteria, all IPCs met their acceptance criteria or action limits, all CPPs and non-CPPs were maintained within their acceptable ranges (except for planned challenge conditions), and process performance was consistent among the PPQ batches. Challenge was conducted for the additional GMP batches, only.

Process design studies support the process parameter classification and acceptable ranges. Microbial hold studies were conducted covering the thawing and homogenization time and the hold time of drug product solution in the filtration vessel. Study results for bioburden and endotoxin support the drug substance thawing and homogenization, and subsequent storage. To verify that aseptic processing effectiveness is maintained, routine media fills are performed at least twice a year. Results for recent media fills confirm aseptic processing

The results of the environmental monitoring tests show that the environmental conditions are well controlled. Results of environmental microbiological monitoring showed no action-level excursions.

Performance qualification for autoclaves, dry heat depyrogenation tunnel, vial washer, and capping machine support the performance of sterile operations .

Product specification, analytical procedures, batch analysis

The release specification for ranibizumab PDS drug product include tests for appearance (physical state, colour, clarity/opalescence), identity (identity by cIEF and content of protein), purity and impurities (SE-HPLC, IE-HPLC, non-reduced CE-SDS), quantity (content of protein by UV), potency (bioassay; inhibition of proliferation assay by HUVEC), general attributes (volume in container, pH, osmolality, sub-visible particles, visible particles) and microbial safety (bacterial endotoxins, sterility). Ranibizumab PDS is formulated with polysorbate 20 as a stabilizer. The polysorbate 20 concentration is tested both at drug product release and stability.

The stability specification for ranibizumab PDS drug product comprises a reduced set of parameters: physical state, volume in container, osmolality, identity, protein content, sterility and bacterial endotoxins are not monitored. SE-HPLC, IE-HPLC, non-reduced CE-SDS methods have been demonstrated to be stability-indicatingThe panel of quality attributes proposed for release and stability testing of ranibizumab PDS drug product is considered adequate and in line with ICH Q6B and EMA/CHMP/BWP/532517/2008 guidelines, and Ph. Eur. 2031. Acceptance criteria are considered justified and sufficient to control drug product quality.

Descriptions of the compendial and in-house analytical methods are sufficiently detailed and acceptable. For the compendial methods (color, clarity/opalescence, pH, sub-visible particles, visible particles, bacterial endotoxins and sterility) reference has been made to the respective Ph. Eur monographs. For both the compendial and the internal methods, a reference to the respective in-house SOP and a brief description of the method has been provided.

All analytical methods used for release testing of the drug product have been appropriately validated based on the principles provided in ICH Q2 (R1) guideline. Established pharmacopoeial analytical procedures, including those for colour, clarity/opalescence, pH, visible and sub-visible particles, bacterial endotoxins and sterility are performed in accordance with the specified compendial method and have not been validated. The methods have been verified. The analytical procedures used for bacterial endotoxin, sterility, and container closure integrity test have been validated for the ranibizumab drug product to determine their suitability. The presented validations for analytical methods are acceptable and demonstrate the suitability of the analytical procedures for their intended use.

Batch release data are presented for three PPQ drug product batches manufactured according to the intended commercial manufacturing process. Overall, the batch release data shows consistent and comparable quality of ranibizumab PDS drug substance manufactured across all batches. All the drug substance batches comply with the pre-established specifications valid at the time of testing.

No new impurities have been introduced during the drug product manufacturing process; reference is made to section 3.2.S.3.2 of the dossier. This is acceptable. Furthermore, elemental impurities have been addressed in these sections, extractables/leachables have been addressed in section 3.2.P.2 and nitrosamines have been addressed in module 1 of the dossier.

A risk assessment for elemental impurities (all considered not intentionally added) has been conducted and no risk was identified. To confirm the predicted absence of risks associated with elemental impurities incorporation into the drug product, one drug product batch was tested for the 10 elementsusing ICP-MS. All results were below the control threshold for injection products.Extractables and leachables studies were performed for the type I glass vial and the fluororesin-coated rubber stopper. The leachables study

is still ongoing. To date, leachables were below the safety concern threshold limit for the compounds or were not detectable.

A short summary of the conducted nitrosamine risk assessment was provided in a separate document in Module 1 ("Nitrosamines Annex"). Ranibizumab PDS was assessed for the risk of nitrosamine impurities according to the principles outlined in *CHMP Article 5[3] Opinion EMEA-H-A5[3]-1490 and the revised EMA Questions and Answers for Marketing Authorization Holders on the CHMP Opinion for the Article 5[3] of Regulation [EC] No 726/2004 Referral on Nitrosamine Impurities in Human Medicinal Products*. No risk was identified for the presence of nitrosamines in Ranibizumab PDS drug product.

The DP specification acceptance criteria were established taking the following considerations into account: clinical experience, stability and process effects, product-specific knowledge, prior knowledge, current compendia or regulatory guidelines, and formulation development studies. Overall, the specifications are deemed sufficient to control the quality of ranibizumab drug product.

Currently, for ranibuzumab drug product specifications, the stability of the drug product within the implant has not been taken into account. Although the implant is not considered an integral drug-device combination, the ranibizumab-filled implant remains in patients' eyes for several months and is refilled with ranibizumab every 6 months. This means that ranibizumab drug product has to remain stable over 6 months at ~ 37°C. Results from simulated in-use studies are presented in section R.4. It is agreed that the specifications of ranibizumab PDS drug product have been "clinically qualified". Nevertheless, taking into account the "Note for guidance on in-use stability testing of human medicinal products", the simulated in-use stability study should also be conducted at the end of shelf-life of ranibizumab drug product using batches at the limit of the proposed commercial stability specifications.

Container closure system

The primary container closure system for ranibizumab PDS consists of a USP/Ph. Eur./JP Type I glass vial with a rubber stopper. The rubber stopper is crimped with an aluminium seal fitted with a plastic flip-off cap. The seal and cap do not come into contact with the drug product. The specifications of the glass vial, rubber stopper, and flip-off seal along with the technical drawings are provided. The glass vial and rubber stopper comply with compendial requirements.

Extractables and leachables studies were performed for the product contact materials. (Information with regard to the sterilization of the primary container closure system is provided in section P.3.5 Process validation and/or evaluation. The primary container closure system is considered suitable for use with ranibizumab PDS.

The secondary packaging is a printed folding box that contains a single labeled vial co-packaged with an initial fill needle or a refill needle. Additionally, specific non-integral devices (an intraocular implant, insertion tool, and explant tool) are also required for administration of ranibizumab PDS drug product.

Stability of the product

The proposed long term storage condition for ranibizumab PDS drug product is 2-8°C, protected from light. A shelf-life of 24 months is proposed, based on long-term primary stability data (real-time recommended storage conditions) generated from clinical batches and process performance qualification (PPQ) batches. The available stability data for samples stored at the recommended storage conditions (2-8°C) show good stability with no (significant) trends observed. A shelf-life of 24 months at the recommended storage conditions is claimed. The presented data for ranibizumab PDS drug product manufactured at the commercial facility support the intended shelf-life of 24 months.

To further support the shelf-life, a temperature cycling study has been initiated to support potential temperature excursions/time out of recommended storage condition relevant for manufacturing, shipping, and handling of drug product vials. All current results are within specifications. The data obtained support the proposed maximum allowable time outside of the recommended storage conditions. In the SmPC it is stated that "Prior to use, the unopened vial may be kept at 9 °C to 30 °C for up to 24 hours". This time out-of-refrigerator is covered by the temperature cycling study.

Photostability: Stability of the drug product when exposed to light was investigated. It has been shown that ranibizumab PDS drug product is light sensitive. The packaging configuration adequately protects the drug product vials from light. The product label contains a note to store the product in the outer carton to protect from light.

A post-approval stability commitment has been provided. The Applicant commits to add at least one commercial drug substance batch to the stability program annually at the recommended storage condition of 2-8°C if commercial production occurs during the calendar year.

Post approval change management protocol(s)

This section is not applicable.

Adventitious agents

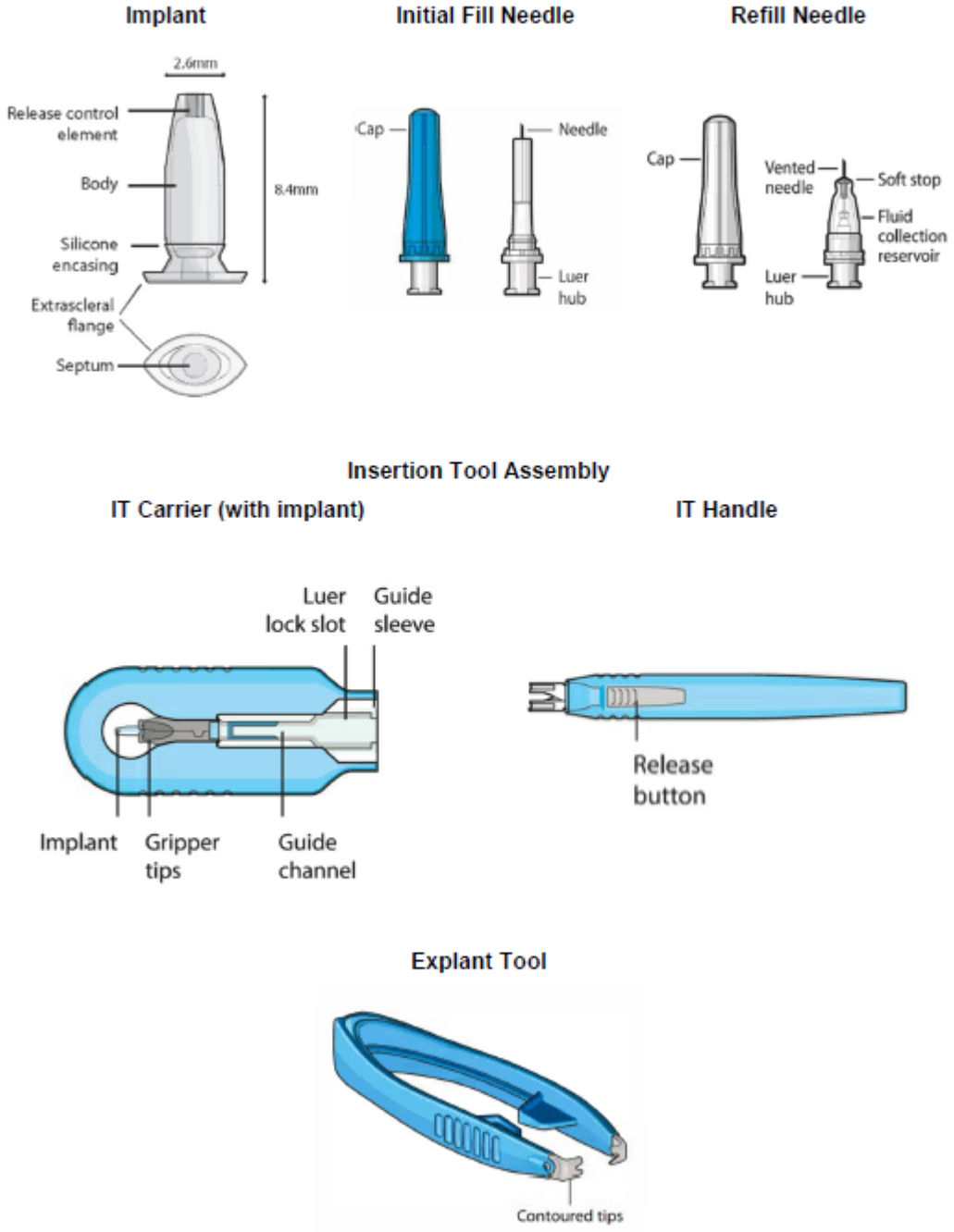
The fermentation process of ranibizumab PDS is in a medium. The cells used for production of ranibizumab PDS are of bacterial origin (*E. coli*), therefore no virus safety testing on cell banks and un-processed bulk has been performed.

In summary, the safety of ranibizumab PDS has been sufficiently demonstrated.

Medical devices

The Port Delivery System with ranibizumab (PDS) is a novel drug delivery system that consists of an intraocular implant, a customized formulation of ranibizumab for Port Delivery System (ranibizumab PDS) (100 mg/mL), and four ancillary devices used to fill, insert, refill, and explant the implant: i.e., an initial fill needle [IFN], an insertion tool assembly [ITA], a refill needle [RFN], and an explant tool [ET], respectively. The PDS implant is a refillable, permanent intraocular device uniquely designed for the continuous delivery of ranibizumab (100 mg/mL).

Figure 2.3-1 Device Constituents of PDS



Note: Images of devices not to scale.

Device descriptions, principles of operation, packaging description, a summary of safety and performance testing, information on design verification and the manufacturing process and controls is provided in Module R.4 of the dossier. Within the scope of the design verification studies, drug product compatibility with the IFN and RFN has been evaluated.

The results demonstrate that PDS drug product is physically and chemically stable under the tested conditions.

Drug release from the implant was evaluated in several studies. Accelerated and real-time aging studies have been conducted for the device parts functionality up to three years. The stability of the implant

itself and its capability to release ranibizumab to the vitreous humour has been tested in in vitro characterization studies up to three refills (~2 years).

Since ranibizumab is light sensitive, and it stays in the implant and/or eye up to 6 months, photostability testing was performedA stability study was also conducted for ranibizumab in vitreous humor.Overall, PDS is considered a drug-device combination, which includes ranibizumab, a medicinal product provided in a vial, and five non-integral medical devices. The Applicant has contracted a third party company , to be the legal manufacturer for the PDS devices. The EC Certificate/Declaration of Conformity for the PDS devices will be obtained prior to commercialization of PDS in the EU. For the IFN and RFN needles which are co-packed with ranibizumab PDS, the Applicant should provide evidence that relevant standards have been met e.g. EU Declaration of Conformity or EU certificate, confirming compliance with relevant GSPRs. Additionally, in view of the risk associated with the combined use of the medicinal product with the implant, the EU certificate for the implant is expected to be provided to confirm compliance with the GSPRs. **(OC)**

A safety report concerning ranibizumab PDS, specifically related to the device (septum dislodgement) was submitted by the Applicant on 28th February 2022. Septum dislodgement might have an impact on drug product quality within the implant and/or release of the drug product from the implant. Therefore, the Applicant should confirm that the legal manufacturer is liaising with the Notified Body and timely share any updates of this interaction. Furthermore, a risk assessment on the impact on quality of the product and a root cause analysis needs to be provided. **(part of multidisciplinary MO)**

GMO

This section is not applicable.

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

From the quality perspective, Ranibizumab PDS is currently not approvable as a major objection with regard to the quality of the product within the implant has been raised.

3.2. *Non clinical aspects*

3.2.1. Pharmacology

Ranibizumab, a recombinant humanized IgG1 monoclonal antibody Fab targeted against VEGF, is considered a known active substance. Ranibizumab administered via intravitreal injection was first approved for use in nAMD under the tradename Lucentis in January 2007. During the approval process the non-clinical studies were thoroughly evaluated with regard to PD, PK, Safety and Efficacy. It is acknowledged that relevant studies were included in the current submission for completeness but the assessment is focused on PK (due to the PDS) and the nonclinical studies conducted specifically with the PDS. The applicant uses a customized formulation of ranibizumab, which differs from the formulation used for Lucentis. No novel excipients are used in this customized formulation and no significant impact on PD, PK is expected by the new formulation. It is therefore considered acceptable to refer to the legacy studies evaluating ranibizumab nonclinical pharmacology and ranibizumab administration via intravitreal injection in rabbits and cynomolgus monkeys.

Clinical PK data with Susvimo demonstrated serum, aqueous humor and predicted vitreous concentration with PDS 100 mg/ml Q24W are maintained within the range (Cmax-Cmin) experienced with monthly intravitreal ranibizumab 0.5 mg.

3.2.2. Pharmacokinetics

The main pharmacokinetic (PK) findings are derived from animal studies from the original development of ranibizumab administered via intravitreal injection. Two studies are conducted in minipigs following administration via the PDS. The method for the quantification of ranibizumab in minipig serum is an ELISA. The minimum quantifiable concentration of ranibizumab in vitreous humor was determined to be 1.56 ng/mL in minipigs. For the Detection of Antibodies to Ranibizumab in Minipig Serum two conjugated reagents to capture antibodies directed against ranibizumab are used: biotin-conjugated ranibizumab and digoxigenin (DIG)-conjugated ranibizumab. The relative assay sensitivity was determined to be 59.0 ng/mL. The assay was able to detect 2500 ng/mL of the surrogate antibody in the presence of 100 µg/mL of ranibizumab.

A study in female mini-pigs was conducted to compare the pharmacokinetics of ranibizumab following a single intravitreal (ITV) injection, intravenous (IV) administration, or repeat ocular administration via the PDS. Dose administered to minipigs (0.5 mg/eye ITV and 2.3 mg with PDS implant) are similar to those administered to humans (0.5 mg/eye ITV and 2 mg with PDS implant). Despite differences in vitreous volumes between Yucatan minipigs and humans are not referenced, the applicant stated that based on species differences in vitreous volume, the 2.3 mg/eye dose in minipig is equivalent to 4.2 mg/eye in humans. At this stage of the clinical development, exposure data are more reliable than comparison of animal and human doses to extrapolate animal data to humans and to estimate safety margins.

Following IV administration, ranibizumab is eliminated quickly, with a half-life of approximately 0.2 days (5 hours). Following ITV administration, ranibizumab enters the systemic circulation with an ocular half-life of approximately 6.8 days. Following PDS implant, there is a steady increase in initial serum ranibizumab concentrations prior to Day 12. After Day 12, the serum concentration data were confounded by the presence of serum anti-ranibizumab antibodies but the continuing increase in serum concentrations over 40 days confirms the long-term sustained drug release ability of the PDS. In conclusion, the pharmacokinetic profile of ranibizumab delivered by the implant (higher Cmax, $AUC_{0\text{-last}}$, vitreous humor concentration at the last time point and $T_{1/2}$) supports longer intervals between doses with the implant compared to ITV administration, but the study duration (18 and 61 days after ITV and PDS implantation, respectively) is not enough to estimate the posology used in clinical trials (refills every 24 weeks). This issue was investigated from the clinical point of view; patients from the study GX28228 were monitored monthly for assessment of the protocol-defined refill criteria and additional non-clinical studies are not warranted.

A GLP 6-month toxicity study in Yucatan minipigs was conducted to evaluate the toxicokinetics of ranibizumab 2.3 mg/eye delivered via the implant, which was either filled once prior to implant insertion (Group 2) or refilled monthly for seven total doses (Group 3). The exposure to ranibizumab via PDS was similar in animals from Groups 2 and 3 after the first dose. After the initial administration of ranibizumab via PDS implant, ranibizumab mean Tmax values were 27.0 days for Group 2 and approx. 21 days for Group 3. After the final administration of ranibizumab via PDS implant on TK Study Day 168, ranibizumab mean T_{max} value was approx. 168 days for animals in Group 3. Following monthly dosing, ranibizumab via PDS had an accumulation ratio over the first dose of 15.3 and 20.5 for C_{max} and AUC, respectively based on data from one animal. The levels of circulating drug levels are influenced by the presence of ADAs. Higher ADA titers correlated with higher serum ranibizumab concentrations for the first 14-28 days. However, after monthly refill of the implant, higher ADA titers correlated with reduced or

undetectable ranibizumab serum concentrations. Despite the mechanisms underlying the PK observations are not known, the ADA effects on PK do not seem clinically relevant because clinical exposures remain within a range that has been demonstrated to be safe for long-term use.

Safety margins are based on serum data from the repeat-dose (every 2 weeks [Q2W]) chronic intravitreal toxicology study in cynomolgus monkeys (Study 01-463-1757) and the clinical study of the PDS refilled Q24W from the Phase III Study GR40548, Report 1100486. The calculated safety factor for systemic exposure following PDS 100 mg/mL Q24W ranged from 1500 to 2100 based on Cmax and $AUC_{\tau,SS}$, respectively, suggesting a lower clinical systemic exposure of ranibizumab via the PDS in humans than exposures in cynomolgus monkey via intravitreal injection. The estimated ocular safety factors are 32-fold based on Cmax, and 10-fold based on $AUC_{\tau,SS}$. Ocular inflammatory reactions were observed in all groups treated with ranibizumab and a NOAEL was not determined. However, safety margins can be calculated for systemic toxicity. Based on study 14-2350 (6-Month Ocular Toxicity Study with the Ranibizumab Port Delivery System in Female Yucatan Minipigs), the safety margin for systemic safety is lower than when compared to intravitreal injections in cynomolgus monkeys but enough to assess safety in humans.

No dedicated nonclinical absorption, distribution, metabolism, or excretion studies were conducted for ranibizumab (administered via intravitreal injection or the PDS). The absorption from the eye into systemic circulation has been characterized in the PK or TK studies.

3.2.3. Toxicology

To support the original development of ranibizumab administered via intravitreal injection, the safety of ranibizumab was characterized in legacy nonclinical studies including single-dose toxicity studies in New Zealand White rabbits, repeat-dose toxicity studies in cynomolgus monkeys), and an embryo-fetal development study.

Toxicology studies with the PDS include a 6-month chronic toxicity study in minipigs and two tolerability studies in rabbits using surrogate PDS implants). Surrogate PDS implants were made from the same materials used in the manufacture of the PDS implant, but they were non-functional and scaled one-third size to match the smaller size of the rabbit eye. An investigative surgery study was performed to qualitatively evaluate various surgical techniques for decreasing the post-operative vitreous hemorrhage rate observed in Yucatan minipigs).

The Yucatan minipig was selected as the appropriate species to assess PDS chronic toxicity and toxicokinetic because the eye of minipigs is large enough for the PDS. Porcine VEGF is more than 90% homologous with human VEGF by DNA sequence and is predicted to differ from human VEGF by five amino acids. The contact residues for ranibizumab binding to VEGF are conserved between human, macaques, and pigs. Ranibizumab also binds pig VEGF (average in vitro K_D values of 128.33 and 75.91 pM to recombinant pig and human VEGF, respectively). New Zealand White rabbits were selected as an appropriate species to assess long-term PDS tolerability.

Sham surgery procedure alone was associated with some ophthalmic abnormalities, while insertion of the implant was associated with more significant findings.

Procedure for implant insertion without ranibizumab was associated with conjunctival hyperemia and chemosis in minipigs and rabbits and mucoid ocular discharge, vitreous hemorrhage and condensation of white vitreous floaters and vitreous cells in rabbits. In minipigs, conjunctival hyperemia was more prolonged in eyes with PDS implant and after multiple doses of ranibizumab, suggesting that the implant and ranibizumab are related with the response. Vitreal hemorrhage was associated with implantation in minipigs, but it was not noted in sham operated eyes. Based on finding in rabbits, the effect could also be associated with the procedure and worsened by implant insertion. Conjunctival hyperemia, eye

discharge and vitreal hemorrhage have been also observed in patients and the risks are described in SmPC (section 4.8).

Two different implants were used during clinical development; the implant used in the Phase I clinical trial was composed of polymethyl methacrylate, silicone and 316L stainless steel, while the implants used in phase II and III clinical trials were composed of polysulfone, silicone and titanium. he tolerance of materials used in the implants selected to be marketed was assessed in rabbits for 6 months and in minipig for 6 months. Moreover, no significant differences were observed in tolerance to implants used in minipigs compared to those used in rabbits.

Implants-associated adverse events in non-clinical studies were fibrosis and risk of implant protusion/extrusion. A thin layer of fibrous connective tissue aligning the surface of the intraocular portion of the implant was noted in rabbits at 3-months but not at 6 months, indicating fibrosis could be a response to the implant. In addition, implant site fibrosis was observed in humans and administration of single or multiple doses of ranibizumab via PDS was associated with increased severity of peri-PDS implant fibrosis in minipig. Altogether indicate fibrosis is a risk of ranibizumab treatment via PDS and should be described in section 5.3 of the SmPC (OC).

An investigative surgical study in minipigs identified the size of scleral incision and scleral dissection followed by cauterization of the choroid as critical steps during the surgical procedure to manage the risk of implant migration and vitreous hemorrhage, respectively. Additionally, pars plana laser ablation following scleral dissection was determined to be the most appropriate and effective way to mitigate the risk of post-operative vitreous hemorrhage in minipigs. Longer scleral incision may have contributed to device dislocation observed in patients and laser treatment of the pars plana was added after scleral dissection in clinical trials to reduce the incidence of vitreous haemorrhage in humans.

Cataracts were observed in two eyes administered multiple doses of ranibizumab via PDS. Despite they could be secondary to contact between the intraocular portion of the implant and the peripheral lens, cataracts are a known risk of ranibizumab by intravitreal administration and were only observed following refill of the PDS implant. These observations support that cataracts are associated with ranibizumab treatment and should be described in section 5.3 of the SmPC (OC).

Administration of single or multiple doses of ranibizumab via PDS was associated with increased severity of ocular inflammation, which necessitated unscheduled euthanasia for one animal. Inflammatory reactions could be explained by the presence of ADAs and inflammation is the main adverse reaction observed in patients treated with ranibizumab IVT or via PDS.

Other microscopic findings related to administrations of ranibizumab included retinal detachment, optic nerve traction and swelling, and photoreceptor nuclei drop down. They were concomitant to inflammation, but the Applicant should further argue that these findings are secondary to inflammation and/or discuss other potential causes in order to assess their clinical relevance and the wording of SmPC. In case the Applicant justifies adequately that retinal detachment, optic nerve traction and swelling and photoreceptor nuclei drop down were secondary to immune mediated inflammation, the paragraph could include that the inflammation and its associated effects such as retinal detachment, optic nerve traction and swelling and photoreceptor nuclei drop down were considered related to an immune-mediated response to a humanised protein, which may be clinically irrelevant. On the contrary case, wording should be justified (OC).

Per current ICH S6(R1) Guidance on the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH 2011), no genotoxicity studies with ranibizumab were conducted. No carcinogenicity studies have been conducted with ranibizumab, consistent with ICH Guideline S6(R1) (ICH 2011).

With regard to reproductive and developmental toxicity the applicant refers to the toxicity study, which was performed with ranibizumab administered via intravitreal injection in pregnant cynomolgus

monkeys. Pregnant animals received bilateral intravitreal injections of ranibizumab every 14 days starting on Day 20 through Day 62 of gestation at a dose of 0, 0.125, and 1.0 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at low incidence in fetuses from dams given ranibizumab 1.0 mg/eye; no skeletal abnormalities were seen at the lower dose of 0.125 mg/eye which resulted in a trough concentration of 0.33 ng/ml (0.3-fold the maximum serum ranibizumab exposure in humans after treatment with Susvimo). Since the dose of 0.125 mg/eye does not provide enough safety margin to discard the risk in humans, information regarding the dose of 0.125 mg/eye is not considered clinically relevant and could be deleted in the SmPC (see comments to SmPC). VEGF is an angiogenic factor involved in the formation of new blood vessels during embryonic and fetal development and placentation, and ranibizumab can reach the systemic circulation and inhibit VEGF systemically. Despite available data indicating effects on embryo-foetal development are likely with ranibizumab treatment, the risk for patients treated with 2 mg of ranibizumab via the implant with refills administered every 24 weeks is considered to be low based on the low systemic levels reached.

No reproductive and developmental toxicity studies with the implant have been conducted (in accordance with ISO 10993-1) but the 6-month necropsy findings from the PDS toxicity study in minipigs did not identify any macroscopic or microscopic abnormalities in reproductive organs in sexually mature animals.

Fertility studies have not been performed with ranibizumab. In the repeat-dose IVT toxicology studies in monkeys, male and female reproductive organs did not display abnormalities. Since minipig is a relevant species to assess safety of ranibizumab (it binds to VEGF in pigs) and it is a suitable species for serial semen sampling and mating studies, fertility studies could be performed in this species. However, taking also into account the median age (above 70 years) of the targeted AMD population, the absence of specific fertility studies with ranibizumab can be considered as justifiable and the risk for human fertility can be assessed based on the weight of evidence.

Despite low systemic levels of ranibizumab are reached in patients when it is delivered by PDS, the embryofetal toxicity study demonstrated that low ranibizumab systemic levels reached after ITV administration were enough to induce skeletal abnormalities in fetuses and toxicity and non-clinical studies with other VEGF inhibitors (Bevacizumab SmPC) support that inhibition of VEGF in human female reproductive tissues could potentially impair fertility. The risk for female fertility is adequately stated in the SmPC, but the Applicant should perform a bibliographic search about potential effects of VEGF inhibition in male reproductive impairment and justify the wording of sections 4.6 and 5.3 of SmPC based on this discussion (OC).

3.2.4. Ecotoxicity/environmental risk assessment

N/A

3.2.5. Discussion on non-clinical aspects

Ranibizumab administered via intravitreal injection was first approved for use in nAMD under the tradename Lucentis by the European Medicines Agency (EMA) in January 2007. In this context the safety and efficacy of ranibizumab were characterized extensively in nonclinical and clinical studies using intravitreal injection ranibizumab. The applicant uses a customized formulation of ranibizumab, which differs from the formulation used for Lucentis. No novel excipients are used in this customized formulation and no significant impact on PD, PK is expected by the new formulation. It is therefore considered acceptable to refer to the legacy studies evaluating ranibizumab nonclinical pharmacology and ranibizumab administration via intravitreal injection in rabbits and cynomolgus monkeys.

The Port Delivery System with ranibizumab (PDS) is a drug delivery technology that enables physicians to use a customized formulation of ranibizumab to provide a continuous drug delivery profile. The nonclinical PDS program focused on the safety of the combination of the PDS implant with ranibizumab or the implant alone.

Toxicology studies with the PDS include a 6-month chronic toxicity study in minipigs and two tolerability studies in rabbits using surrogate PDS implants. Overall it can be concluded that the implant itself is tolerated but there are risks for infections, ocular irritation etc. related to the surgery process. These aspects are reflected in the clinical assessment. Considering the findings in the 6-Month Ocular Toxicity Study with the PDS in Female Yucatan Minipigs it needs to be carefully evaluated whether the benefit of less visits outweighs the additional risk associated with surgery, implant insertion, and the re-fill procedure.

3.2.6. Conclusion on non-clinical aspects

From non-clinical point of view the application for Susvimo is approvable as no major objections have been raised, however several other concerns should be addressed (please see LoOI).

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Clinical evidence supporting the marketing authorisation application is primarily based on the ongoing pivotal Phase III clinical study (GR40548/ Archway) investigating the efficacy, safety and pharmacokinetics of the PDS in patients with wet AMD. In addition, results from the dose-finding Phase II Study (GX28228/ Ladder, study complete) and the long-term extension Study (GR40549/ Portal, study ongoing) are also provided to further substantiate the efficacy, safety and the B/R profile of PDS.

1.2 OVERVIEW OF STUDIES CONTRIBUTING TO THE EVALUATION OF EFFICACY

Table 1 Summary of Studies Contributing to Efficacy Evaluation

Study No.	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen
GR40548 (Archway) pivotal study	Phase III, Randomized, multicenter, open-label (VA–masked), active-comparator study (ongoing)	Patients with nAMD responsive to anti-VEGF treatment with maximum 9 months since diagnosis; BCVA 20/200 or better; any type of macular CNV	418 patients randomized [a] -PDS 100 mg/mL Q24W: 248 patients -Intravitreal ranibizumab injection (0.5 mg) Q4W: 167 patients -3 patients not treated	PDS 100 mg/mL Q24W Intravitreal ranibizumab injection (0.5 mg) Q4W
GX28228 (Ladder main study) supportive study	Phase II, Multicenter, dose-ranging, randomized, active treatment (monthly intravitreal injection)–controlled study (complete)	Patients with nAMD responsive to anti-VEGF with maximum 9 months since diagnosis; BCVA 20/20 to 20/200; subfoveal CNV or juxtafoveal with subfoveal component	232 patients randomized [b] -PDS 10 mg/mL PRN: 58 patients -PDS 40 mg/mL PRN: 62 patients -PDS 100 mg/mL PRN: 59 patients -Intravitreal ranibizumab injection (0.5 mg) monthly: 41 patients -5 patients not treated -7 patients treated at a non-compliant site	PDS 10 mg/mL, PRN [c] PDS 40 mg/mL, PRN [c] PDS 100 mg/mL, PRN [c] Intravitreal ranibizumab injection (0.5 mg) monthly

Study No.	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen
GR40549 (Portal) extension study	Phase III, Multicenter, open-label, VA–masked, multiple-cohort extension study (ongoing)	Patients with nAMD who have completed either Phase II Study GX28228 (Ladder) or Phase III Study GR40548 (Archway)	220 patients enrolled [d] -PDS 100 mg/mL Q24W: 217 patients -13 patients from Archway -189 patients from Ladder main study -4 patients from non-compliant Ladder site not included in analyses -11 patients from OATS -3 patients not treated	PDS 100 mg/mL Q24W

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; nAMD = neovascular age-related macular degeneration; PDS = Port Delivery System with ranibizumab; PRN = pro re nata; Q4W = every 4 weeks; Q24W = every 24 weeks; VA = visual assessor; VEGF = vascular endothelial growth factor.

[a] 418 patients were enrolled and randomized; however, 3 patients randomized to the PDS 100 mg/mL arm were never treated or analyzed.

[b] This includes patients from the main study only. 7 patients randomized at a non-compliant site were excluded from efficacy analyses. 5 patients randomized to the PDS groups decided not to undergo implantation because of the unexpectedly high incidence of vitreous hemorrhage before optimization of the Instructions for Use.

[c] According to protocol-specified refill-criteria.

[d] Five patients from the main study of Study GX28228 were not included in the efficacy population in this SCE due to being from a non-compliant site (n = 4) or untreated (n=1) and 11 non-randomized patients from the oral anti-thrombotic (OAT) sub-study were excluded from the analyses in this SCE leaving 189 GR40549 patients in the pooled analysis population; 15 patients enrolled from Study GR40548 (2 not treated) were not included in the efficacy evaluation included in this SCE, due to their short duration of participation in Study GR40549 and therefore limited follow-up data available, as of the CCOD of 11 September 2020.

Table 1 from Summary of Clinical Efficacy]

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

The applicant has developed PDS as an innovative drug delivery system providing continuous drug delivery of ranibizumab. The PDS has the same active pharmaceutical ingredient as the commercial intravitreal injection (ranibizumab), for which PK characteristics have been previously characterized extensively in clinical trials in neovascular age-related macular degeneration (nAMD) and other indications (Xu et al. 2013, Zhang et al. 2014). Due to continuous release of ranibizumab administered by PDS, the PK profile differs from that of ranibizumab administered via intravitreal injection.

The clinical pharmacology package supporting this submission comprises data on characterization of serum ranibizumab PK from Studies GX28228 and GR40548 by non-compartmental analysis (NCA), population PK (PopPK) analyses to characterize ranibizumab release into the vitreous via the PDS

implant, a PopPK/PD model to explore the relationship between vitreous concentrations and response in terms of central subfield thickness (CST), and the evaluation of immunogenicity.

The proposed dosing regimen in the label is 2 mg of Susvimo (0.02 mL of a 100 mg/mL solution) continuously delivered via the implant with refills administered every 24 weeks.

Analytical methods

Analytical assays methods to measure ranibizumab concentrations in serum and aqueous humor and to analyse anti-ranibizumab antibodies were developed and validated.

Assays used for quantification of ranibizumab concentrations

Total ranibizumab concentrations in human serum were quantified by ELISA. The assay was developed at Genentech, Inc. and validated at PPD. Assay quantification range was 15.0 pg/mL to 600 pg/mL. Both precision and accuracy of each of the 7 QC samples tested (15.0, 20.0, 30.0, 100, 400, 500, 600 pg/mL) was within 20%. Selectivity of the assay was found to be acceptable in matrices of different disease states (age-related macular degeneration (AMD), retinal vein occlusion (RVO), and diabetic macular edema (DME)). No interference with haemolytic or lipemic samples was observed at tested concentrations. However, interference was observed with bevacizumab and rhVEGF at concentrations of 100 pg/mL or greater and 100 ng/mL or greater, respectively. Dilutional linearity was demonstrated for dilutions up to 1:1500. Long-term stability at -80°C was demonstrated for 1882 days. All serum study samples were analyzed within the demonstrated long-term storage stability period.

Ranibizumab concentrations in human aqueous humor were also measured by an ELISA method that was developed at Genentech, Inc. and validated at PPD. The quantification range for this assay was 20,000 – 800,000 pg/mL and the assay performed with adequate precision and accuracy. No relevant matrix effect and no interference with VEGFR1, VEGFR2 and rhVEGF and aflibercept was observed. However, interference with bevacizumab was evident at LQC (30,000 pg/mL) at bevacizumab concentrations of 20 ng/mL and 200 ng/mL, at HQC (400,000 pg/mL) interference of bevacizumab concentrations at 200 ng/mL was evident. Long-term stability at -80°C was demonstrated for 1105 days. All aqueous humor study samples were analyzed within the demonstrated long-term storage stability period.

Assays used for determination of anti-ranibizumab antibodies

The ADA assay strategy used a tiered approach for analysis, consistent with current health authority guidance for biotherapeutics. Samples were tested in a sequential fashion: screening assay, followed by confirmatory assay, followed by ADA titration. Samples that were positive in the confirmatory assay were further analysed for neutralizing activity.

For the qualitative determination of anti-ranibizumab antibodies in human serum, a bridging antibody ELISA was developed and validated. The following assay parameters were tested: cutpoint, immunodepletion, relative sensitivity, drug tolerance, recovery, selectivity, precision, and stability of assay reagents and samples. In PPD project FHX4, the initially developed method was partially validated in AMD-disease-state human serum. Additional experiments were required to re-evaluate the assay's cut point factors in AMD-disease-state human serum, as well as the relative assay sensitivity and drug tolerance using new lots of Biotin and DIG conjugate stock received. Sensitivity of the assay, relative to the positive control used, was 4.27 ng/mL. Precision of the assay was adequate. The assay tolerated up to 100 ng/mL ranibizumab for adequate detection of 30 ng/mL or 500 ng/mL ADA. For inhibition of interference and cross-reactivity of VEGF in the assay, anti-VEGF mAb G6-23m was added. No interference was observed with haemolysed or lipemic samples.

For the detection of neutralizing antibodies to ranibizumab, an ELISA-based assay was developed with a preceding step in which all VEGF present in the sample is removed by magnetic bead extraction. This

step was necessary to avoid interference of VEGF with the detection of NAb. Validation experiments revealed that the assay performed with adequate precision. No interference was observed with haemolysed or lipemic samples, rhVEGF, aflibercept and soluble VEGFR2. Interference was observed at low (150 ng/mL) and high (800 ng/mL) level of NAb with 1000 ng/mL VEGFR1 and with 100 ng/mL bevacizumab. Similar to the ADA assay, ranibizumab tolerance was determined to be 100 ng/mL in presence of 800 ng/mL NAb positive control and 12.5 ng/mL in presence of 250 ng/mL NAb positive control.

Noncompartmental analyses (NCA)

NCA was conducted using serum ranibizumab concentrations in Studies GX28228 and GR40548. Estimated PK parameters included the maximum serum concentration of ranibizumab (Cmax), the time to reach the maximum serum concentration (tmax), the minimum serum concentration of ranibizumab (Cmin), the area under the curve concentration of ranibizumab from time zero to a selected time (AUCt), and terminal half-life (t1/2).

Due to the long systemic half-life of bevacizumab and bevacizumab detection in the ranibizumab PK assay prior intravitreal bevacizumab can impact interpretation of serum ranibizumab concentrations. In addition, serum ranibizumab concentrations are impacted by fellow eye treatment. PK-Evaluable populations were defined to exclude patients with these confounding effects.

Population PK model analysis

The objectives of this analysis were to develop a pharmacokinetics (PK) model that could describe ranibizumab PK in serum and predict ranibizumab concentrations in the vitreous and to explore covariate effects on the PDS release rate, as well as ranibizumab drug disposition following treatment with PDS.

For model development, population pharmacokinetics (PopPK) analysis was executed on data from the clinical Phase 2 study GX28228 (Ladder). The analysis dataset included 220 subjects with PK samples. Out of these subjects, 56 were previously treated with intravitreal bevacizumab, and due to the long systemic half-life of bevacizumab and bevacizumab detection in the ranibizumab PK assay, they were not included in the analysis; leaving 164 patients.

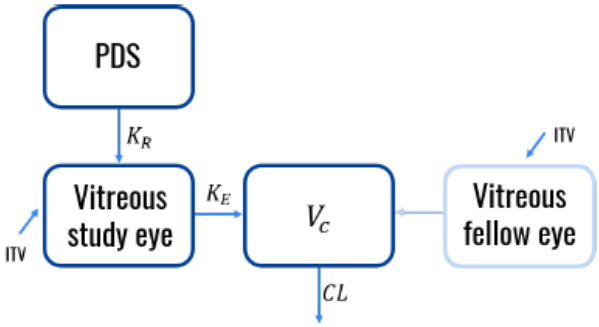
The number of serum concentration observations obtained from the included patients was 4069 and out of these 532 (13.1%) were below the lower limit of quantification (LLOQ). BQL values were excluded from the analysis without further assessment of their impact on parameter estimates.

In addition, 28 patients providing 62 samples of ranibizumab from aqueous humor were used as assessment of the predictions of vitreous concentrations.

The already established PopPK model for intravitreal injection was used as a starting point (M. Kagedal and T. Lu. Population pharmacokinetics of ranibizumab in age-related macular degeneration: an update, 2020). A non-linear mixed effect modeling approach was taken. The following covariate relationships were tested: creatinine clearance (CRCL) on clearance (CL), as well as age and gender on device release rate (kr). Drug release from the PDS implant was modeled as a modified first order release rate (kr) into vitreous followed by a first order release (vitreous distribution rate constant (kE)) into serum from vitreous.

A one-compartment disposition model with first-order absorption into and first-order elimination from the systemic circulation was able to describe the serum concentration-time profile of ranibizumab, illustrated in Figure 1. Solely CRCL was found to be an influential covariate on systemic clearance from serum, confirming previous findings. Parameter estimates are tabulated in Table 9.

Figure 1 Structural Starting Point Model



The serum PK profile of ranibizumab was described by a one-compartment disposition model. The model included two vitreous compartments linked to the serum, one for study eye and one for fellow eye. A PDS compartment was linked to the vitreous compartment of the study eye. CL: Clearance. V_c: Volume of distribution. k_E: Vitreous distribution rate constant. k_r: Device release rate. PDS: Port delivery system. ITV: Intravitreal injection.

Table 1 Parameter Estimates, Final Model

Parameter	Label	Estimate	Unit	CI95
θ_2	CL	21800	mL/day	(20600 - 22900)
θ_4	k_r,0	0.00445	d^{-1}	(0.00418 - 0.00473)
θ_8	Time slope k_r	0.664	Proportion/year	(0.568 - 0.777)
θ_{10}	Concentration slope-k_r*	-0.00369	Proportion/(mg/μL)	(-0.00565 - -0.001705)
θ_9	CrCL-CL	0.639	-	(0.501 - 0.778)
θ_5	Early residual error	0.738	Proportion	(0.723 - 0.753)
θ_6	Residual error	0.285	Proportion	(0.278 - 0.291)
θ_7	Rate constant early error	0.208	d^{-1}	(0.199 - 0.216)
ω_1	IIV Residual Error	0.699	SD	(0.633 - 0.765)
ω_3	IIV CL	0.257	SD	(0.245 - 0.269)
ω_4	IIV k_r	0.162	SD	(0.151 - 0.173)
ω_{29}	IIV Time slope	0.414	SD	(0.253 - 0.575)

k_r: Device (implant) release rate. IIV: Inter-individual variability. CrCL: Creatinine clearance. CL: Systemic clearance. SD: Standard deviation, log-normally distributed.

PopPK/PD model

A PopPK/PD model was developed to explore the relationship between concentration in the vitreous and the efficacy endpoint CST. Available data from patients in Studies GX28228, GR40548, and GR40549 were included for this analysis.

The PKPD analysis included the Phase II study GX28228 (Ladder) as well the open-label extension, study GR40549 (Portal) with 100 mg/mL PDS with refills administered every twenty four weeks (Q24W). At the time of the analysis, study GR40549 only included patients who were previously enrolled in study GX28228.

Table 2 Data Included in CST PKPD Analysis

Study	Dose	N Subjects	N Obs
Ladder (GX28228)	ITV 0.5 mg	41	980
Ladder (GX28228)	PDS 10 mg/mL	58	1446
Ladder (GX28228)	PDS 40 mg/mL	62	1564
Ladder (GX28228)	PDS 100 mg/mL	70	1597
Portal (GR40549)	PDS 100 mg/mL	198	2243
Total		231	7830

Obs: Observations. LLOQ: Lower Limit of Quantification. ITV: Intravitreal. PDS: Port Delivery System with Ranibizumab. Note all subjects in study GR40549 (Portal) were previously part of the study GX28228 (Ladder). In total, 231 unique individuals were included in the analysis. For more information consult the clinical study reports or protocols.

Table 2: Data Included in CST Model Validation

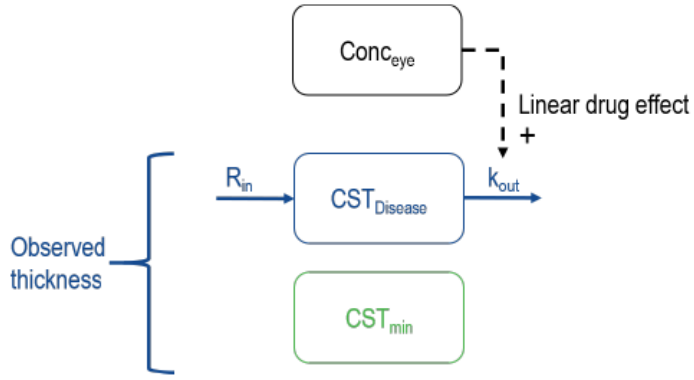
Dose	N Subjects	N Obs
PDS 100 mg/mL	247	5385
ITV 0.5 mg	167	3449
Total	414	8834

Obs: Observations. LLOQ: Lower Limit of Quantification. ITV: Intravitreal. PDS: Port Delivery System with Ranibizumab.

The Phase III study GR40548 (Archway) with 100 mg/mL PDS administered every 24 weeks compared to monthly intravitreal ranibizumab 0.5 mg injections, was used for external validation (see below "Evaluation and Qualification of Models").

Ranibizumab effect on CST was modeled using indirect response models. An indirect response model with a linear drug effect on kout described the data adequately. Population pharmacokinetics (PK) parameters were used to obtain ranibizumab concentrations in vitreous to drive the effect. No covariate effect for Sex or Age on drug effect appeared to be present; hence no covariate modeling in NONMEM was performed.

Figure 2: Schematic of the Final CST Model



R_{in} - Production rate of thickness; k_{out} - removal of thickness rate constant

CST Dose Response Simulations

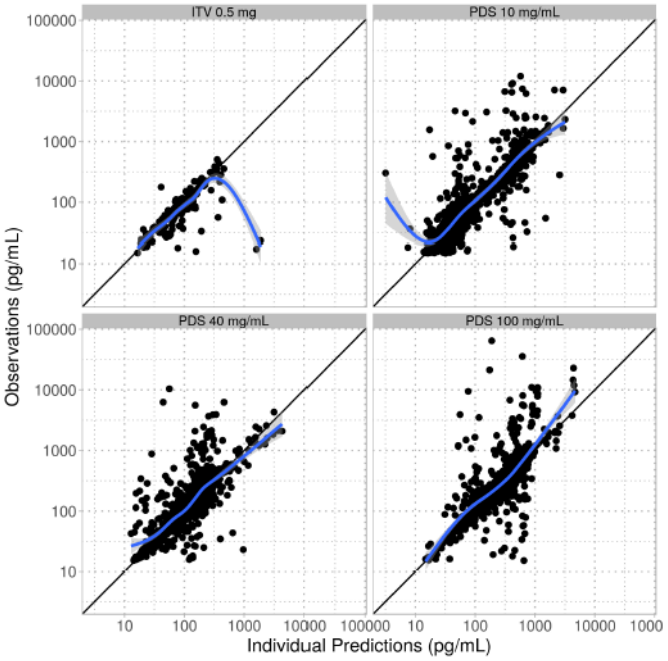
Based on the CST model, Monte-Carlo simulation of four different treatment regimens for ranibizumab was performed. Initially all subjects received 2 (Q4W) intravitreal injections of 0.5 mg followed by intravitreal 0.5 mg injections (Q4W) or PDS of 10, 40 and 100 mg/mL that was refilled every Q16W, Q24W, Q36W or Q48W months. 10,000 subjects were simulated with IIV and residual unexplained variability (RUV), each subject received all four dose levels.

Evaluation and Qualification of Models

PopPK model

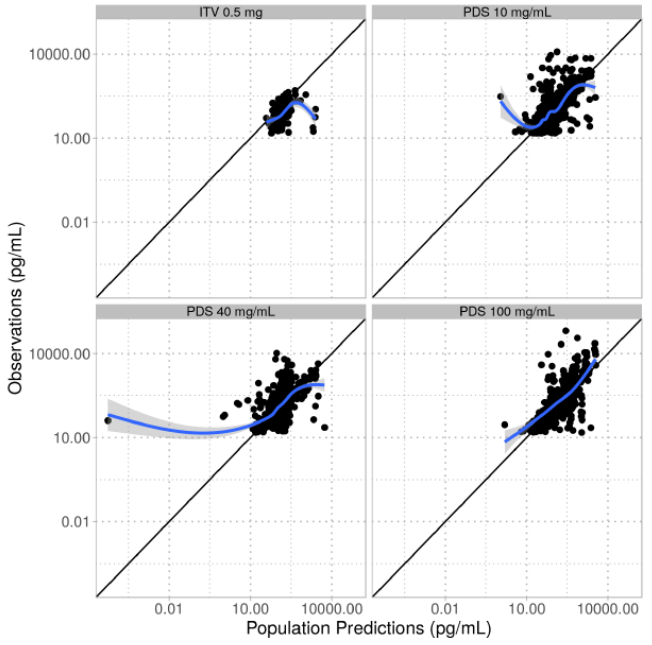
Goodness-of-fit plots by nominal dose level are presented in Figure 3 (linear scale) and Figure 4 (log scale).

Figure 3 Observed vs. Individual Predicted by Nominal Dose, Final Model



Solid line: LOESS smooth. **Shaded area:** 95% confidence interval of the LOESS smooth. **Black dots:** Individual parameter estimates.

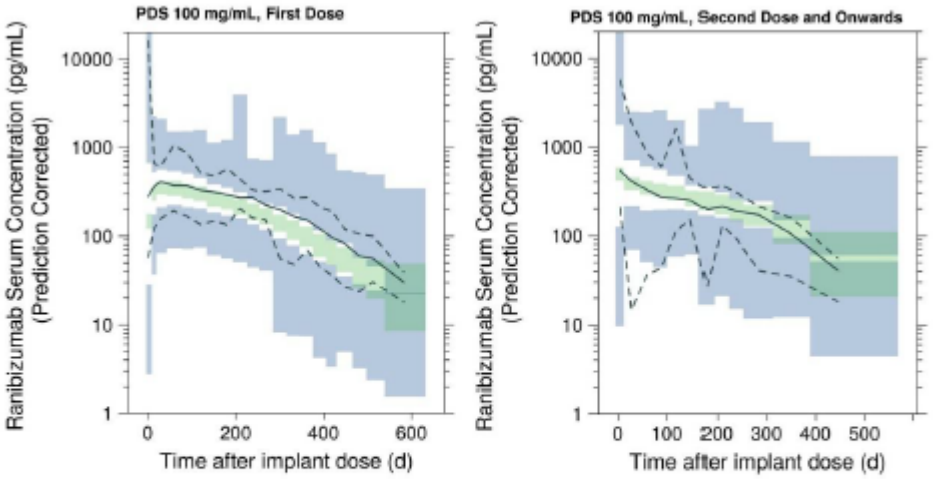
Figure 4 Observed vs. Population Predicted by Nominal Dose, Final Model



Solid line: LOESS smooth. **Shaded area:** 95% confidence interval of the LOESS smooth. **Black dots:** Individual parameter estimates.

The goodness of fit of the final model was judged acceptable with no apparent bias in visual predictive checks (VPCs) following refills, although observed serum concentrations with the highest dose (100 mg/mL) were slightly higher than predicted following implantation (Figure 5).

Figure 5 VPC for PDS 100 mg/mL arm in Study GX28228 After First Dose (left), and After Second Dose and Onwards (right), Final Model



PDS = Port Delivery System with ranibizumab; VPC = visual predictive check

Note: Solid line represents median of the observed concentrations; dashed lines represent 2.5th and 95th percentiles of the observed concentrations; shaded area indicates the 95% confidence interval around the median (green area), and 2.5th and 97.5th percentiles of the simulated concentrations (blue areas).

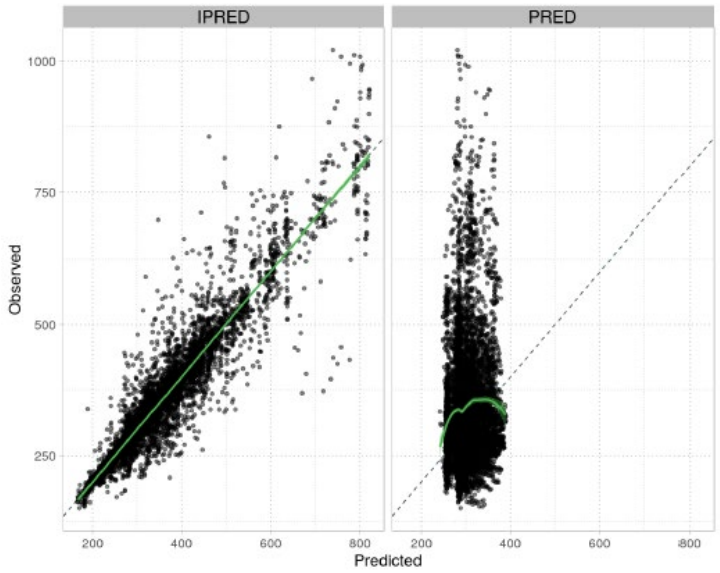
Adapted from Report 1104046, Figure 48 and Figure 49

The performance of the final model using the validation dataset from Study GR40548 was adequate with no major trends in goodness of fit plots. As seen with the VPCs using Study GX28228 data, the model slightly under-predicts concentrations following the first dose (after PDS implant insertion), while subsequent doses demonstrated a reasonable model fit. For respective graphs, please refer to the clinical assessment report.

PopPK/PD model

The performance of the model prior to inclusion of any covariates was deemed adequate following that no major trends could be identified in goodness-of-fit plots. Individual predictions describe the data well but the population predictions do not fall on the line of identity (Figure 6). The population prediction from an indirect response model is dependent on the pre-treatment baseline value. The entire curve is misrepresented if the pre-treatment baseline is poorly described for a subject, especially in the presence of large IIV estimates, as seen in this model.

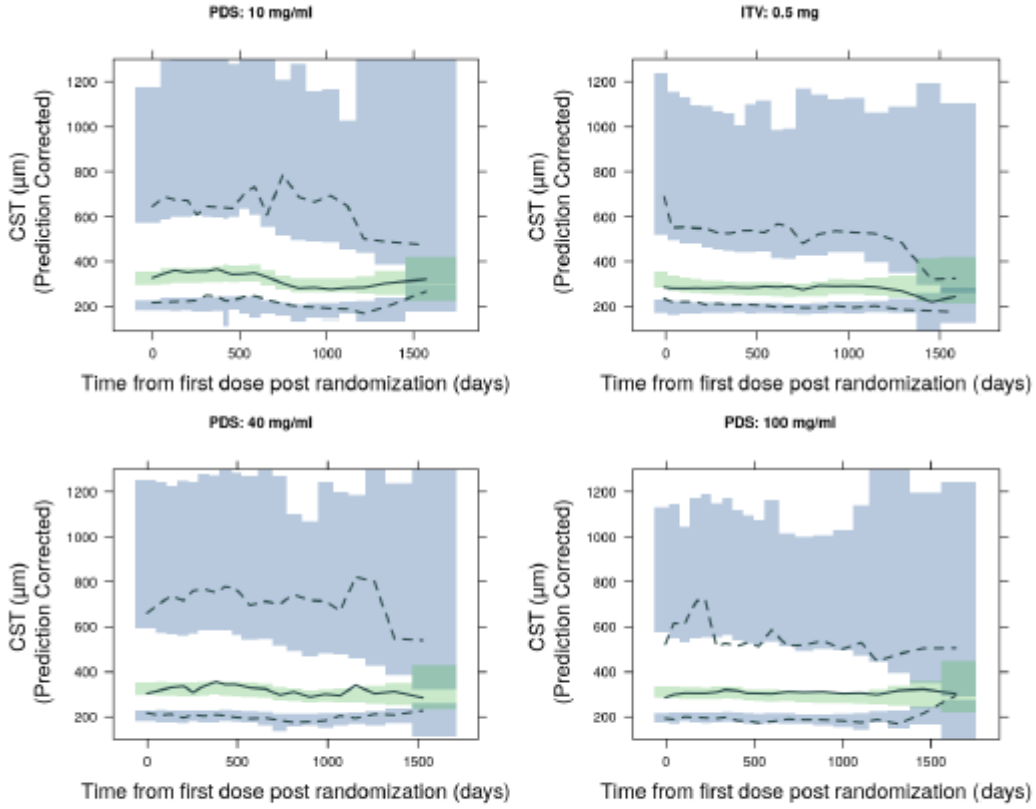
Figure 6 Observations vs IPRED and PRED



Green line is a loess smooth with 95% confidence interval, PRED: Population Predictions, IPRED: Individual Predictions

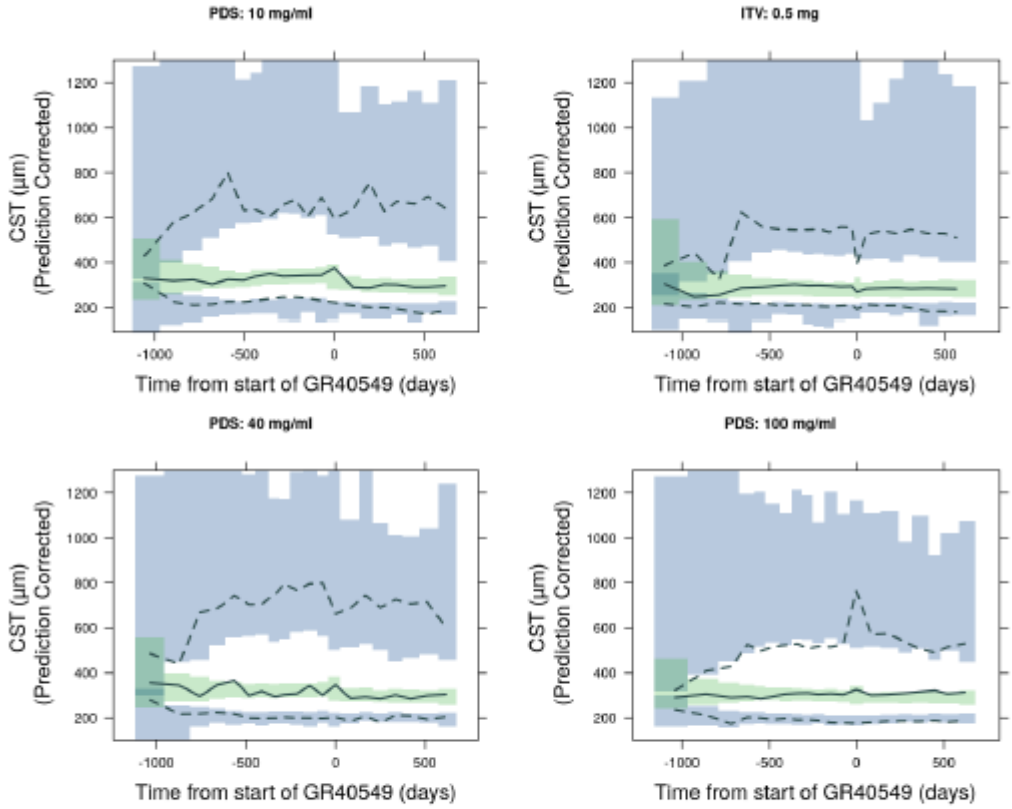
Simulation based diagnostic plots (VPCs) stratified by nominal dose level show that the median as well as the variability is adequately described, however the CI of the upper percentile is rather wide (Figure 7). The upper percentile is slightly overpredicted for PDS 100 mg/mL around 400 days after first dose post randomization. The model captures the decrease in CST well when the PDS 10 and 40 mg/mL dose groups enters GR40549 and receive the PDS 100 mg/mL dose (Figure 8). The VPCs do not show the initial decrease in CST since there are no observations during that time.

Figure 7 VPC by Nominal Dose, Time From First Dose Post Randomization



ITV: Intravitreal, PDS: Port Delivery System with Ranibizumab. Solid Black Line: Median of the observed CST. Dashed Lines: 2.5^{th} and 97.5^{th} percentiles of the observed CST. Shaded Area: 95% CI around the median (green area), 2.5^{th} and 97.5^{th} percentiles of the simulated CST (blue areas). All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. [5].

Figure 8 VPC by Nominal Dose, Time From Start of GR40549



ITV: Intravitreal, PDS: Port Delivery System with Ranibizumab. Solid Black Line: Median of the observed CST. Dashed Lines: 2.5^{th} and 97.5^{th} percentiles of the observed CST. Shaded Area: 95% CI around the median (green area), 2.5^{th} and 97.5^{th} percentiles of the simulated CST (blue areas). All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. [5].

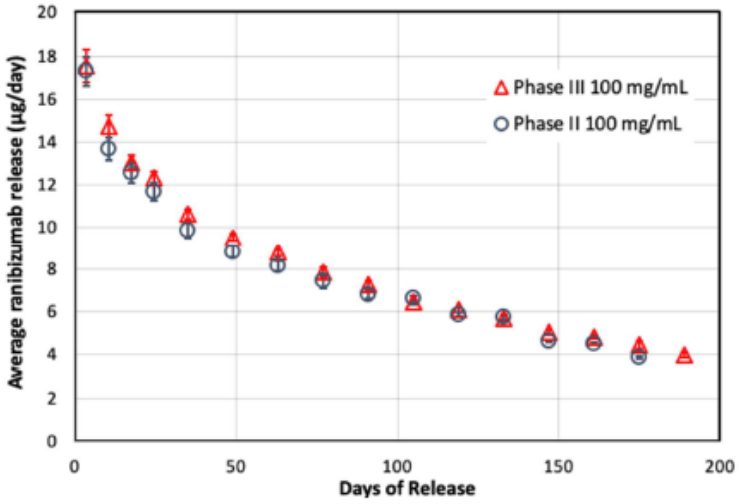
CST data from Study GR40548 study was evaluated with the final model described above. The VPCs show that the median is well described for both nominal dose levels but the variability is slightly overpredicted, as seen in the development dataset. Similar to the development dataset, individual predictions described the data well but the population predictions did not fall on the line of identity. No covariate effects appeared to be present in the external validation. IIV on the residual error magnitude was not centered around zero, which indicated a lower residual error for the external validation data.

ADME

In vitro drug release characterization

The ranibizumab release from the PDS implant has been characterized in vitro. The estimated release rate based on this in vitro characterization is 3.55 µg/days at 26 weeks. Over the course of 24 weeks, the cumulative release is around 66%; 1.3 mg ranibizumab is released from the PDS implant when filled with 2 mg ranibizumab (20 mL of 100 mg/mL). Evaluation of total ranibizumab release demonstrates consistent release profiles (Figure).

Figure 9 Total Drug Release Rates with Phase II and Phase III Formulations



Results on relevant absorption parameters

For the 100 mg/mL PDS in **study GX28228**, ranibizumab Cmax (geometric mean) in serum in the full PK population was 1067.43 pg/mL after implantation and 1125.99 pg/mL after refill (total). Median Tmax was 27.44 days after implantation and 6.91 days after refill. In the PK population with exclusions, Cmax in serum was 1080.7 pg/mL after implantation and 1131 pg/mL after refill. Median Tmax in this population was 29 days after implantation and 6.97 days after refill.

In **study GR40548,** the observed geometric mean Cmax and the median Tmax in the PK-Evaluable Population for the patients from selected study sites with additional PK sampling in the PDS 100 mg/mL arm was 450 pg/mL and 26.1 days, respectively.

As per **population PK analysis**, Cmax in serum was predicted to be 478 pg/mL and Cmax in vitreous humour was predicted to be 25.5 µg/mL.

For both PDS and intravitreal ranibizumab injections, serum concentrations were rate-limited by either release rate, in the case of PDS, or by vitreous elimination, in the case of intravitreal injections. PDS release rate and vitreous elimination rate were much slower than systemic elimination, resulting in flip-flop kinetics of ranibizumab.

Distribution

Vd was not determined by noncompartmental analyses. In the popPK model, volume of distribution (Vc) was fixed to 3270 mL.

Elimination

Clearance was not determined by NCA. The apparent terminal half-life of ranibizumab, when administered by PDS at 100 mg/mL, was determined to be 119.07 days after implantation and 143.87 days after refills in study GX28228 and 482.22 days in study GR40548.

In the popPK analysis, typical systemic clearance was estimated to be 21800 mL/day (CI 95%: 20600 - 22900), which was comparable with the previously estimated value following intravitreal administration (24100 mL/day). Half-life was not determined with the new popPK model.

Dose proportionality and time dependency

The release rate constant kr and any PK parameters that depend on that constant are both dose- and time-dependent. As such, an increasing kr over time and a decreasing kr with dose in the implant was observed. As concentration is highest initially after implantation/refill, both effects work in tandem and

affect kr in the same direction over time, however, the time effect is the more important effect, over time kr changes more than the difference between dose levels at start.

Figure 10 Release Rate Constant (kr) Time and Concentration Dependency with 24 Weeks (168 Days) Refill Interval

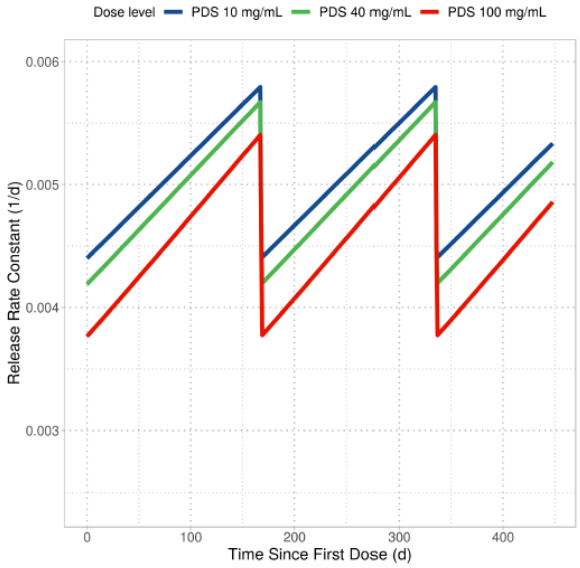
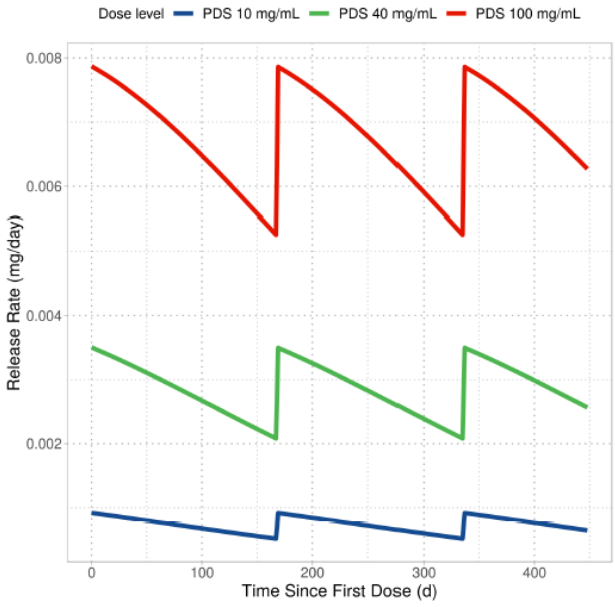


Figure 11 Release Rate Time and Concentration Dependency with 24 Weeks (168 Days) Refill Interval



Intra- and inter-individual variability

High variability in ranibizumab concentrations was observed early after dose (implantation/refill): some administrations showed large concentration spikes after dose while others did not. This is also resembled in a large %CV of Cmax in study GX28228 (256.6 – 272.5%). Variability described as %CV on AUC per dosing interval was 37 – 71% in studies GX28228 and GR40548.

In the final popPK model, the residual error model consists of a constant part (0.285 (CI 95%: 0.278 - 0.291) as additive on log-scale) and one part with a high initial value, 0.738 (CI 95%: 0.723 - 0.753), that declines with a rate constant 0.208 d^{-1} (CI 95%: 0.199 - 0.216), which corresponds to a half-life of

3.33 days. Inter-individual variability in release rate was estimated to be rather small at 16.2%. IIV on Clearance was estimated to be 25.7%.

Pharmacokinetics in target population

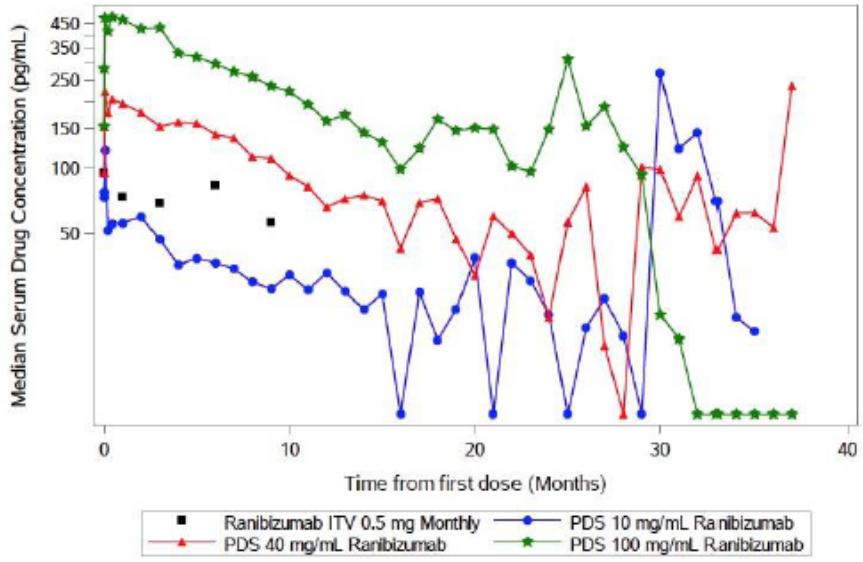
STUDY GX28228

Study GX28228 was a Phase II, multicenter, dose-ranging, randomized, active treatment-controlled study to evaluate the efficacy, safety, and pharmacokinetics of ranibizumab delivered via the PDS implant using three ranibizumab formulations arms (10 mg/mL, 40 mg/mL, and 100 mg/mL) with PRN (pro re nata; 'as needed') refill-exchanges compared with a monthly intravitreal ranibizumab 0.5 mg injection control arm (intravitreal arm) in patients with nAMD. Prior to enrollment into the study, patients had to receive at least two prior anti-vascular endothelial growth factor (VEGF) intravitreal injections into their study eye, with the most recent injection being an intravitreal ranibizumab 0.5 mg injection at screening.

Serum PK Results

The median serum concentration-time profiles based on time in study (i.e., independent of whether or when a refill-exchange procedure was performed) are shown in Figure 12. This figure illustrates the overall serum ranibizumab exposure across PDS arms and the minimum concentration for the intravitreal ranibizumab injections arms; however, given the PRN dosing regimen in this study, this concentration-time profile does not illustrate the release of ranibizumab from the PDS implant. Figure 13 shows the median serum concentration-time profile including data up to first refill-exchange procedure in the PK population with exclusions. A summary of PK parameter estimates for the PDS arms based on NCA is shown in Table 12.

Figure 12 Median Serum Concentration-Time Profile (Log-Scale) by Time on Study in Full PK Population, Study GX28228

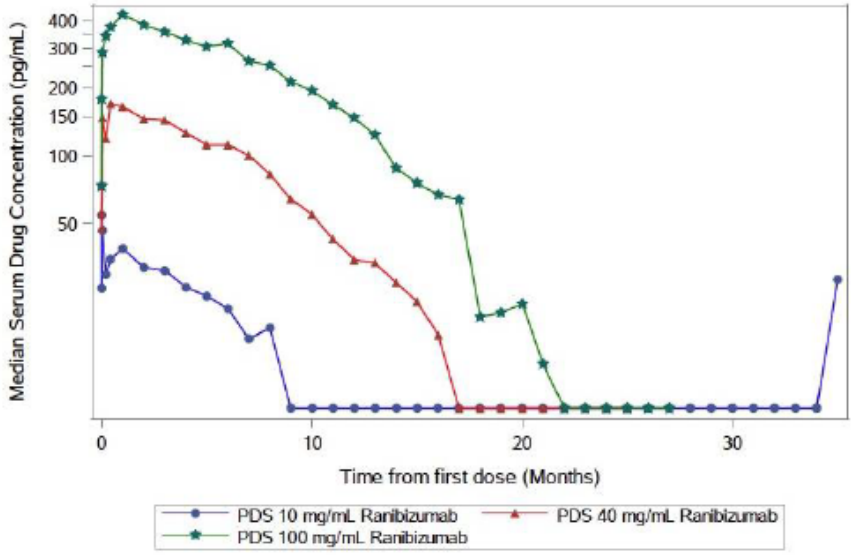


ITV = intravitreal; PDS = Port Delivery System with ranibizumab

Note: Samples taken following refill (1 to 2 days after refill, and 7 days after refill) were not included in this plot since limited number of patients had these samples between any given month.

Source: GX28228 CSR: Figure 7

Figure 13 Median Serum Concentration-Time Profile (Log-Scale) by Time Since Implantation up to First Refill in PK Population with Exclusions, Study GX28228



PDS = Port Delivery System with ranibizumab

Source: GX28228 CSR: Figure 8

Table 4 Pharmacokinetic Parameters [Geometric Mean (CV%)] in PK Population with Exclusions

Cohort	Refill Number	n[a]	C_{max} (pg/mL)	t_{max}[b] (day)	C_{trough} (pg/mL)	AUC_{Last}[c] (ng • day/mL)	$t_{1/2}$[d] (day)
PDS 10 mg/mL	Implantation	16	105.52 (258.0)	11.45 (0 – 688.1)	14.96 (76.4)	5.89 (225.1)	168.20 (163.3)
	All refills	40	91.47 (187.2)	4.87 (0 – 688.1)	11.58 (65.7)	3.43 (176.8)	162.36 (129.3)
PDS 40 mg/mL	Implantation	24	220.87 (46.4)	12.87 (0 – 86.0)	61.64 (95.8)	28.39 (107.6)	88.30 (46.7)
	All refills	61	297.61 (115.2)	6.71 (0 – 91.1)	105.07 (77.4)	22.93 (96.9)	118.87 (76.2)
PDS 100 mg/mL	Implantation	27	1080.69 (272.5)	29.01 (0.8 – 180.3)	129.63 (149.2)	90.83 (64.7)	119.07 (128.4)
	All refills	70	1131.01 (256.6)	6.97 (0.8 – 180.3)	62.19 (345.2)	66.12 (71.4)	143.87 (171.4)

AUC_{Last} = area under the concentration-time curve from dosing (implant or refill) to last observation before next refill or exiting the study; C_{max} = maximum concentration; C_{trough} = concentration at trough, before next refill; CV = coefficient of variation; PDS = Port Delivery System with ranibizumab; $t_{1/2}$ = half-life; t_{max} = time of maximum concentration

Note: Parameters are geometric means unless otherwise noted, with geometric mean CV% in parenthesis. This summary is for patients who did not have prior treatment with bevacizumab, did not have fellow eye treatment, and did not have supplemental intravitreal ranibizumab.

[a] For implantation n refers to number of patients; for all refills, n refers to number of refill cycles (implantation to first refill, first refill to second refill, etc.). The number of refill cycles per patient varies.

[b] Median (range) is reported.

[c] The interval between each refill cycle (implantation to first refill, first refill to second refill, etc.) is variable between patients.

[d] Apparent terminal half-life.

Source: GX28228 CSR : Table 34

STUDY GR40548

Study GR40548 is an ongoing Phase III multicenter, randomized, visual assessor-masked, active-comparator study designed to evaluate the efficacy, safety, and pharmacokinetics of PDS 100 mg/mL Q24W compared with intravitreal ranibizumab 0.5 mg injections Q4W in patients with nAMD. Prior to enrollment into the study, patients were treated with at least 3 injections in their study eye with any anti-VEGF agent within the last 6 months prior to screening.

The results summarized here focus on the data available as of the CCOD of 11 September 2020.

Serum PK Results

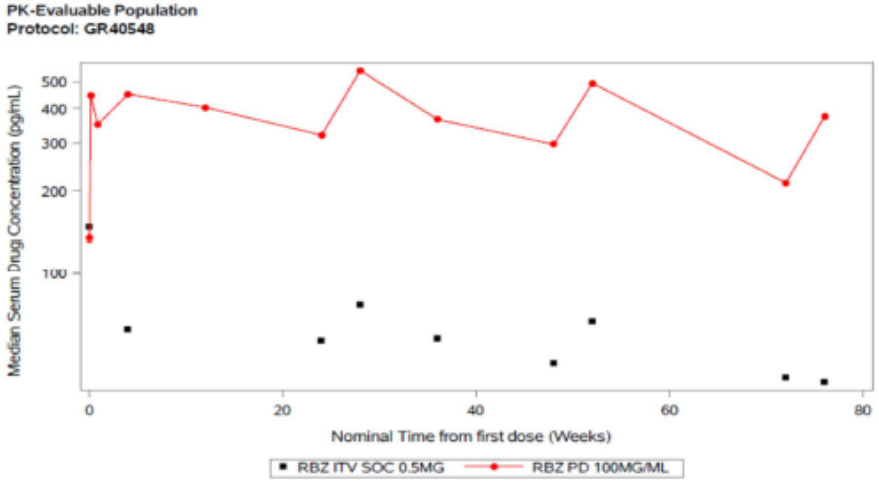
Following implant insertion in the PDS 100 mg/mL arm, measurable serum ranibizumab concentrations are observed across the time points where samples were collected up to Week 72 in the PK-Evaluable Population (Figure 14), which supports that PDS is continuously delivering ranibizumab throughout each dosing interval.

The serum ranibizumab concentration-time profile in the PDS 100 mg/mL arm was consistent across implantation and subsequent refills. In the PK-Evaluable Population, the geometric mean serum ranibizumab concentration was 416 pg/mL at Week 4 (4 weeks after implantation), 558 pg/mL and 479 pg/mL at Weeks 28 and 52, respectively (4 weeks after 1st and 2nd refill-exchange, respectively). The geometric mean serum ranibizumab concentration was 330 pg/mL at Week 24 (24 weeks after implant insertion) and 250 pg/mL and 210 pg/mL at Weeks 48 and 72 (24 weeks after 1st and 2nd refill-exchange, respectively). These results indicate that ranibizumab did not accumulate in the serum when administered with refill-exchange every 24 weeks.

In the intravitreal arm PK-Evaluable Population, observed geometric mean Cmax was 1840 pg/mL based on samples collected between 1 to 5 days after intravitreal injection. The observed geometric mean Ctrough ranged from 28.8 - 58.9 pg/mL across the time points where samples were collected up to Week 72. In the PK-Evaluable Population for the patients from selected study sites with additional PK sampling in the PDS 100 mg/mL arm, the observed geometric mean Cmax and Cmin were 450 pg/mL and 300 pg/mL, respectively. Thus, the serum ranibizumab concentrations in patients treated with PDS 100 mg/mL Q24W are within the range experienced with monthly intravitreal ranibizumab 0.5 mg, as shown in a median serum PK concentration-time profile for the PDS 100 mg/mL arm overlaid with intravitreal arm in the PK-Evaluable Population (Figure 15, Table 5).

Due to the relatively small change in serum concentrations over the 24-week refill-exchange interval and limited PK sample collection after tmax, estimation of t1/2 was available only from 5 patients (Table 5); therefore, the reported t1/2 in Study GR40548 should be interpreted with caution.

Figure 14 Plot of Log-Scale Median Serum Ranibizumab Concentrations by Treatment for PK-Evaluable Population, Study GR40548



Note: Timepoints with at least 5 subjects are included in this plot. The serum concentration (290000 pg/mL) on wk 48 for a patient was considered as an outlier (compared with the median serum concentration on wk 48 [~300 pg/mL]) and excluded from data summary.

ITV = intravitreal; PDS = Port Delivery System with ranibizumab; PK = pharmacokinetic; RBZ = ranibizumab

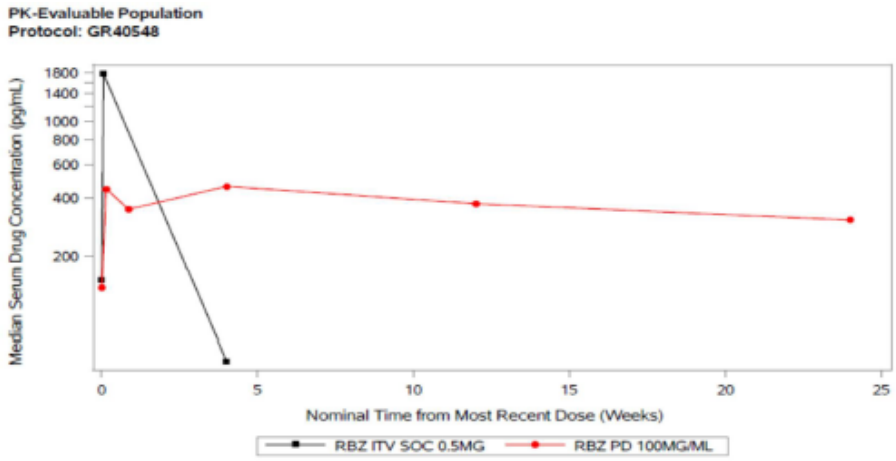
Note: Timepoints with at least 5 subjects are included in this plot.

Based on the sampling approach and available data at the time of the clinical cutoff date, the number of samples per timepoint range from 18 to 85 serum samples for the timepoints up to Week 72, while the last timepoint at Week 76 has only 7 serum samples.

RBZ PD 100MG/ML is the same as PDS 100 mg/mL.

Source: GR40548 Update CSR: Figure 7

Figure 15 Plot of Log-Scale Median Serum Ranibizumab Concentrations from Most Recent Dose Time by Treatment for PK-Evaluable Population, Study GR40548



Note: Timepoints with at least 5 subjects are included in this plot. For the purpose of plotting, ITVPKO samples collected at 1-5 days postdose in the intravitreal arm was assigned as 3 days (or 0.4 week) postdose.
The serum concentration (290000 pg/mL) on wk 48 for patient was considered as an outlier (compared with the median serum concentration on wk 48 [~300 pg/mL]) and excluded from data summary.

ITV = intravitreal; PDS = Port Delivery System with ranibizumab; PK = pharmacokinetic; RBZ = ranibizumab

Note: Timepoints with at least 5 subjects are included in this plot. ITVPKO samples collected at 1-5 days postdose in the intravitreal arm was assigned as 3 days (or 0.4 weeks) postdose.

RBZ PD 100MG/ML is the same as PDS 100 mg/mL

Source: GR40548 Update CSR: g_pkc_median4

Table 5 Summary of Serum Ranibizumab PK Parameters for Patients in the PDS 100 mg/mL arm from Selected Sites with Additional PK Sampling in the PK-Evaluable Population, Study GR40548

	C_{max} (ng/mL)	T_{max} (day)	C_{min} [a] (ng/mL)	$AUC_{0\text{-}168\ Day}$ (day.ng/mL)	$t_{1/2}$ [b] (day)
n	29	29	29	29	5
Mean (SD)	0.48 (0.17)	28.45 (28.24)	0.31 (0.08)	59.48 (18.99)	537.95 (273.75)
CV% Mean	35.5	99.3	26.0	31.9	50.9
Geometric Mean	0.45	11.38	0.30	56.27	482.22
CV% Geometric Mean	34.2	467.3	29.7	37.0	57.7
Median (Min - Max)	0.45 (0.2 - 1.0)	26.06 (0.8 - 88.8)	0.31 (0.1 - 0.5)	59.50 (18.3 - 117.7)	469.95 (225.3 - 950.2)

$AUC_{0\text{-}168Day}$ = area under the concentration-time curve from 0 to 168 days; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; $t_{½}$ = half-life; T_{max} = time of maximum concentration

Note: Due to a numerical error from the source document, $AUC_{0\text{-}128\ Day}$ has been changed to $AUC_{0\text{-}168\ Day}$ in this document.

[a]: same as C_{trough}

[b]: apparent terminal half-life

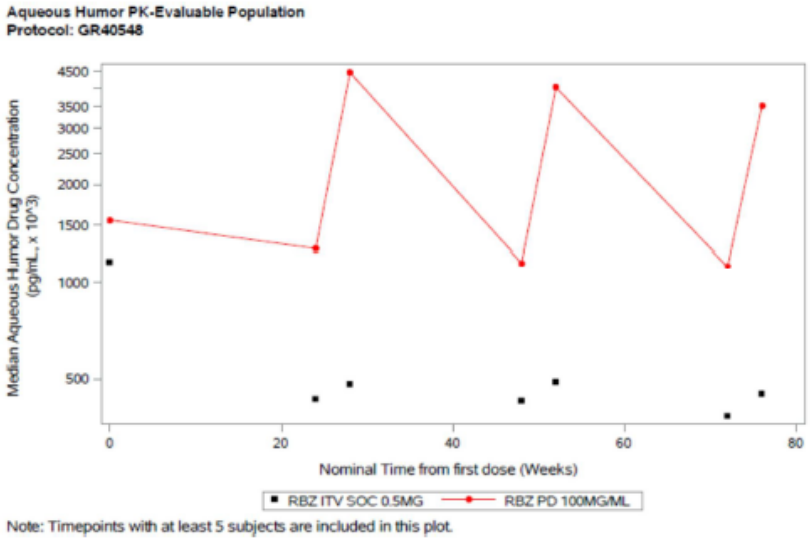
Source: GR40548 Update CSR: Table 17

Aqueous Humor PK Results

The ranibizumab pharmacokinetics in aqueous humor are generally consistent with the pharmacokinetics in serum. Specifically, the aqueous humor pharmacokinetics support that the PDS continuously delivers ranibizumab over the 24-week dosing interval and that the concentration-time profile in the PDS 100 mg/mL arm was consistent across implant insertion and subsequent refill-exchanges (Figure 16). In both the PDS 100 mg/mL arm and intravitreal arm, the aqueous humor and serum pharmacokinetics are consistent with flip-flop kinetics, with serum ranibizumab concentrations approximately 3000-9000 fold lower than aqueous humor concentrations (Table 6).

In the PDS 100 mg/mL arm of the Aqueous-Humor PK-Evaluable Population, the aqueous-humor ranibizumab geometric mean Ctrough was 1350 ng/mL at Week 24 (24 weeks after implant insertion) and ranged from 671-1320 ng/mL at Weeks 48 and 72 (24 weeks after 1st and 2nd refill-exchange procedure), indicating that PDS continuously releases ranibizumab over the 24-week refill-exchange interval and that ranibizumab did not accumulate in the aqueous humor when administered with refill-exchange every 24 weeks (Table 6). The observed ranibizumab geometric mean concentration was 4530 ng/mL and 3050 ng/mL at Weeks 28 and 52 (4 weeks after the 1st and 2nd refill-exchange procedure), respectively. These results support that the ranibizumab concentration-time profile in the PDS 100 mg/mL arm was consistent across refill-cycles (Figure 16).

Figure 16 Plot of Log-Scale Median of Aqueous Humor Ranibizumab Concentrations by Treatment, Study GR40548



Note: Timepoints with at least 5 subjects are included in this plot.

ITV = intravitreal; PDS = Port Delivery System with ranibizumab; PK = pharmacokinetic; RBZ = ranibizumab

Note: Timepoints with at least 5 subjects are included in this plot.

Based on the sampling approach and available data at the time of the clinical cutoff date, the number of samples per timepoint range from 9 to 38 aqueous humor samples for the timepoints up to Week 72, while the last timepoint at Week 76 has only 7 serum samples.

RBZ PD 100MG/ML is same as PDS 100 mg/mL

Source: GR40548 Update CSR: Figure 8

Table 6 Summary of Ranibizumab Concentrations by Matrix and Treatment, Study GR40548

		Geometric Mean (%CV) Ranibizumab Concentration in ng/mL					
Treatment Arm	Matrix	Randomization	Week 24 prerefill-exchange	Week 28	Week 48 prerefill-exchange	Week 52	Week 72 prerefill-exchange
PDS 100 mg/mL (2 mg Q24W)	Aqueous Humor (N=40)	1140 (116)	1350 (81.4)	4530 (37.9)	1320 (67.2)	3050 (88.0)	671 (152)
	n	38	33	29	26	19	9
	Serum (N=40)	0.126 (113)	0.394 (70.2)	0.558 (40.3)	0.284 (89.5)	0.479 (47.2)	0.206 (92.1)
	n	40	37	29	29	18	15
		Randomization	Week 24 predose	Week 28 predose	Week 48 predose	Week 52 predose	Week 72 predose
Intravitreal ranibizumab 0.5 mg Q4W	Aqueous Humor (N=46)	982 (111)	351 (218)	482 (225)	407 (225)	409 (240)	239 (265)
	n	37	37	35	36	35	20
	Serum (N=46)	0.117 (78.5)	0.0566 (188)	0.0581 (178)	0.0589 (149)	0.0562 (114)	0.0288 (140)
	n	46	45	35	38	34	20

PDS = Port Delivery System with ranibizumab; Q24W = every 24 weeks; Q4W = every 4 weeks

N = numbers of treated patients; n = numbers of aqueous humor or serum samples at a given timepoint

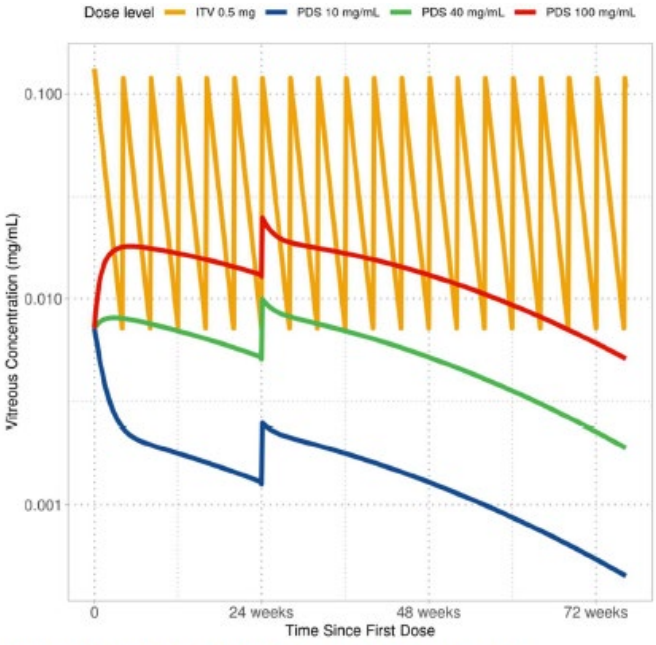
Source: GR40548 Update CSR: Table 18

Population PK analysis

The PopPK model predicts continuous release of ranibizumab into the vitreous for the duration of a Q24W refill-exchange interval. For PDS 100 mg/mL, population mean vitreous profiles are predicted to exceed the minimum concentrations of monthly intravitreal ranibizumab 0.5 mg injections at 24 weeks post implantation or refill-exchange (Figure 17). While 10 and 40 mg/mL doses do not exceed intravitreal trough level over the dosing interval, the 100 mg/mL dose covers two dosing intervals. The concentration time profiles for vitreous and serum are parallel, thus when comparing between regimens the conclusions will be the same regardless of matrix. Simulated serum (Table 7) and vitreous (Table 8) exposures indicate that the total exposure (as summarized with AUCt) and maximum concentrations experienced with PDS 100 mg/mL Q24W are lower than that experienced with monthly intravitreal ranibizumab 0.5 mg injections. Alternatively stated, this model demonstrates that the delivery of ranibizumab with the

PDS is durable and that exposure, with refill-exchanges Q24W, is expected to be within the range (Cmax - Cmin) of monthly intravitreal ranibizumab 0.5 mg injections.

Figure 17 Simulated Typical Vitreous Concentration-Time Profiles of Two PDS Doses 24 Weeks Apart and of Intravitreal Doses Every 4 Weeks



ITV = intravitreal injection, PDS = Port Delivery System with ranibizumab
Source: Report 1104046: Figure 52

Table 7 Simulated Serum Exposures

	Unit	PDS 100 mg/mL Q24W	Intravitreal Ranibizumab 0.5 mg Q4W	Relative Exposure (PDS/ITV)
AUC_t	pg/mL*day	53,900	138,000	39.2%
C_{max}	pg/mL	478	2,360	20.2%
C_{min}	pg/mL	249	141	177%

AUC_t = Area Under the Concentration-time curve in the last PDS dosing interval (from 504 to 672 days); C_{max} = maximum concentration; C_{min} = minimum concentration; ITV = intravitreal; PDS = Port Delivery System with ranibizumab; Q24W = every 24 weeks; Q4W = every 4 weeks
Source: Report 1104046: Table 14

Table 8 Simulated Vitreous Exposure

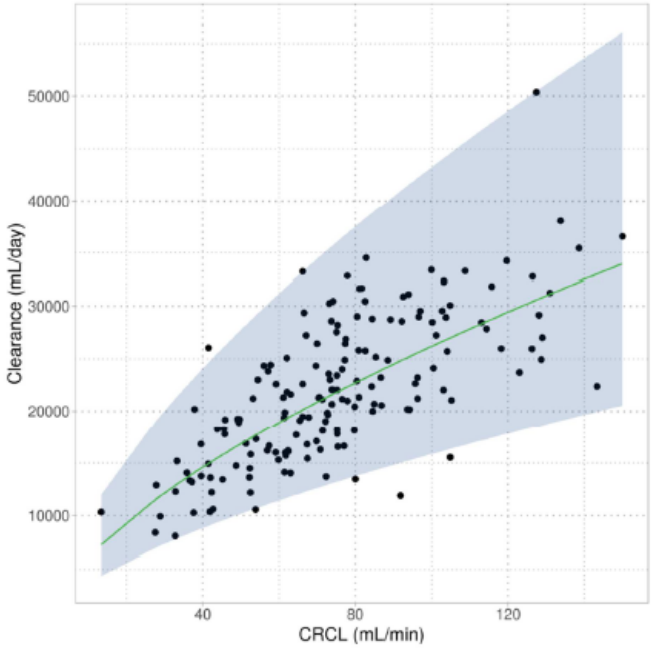
	Unit	PDS 100 mg/mL Q24W	Intravitreal Ranibizumab 0.5 mg Q4W	Relative Exposure (PDS/ITV)
AUC_t	µg/mL*day	2,820	7,210	39.2%
C_{max}	µg/mL	25.5	132	19.3%
C_{min}	µg/mL	13	7.3	178%

AUC_t = Area Under the Concentration-time curve in the last PDS dosing interval (from 504 to 672 days); C_{max} = maximum concentration; C_{min} = minimum concentration, ITV = intravitreal, PDS = Port Delivery System with ranibizumab; Q24W = every 24 weeks; Q4W = every 4 weeks
Source: Report 1104046: Table 15

PK in special populations

In the former PopPK model developed for the intravitreal ranibizumab regimen, the following covariates were analysed: demographic factors (age, gender, race, height, total body weight), pathophysiology (choroidal neovascularization [CNV] type, lesion size, area of CNV, leakage with retinal pigment epithelium staining), clinical chemistry variables (serum CrCL, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, albumin, and uric acid), and concomitant treatment (verteporfin photodynamic therapy [PDT], intraocular pressure [IOP]-lowering medications). None of these, except for CrCL, were found to have a significant impact on ranibizumab exposure. Due to prior knowledge, CrCL was also assessed as covariate in PDS clinical trials. Indeed, CrCL was found to be a significant covariate in the model, as higher CrCL led to an increase in ranibizumab CL.

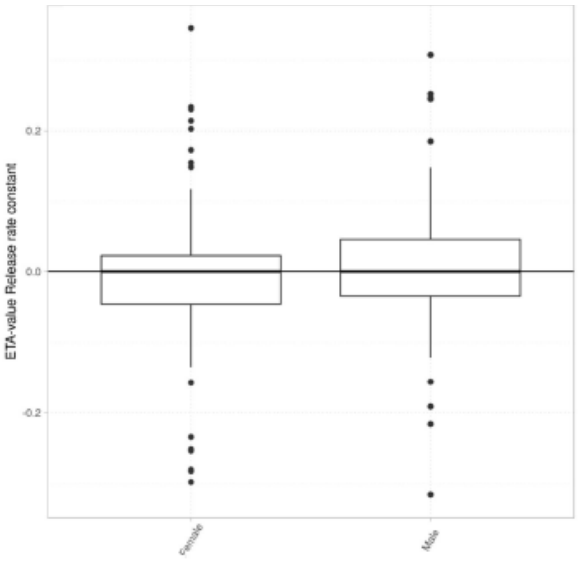
Figure 18 Estimated Covariate Relationship Clearance-Creatinine Clearance



CrCL = creatinine clearance
Green line: Typical relationship, Area: 95% prediction interval, Black dots: Individual parameter Estimates/covariate value.
Source: Report 1104046: Figure 32

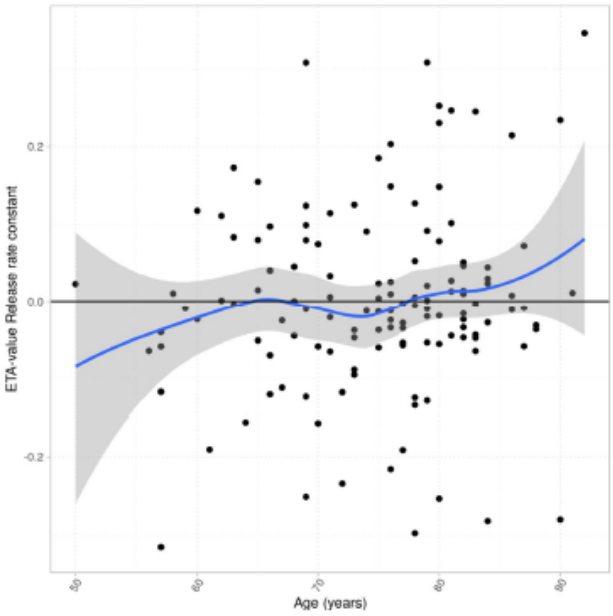
Given the mechanism of drug release for PDS implant (driven by ranibizumab diffusion), an impact of patient factors on the release rate was considered unlikely. The assessment of covariates on the PDS implant release rate was therefore limited covariates of clinical interest, which are age and sex. Both were found to have no significant influence on PDS release rate.

Figure 19 Random Effect for Release Rate Constant vs. Sex



ETA = random effect model component
Source: Report 1104046: Figure 31

Figure 20 Random Effect for Release Rate Constant vs. Age



ETA = random effect model component.
Blue line is loess smooth with 95% confidence interval.
Source: Report 1104046: Figure 30

Exposure relevant for safety evaluation

When administered by PDS 100 mg/mL, ranibizumab concentrations were contained within the Cmax-Cmin range of the monthly intravitreal dosing regimen at 0.5 mg ranibizumab. Referring to the SmPC of Lucentis, serum ranibizumab Cmax, attained approximately 1 day after dosing, is predicted to generally range between 0.79 and 2.90 ng/mL, and Cmin is predicted to generally range between 0.07 and 0.49 ng/mL. For the PDS at dose 100 mg/mL, Cmax was predicted to be 0.478 ng/mL and Cmin was predicted to be 0.249 ng/mL. PopPK analyses further predicted that AUCt achieved with PDS 100 mg/mL was lower than AUC of the monthly intravitreal regimen over the same time span (Q4Wx6=Q24W).

3.3.1.2. Pharmacodynamics

No specific pharmacodynamic studies were performed in humans.

For the assessment of PD parameters such as central subfield thickness (CST), center point thickness (CPT) investigated in studies GX28228, GR40548 and GR40549, please refer to the assessment of clinical efficacy.

Further PD investigations included the analysis of immunogenicity and a population PK/PD analysis of CST.

Immunogenicity

The potential for the PDS to induce an immunogenic response to ranibizumab was assessed in Studies GX28228 and GR40548.

In Study GX28228, the mean duration of study treatment was 20.95 months (range, 0.26-37.52 months) for patients in the PDS arms and 21.58 months (range, 5.98-37.32 months) for patients in the intravitreal arm. Incidence of treatment-emergent ADA to ranibizumab over the course of the study was 4 of 58 patients (6.9%), 9 of 62 patients (14.5%), 9 of 59 patients (15.3%), 22 of 179 patients (12.3%), and 6 of 41 patients (14.6%) in the PDS 10, 40, 100 mg/mL arms, all PDS arms combined, and the intravitreal arm, respectively.

Overall, the incidence of treatment-emergent NAb to ranibizumab in Study GX28228 was low: 2 of 58 patients (3.45%), 1 of 62 patients (1.61%), 2 of 59 patients (3.39%), 5 of 179 patients (2.79%), and 0 of 41 patients (0%) in the PDS 10, 40, 100 mg/mL arms, and in all PDS arms combined, and intravitreal arm, respectively.

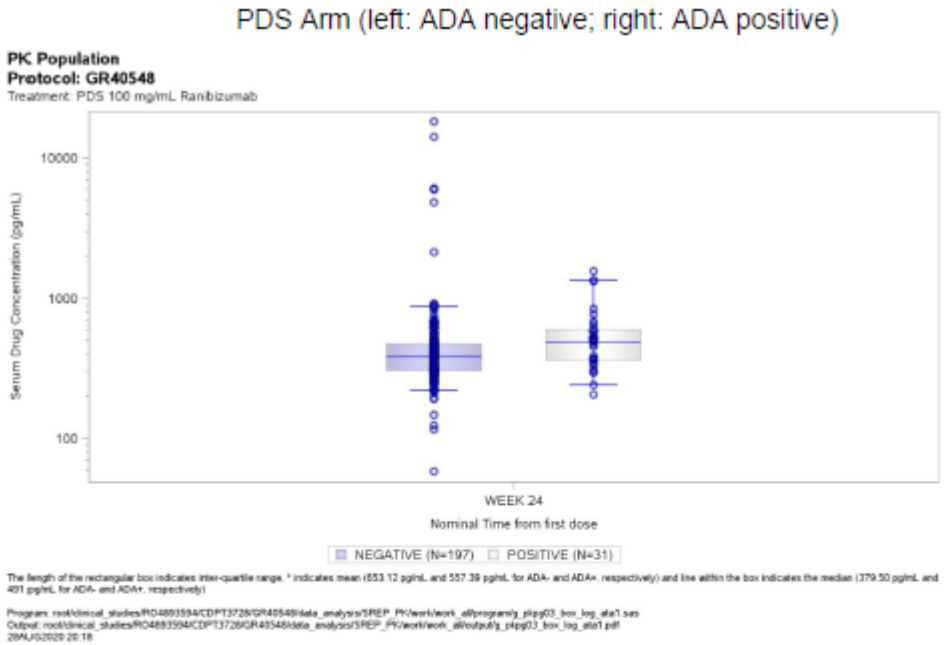
In Study GR40548, the overall mean time on study was 80.0 weeks in the PDS 100 mg/mL arm and 78.5 weeks in the intravitreal arm through the CCOD (11 September 2020 CCOD). Based on this CCOD, incidence of treatment emergent ADA to ranibizumab was 29 of 247 patients (11.7%) and 10 of 165 patients (6.1%) in the PDS 100 mg/mL arm and intravitreal ranibizumab 0.5 mg arm, respectively.

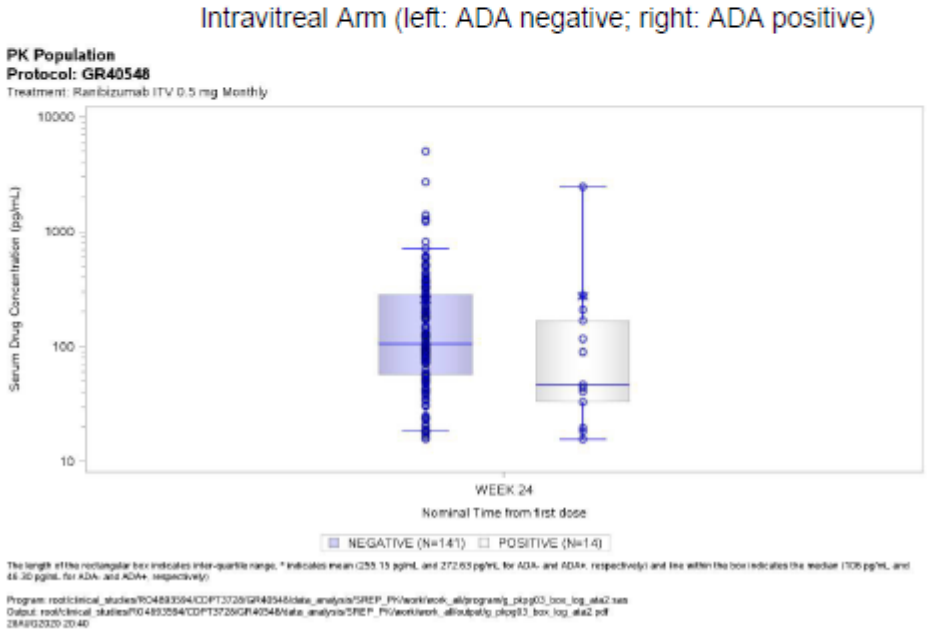
Overall, the incidence of treatment-emergent NAb to ranibizumab in Study GR40548 was low: 13 of 247 patients (5.3%) in the PDS 100 mg/mL arm, and 4 of 165 patients (2.4%) in the intravitreal arm.

Potential Impact of ADAs on PK

ADA impact on ranibizumab serum concentrations was evaluated in the PK population based on serum ranibizumab concentrations at Week 24 (representing a trough sample in both PDS and intravitreal arms). No apparent impact of ADA status on serum PK was observed in either treatment arm (Figure 21).

Figure 21 Plot of Serum Ranibizumab Concentrations at Week 24 by Treatment and ADA Status





Source: Primary CSR Study GR40548, Section 8.1

Potential Impact of Immunogenicity on Efficacy

Given the low number of patients with a positive ADA or NAb response to ranibizumab in Study GR40548, it is not possible to make definite conclusions on the impact of ADAs or Nabs on efficacy; however, there did not appear to be a meaningful difference in change from baseline in best corrected visual acuity (BCVA) in the study eye at Week 40, between ADA-positive and ADA-negative, or between NAb-positive patients and NAb-negative patients (Table 9).

Table 9 Summary of Change from Baseline in BCVA at Week 40 by ADA and NAb Status

Study GR40548 (CCOD: 27March2020)		
	PDS 100 mg/mL Arm (N = 247)	Intravitreal Arm (N = 167)
ADA Negative, n	213	149
Change from baseline in BCVA at Week 40		
Mean (SD)	0.2 (9.05)	0.4 (7.34)
95% CI	(-1.0, 1.5)	(-0.8, 1.6)
ADA Positive, n	34	15
Change from baseline in BCVA at Week 40		
Mean (SD)	0.0 (7.86)	2.9 (4.45)
95% CI	(-2.8, 2.8)	(0.4, 5.5)
NAb Negative, n	18	7
Change from baseline in BCVA at Week 40		
Mean (SD)	0.5 (7.00)	4.1 (4.26)
95% CI	(-3.0, 4.0)	(0.2, 8.1)
NAb Positive, n	14	7
Change from baseline in BCVA at Week 40		
Mean (SD)	-1.2 (9.36)	1.8 (5.04)
95% CI	(-6.9, 4.4)	(-3.5, 7.1)

ADA = anti-drug antibody; BCVA = best corrected visual acuity letter score; CCOD = clinical cut-off date; NAb = Neutralizing antibody; PDS = Port Delivery System with ranibizumab; SD = standard deviation.

Source: Study GR40548 Primary CSR Section 8.2.

Potential Impact of ADA on Safety

There were no major differences in the ocular or non-ocular adverse event (AE) profiles between ADA-positive patients in PDS 100 mg/mL arm and ADA-positive patients in intravitreal arm. However, the low number of patients with a positive ADA response precludes firm conclusions. As immunogenicity to intravitreally administered recombinant therapeutics may result in development of intraocular inflammation, summaries of intraocular inflammation by ADA and NAb status were performed (Table 10).

Table 10 Summary of Intraocular Inflammation in Study Eye by ADA and NAb Status

Study GR40548 (CCOD: 11 Sept 2020)				
	PDS 100 mg/mL Arm (N = 247)		Intravitreal Arm (N = 165)	
	Through 37 days	Day 38 to Day 294	Through 37 days	Day 38 to Day 294
ADA Negative				
# of Patients with intraocular inflammation/ADA Negative patients (%)	49/213 (23.0%)	12/213 (5.6%)	1/149 (0.7%)	0
ADA Positive				
# of Patients with intraocular inflammation/ADA Positive patients (%)	8/34 (23.5%)	1/34 (2.9%)	0	0
NAb Negative				
# of Patients with intraocular inflammation/NAb Negative patients (%)	4/18 (22.2%)	1/18 (5.6%)	0	0
NAb Positive				
# of Patients with intraocular inflammation/NAb Positive patients (%)	3/14 (21.4%)	0	0	0

ADA = anti-drug antibody; CCOD = clinical cut-off date; NAb = Neutralizing antibody; PDS = Port Delivery System with ranibizumab.

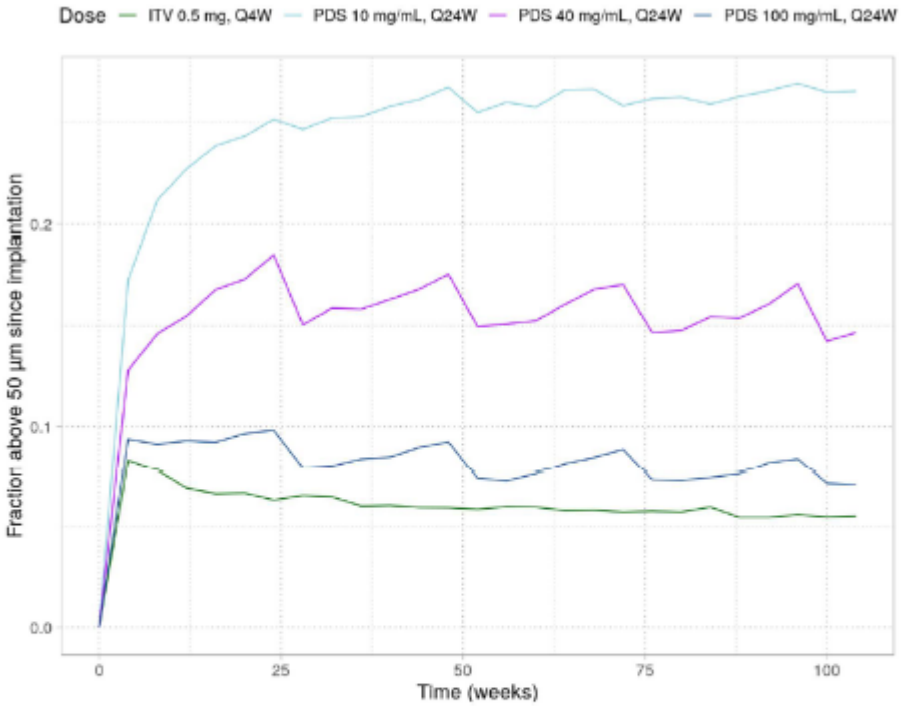
Intraocular inflammation was defined based on selected preferred terms according to the Standardization of Uveitis Nomenclature (SUN) (Jabs et al. 2005). Intraocular inflammation was defined as anterior uveitis (included iritis, iridocyclitis, anterior cyclitis, anterior chamber cell, flare, and inflammation); intermediate uveitis (included pars planitis, posterior cyclitis, hyalitis, vitritis, vitreous haze); posterior uveitis (included choroiditis, chorioretinitis, retinochoroiditis, retinitis, neuroretinitis, retinal vasculitis); panuveitis (included endophthalmitis) and events which were not otherwise specified (included eye inflammation, uveitis, post procedural inflammation, incision site inflammation, inflammation of wound, ocular vasculitis).

Population PK/PD analysis of CST

A population PK/PD model was developed where the concentration time-course profile in vitreous were related to the efficacy endpoint CST. The model was used to simulate how CST changes over time with different PDS dosing regimens compared to intravitreal ranibizumab 0.5 mg Q4W.

Two intravitreal injections of 0.5 mg ranibizumab (Q4W) followed by Q4W intravitreal injections of 0.5 mg or PDS of 10, 40 and 100 mg/mL refilled every 24 weeks were administered. CST was observed Q4W. Figure 23 shows the simulated average change from pre-treatment baseline over time for the different dose levels. This plot shows that PDS 100 mg/mL Q24W is predicted to give a similar reduction in CST as monthly intravitreal ranibizumab 0.5 mg, while PDS 10 mg/mL Q24W is predicted to give an increase in CST after the two initial intravitreal injections. Figure 22 shows the fraction of subjects that are predicted to have an increase more than 50 µm in CST since time of implantation. About 27% of the subjects receiving the lowest PDS dose of 10 mg/mL Q24W are predicted to have an increase of more than 50 µm. Only 7% of the subjects in the highest PDS dose of 100 mg/mL Q24W are predicted to have an increase of more than 50 µm.

Figure 22 Simulated Fraction of Patients with an Increase of CST Above 50 µm since Randomization vs Time From Randomization

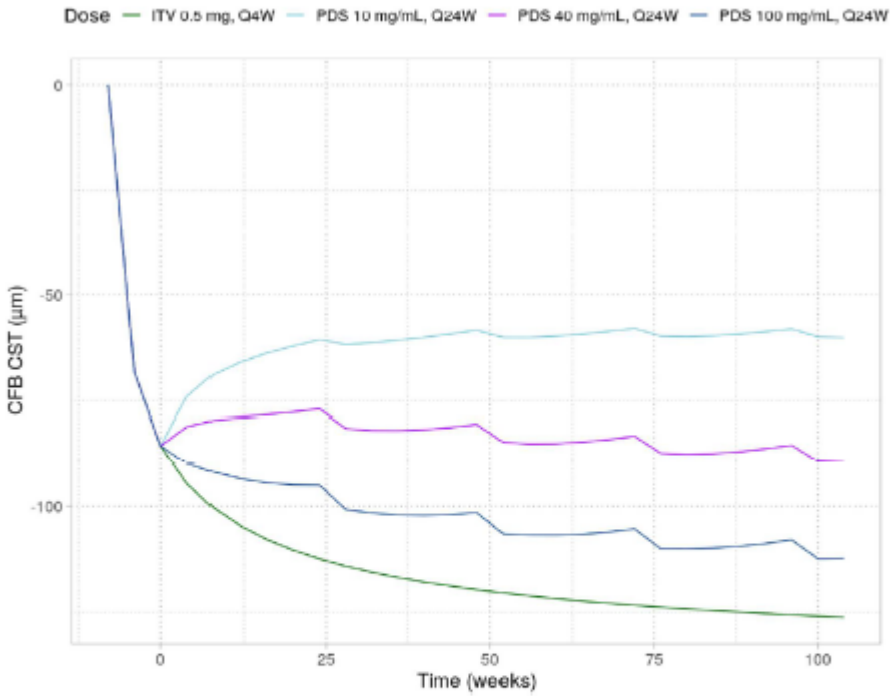


CST = central subfield thickness; ITV = Intravitreal; PDS = Port Delivery System with ranibizumab, Q4W = every 4 weeks; Q24W = every 24 weeks.

Note: Simulation of two initial administrations of intravitreal ranibizumab 0.5 mg followed by randomization to either intravitreal ranibizumab 0.5 mg Q4W or PDS with 10, 40 and 100 mg/mL refilled Q24W (n=10,000 patients/arm). Plot includes both inter-individual variability and residual unexplained variability.

Source: Report 1104047: Figure 21

Figure 23 Simulated Mean Change in CST from Initial nAMD Diagnosis versus Time from Randomization



CFB = change from baseline; CST = central subfield thickness,
ITV = Intravitreal; PDS = Port Delivery System with ranibizumab; Q4W = every 4 weeks;
Q24W = every 24 weeks.

Note: Simulation of two initial administrations of intravitreal ranibizumab 0.5 mg followed by randomization to either intravitreal ranibizumab 0.5 mg Q4W or PDS with 10, 40 and 100 mg/mL refilled Q24W (n=10,000 patients/arm)

Source: Report 1104047: Figure 19

3.3.2. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetics of ranibizumab administered via the PDS were investigated in three clinical studies: study GX28228 (Ladder), study GR40548 (Archway; pivotal efficacy study), and study GR40549 (Portal; extension study). The PDS is designed to provide continuous delivery of ranibizumab in the vitreous, therefore, the PK profile of ranibizumab administered via the PDS differs from that of ranibizumab administered via intravitreal injection.

PK was characterized by noncompartmental analysis in studies GX28228 and GR40548. In addition, PopPK analyses were conducted to describe ranibizumab PK in serum and predict ranibizumab concentrations in the vitreous and to explore covariate effects on the PDS release rate, as well as ranibizumab drug disposition following treatment with PDS.

The recommended dose of Susvimo is 2 mg (0.02 mL of 100 mg/mL solution) continuously delivered via the implant with refills administered every 24 weeks (approximately 6 months).

Analytical methods

ELISA-based methods were used for the quantification of ranibizumab in human serum and aqueous or vitreous humor. Both methods were adequately validated and investigated; performance parameters met the acceptance criteria of the EMA guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

For the qualitative determination of anti-ranibizumab antibodies in human serum, a bridging antibody ELISA was developed and validated. The assay performed with adequate precision and sufficient drug tolerance. For the detection of neutralizing antibodies to ranibizumab, an ELISA-based assay was developed with a preceding step in which all VEGF present in the sample is removed by magnetic bead extraction. Validation was overall acceptable. Interference was observed in the presence of 100 ng/mL of bevacizumab. It is possible that prior intravitreal injections of bevacizumab could have impacted NAb results for timepoints early in the studies (Randomization, Day 14, and Month 1). The Applicant is asked to present data on NAb status of ADA-positive samples from early study timepoints (randomization, Day 14, Week 4/Month 1) from studies GX28228 and GR40548 **(LoOI).**

PopPK / PopPK/PD model

For the population PK model, data from Study GX28228 (Ladder) were used for model development, while data from Study GR40548 (Archway) were used for validation of the final model. Patients previously treated with intravitreal bevacizumab were excluded due to bevacizumab interference in the ranibizumab PK assay, which is endorsed. Nevertheless, all patients having received prior intravitreal bevacizumab and additionally all patients with on study fellow eye treatment or on study supplemental intravitreal ranibizumab injections were excluded in NCA, which was not the case for population PK modelling. In response to the Day 120 LoQ, the applicant presented data confirming that fellow eye treatment or supplemental intravitreal ranibizumab injections were adequately captured in the model.

The serum PK profile of ranibizumab was described by a one-compartment disposition model with first-order absorption into and first-order elimination from the systemic circulation. Model development is considered adequate. In covariate testing, CRCL was found to be an influential covariate on ranibizumab clearance from serum, confirming earlier findings.

Deviations of the PopPK model were identified in goodness-of-fit (GOF) and visual predictive check (VPC) plots. Overall, it is questioned whether the model, due to the observed deviations in predicted ranibizumab concentrations as compared to observed concentrations, provides adequate estimates of ranibizumab concentrations on the population level. It is suggested that mechanisms involved in ranibizumab kinetics when administered by PDS, especially regarding drug release, are even more complex than could be described by this "simple" model.

The final population PK model incorporates two main aspects that required further clarification by the Applicant:

- a time- and concentration-dependent release rate constant (kr) was assumed based on the experimental data. The concentration dependence on kr has been properly justified and it might be scientifically plausible. However, the impact on PK profiles and scientific rationale of a time-dependency on kr was lacking. The Applicant clarified that the time-dependency effect on release rate constant is refill independent and the time-dependency effect was considered to accommodate a structural deviation in the release rate within a refill-exchange interval. No additional information has been provided to clarify why this process is affecting the release rate. However, based on the impact of the time-dependency effect and the lack of any significant difference across refills, the issue is not further pursued.
- large residual unexplained variability has been observed, which was characterized through a residual error (28%), early residual error (74%), a time-dependent rate constant early error (0.2 d^{-1}) and IIV on residual error (~70%). The early residual error component helps to characterize the higher concentrations (outliers) that could not be described through the structural model. Therefore, the use of an early residual error could highlight a structural model misspecification. A justification was provided in response to the Day 120 LoQ. Uncertainty with regard to the high residual error remains, since the Applicant recognized that the shunt model was able to describe

better the initial high observations following the very first days after implantation or refill-exchange. However, the final model does not incorporate the shunt component to characterize such concentrations, despite both models providing similar performance in the long-term concentrations. The model comparison demonstrates that the large residual error model in the final popPK model is partially explained by the shunt component and this should be considered in the final popPK model (**LoOI**). Only if minimization errors occur or large condition number is present in the final model including the shunt component vs the current final popPK model, a more parsimonious model could be accepted.

A slight model misspecification was identified at > 6 months after implantation, but this posology is not claimed by the Applicant. The model evaluation analyses considering the pooled dataset including both Study GX28228 and GR40548 showed the adequacy of the model to capture the experimental observations of ranibizumab for all dose levels tested, especially after the second dose and onwards. The characterization of observations below the lower limit of quantification is adequate. Therefore, the current popPK model supports the PDS administration over the 6-month dosing interval across the dose levels tested.

In addition, a population PK/PD model was developed to explore the relationship between concentration in the vitreous and the efficacy endpoint central subfield thickness (CST). PKPD analysis included the Phase II study GX28228 and study GR40549. The final CST model was an indirect response model with a linear drug effect on kout. No covariate relationships were seen for the drug effect. GOF plots from the final model as well as from model validation with GR40548 study data reveal that CST on the population level may not be reliably estimated by the model. As discussed by the applicant, the population prediction from an indirect response model is dependent on the pre-treatment baseline value. CST at baseline is considered to be highly variable (large IIV estimates) and thus, the entire curve is misrepresented if the pre-treatment baseline is poorly described for a subject. As a result, a fixed CSTmin was included in the model, presumably to create a functional model which allows predictions at all. However, this is not considered to truly reflect the in vivo situation.

Additionally, the popPK/PD model incorporates large inter-individual random effects that could affect the application of the popPK/PD model for dose selection. Eta-shrinkage values were provided and considered adequate for covariate evaluation.

Overall, the informative value of the described PopPK/PD model is considered questionable, but data may be seen as supportive.

ADME

Drug release rate from PDS was characterized in vitro and revealed that the PDS implant continuously released ranibizumab down to 3.55 µg/day for at least 24 weeks. Diffusion of ranibizumab was however dependent on the formulation composition and higher release was seen during the first weeks after implantation. PK parameters such as Cmax and Tmax describing ranibizumab absorption or appearance in serum are dependent on release from PDS/vitreous compartment. According to PK data from study GX28228 in both the full PK population and PK population with exclusions, peak serum ranibizumab concentrations are detected approx. one month post implantation. After refill however, median Tmax was about 7 days. The Applicant explained that maximum serum concentrations after a refill-exchange procedures could be earlier than after implantation due to the refill bolus, by which a small dose (~2.5%) of ranibizumab is released through the release control element into the vitreous at the time of a refill-exchange procedure. The identification of a clear Tmax was generally challenging due to the relatively flat concentration-time profile and small differences in the profile could have led to large differences in observed Tmax. Results for Cmax were however judged to be reliable since this parameter is less sensitive to the exact sampling time. This is endorsed.

In study GR40548 and the PopPK analysis, Cmax was approx. 50% lower as compared to Cmax described in study GX28228. It was explained that large data variability of Cmax contributed to the higher mean or geometric mean Cmax described in Study GX28228 as compared to Study GR40548. The lower variability seen in Study GR40548 is a result of fewer observed high initial spikes after implant insertion. It is suggested that the high initial spikes observed in Study GX28228 are caused by the transfer of a small amount of drug directly to serum, potentially due to transient direct access to blood circulation through the needle wound. This can be followed, although it seems unexpected that high spikes have only been observed in Study GX28228 and not in Study GR40548. Since the sample size for Cmax in both studies is low (n=27-29), no valid conclusions may be drawn at this point. The Applicant is however asked to further elaborate on this issue and should discuss whether high initial spike concentrations were anyhow related to previous versions of instructions for use (prior to IFU version 10/before May 2016) and simultaneously occurring high rates of vitreous haemorrhages (**LoOI**).

Vd was not determined by noncompartmental analyses and was fixed to the previous value of 3270 mL in the popPK model. The apparent half-life of ranibizumab administered by PDS 100 mg/mL in study GX28228 was 119.07 days after implantation and 143.87 days after refills, but should be interpreted with caution, given the low numbers of patients and rather infrequent sampling.

Dose-proportionality

The release rate constant kr and any PK parameters that depend on that constant are both dose- and time-dependent. As such, an increasing kr over time and a decreasing kr with dose in the implant was observed. As concentration is highest initially after implantation/refill, both effects work in tandem and affect kr in the same direction over time, however, the time effect is the more important effect, over time kr changes more than the difference between dose levels at start.

In general, PK of ranibizumab in serum after administration by PDS appeared dose-proportional; an evaluation additionally provided by the Applicant on data from Study GX28228 (AUC0-inf and Cmax) showed a linear relationship across the dose levels evaluated (10-100 mg/mL).

Intra- and inter-individual variability

High variability in ranibizumab concentrations was observed early after dose (implantation/refill): some administrations showed large concentration spikes after dose while others did not. This is also resembled in a large %CV of Cmax in study GX28228 (256.6 – 272.5%). Variability described as %CV on AUC per dosing interval was 37 – 71% in studies GX28228 and GR40548.

Similarly, in the final popPK model, the residual error model consists of a constant part (0.285) and one part with a high initial value (0.738) that declines with a rate constant 0.208 d^{-1}.

The between patient variability in vitreous concentrations is primarily a result of the estimated variability in PDS release rate which is informed by the observed rate of decline in serum. Inter-individual variability in release rate was estimated to be rather small at 16.2%. IIV on Clearance was estimated to be 25.7%.

PK in the target population

In **study GX28228**, Cmax in the PK population with exclusions was 1080.7 pg/mL after implantation and 1131.01 pg/mL after refills. The AUC(0-last) throughout the different dosing intervals was 90.83 ng*day/mL after implantation and 66.12 ng*day/mL after refills.

In **study GR40548**, the serum ranibizumab concentration-time profile in the PDS 100 mg/mL arm appeared consistent across implantation and subsequent refills with no accumulation observed. As such, the geometric mean serum ranibizumab concentration was 330 pg/mL at Week 24 (24 weeks after implant insertion) and 250 pg/mL and 210 pg/mL at Weeks 48 and 72 (24 weeks after 1st and 2nd refill-exchange, respectively).

In the PK-evaluable population, the geometric mean of serum Cmax was 450 pg/mL for the 100 mg/mL PDS. Serum Cmin was determined to be 300 pg/mL. In contrast, the geometric mean of Cmax, determined in serum on Day 2 (1-5 days post dose) was 1840 pg/mL for intravitreal ranibizumab injections. Serum Cmin was 28.8 – 58.9 pg/mL throughout the treatment period up to Week 72. Thus, it is suggested that ranibizumab serum concentrations achieved with the PDS are contained within the concentration range achieved with monthly intravitreal ranibizumab injections at the 0.5 mg dose.

The change in serum concentrations over the 24-week refill-exchange interval was relatively small. In addition, Ctrough levels after 24 weeks with the 100 mg/mL PDS were largely above the Ctrough reached with monthly intravitreal injections of 0.5 mg ranibizumab. In this regard, less frequent dosing, as for example conducted in study GX28228, could have been considered as well. Still, the proposed dosing regimen currently does not give rise to safety concerns based on ranibizumab exposure, as no accumulation is observed and serum concentrations achieved with the PDS are contained within the concentration range achieved with monthly intravitreal ranibizumab injections at the 0.5 mg dose.

AUC(0-168days) for the PDS in the PK-evaluable population was 56.27 ng*day/mL.

PK analysis in aqueous humor confirmed that ranibizumab did not accumulate in the aqueous humor when administered with refill-exchange every 24 weeks.

Based on trough concentrations determined at Week 24, 48 and 72 in aqueous humor, ranibizumab concentrations reached with the 100 mg/mL PDS (671 – 1350 ng/mL) were approx. 3-fold higher than concentrations reached with intravitreal injections of 0.5 mg/mL (239 – 407 ng/mL). Peak concentrations of ranibizumab in aqueous humor after intravitreal injection have not been measured in this study. However, referring to literature, ranibizumab Cmax after intravitreal injection of 0.5 mg ranibizumab was 56,100 ng/mL (peak on Day 1 post injection). Thus, ranibizumab concentrations reached in aqueous humor with the 100 mg/mL PDS are also within the range of intravitreal ranibizumab.

In response to the Day 120 LoQ, an update on PK data from Study GR40548, including Week 96 assessments, was provided. Over time (up to study week 96), a slight decrease in both the median serum concentrations and median aqueous humor concentrations was observed for the PDS 100 mg/mL arm. However, serum concentrations consistently remained above the Ctrough serum concentrations observed in the intravitreal arm and were thus maintained within the range experienced with monthly intravitreal ranibizumab 0.5 mg injection. Nevertheless, the Applicant should further discuss whether decreasing serum and ocular ranibizumab concentrations could originate from changes in the implant or implant kinetics (**LoOI**).

An update on PK data was also provided for the extension study GR40549. However, the study has not yet been completed and patient numbers are overall too low to draw any valid conclusions. Given that a decrease in ranibizumab concentrations was observed with the PDS over time in Study GR40548 and it is currently not clear whether ranibizumab concentrations would (and to which extent) decrease further, the Applicant should commit to provide the full PK data set from Study GR40549 as post-authorization measure, once the study has been completed and the CSR is finalized (**LoOI**).

PopPK-derived simulations revealed that the 10 mg/mL PDS dose is below the ranibizumab trough concentrations of the intravitreal regimen, while the 40 mg/mL dose remains above the trough values of the intravitreal regimen for 8 weeks. For the 100 mg/mL PDS dose, concentrations remain above the trough values of the intravitreal regimen for approx. 42 weeks. As mentioned earlier in assessor's comment regarding study GR40548, the presented results indicate that longer treatment intervals could also be appropriate. Cmax of the 100 mg/mL PDS was estimated to be below Cmax achieved with the intravitreal regimen. In addition, AUCt for the last PDS dosing interval (Week 72-96) and average ranibizumab concentrations were lower for the PDS 100 mg/mL than for the intravitreal regimen. Overdosing due to Q24W PDS refills may therefore be excluded.

The popPK model was further used to analyse vitreous ranibizumab concentrations. Vitreous ranibizumab concentrations were predicted to be approx. 52,000-fold higher than ranibizumab concentrations in serum. A model comparison performed between intravitreal and PDS administration using the final and pooled models in the vitreous suggested minor differences in exposure for PDS administration with less oscillation compared to intravitreal injections.

PK in special populations

Due to prior knowledge, CrCL was assessed as covariate in PDS clinical trials. Similar to the previous model developed for intravitreal ranibizumab injections, CrCL was found to be a significant covariate in the PopPK model, as higher CrCL led to an increase in ranibizumab CL. However, this effect was not considered clinically relevant, given the large intersubject variability in systemic clearance and the generally low serum ranibizumab concentrations. Consequently, no dose adjustments are deemed necessary in case of renal impairment. This is agreed.

Given the mechanism of drug release for PDS implant (driven by ranibizumab diffusion), an impact of patient factors on the release rate was considered unlikely. The assessment of covariates on the PDS implant release rate was therefore limited covariates of clinical interest, which are age and sex. Both were found to have no significant influence on PDS release rate.

Pharmacodynamics

No specific pharmacodynamic studies were performed in humans. PD parameters investigated in studies GX28228, GR40548 and GR40549 (CST, CPT) are assessed in the section on clinical efficacy.

Immunogenicity

In Study GX28228, the treatment-emergent ADA incidence among patients treated with PDS 100 mg/mL PRN was 15.3%, while the incidence of treatment-emergent ADA after intravitreal injection of 0.5 mg ranibizumab was 14.6%. Treatment-emergent NAb incidence was 3.39% and 0% for the PDS and for the IVT 0.5 mg regimen, respectively.

In Study GR40548, the treatment-emergent ADA incidence among patients treated with PDS 100 mg/mL Q24W was 13.4%, while the incidence of treatment-emergent ADA after intravitreal injection of 0.5 mg ranibizumab was 9.1%. Treatment-emergent NAb incidence was 6.1% and 2.4% for the PDS and for the IVT 0.5 mg regimen, respectively.

As mentioned earlier, all ranibizumab ADA samples that were collected and analysed had corresponding ranibizumab concentrations that were unlikely to interfere in the ADA assay.

Overall, the incidence of ADA and NAb to ranibizumab was rather low and no meaningful differences were observed between PDS and IVT route of administration. In studies GX28228 and GR40548, a similar ADA incidence range for the IVT regimen as previously observed (2.0-9.4%) in the intravitreal ranibizumab clinical studies was confirmed.

The incidence of ADA and NAb is slightly higher using PDS vs IVT administration (15.3% vs 14.6% (ADA) and 3.4% vs 0 (NAb)-Study GX28228; 13.4% vs 9.1% (ADA) and 6.1% vs 2.4% (NAb)-Study GR405448).

No impact of ADA positivity on ranibizumab exposure at Week 24, efficacy (as evaluated by change from baseline in BCVA at Week 40) or safety (intraocular inflammation) was observed. Nonetheless, it is agreed with the applicant that due to the low incidence of ADAs observed to date, the results do ultimately not provide definitive conclusions.

PK/PD analysis

Population PK/PD analysis was conducted to simulate the relationship between the different ranibizumab dosing regimens (PDS at the 10 mg/mL, 40 mg/mL, and 100 mg/mL and intravitreal regimen at 0.5 mg Q4W) and the efficacy endpoint central subfield thickness (CST). Simulations illustrated that a PDS dose of 100 mg/mL refilled Q24W resulted in similar reduction of CST as Q4W intravitreal injections of 0.5 mg, while PDS 10 mg/mL gives an increase in CST after the two initial intravitreal injections. Additionally, the fraction of subjects that increase more than 50 µm in CST since time of implantation was analysed. Simulations revealed that approx. 27% of the subjects receiving the lowest PDS dose of 10 mg/mL increased more than 50 µm, while only 7% of the subjects in the highest PDS dose of 100 mg/mL increased more than 50 µm. These results support the choice of the 100 mg/mL PDS regimen. The difference in change from baseline CST appears only marginal with PDS 100 mg/mL at refill intervals of Q36W as compared to refill intervals of Q24W.

The results suggest the adequacy of the dose selected (100 mg/mL) in order to achieve similar central subfield thickness reduction compared to ITV administration of ranibizumab. Surprisingly, sustained levels of ranibizumab achieved with the PDS dose of 100 mg/mL did not achieve the same CST reduction nor the fraction of subjects that increase more than 50 µm in CST since time of implantation compared to ITV administration.

However, the PDS dose of 100 mg/mL predictions could be under-predicted, since the popPK model under-predicted the observed levels. This is of great relevance, since it would affect both the efficacy levels evaluated (CST and fraction of subjects that increase more than 50 µm in CST since time of implantation) and the safety levels.

In response to the Day 120 LoQ, the Applicant provided a Monte-Carlo simulation evaluating the impact of different dose schedules of PDS on CST reduction and the fraction above 50 µm since implantation. The analyses showed that ITV 0.5 mg Q4W shows higher efficacy on both endpoints over the time-range evaluated. On the other hand, PDS 100 mg/mL Q16W was the regimen more close to the ITV arm. It is acknowledged that very similar results were obtained between Q16W and Q24W, which may benefit patient's treatment and refill in clinical practice. In general, the proposed schedule of PDS 100 mg/mL Q24W showed less than 10% of fractions above 50 µm and central subfield thickness change from baseline of 100 µm. Therefore, the current dose regimen proposed could be considered as adequate based on the model-predicted efficacy status achieved compared to ITV administration.

Still, the described model deficiencies should be kept in mind in the interpretation of PopPK/PD derived data.

3.3.3. Conclusions on clinical pharmacology

Overall, pharmacokinetics and pharmacodynamics of ranibizumab delivered intravitreally by PDS has been adequately characterized.

Several outstanding issues remain which need to be addressed in more detail.

3.3.4. Clinical efficacy

Dose-response study

Study GX28228 (Ladder) is a Phase II, multicenter, dose ranging, randomized, active treatment-controlled study. This study evaluated the efficacy, safety, and pharmacokinetics of ranibizumab delivered through the PDS using three different ranibizumab formulation arms (10 mg/mL, 40 mg/mL, and 100 mg/mL), refilled on a PRN (pro-re nata, as needed) regimen, compared with the control arm (0.5 mg monthly intravitreal injections of 10 mg/mL ranibizumab formulation) in patients with nAMD. The study also evaluated the safety of the PDS.

Study [Status]	Overall Design	Patient Population (Number of Patients)	Dose, route and Regimen: Number of Patients	Objectives	Analysis/Data Cut-off/CSR
GX28228 [d] (Ladder main study) (Supportive study) [Completed]	Phase II, dose-ranging, randomized, active treatment-controlled, multicenter study	nAMD responsive to anti-VEGF with maximum 9 months since diagnosis; BCVA 20/20 to 20/200; subfoveal CNV or juxtafoveal with subfoveal component (232 patients randomized and 220 treated excluding 7 patients treated at a non-compliant site) [e]	PDS 10 mg/mL PRN: 58 patients PDS 40 mg/mL PRN: 62 patients PDS 100 mg/mL PRN: 59 patients Intravitreal ranibizumab injection (0.5 mg) monthly: 41 patients	Primary efficacy: • Time to first PDS refill See protocol for the full list including safety and PK	Final Analysis/ GX28228 Final CSR, Report 1097181 GX28228 Addendum CSR, Report 1097181

[d] Data on the performance of the PDS devices were derived from Study GX28228.
[e] Five patients randomized to the PDS groups decided not to undergo implantation because of the unexpectedly high incidence of vitreous hemorrhage before optimization of the Instructions for Use. Seven patients from a non-compliant site were randomized and treated but were not analyzed.

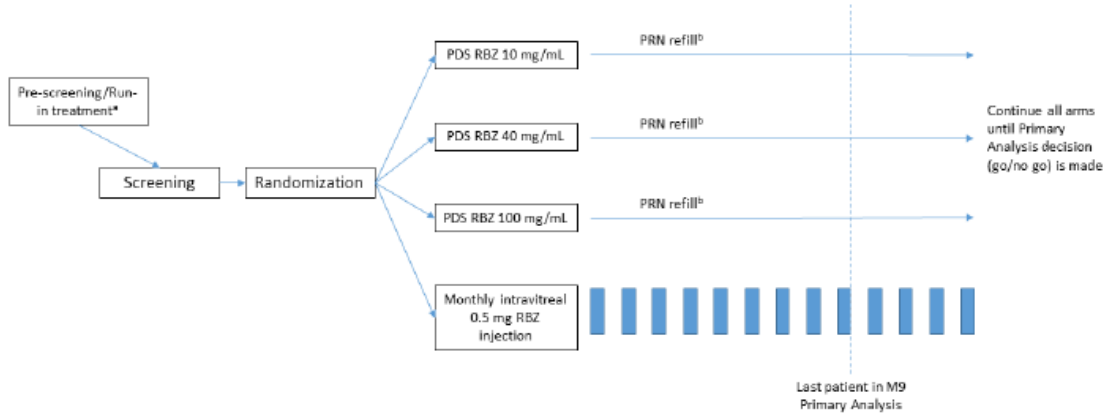
[Table 3 from Clinical Overview]

Approximately 220 patients at up to 60 sites in the United States were planned to be randomized in a 3:3:3:2 ratio to PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms and ranibizumab IVT arm, respectively, within an approximate 24-month period of time.

The study has been completed.

Study design

Figure 1 Study Schema (Main Study)



M9 = Month 9; PRN = as needed (as per the refill criteria); PDS = Port Delivery System with ranibizumab
[a] See Section 3.6.3 for details of pre-screening/run-in treatment with intravitreal ranibizumab
[b] See Section 3.6.1 for details of refill criteria

[Figure 1 from final CSR]

Patients had the implant (prefilled with approximately 20 µL of either the 10 mg/mL [approximately 0.2 mg dose], 40 mg/mL [approximately 0.8 mg dose], or 100 mg/mL formulation [approximately 2-mg dose] of ranibizumab) surgically inserted in the study eye at the Day 1 visit following their randomization visit.

Starting at the Month 1 visit, patients were evaluated monthly for the need for implant refill with the 10 mg/mL, 40 mg/mL, or 100 mg/mL formulations of ranibizumab according to their randomization as per protocol-specified refill criteria (see below). If the criteria were not met, no implant refill was given. At each refill, a volume of approximately 100 µL of ranibizumab was injected in situ into the implant through the septum to exchange the remaining contents of the implant with newly introduced ranibizumab. The volume of newly introduced ranibizumab remaining in the implant after the refill-exchange procedure

was approximately 20 µL. After the initial fill of the implant with ranibizumab, patients were evaluated for their implant refill according to protocol-specified refill criteria (see below) at each of their scheduled visits until the study treatment completion.

A protocol amendment (Version 5) allowed enrollment and implant insertion surgeries to be paused to enable real-time review of post-implant insertion safety data by the Internal Monitoring Committee (IMC). The high rate of vitreous hemorrhage observed prompted a modification to the Instructions for Use (IFU). On implementation of this pause, dosing continued as per the protocol for patients who had already received study drug (e.g., patients who have performed Day 1 visit), while patients who had not yet received study drug stayed in Pre-Screening, Run-In, Screening, or Randomization period (as applicable) and received monthly open-label intravitreal ranibizumab treatment until enrollment and implant insertion surgeries were restarted. Patients who had been randomized but not yet received the study drug repeated the Randomization assessments after enrollment and implant insertion surgeries recommenced, and before receiving the study drug according to optimized IFU.

After Version 7 of the protocol was implemented, if a study patient met criteria for lack of clinical efficacy, he or she received a supplemental injection (referred to as rescue injections in the protocol) with open-label ranibizumab (0.5-mg intravitreal injection of 10 mg/mL formulation) followed by a refill with the 100 mg/mL formulation one month later. After that, he or she received the 100 mg/mL formulation for all future refills, when refill criteria were met.

Refill Criteria

Starting at the Month 1 visit, all randomized patients were assessed monthly for refill.

At 1 month after initial fill, patients randomized to the PDS arms had their implant refilled only if **any** of the following criteria was met:

- Decrease of ≥ 10 letters in BCVA at the current visit compared with the baseline BCVA, due to nAMD disease activity

OR

- Increase in CFT of ≥ 100 µm at the current visit compared with the baseline CFT, due to nAMD disease activity

OR

- Presence of new macular hemorrhage, due to nAMD disease activity

For subsequent assessments, patients randomized to the PDS arms had their implant refilled only if **any** of the following criteria was met:

- Increase in CFT of ≥ 75 µm on SD-OCT at the current visit compared with the average CFT over the last 2 available measurements, due to nAMD disease activity

OR

- Increase in CFT of ≥ 100 µm from the lowest CFT measurement on study, due to nAMD disease activity

OR

- Decrease of ≥ 5 letters in BCVA at the current visit compared with the average BCVA over the last 2 available measurements, due to nAMD disease activity

OR

- Decrease of ≥ 10 letters from best recorded BCVA on study, due to nAMD disease activity

OR

- Presence of new macular hemorrhage, due to nAMD disease activity

CFT measurements used to determine need for refill were assessed by the investigator. From 14 January 2017, CFT measurements were assessed by the investigator and then confirmed by a central reading center.

Patients assigned to the PDS arms were scheduled for a safety evaluation visit 7 (± 2) days after each refill.

Management of Patients Who Met Lack of Clinical Efficacy Criteria

Criteria for meeting lack clinical efficacy are shown in Table 6 (as per the protocol version at the time of the final analysis, these criteria were amended in Version 6 of the Protocol).

Patients who met criteria for lack of clinical efficacy received supplemental treatment with intravitreal injection of open-label ranibizumab. One month after meeting criteria for lack of clinical efficacy and receiving a supplemental intravitreal ranibizumab injection, the patient received a mandatory refill with the 100 mg/mL ranibizumab formulation. At the next monthly visit and until the end of the study, the patient received a refill with the 100 mg/mL ranibizumab formulation if the patient met the protocol-defined refill criteria.

Table 6 Lack of Clinical Efficacy Criteria

Event	
Lack of clinical efficacy	Loss in BCVA of ≥ 15 letters from the best recorded BCVA on study following 2 consecutive ranibizumab implant refills (as per protocol-specified refill criteria) occurring 1 month apart due to nAMD disease activity and not attributable to a change in the ocular media (i.e., cornea, lens, aqueous or vitreous humor, epiretinal membrane development, etc.) unless there was at least a five-letter increase in BCVA, in which case a refill occurred. and/or Increase in CFT ≥ 150 μm from the lowest CFT measurement on study following 2 consecutive ranibizumab implant refills (as per protocol-specified refill criteria) occurring 1 month apart due to nAMD disease activity and not attributable to a change in the ocular media (i.e., cornea, lens, aqueous or vitreous humor, epiretinal membrane development, etc.) unless there was a decrease in CFT ≥ 75 microns from the last refill, in which case a refill occurred.

[Table 6 from final CSR]

The study was to continue until the Sponsor decided, based on the primary analysis results, to either terminate the study and discontinue study treatment or to offer patients entry into the PDS Extension study (GR40549 [Portal]). Study participation for patients in the implant arms (excluding screening period) was expected to last approximately 13-38 months dependent on the date of their randomization to the study.

Study population

Patients with subfoveal neovascularization secondary to AMD diagnosed within 9 months and treated with and responsive to intravitreal anti-VEGF agents were enrolled in the study.

The key inclusion criteria were as follows:

- Age ≥ 50 years

- Newly diagnosed with nAMD within 9 months prior to screening visit

- Patient must have received at least 2 prior anti-VEGF injections (including ranibizumab, aflibercept or bevacizumab). However, the most recent anti-VEGF injection must have been ranibizumab and must have occurred at least 7 days prior to the screening visit.

- Demonstrated response to prior intravitreal anti-VEGF treatment, as evidenced by the following:

Decrease in central foveal thickness (CFT) of >50 µm since commencing intravitreal anti-VEGF treatment

OR

Stable or improved BCVA since commencing intravitreal anti-VEGF treatment

- BCVA using ETDRS charts of 20/20 - 20/200 Snellen equivalent

- All macular CNV lesions were permitted

The key exclusion criteria were as follows:

- Subfoveal fibrosis, subfoveal atrophy, or subretinal hemorrhage (greater than 2.54 mm^2 involving the center of the fovea) in the study eye

- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye

- Use of anticoagulants, antiplatelets (other than aspirin), or medications known to exert similar effects at the time of study entry for a pre-existing condition

The study population enrolled in the Phase II study GX28228 was overall comparable to the population enrolled in the Phase III study with regard to ocular eligibility criteria. In addition, patients must have demonstrated response to any anti-VEGF intravitreal therapy within 9 months prior to screening.

However, in study GX28228 a minimum of 2 prior anti-VEGF injections (including ranibizumab, aflibercept or bevacizumab) was required for inclusion in the study, in contrast to the Phase III study, where at least 3 prior injections and one additional ranibizumab IVT injection at screening were required in order to increase the likelihood for patients to reach a vision plateau prior to randomization. Thus, patients in the Phase II study had most likely not yet reached their vision plateau.

Study objectives

Table 3 Efficacy Objectives and Corresponding Endpoints for Study GX28228

Primary Efficacy Objective	Corresponding Primary Endpoint
• To evaluate the relative efficacy of 10 mg/mL, 40 mg/mL, and 100 mg/mL formulations of ranibizumab, delivered via the implant [a]	• Time until a patient first requires the implant refill according to protocol-defined refill criteria
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate and compare the relative efficacy of 10 mg/mL, 40 mg/mL, and 100 mg/mL formulations of ranibizumab, delivered via the implant, to that of 10 mg/mL (0.5 mg dose) monthly intravitreal ranibizumab injections, as assessed by visual acuity	• Change in BCVA from baseline at Month 9 • Average change from baseline in BCVA over time • Change in BCVA from baseline over time
• To evaluate the efficacy of 10 mg/mL, 40 mg/mL, and 100 mg/mL formulations of ranibizumab, delivered via the implant, with that of 10 mg/mL (0.5 mg dose) monthly intravitreal ranibizumab injections over time, as assessed by CFT on SD-OCT	• Change from baseline in CFT (defined as the retinal thickness in the center of the fovea) over time, as assessed on SD-OCT by the central reading center
• To evaluate the proportion of patients with an improvement of ≥ 15 letters in BCVA from baseline	• Proportion of patients with an improvement of BCVA from baseline of ≥ 15 letters over time
• To explore time to subsequent implant refills according to protocol-defined refill criteria [a]	• Time to subsequent implant refills according to protocol-defined refill criteria

BCVA = best corrected visual acuity; CFT = central foveal thickness; SD-OCT = spectral-domain optical coherence tomography.

[a] The endpoints supporting these objectives are not presented in the SCE and can be found in the Study GX28228 Final CSR.

[Table 3 from Summary of Clinical Efficacy]

The main objective of the dose-finding study GX28228 was to identify the most appropriate dose and regimen for the PDS for the subsequent pivotal Phase III study. The study assessed the time to first refill (TTFR) as primary endpoint with 10 mg/mL, 40 mg/mL, and 100 mg/mL ranibizumab formulations.

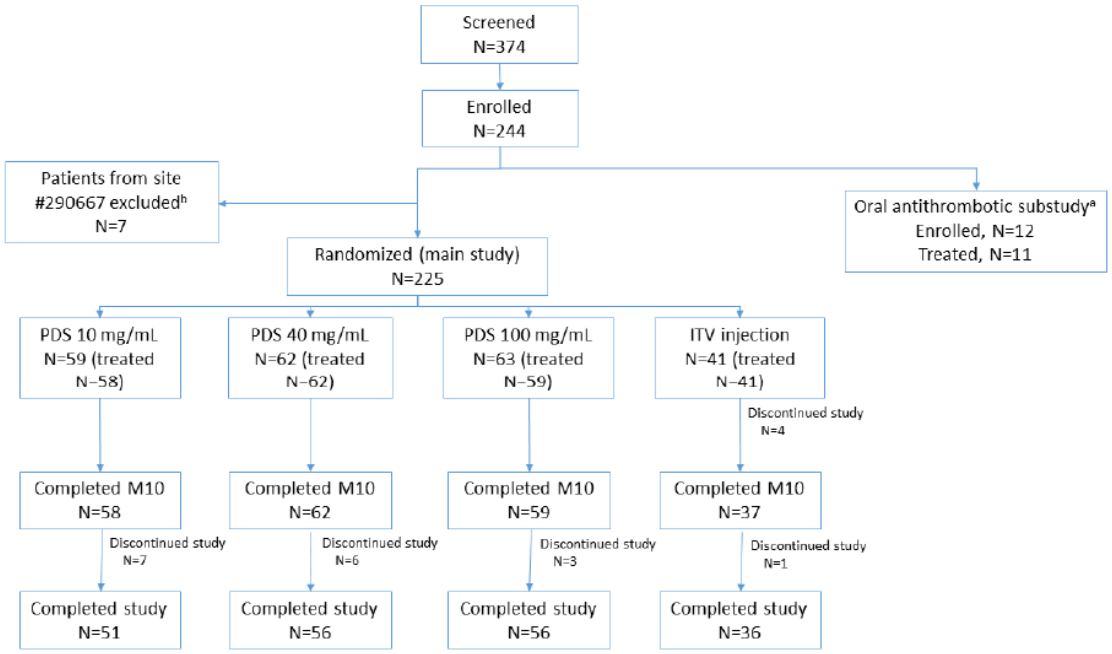
Furthermore, visual acuity and anatomical outcomes were evaluated as secondary endpoints.

In order to demonstrate the consistency of the results between study GX28228 and the pivotal Phase III study GR40548, the Applicant has presented additional supportive analyses of BCVA of study GX28228 performed using similar statistical methods as in study GR40548.

Disposition of subjects

Between 28 September 2015 and 21 August 2018, 244 patients were enrolled at up to 60 sites in the US. Of those 244 patients, 12 patients were enrolled in the non-randomized OAT substudy – see Figure 2 below. Thus, overall 232 patients were enrolled in the main study – see Table 15 below. Seven of these were randomized at a non-compliant site and were thus excluded from further analysis. Finally, 225 patients were randomized in a 3:3:3:2 ratio to PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms and to the ranibizumab IVT arm, respectively.

Figure 2 Patient Disposition



[a]Oral antithrombotic substudy results are presented separately in Section 9
[b]See Section 3.9.7.5 and Section 4.3
Source: t_anlpop, t_ds_m10, t_ds

[Figure 2 from final CSR]

The randomized population comprised 225 patients. Five of them, who were randomized into the PDS arms, decided not to undergo implantation because of the unexpectedly high incidence of vitreous haemorrhage. Apart from these 5 patients, all others were treated with study treatment as randomized, leading to 220 patients in the Efficacy Population (see below).

The primary analysis was performed after the last patient's Month 9 visit occurred based on the 28 June 2018 snapshot data. The final analysis was performed after the database lock occurred on 2 May 2019, based on the Study GX28228 Statistical Analysis Plan (SAP) Version 3.

Numbers analysed

Table 15 Overview of Analysis Populations (Main Study)

	PDS 10 mg/mL	PDS 40 mg/mL	PDS 100 mg/mL	Intravitreal ranibizumab	All patients
All patients enrolled	63	63	63	43	232
Enrolled at non-compliant site	4	1	0	2	7
Randomized Population	59	62	63	41	225
Efficacy Population	58	62	59	41	220
Safety Population	58	62	59	41	220

Source: t_anlpop

[Table 15 from final CSR]

The Efficacy Population was defined as all patients who were randomly assigned to study treatment and received at least one study treatment. Patient data were summarized by treatment arm and analyzed according to the treatment actually received and not according to the treatment to which they were

randomized, in the event of a discrepancy. Patients who received an implant were considered PDS patients.

Demographic characteristics

Overall, in the Efficacy Population, the mean (SD) age of the patients was 73.8 (8.4) years; 141 (61.4%) were female; and the majority of patients were White (215 patients [97.7%]). Baseline demographics were generally balanced across treatment groups.

Baseline ocular characteristics/ Prior and concomitant treatments

Baseline ocular characteristics were generally balanced across treatment groups. Overall, 145 patients (65.9%) had 20/40 or better vision at baseline (after receiving initial anti-VEGF intravitreal treatment to check for treatment response)

The mean number of anti-VEGF injections prior to randomization in the study eye was 2.7-3.1 in the PDS arms and 2.9 in the intravitreal arm, and all patients had received at least 1 prior dose of intravitreal ranibizumab in the study eye as per protocol. Forty-four patients (20.0%) received intravitreal bevacizumab as part of the pre-screening anti-VEGF treatment with no marked imbalances.

Prior surgical procedures in the study eye were reported in 69 patients overall (31.4%) and were generally balanced across treatment arms. The most common surgical procedure in the study eye before screening was cataract surgery.

In the first 10 months, concurrent ocular procedures were performed in 28 patients in the PDS arms (15.6%) and in no patients in the intravitreal arm. The most frequently reported concurrent ocular procedure was vitrectomy for vitreous hemorrhage or retinal detachment (13 patients [5.9%] in the PDS arms).

Previous and Concurrent Diseases

The most frequently reported diseases in the medical history were systemic hypertension (147 [66.8%]) and diabetes (40 [18.2%]). During the study, eye disorders were observed more frequently in the PDS arms, including cataracts (reported in 77.6%-86.4% of patients in the PDS arms compared with 70.7% of patients in the intravitreal arm) and vitreous detachment (reported in 46.8%-56.9% in the PDS arms compared with 39.0% in the intravitreal arm).

Efficacy results

Primary endpoint

The primary endpoint, **TTFR** (time from implant insertion until a patient first requires the implant refill according to protocol-defined refill criteria), was analyzed both at the primary analysis, which was conducted after the last patient's Month 9 visit occurred, and at the final analysis. Both analysis results were similar. The final analysis results are depicted below.

Table 20 Time to First Required Refill (TTFR) (Efficacy Population)

	PDS 10 mg/mL	PDS 40 mg/mL	PDS 100 mg/mL
At the Primary Analysis (conducted after the last patient's Month 9 visit occurred with a cut-off date of 28JUN2018)			
Median, months	8.7	13.0	15.0
HR (70% CI), Log-rank p-value			
vs. PDS 10 mg/mL		0.60 (0.46, 0.78) p=0.0415	0.50 (0.38, 0.66) p=0.0066
vs. PDS 40 mg/mL			0.92 (0.69, 1.22) p=0.7523
At the Final Analysis			
Median, months	8.7	13.0	15.8
HR (70% CI), Log-rank p-value			
vs. PDS 10 mg/mL		0.67 (0.52, 0.85) p=0.0875	0.56 (0.43, 0.72) p=0.0166
vs. PDS 40 mg/mL			0.89 (0.69, 1.15) p=0.6374

CI=confidence interval; HR=hazard ratio; PDS=Port Delivery System with ranibizumab

The p-values were from stratified log-rank tests. The HR for each pairwise comparison of the treatment arms was estimated using the Cox proportional hazards model. Both analyses are stratified by baseline best corrected visual acuity (BCVA) score (≤65 letters vs. ≥66 letters) and number of prior anti-VEGF intravitreal injections (≤3 vs. ≥4).

Sources: Campochiaro et al. 2019 (primary analysis datacut), t_ef_tte (final analysis)

[Table 20 from final CSR]

The median TTFR was 8.7, 13.0, and 15.8 months for the PDS 10 mg/mL, 40 mg/mL and 100 mg/mL arms, respectively (final analysis).

A dose response was observed: PDS 40 mg/mL and 100 mg/mL arms tended to have a longer time to first required refill, compared with PDS 10 mg/mL arm with HR=0.56 (70% CI: 0.43, 0.72) and log-rank p-value = 0.0166 between PDS 100 mg/mL and 10 mg/mL arms and HR=0.67 (70% CI: 0.52, 0.85) and log-rank p=0.0875 between PDS 40 mg/mL and 10 mg/mL arms (final analysis). TTFR in the PDS 100 mg/mL arm tended to be longer than that in the PDS 40 mg/mL arm (HR=0.89 with 70% CI: 0.69, 1.15 at the final analysis), but with larger uncertainty in estimation accuracy.

At Month 6, 62%, 70%, and 80% of patients did not require a refill per protocol defined criteria for the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms, respectively (see Table below).

Table 21 Kaplan-Meier Estimated Rates for Patients Not Meeting the First Refill Criteria by Months 6, 9 and 12 at Final Analysis (Efficacy Population)

Event Rate (80% CI)	PDS 10 mg/mL (N=58)	PDS 40 mg/mL (N=62)	PDS 100 mg/mL (N=59)
6 Months	61.6 (52.4, 69.6)	69.6 (61.2, 76.5)	79.8 (71.8, 85.8)
9 Months	42.4 (33.5, 50.9)	61.1 (52.5, 68.7)	68.7 (59.8, 76.0)
12 Months	28.9 (21.1, 37.1)	56.0 (47.3, 63.8)	59.4 (50.3, 67.3)

CI=confidence interval; PDS=Port Delivery System with ranibizumab

Source: t_ef_tte

[Table 21 from final CSR]

Sensitivity analyses were performed for the primary endpoint with additional censoring at the time of dosing errors, as well as with censoring after explant only. The sensitivity analyses supported the results from the primary analysis, confirming the dose response.

During the first 10 months, 38 patients (65.5%), 25 patients (40.3%) and 22 patients (37.3%) in the PDS 10 mg/mL, 40 mg/mL and 100 mg/mL arms, respectively, met at least one protocol-defined refill criterion (Table 23). The most frequent reason for refill was an increase in CFT (ranging from 44.2% to 50.0% of refills in each PDS treatment arm).

Table 23 Specific Protocol-Defined Refill Criteria During the First 10 Months at Final Analysis (Efficacy Population)

	PDS 10 mg/mL (N=58)	PDS 40 mg/mL (N=62)	PDS 100 mg/mL (N=59)
Number of patients meeting ≥ 1 refill criteria	39 (67.2%)	25 (40.3%)	22 (37.3%)
Number of visits refill criteria met	78	53	43
BCVA only[a]	15 (19.2%)	14 (26.4%)	11 (25.6%)
CFT only[a]	39 (50.0%)	24 (45.3%)	19 (44.2%)
New macular hemorrhage only[a]	1 (1.3%)	1 (1.9%)	7 (16.3%)
BCVA and CFT[a]	20 (25.6%)	10 (18.9%)	3 (7.0%)
BCVA and new macular hemorrhage[a]	0	0	0
CFT and new macular hemorrhage[a]	1 (1.3%)	4 (7.5%)	0
BCVA, CFT, and new macular hemorrhage[a]	2 (2.6%)	0	3 (7.0%)

BCVA=best corrected visual acuity; CFT=central foveal thickness; PDS=Port Delivery System with ranibizumab

[a] Percentage is with respect to the total number of times the refill criteria were met.

Source: t_ex_rf_m10_SE

[Table 23 from final CSR]

Secondary endpoints

Visual acuity

The mean BCVA changes from baseline at Month 9 in the PDS 10 mg/mL, 40 mg/mL and 100 mg/mL groups, based on all observed data, were -3.1, 0.2, and 4.8 letters, respectively, which support a dose response. The change in BCVA in the PDS 100 mg/mL arm was comparable to that in the intravitreal arm, with mean difference of 1.6 letters (95% CI: ±1.8, 4.9). The results were similar for analyses with censoring for intravitreal anti-VEGF injection in the study eye, use of selected prohibited medication, or receiving an explant.

With regard to the change in BCVA from baseline over time, there was a decrease in BCVA observed in the PDS arms immediately after implant insertion, as expected from any vitreo-retinal surgery. By Months 2-3, BCVA in the PDS arms, on average, recovered to baseline values. Change in BCVA generally remained stable afterwards in the PDS 10 mg/mL and 40 mg/mL arms. The change in BCVA in the 100 mg/mL arm remained stable and was generally comparable to the intravitreal arm after Month 4.

The change from baseline in BCVA averaged over Month 1 through Month 10 supported the main analysis findings of a dose response in PDS arm and similar change in BCVA outcome between PDS 100 mg/mL and the intravitreal arms after recovery from the surgery.

The proportions of patients losing <15 letters, <10 letters, <5 letters, and <0 letters and gaining ≥15 letters over time through Month 10 were also supportive of the main analysis findings of a dose response in PDS arms and similar change in BCVA outcome between PDS 100 mg/mL and the intravitreal arms after recovery from the surgery.

Additional supportive analyses were performed for BCVA, following those BCVA analyses performed in the pivotal Phase III study GR40548, using the MMRM method as well as the trimmed mean approach:

With regard to the change from baseline in BCVA score averaged over Month 9 and Month 10 analyzed with MMRM, the findings were similar to the main analysis results described above, with the change in BCVA in the PDS 100 mg/mL arm being comparable to the IVT arm, with adjusted mean difference of 1.8 (95% CI: -1.7, 5.2). The findings from the MMRM analyses with BCVA with data censored after supplemental intravitreal anti-VEGF injection in the study eye, select prohibited therapy, or explant were also similar to the main analysis.

The trimmed means approach was used to evaluate the difference in change in BCVA averaged over Months 9 and 10 between PDS 100 mg/mL and the intravitreal arm (ranibizumab 0.5 mg). 10% of patients who were considered to have the worst outcomes were trimmed from analysis, including those patients in the PDS arm who received a supplemental intravitreal anti-VEGF injection in the study eye, received any prohibited therapy (other than oral corticosteroids more than 10 mg/day or any fellow eye treatment), or underwent explantation; or if patients in any treatment arm discontinued study treatment due to lack of clinical efficacy or adverse event. 6.8% of patients in the PDS 100 mg/mL arm met the "must be trimmed" criteria. The trimmed mean changes from baseline averaged over Month 9 and Month 10 were +6.0 and -+5.4 letters for the PDS 100 mg/mL and the intravitreal arms, respectively, with the adjusted difference in mean changes (95% CI) of 0.6 letters (-2.2, 3.4).

Anatomical outcomes

The mean change from baseline in CFT, excluding both retinal pigment epithelium (RPE) and pigment epithelial detachment (PED) height (i.e., measured between the internal limiting membrane and the inner third of the RPE), through 24 months showed little change in the PDS 40 mg/mL, PDS 100 mg/mL, and intravitreal arms, and increased modestly in the PDS 10 mg/mL arm.

Based on all observed data, the mean change from baseline in CFT without RPE and PED height in the PDS 10 mg/mL, 40 mg/mL, 100 mg/mL, and intravitreal arms, were 28.0, 2.9, -3.4, and -6.9 microns respectively, indicating very little difference between the PDS 40 mg/mL, 100 mg/mL, and intravitreal arms.

There was a bigger difference in mean change from baseline in CFT if the measurement included RPE and PED height (i.e., measured between the internal limiting membrane and the Bruch's membrane) between the PDS groups and the intravitreal group; specifically, the mean change from baseline in CFT at Month 9 were 21.9, 23.6, 7.5 and -29.6 microns in the PDS 10 mg/mL, PDS 40 mg/mL, PDS 100 mg/mL and intravitreal arms, respectively.

Implant functionality

Among the 15 explanted implants (mostly due to lack of clinical efficacy, see CSP Section 5.4.4), 12 were analyzed for functionality by in-vitro release testing. No evidence of implant clogging was observed in any of the examined implants.

Overall, for primary and secondary endpoints, a dose response was observed across the PDS treatment arms. In addition, clinical benefit in terms of visual acuity (BCVA) and anatomical changes observed for patients in the PDS 100 mg/mL arm was comparable to monthly ranibizumab injections. Therefore, the 100 mg/mL concentration was chosen for the PDS arm in the pivotal Phase III study. Choosing this dose is overall considered adequate, based on the available data from study GX28228.

However, the rationale for choosing the Q24W refill regimen for further clinical development is not fully understood, based on the fact that in the PDS 100 mg/mL arm, more than 68% of patients proceeded 9 months and more than 59% went even 12 months not meeting the refill criteria. Furthermore, the median time to first implant refill was 15.8 months in the PDS 100 mg/mL arm. For those patients, a Q24W refill interval might bear the risk of overdosing. Within this context, a longer time to refill might have been adequate for further clinical development, also against the background of less frequent

burdening refill-exchange procedures. The Applicant was requested to further discuss on the potential specific characteristics of the patients that proceeded beyond the 24 week for the refill and/or their predictability and the potential for overdose. The Applicant argues that vision deterioration with pro-re-nata (PRN) treatment was seen in Ladder Study PDS 100 mg/mL PRN arm after patients rolled over into Study GR40549 and that the initial BCVA gains were lost at Month 21 post-implantation when the mean BCVA went back to pre-implantation levels, concluding that this loss in BCVA was most likely due to the long-term effect of the initial PRN regimen used in Ladder Study, where a clinically meaningful nAMD worsening had to be observed before receiving a refill-exchange. The justification provided by the Applicant for the risk of overdosing is considered acceptable. However, the appropriateness of the 24W regimen should be balanced against the PDS associated risks in comparison with other regimens. The Applicant is requested to comment on this aspect. (**LoOI**)

Main study

GR404548/ Archway

Study GR40548 (Archway) is a Phase III, randomized, multicenter, open-label (visual assessor [VA]-masked), active-comparator study designed to assess the efficacy, safety and pharmacokinetics of ranibizumab 100 mg/mL every 24 weeks (Q24W) delivered via the PDS compared with ranibizumab 0.5 mg administered via IVT injection every 4 weeks (Q4W) in patients with nAMD. A total of 418 patients were randomized in a 3:2 ratio, and 415 received treatment at 78 centres in the US.

The study had an expected duration of 96 weeks. With the initial MAA submission, the primary CSR with a clinical cut-off date of 27 March 2020 has been submitted, including data through week 40. In addition, an updated CSR with a CCOD of 11 September 2020 has been provided, including data through week 48.

Study [Status]	Overall Design	Patient Population (Number of Patients)	Dose, Route and Regimen: Number of Patients	Objectives	Analysis/Data Cut-off/CSR
GR40548 (Archway) (Pivotal study) [Ongoing]	Phase III, randomized, multicenter, open-label (visual assessor [VA-masked]), active-comparator	nAMD responsive to anti-VEGF treatment with maximum 9 months since diagnosis; BCVA 20/200 or better; all subtypes of lesions (type I, type II, type III, or mixed per OCT) (418 patients randomized and 415 treated [a])	PDS 100 mg/mL Q24W: 248 patients Intravitreal ranibizumab injection (0.5 mg) Q4W: 167 patients	Primary efficacy: • BCVA change at the average of Weeks 36 and 40 (4.5L margin) Secondary efficacy (requested by EMA): • BCVA change at the average of Weeks 36 and 40 (3.9L margin) • BCVA change at the average of Weeks 44 and 48 (3.9L margin) See protocol for the full list including safety and PK	Primary analysis at Week 36-40[b]/ 27 March 2020/ GR40548 Primary CSR, Report 1100486 Week 44-48 Analysis [b] 11 September 2020/ GR40548 Update CSR, Report 1104956

AE=adverse event; BCVA=best-corrected visual acuity; CFT=central foveal thickness; CNV=choroidal neovascularization; CPT=center point thickness; CSR=clinical study report; nAMD=neovascular age-related macular degeneration; PDS=Port Delivery System with ranibizumab; PK=pharmacokinetic; PRN=pro re nata (as needed); VEGF=vascular endothelial growth factor.

[a] A total of 418 were enrolled and randomized; however, 3 patients randomized to the PDS 100 mg/mL arm were not treated.

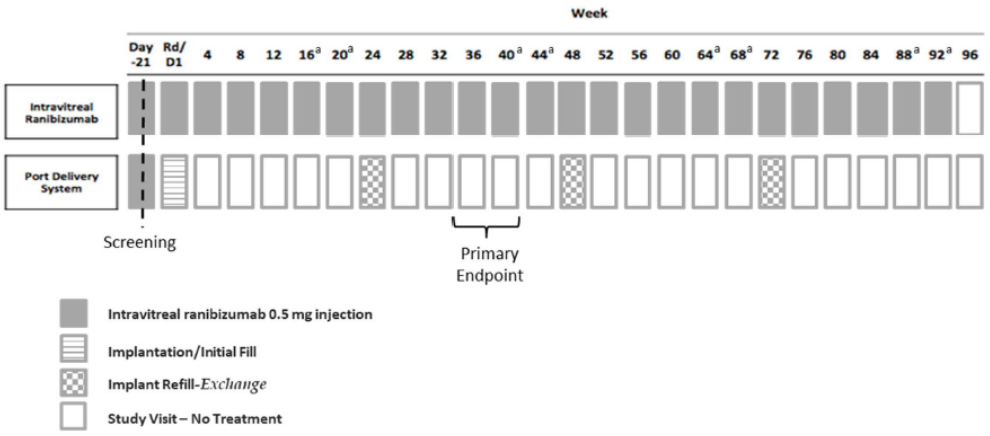
[b] Primary and Update CSRs for Study GR40548 include data through to their respective CCODs.

[Table 3 from Clinical Overview]

Study GR40548 was designed to investigate if continuous delivery of ranibizumab from the implant, with a Q24W fixed period between refill-exchange intervals, results in less frequent need for treatment while maintaining optimal visual outcomes in patients with nAMD responsive to anti-VEGF treatment.

The primary efficacy endpoint (mean change in BCVA score from baseline) was assessed at Weeks 36 and 40, with BCVA assessed using the ETDRS chart at a starting distance of 4 meters.

Figure 1 Study Schema



D = day; Rd = randomization.

[a] Patients in the PDS 100 mg/mL arm may be eligible for supplemental treatment with intravitreal ranibizumab 0.5 mg at Weeks 16, 20, 40, 44, 64, 68, 88, and 92.

[Figure 1 from Primary CSR]

Methods

Study Participants

Ranibizumab is, among others, approved for the treatment of adult patients with neovascular AMD; therefore, this patient population was selected to evaluate the PDS with ranibizumab 100 mg/mL.

Key Inclusion and Exclusion Criteria

The key inclusion criteria were as follows:

- Age ≥50 years, at time of signing Informed Consent Form

- Initial diagnosis of exudative nAMD within 9 months prior to the screening visit

- Previous treatment with at least three anti-vascular endothelial growth factor (VEGF) intravitreal injections in study eye (e.g., ranibizumab, aflibercept or bevacizumab) for nAMD per standard of care within 6 months prior to the screening visit

A run-in phase with intravitreal ranibizumab treatment was available to patients to meet this specific criterion.

- Demonstrated response to prior anti-VEGF intravitreal treatment since diagnosis, as evidenced at screening by the following:

Overall decrease in nAMD disease activity detected on spectral domain optical coherence tomography (SD-OCT), as assessed by the investigator and confirmed by the central reading center, and stable or improved BCVA

- All macular choroidal neovascularization (CNV) lesions were permitted

- BCVA of 34 letters or better (20/200 or better approximate Snellen equivalent),-using Early Treatment Diabetic Retinopathy Study (ETDRS) chart

The key exclusion criteria were as follows:

- Subfoveal fibrosis, subfoveal atrophy, or subretinal hemorrhage (greater than 1.27 mm2 involving the center of the fovea) in the study eye

- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye

The study population was restricted to patients with an initial diagnosis of wet AMD within 9 months prior to screening, to avoid inclusion of a very advanced patient population.

Furthermore, the patients enrolled in Study GR40548 were required to have received at least 3 anti-VEGF intravitreal injections (e.g., ranibizumab, aflibercept or bevacizumab) for nAMD per standard clinical practice within 6 months prior to the screening visit, plus one additional intravitreal ranibizumab 0.5 mg injection required at screening. This is overall agreed, since this requirement assures that patients are in general responsive to anti VEGF treatment, and it increases the likelihood that the patients have reached a stable vision plateau by the time of enrollment in Study GR40548.

However, those restrictions will, of course, have an impact on the indication wording that will be approved at the end of this procedure. Please refer to Section 3.3.6 "Discussion on clinical efficacy" below for details.

Treatments

PDS and customized formulation of ranibizumab 100 mg/mL used to fill or refill-exchange the implant

The PDS and ranibizumab 100 mg/mL for the PDS were supplied by the Sponsor for the initial fill and refill-exchange of the implant. Ranibizumab was formulated as a sterile solution aseptically filled in a sterile 2-mL stoppered glass vial. Each vial contained 0.5 mL of the 100 mg/mL formulation of ranibizumab aqueous solution in 10 mM histidine hydrochloride, 240 mM sucrose, and 0.01% polysorbate 20, pH 5.5.

Table 2 Components of the PDS

Drug Constituent	Description
Ranibizumab, 100 mg/mL	Ranibizumab is the Fab of a recombinant humanized monoclonal antibody anti-VEGF. It consists of a 214 residue light chain linked by a disulfide bond at its C-terminus to the 231 residue N-terminal segment of the heavy chain. Ranibizumab is not glycosylated and has a molecular mass of 48,380 Da.
Device Constituent	**Intended Use**
Implant	To provide continuous release of ranibizumab to the vitreous over time. The implant is intended to be permanent.
Insertion Tool Assembly	To facilitate handling of the implant during initial filling and insertion procedures (consists of insertion tool handle and insertion tool carrier).
Initial Fill Needle	To fill the implant with ranibizumab prior to insertion.
Refill Needle	To refill (*in situ*) the implant with ranibizumab when needed.
Explant Tool	To grasp and securely hold the implant flange during implant removal.

[Table 2 from Clinical Overview]

Formulation of intravitreal ranibizumab 10 mg/mL

Ranibizumab for intravitreal injection was supplied by the Sponsor and was formulated as a sterile, colorless to pale yellow solution. Ranibizumab was supplied as a preservative-free, sterile solution in a single-use contained designed to deliver 0.05 mL of ranibizumab 10 mg/mL solution with mM histidine hydrochloride, % α,α-trehalose dihydrate,% polysorbate 20, pH.

Study drug dosage and administration

PDS with ranibizumab

The study-specific implant initial filling, insertion, refill-exchange and implant removal procedures are outlined in the PDS Instructions for Use (IFU) document.

Prior implantation, the implant was filled with approx. 20µl of the 100 mg/mL formulation of ranibizumab (approximately 2-mg dose of ranibizumab). Then, the implant was surgically inserted in the patient's study eye at the Day 1 visit following their randomization visit. After the initial fill of the implant with ranibizumab, patients received implant refill-exchanges at fixed 24-week intervals.

At each refill-exchange, a volume of approximately 100 µL ranibizumab was injected in situ into the implant through the septum to exchange the contents of the implant with newly introduced ranibizumab. The volume of newly introduced ranibizumab in the implant after the refill-exchange procedure was approximately 20 µL. Missed implant refill-exchanges were made up no later than the next scheduled study visit. Subsequent refill-exchanges were administered according to the study treatment schedule relative to Day 1 as outlined in Protocol Appendix 1 until study completion.

Supplemental treatment

Patients randomized to the PDS 100 mg/mL arm were eligible for supplemental treatment with intravitreal ranibizumab (0.5 mg intravitreal injections of 10 mg/mL formulation) at Weeks 16 and 20 (after implant insertion) and at Weeks 40, 44, 64, 68, 88, and 92 if any of the following criteria were met in the study eye:

- Decrease of ≥15 letters from the best recorded BCVA in the study, due to nAMD disease activity.

OR

- Increase of ≥150 µm in central subfield thickness (CST) on spectral domain optical coherence tomography (SD-OCT) from the lowest CST measurement in the study, due to nAMD disease activity.

OR

- Increase of ≥100 µm in CST on SD-OCT from the lowest CST measurement in the study associated with a decrease of ≥10 letters from the best recorded BCVA during the study, due to nAMD disease activity.

(CST was assessed by central reading center with boundaries of the inner limiting membrane (IML) to Bruch´s Membrane)

Ranibizumab IVT injection

Ranibizumab (10 mg/mL), supplied by the Sponsor, was used in the study eye as follows:

- during the run-in period and at the screening visit for applicable patients (CSR Section 3.6.2.3),

- as study treatment for patients in the IVT arm; as supplemental treatment for the PDS 100 mg/mL arm (CSR Section 3.6.2.1),

- if delaying surgery was required,

- as nAMD treatment in the fellow eye for patients, per investigator's discretion;

- and if a patient in the PDS 100 mg/mL arm discontinued study treatment and started receiving ranibizumab IVT injections in the study eye, per investigator's discretion.

Commercially available intravitreal ranibizumab 0.5 mg supply was used only if an IVT ranibizumab injection was necessary per protocol and study supply was not available at the site.

Patients in the intravitreal arm received their first IVT injection of 50 µL of the ranibizumab 10 mg/mL (0.5 mg dose) at the Day 1 visit, which occurred at the conclusion of the randomization visit. Afterward, patients received intravitreal ranibizumab injections of 50 µL of the 10 mg/mL formulation Q4W at each scheduled study visit until Week 92 (see Protocol Appendix 2 for Schedule of Activities). Missed treatments were not made up.

Monthly injections of ranibizumab are consistent with the EU-approved label and have shown to be an effective therapy for wet AMD.

Intravitreal dosing prior to screening

There were 5 eligibility scenarios based on prior intravitreal anti-VEGF treatment history:

1. *Patients newly diagnosed with nAMD who are anti-VEGF treatment-naive*

If patients in this group satisfied all other eligibility criteria (other than prior anti-VEGF treatment criteria in the study eye, see List of Inclusion Criteria) and sign the Informed Consent Form, patients:

- Received 3 monthly (28 [±7] days) IVT ranibizumab 0.5 mg injections in the run-in period to determine whether they demonstrated response to anti-VEGF treatment as outlined per the eligibility criteria (see Protocol Appendix 3).

- After the third run-in IVT ranibizumab 0.5 mg injection, patients proceeded to screening, scheduled 28 (±7) days from the last administered IVT ranibizumab 0.5 mg injection, and received an additional IVT ranibizumab 0.5 mg injection at the end of the screening visit.

- If all eligibility criteria were then met, patients proceeded to the randomization visit.

2. *Patients diagnosed with nAMD in the study eye within 9 months prior to screening who had been treated with one or 2 intravitreal anti-VEGF injections within the last 6 months*

If patients in this group satisfied all other eligibility criteria (other than prior anti-VEGF treatment criteria in the study eye, see Section 3.5) and sign the Informed Consent Form, patients:

- Received up to 3 IVT ranibizumab 0.5 mg injections in the run-in period to meet the required 3 anti-VEGF intravitreal injections within 6 months prior to screening (see Protocol Appendix 3).

- After completing the required run-in treatments, patients proceeded to screening, scheduled 28 (±7) days from the last administered IVT ranibizumab 0.5 mg injection, and received an additional IVT ranibizumab 0.5 mg injection at the end of the screening visit.

- If all eligibility criteria were then met, patients proceeded to the randomization visit.

3. *Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with 3 intravitreal anti-VEGF injections within 6 months prior to screening*

If patients in this group satisfied all other eligibility criteria (see Section 3.5) and signed the Informed Consent Form, patients:

- Proceeded directly to screening, scheduled ≥21 days from the last IVT anti-VEGF injection administered per standard of care, and received an additional IVT ranibizumab 0.5 mg injection at the end of the screening visit.

- If all eligibility criteria were then met, patients proceeded to the randomization visit.

4. *Patients diagnosed with nAMD in the study eye within 9 months prior to screening who had been treated with at least 4 intravitreal anti-VEGF injections within 6 months prior to screening and with the most recent dose being aflibercept or bevacizumab*

If patients from this group satisfied all other eligibility criteria (see Section 3.5) and signed the Informed Consent Form, patients:

- Proceeded directly to screening, scheduled ≥21 days from the last IVT anti-VEGF injection, and received an IVT ranibizumab 0.5 mg injection at the end of the screening visit.

- If all eligibility criteria were then met, patients proceeded to the randomization visit.

5. *Patients diagnosed with nAMD in the study eye within 9 months prior to screening who had been treated with at least 4 intravitreal anti-VEGF injections within 6 months prior to screening, with the most recent dose being ranibizumab*

If patients from this group satisfied all other eligibility criteria (see Section 3.5) and signed the Informed Consent Form, patients:

- Proceeded directly to the screening visit, which should be scheduled ≥7 days from the last administered ranibizumab dose, and did not receive another IVT ranibizumab 0.5 mg injection at the screening visit, provided that the randomization and Day 1 visits was completed within 21-28 days after the last ranibizumab dose administered in the study eye prior to screening.

If the randomization and Day 1 visit cannot be completed within the allotted time window, the patient should be scheduled for a screening visit at ≥21 days from the last ranibizumab dose and will receive an additional intravitreal ranibizumab 0.5 mg injection at the end of the screening visit.

- If all eligibility criteria were then met, patients proceeded to the randomization visit.

Criteria for dose interruption or withdrawal from study/ treatment

Patients had the right to voluntarily withdraw from the study at any time for any reason; likewise the investigator could withdraw a patient from the study at any time.

Study treatment dose interruption and/or study treatment discontinuation or study discontinuation following an AE was determined according to the criteria in Table 2 below.

Table 2 Dose Interruption, Study Treatment Discontinuation, or Study Discontinuation Criteria

Event	Dose Interruption Criteria
Intraocular inflammation	Interrupt dose if intraocular inflammation ≥2+ in the study eye (see the definitions of intraocular inflammation in Protocol Section 5.1.2.4).
BCVA decrease	Interrupt dose in the event of a study drug–related decrease of ≥30 letters in BCVA in the study eye compared with the last assessment of BCVA.
Elevated IOP	Interrupt ranibizumab study treatment via intravitreal injection if pre-treatment IOP in the study eye ≥30 mmHg. Treatment was permitted when IOP had decreased to <30 mmHg, either spontaneously or by treatment, as determined by the investigator. Note: In the PDS 100 mg/mL arm, if IOP in the study eye was ≥30 mmHg at an implant refill-exchange visit, study treatment could proceed if the implant was seated in correct position.
Rhegmatogenous retinal break or detachment and macular hole Stages 3 or 4	Interrupt dose in the event of retinal break in the study eye. Treatment could be resumed ≥28 days after the retinal break had been successfully treated. Patients with a rhegmatogenous retinal detachment or Stage 3 or 4 macular holes could require discontinuation from study treatment after consultation with the Medical Monitor.
Local or systemic infection	Interrupt dose in presence of any of the following: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye. Dose could be interrupted if the patient was currently receiving treatment for a severe systemic infection per clinical judgment.
IV corticosteroids	Dose could be interrupted after consultation with the Medical Monitor if patients needed to receive IV corticosteroids. Study treatment could be resumed when the patient had finished IV corticosteroid course.
Intraocular surgery	Dose could be interrupted after consultation with the Medical Monitor if intraocular surgery (except cataract, see Protocol Section 4.4.1) had been performed in the study eye within the previous 28 days.
Observed damage to the implant	If damage to the implant was observed by the investigator, the implant could be explanted even if it did not cause any AE. The patient could be discontinued from the study treatment.
Pregnancy	Discontinue patient's study treatment in the case of positive serum pregnancy test during the study. For patients in the PDS 100 mg/mL arm, a saline flush of implant content could be performed.

BCVA = best corrected visual acuity; IOP = intraocular pressure.

[Table 2 from Primary CSR]

Concomitant therapies

Permitted therapies

Patients were permitted to use the following therapies during the study:

- Intravitreal administration of FDA-approved anti-VEGF agents, including Sponsor-provided ranibizumab 0.5 mg, at the discretion of the evaluating investigator in the fellow eye for nAMD

- Continuous use of aspirin or nonsteroidal anti-inflammatory drug (NSAID) treatment (these treatments were interrupted prior to implant surgery)

- Ongoing anticoagulant or anti-platelet therapy (other than aspirin or other NSAIDs)(these treatments were interrupted prior to implant surgery)

- Cataract surgery in the study eye, if clinically indicated and occurring 7 or more days after the last study treatment, with the next study treatment held for 7 or more days following the surgery

- Treatment, as clinically indicated, for the onset of increased IOP and/or glaucoma in the study eye during a patient's study participation

- Use of topical steroids post-implant insertion or post-implant removal surgery in the study eye

- Conditional use of magnetic resonance imaging scans for patients in the PDS 100 mg/mL arm (for additional information refer to the current PDS

Prohibited therapies

- Concurrent use of any systemic anti-VEGF agents

- Concurrent study eye treatment for nAMD with anti-VEGF agents other than the study-assigned treatment

- Concurrent fellow eye treatment for nAMD with unapproved anti-VEGF therapy

- Concurrent treatment with laser photocoagulation (any type) for nAMD in the study eye

- Concurrent treatment with Visudyne® for nAMD in study eye

- Concurrent use of intravitreal corticosteroids in the study eye

- Concurrent use of subtenon corticosteroids in the study eye (except at the conclusion of PDS implantation or implant removal surgery)

- Concurrent use of and participation in other experimental therapies (except those with minerals and vitamins)

Objectives

The primary objective of Study GR40548 (Archway) was to evaluate the non-inferiority and equivalence in efficacy of ranibizumab delivered via the PDS filled with the 100 mg/mL formulation compared to that of 10 mg/mL (0.5 mg dose) ranibizumab Q4W via IVT injections.

Outcomes/endpoints

The specific efficacy objectives and corresponding endpoints for the study are outlined in the Table below (Table 2 from the SCE).

Table 2 Efficacy Objectives and Corresponding Endpoints for Study GR40548

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the non-inferiority and equivalence in efficacy of ranibizumab delivered via the PDS Q24W with the 100 mg/mL formulation compared with that of 10 mg/mL (0.5 mg dose) Q4W intravitreal ranibizumab injections	• Change from baseline in BCVA score at the average of Week 36 and Week 40, as assessed using the ETDRS visual acuity chart at a starting distance of 4 meters with an NI margin of 4.5 letters and equivalence margins of ± 4.5 letters
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the relative efficacy of ranibizumab delivered via the PDS Q24W with the 100 mg/mL formulation compared with that of 10 mg/mL (0.5 mg dose) Q4W intravitreal ranibizumab injections, as assessed by visual acuity	• Change in BCVA score from baseline averaged over Weeks 36 and 40 assessed using the ETDRS chart at a starting distance of 4 meters with an NI margin of 3.9 letters [a] • Change in BCVA score from baseline averaged over Weeks 44 and 48 assessed using the ETDRS chart at a starting distance of 4 meters with an NI margin of 3.9 letters [a] • Change from baseline in BCVA score over time • Proportion of patients with BCVA score of 38 [b] letters (20/200 approximate Snellen equivalent) or worse at the average over Week 36 and Week 40 • Proportion of patients with BCVA score of 38 [b] letters (20/200 approximate Snellen equivalent) or worse over time • Proportion of patients with BCVA score of 69 letters (20/40 approximate Snellen equivalent) or better at the average over Week 36 and Week 40 • Proportion of patients with BCVA score of 69 letters (20/40 approximate Snellen equivalent) or better over time • Proportion of patients who lose < 10 or < 5 letters in BCVA score from baseline to the average over Week 36 and Week 40 • Proportion of patients who lose < 10 or < 5 letters in BCVA score from baseline over time • Proportion of patients who gain ≥ 0 letters in BCVA score from baseline to the average over Week 36 and Week 40 • Proportion of patients who gain ≥ 0 letters in BCVA score from baseline over time
• To evaluate the relative efficacy of ranibizumab delivered via the PDS Q24W with the 100 mg/mL formulation compared with that of 10 mg/mL (0.5 mg dose) Q4W intravitreal ranibizumab injections, as assessed by CPT on SD-OCT	• Change from baseline in CPT at Week 36 • Change from baseline in CPT over time
• To evaluate the proportion of patients who undergo supplemental treatment with intravitreal	• Proportion of patients in the PDS 100 mg/mL arm who undergo supplemental treatment with intravitreal

ranibizumab 0.5 mg	ranibizumab 0.5 mg before the first, second, third and fourth fixed refill-exchange interval [c] • Proportion of patients in the PDS 100 mg/mL arm that undergo a supplemental treatment that requires at least one additional supplemental treatment during the study
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the impact of supplemental treatment with intravitreal ranibizumab 0.5 mg	• BCVA and CST results over time relative to supplemental treatment
• To evaluate the relative efficacy of ranibizumab delivered via the PDS Q24W with the 100 mg/mL formulation compared with that of 10 mg/mL (0.5 mg dose) Q4W intravitreal ranibizumab injections, as assessed by central subfield thickness on SD-OCT	• Change from baseline in CST at Week 36 • Change from baseline in CST over time
• To evaluate the relative efficacy of ranibizumab delivered via the PDS Q24W with the 100 mg/mL formulation compared with that of 10 mg/mL (0.5 mg dose) Q4W intravitreal ranibizumab injections, as assessed by visual acuity	• Proportion of patients who gain ≥5 letters in BCVA score from baseline over time

BCVA = best corrected visual acuity; CPT = center point thickness; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Scale; NI = non-inferiority; PDS = Port Delivery System with ranibizumab; Q4W = every 4 weeks; Q24W = every 24 weeks; SD-OCT = spectral-domain optical coherence tomography.

[a] Change in BCVA score from baseline averaged over Weeks 36 and 40 and averaged over Weeks 44 and 48 assessed using the ETDRS chart at a starting distance of 4 meters with an NI margin of 3.9 was requested by the EMA as a key secondary endpoint.

[b] 38 letters is in alignment with the Study GR40548 Statistical Analysis Plan Version 2.0.

[c] Data for the third, fourth and fifth refill intervals were not mature at the time of the CCOD and are not included in the SCE.

Note: CPT is defined as the retinal thickness in the center point of the fovea measured between the internal limiting membrane and the inner third of the retinal pigment epithelium layer. CST is defined as the average thickness of the central 1 mm circle of the ETDRS grid centered on the fovea measured between the internal limiting membrane and the Bruch's membrane. CPT and CST were assessed by the central reading center.

[Table 2 from Summary of Clinical Efficacy]

The primary efficacy endpoint is the change in BCVA from baseline averaged over Weeks 36 and 40. This is overall considered adequate. However, during EMA advice the chosen time points were critically reflected. The evaluation of the mean change in BCVA at the time of trough for the PDS (i.e. when the amount of ranibizumab in the implant should be the lowest) just before implant refill was proposed.

In addition, the non-inferiority margin of 4.5 letters was considered too wide by SAWP/ CHMP, since a BCVA loss of 5 letters is a criterion for re-treatment and is thus of clinical relevance.

This was overall followed by the Sponsor: the mean changes in BCVA from baseline averaged over Week 36 and Week 40 and averaged over Week 44 and Week 48 were evaluated as key secondary endpoints, with a NI margin of 3.9 letters. This is acknowledged.

The study was designed for testing the non-inferiority of PDS 100 mg/ml ranibizumab Q24W versus intravitreal ranibizumab 0.5 mg Q4W regimen. The patients at the start of the study should have achieved the main benefit of the treatment during the initial injections before commencing the study. In this situation they had very limited room for further improvement during the course of the study, stabilization being the main target of the treatment. In these circumstances, where the main proof of efficacy relies on a single pivotal study, a primary analysis with a stricter NI margin would have been much more reassuring.

In the EMA Scientific Advice, it was also recommended to the Applicant to add secondary endpoints evaluating efficacy at later time points, such as Week 64 and 68, and Week 88 and 92. This was followed by the Applicant: mean change from BL in BCVA averaged over Wk 60 and Wk 64 was presented as secondary EP in the CSP Version 3 (dated 18 Dec 2019), and mean change from BL in BCVA averaged

over Wk 88 and Wk 92 was introduced as key secondary EP in the SAP Version 2.0 (dated 21 Apr 2020). However, since these analyses were not mature at the time of MAA submission, they were presented with the responses to the D120 LoQ in the final CSR (Sections 5.2.9 and 5.2.1). For both endpoints, mean change from BL in BCVA averaged over Wk 60/ Wk 64 as well as over Wk 88/ 92, non-inferiority was demonstrated in the Efficacy population ("as treated") [pre-defined NI margin of -3.9 letters]. This was supported by supplemental analyses (trimmed mean analysis, MMRM method) and by sensitivity analysis in the PP population. Overall, those analyses indicate that are no hints for loss of efficacy over time for the PDS.

Randomisation and blinding (masking)

Patients were planned to be randomized in a 3:2 allocation to one of the two treatment groups stratified by BCVA score (<74 letters vs. ≥ 74 letters) at Day of patient's randomization visit. Randomisation was planned to be performed through an IxRS.

The randomization scheme is considered acceptable.

This was an open-label study. Patients and study site personnel were not masked with regard to patient assignment because of difficulties of maintaining masking following the surgical procedure. Additional safety visits were added at 1 and 7 days following implantation to visualize the implant in situ and to examine the eye for any potential AEs. BCVA was measured at these visits with VAE masking maintained and this data was not included for efficacy analysis.

The Sponsor explains that at least the visual acuity examiner (VAE) were masked to the treatment as best as possible to patient study eye assignment, study visit eye and patient treatment assignment. The VAE had planned to have no access to patient's BCVA scores from previous visits, (s)he provided no direct or indirect patient care, and patients and unmasked personnel were asked not to discuss the study eye assignment.

As this is an open-label study, placebo effects may lead to bias towards rejecting the null hypothesis.

Statistical methods

Analysis populations:

The Efficacy population is defined as all patients who were randomised and received the study treatment. Patients were analysed according to treatment actually received. The Efficacy population is the primary efficacy population for the primary efficacy analysis.

The per-protocol population was defined as all patients in the Efficacy population who do not have a major protocol deviation that impacts the efficacy evaluation. Patients were analysed according to treatment actually received. The per-protocol population was planned to be used for the sensitivity analysis for the primary endpoint and the key secondary endpoint.

The Safety population was defined as all patients who received the study treatment, with patients grouped according to treatment actually received.

The PK population was defined on a subset of patients in the Safety Population with at least one post study treatment PK sample available.

The PK-evaluable population consisted of all patients in the PK Population excluding patients receiving intravitreal injections of ranibizumab in the study eye post PDS implant, patients with fellow eye ranibizumab or bevacizumab treatment, or prior bevacizumab treatment in either eye.

The primary efficacy population is acceptable for this equivalence trial, especially as a sensitivity analysis for the PP population, defined as all patients from the primary efficacy population without major protocol deviations, is provided.

Primary efficacy analysis:

The primary estimand is defined as follows:

- Population: Adult patients with nAMD diagnosed within 9 months and receiving at least anti-VEGF intravitreal injections (with the last injection being ranibizumab), responsive to prior anti-VEGF treatment
- Variable: Change in BCVA score from baseline averaged over Weeks 36 and 40
- Intercurrent events: Regardless whether or not a patient has the following intercurrent event prior to Week 40 (treatment policy strategy):
    - Receives more than 1 supplemental treatment
    - Receives any prohibited systemic treatment or prohibited therapy in the Study eye
    - Discontinues study treatment due to adverse events (AEs)
    - Discontinues study treatment due to lack of efficacy as per investigator's clinical judgement
- Population-level summary: Difference in adjusted mean between PDS 100 mg/mL and intravitreal groups.

The primary estimand, where intercurrent events are defined to be treated with a treatment policy strategy (regardless whether or not a patient has an intercurrent event), is questionable in the setting of testing equivalence. Especially intercurrent events like 'more than 1 supplemental treatment', that may have a compensatory effect on the outcome, may lead to an underestimation of treatment differences, which is not endorsed in an equivalence trial. On the contrary, intercurrent events that may have a worsening effect on the outcome are acceptable to be treated by the treatment policy estimand. The Applicant was asked to discuss the treatment policy strategy of the four defined intercurrent events regarding its sensitivity of detecting differences between the treatments, and to provide sensitivity analyses for more conservative strategies if necessary. The Applicant acknowledged the CHMP comment that a treatment policy strategy might prevent important differences from being captured in the estimate and provided supplemental analyses under hypothetical estimand strategy. While the results support the Applicant's position that there are no major differences among the estimand strategies, some methodological questions regarding the MNAR scenario remain open. (**LoOI**)

The primary analysis was planned to be performed using the mixed-effect model with repeated measures (MMRM) based on all available data up to week 40. The dependent variable in the MMRM model was the change from baseline in BCVA score at post-baseline visits, up to 40 weeks, and the independent variables are the treatment group, time, treatment-by-time interaction, baseline BCVA score (continuous), and the randomization stratification factor of baseline BCVA (< 74 letters vs. ≥ 74 letters) as fixed effects. The MMRM model was planned with an unstructured covariance structure. If there are convergence problems with the model, then a compound symmetry covariance or a first order autoregressive order (AR [1]) covariance structure was used. Comparisons between the two treatment groups will be made using a composite contrast over Weeks 36 and 40. For the primary efficacy endpoint, if a lower bound of a two-sided 95.03% CI for the difference of two treatments is greater than -4.5 letters (the NI margin), then treatment via PDS is considered non-inferior to monthly intravitreal ranibizumab treatment. If the two-sided 95.03% CI is within - 4.5L and + 4.5L, then the two treatment regimens are considered clinically equivalent.

As a sensitivity analysis the per-protocol analysis will follow the same methods as the primary analysis except the Per-Protocol Population will be used. Further sensitivity analyses were the trimmed mean analysis, and analyses using different handling rules for intercurrent events.

The primary analysis was defined as a mixed-effect model with repeated measures (MMRM) based on all available data up to Week 40, which is acceptable. However, as a sensitivity analysis the Applicant was asked to provide a confidence interval for the differences in treatment arms in the primary endpoint without using statistical modelling and the need of modelling assumptions and without implicitly imputing missing values. The requested analysis was provided with the responses to the D120 LoQ. The results of the sensitivity analysis are in line with the results of the main analysis.

Key secondary analysis:

After achieving NI with respect to the primary endpoint with a 4.5 letter margin the NI test for the key secondary endpoint was performed with an NI margin of 3.9 letters. Analysis of this key secondary endpoint followed the same method as the analysis of the primary endpoint in all respects except for the NI margin.

Multiplicity:

The two primary objectives of non-inferiority and equivalence between the two treatment groups were tested controlling the overall type I error by a fixed sequence testing procedure (Westfall and Krishen, 2001): If the PDS 100mg/mL arm is shown to be non-inferior to the intravitreal arm at the one-sided 0.02485 level, then the equivalence test was conducted using two one-sided 0.02485 tests. The alpha level was adjusted to 0.02485 (one-sided) due to an interim safety monitoring by the iDMC.

The handling of multiple testing is acceptable.

Missing values:

All observed measurements were included in the primary analysis regardless whether or not a patient has an intercurrent event. Missing values were implicitly imputed by the MMRM model, assuming a missing at random mechanism.

Interim analyses:

No interim analyses were planned for the efficacy endpoints.

Secondary endpoints:

The key secondary endpoints of change from baseline in BCVA score averaged over different time points (Week 36 and Week 40, Week 44 and Week 48, Week 88 and Week 92) were analysed according to the primary efficacy analysis. For binary secondary endpoint the following estimand was defined:

- Population: Adult patients with nAMD diagnosed within 9 months and receiving at least 4 anti-VEGF intravitreal injections (with the last injection being ranibizumab), responsive to prior anti-VEGF treatment.
- Variable: Proportion of patients for event of interest
- Intercurrent events: Regardless whether or not a patient has the following intercurrent event prior to visit for endpoint:
    - Receives more than 1 supplemental treatments
    - Receives any prohibited systemic treatment or prohibited therapy in the Study eye
    - Discontinuation study treatment due to AEs
    - Discontinuation study treatment due to lack of efficacy as per investigator's clinical judgement .

- Population-level summary: Difference in proportions between PDS 100 mg/ml and intravitreal groups

The proportion of patients in each treatment group and the overall difference in proportions between treatment groups were estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by randomization stratification factor of baseline BCVA (<74 letters vs. ≥74 letters) using the Cochran-Mantel-Haenszel (CMH) weights (Cochran 1954; Mantel and Haenszel 1959). All observed measurements were included in the analysis regardless whether or not a patient has an intercurrent event.

There were no critical protocol changes regarding the statistical analysis plan during the study conduct.

Results

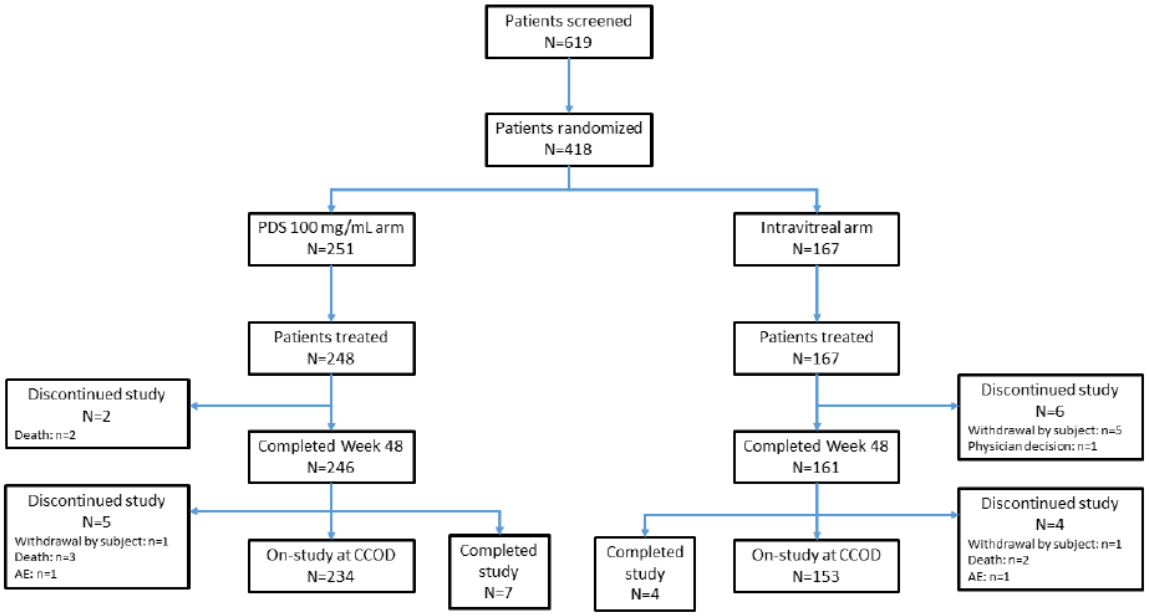
Participant flow

Disposition of patients

A total of 619 patients were screened. Of these, 201 were considered screen failures (the main reasons for screen failure were lack of response to anti-VEGF treatment during run-in phase for patients who had not received at least 3 prior anti-VEGF treatments [n=50], subfoveal fibrosis or atrophy [n=35] and lack of ability and willingness to undertake all scheduled visits and assessments [n=18]) (see Screen Failure list in the primary CSR).

Therefore, 418 patients were enrolled and randomized (251 to the PDS 100 mg/mL arm and 167 to the intravitreal arm) (Figure 2). Due to a high speed of enrollment, combined with a lower screen failure rate than expected, the number of patients enrolled exceeded the number required according to the sample size calculation (n=360). A summary of the number of patients enrolled by 78 sites that are participating in the study has been provided in the CSR.

Figure 2 Patient Disposition



Intravitreal arm: intravitreal ranibizumab 0.5 mg injections every 4 weeks (Q4W)
PDS: Port Delivery System with ranibizumab, refill-exchange every 24 weeks (Q24W)
CCOD=clinical cut-off date (11 September 2020)
Source: t_ds_EP_UPDCSR, t_ds_w48_EP_UPDCSR

[Figure 2 from Updated CSR]

Three patients randomized to the PDS 100 mg/mL arm were never treated (one patient was unable to attend the Day 1 visit in the stipulated timeframe, one experienced atrial fibrillation and was unable to comply with study visits, and one did not have nAMD diagnosis within 9 months). The Efficacy population (i.e. randomized and treated) therefore comprised 415 patients (248 in the PDS 100 mg/mL arm and 167 in the IVT arm).

Prior to Week 48, 2 patients in the PDS 100 mg/mL arm and 6 in the intravitreal arm discontinued the study; thus 99.2% and 96.4%, respectively, were still on study at Week 48. Through Week 48, 94.0% of patients in the PDS 100 mg/mL arm had received an initial fill and 2 refills while patients in the intravitreal ranibizumab arm had received a mean of 12.6 treatments out of a possible 13.

The most common reason for study discontinuation in the PDS 100 mg/mL arm was death (n=5) while the most common reason in the intravitreal arm was withdrawal by patient (n=6). However, it remains unclear which reasons led to withdrawal by subject. Within this context, the Applicant was requested to provide details for withdrawals by subject since there is an obvious imbalance between the treatment arms (n=7 in the IVT ranibizumab arm vs. n=1 in the PDS arm). However, it was clarified by the Applicant that details on the reason for withdrawals by subject were not requested in the Treatment Discontinuation eCRF, hence they were not documented by the Principal Investigator. Thus, no further details can be provided regarding the specific reason for the "Withdrawal by Subject". Since this imbalance concerns the IVT ranibizumab comparator arm, this is considered overall negligible and will not be pursued further.

At CCOD, 7 patients (2.8%) in the PDS 100 mg/mL arm and 4 patients (2.4%) in the intravitreal arm had completed the study. Two additional patients have completed the study and are not recorded in this output because the study completion eCRF was not entered into Electronic Data Capture (EDC) at the time of the data snapshot. Treatment discontinuations are presented below (Table 1).

Eight patients died on study (5 in the PDS 100 mg/mL arm and 2 in the intravitreal arm) prior to CCOD. One additional patient in the intravitreal arm withdrew from the study at Day 187 and later died of pancreatic carcinoma (see Narrative). See AR Safety Section for further details of patients who died.

The overall time on study was balanced across treatment arms (mean 80.0 weeks in the PDS 100 mg/mL arm and mean 78.5 weeks in the intravitreal arm through CCOD).

In the primary CSR, it is stated in Section 4.1 (Disposition of patients) that the mean overall time on study was 40.8 months in the PDS arm versus 39.8 months in the IVT arm through Week 40, and median 54.7 months versus 55.3 months through CCOD. Here, obviously, months and weeks have been mixed up. The Applicant has clarified that mean was erroneously reported as median in the primary CSR, and weeks and months have been mixed up. In the final CSR, this is presented correctly (mean weeks).

Premature withdrawal from study treatment

Eight patients in the PDS 100 mg/mL arm and 6 in the intravitreal arm withdrew from study treatment on or before the Week 48 visit (Table 1). The main reasons for discontinuation of treatment were an AE in the PDS 100 mg/mL arm and withdrawal by subject in the intravitreal arm.

Table 1 Treatment Completion/Early Discontinuation through Week 48, Efficacy Population

	PDS with Ranibizumab 100 mg/mL Q24W (N=248)	Intravitreal Ranibizumab 0.5 mg Q4W (N=167)	All Patients (N=415)
Ongoing at Week 48	240 (96.8%)	161 (96.4%)	401 (96.6%)
Discontinued Treatment in Study Eye Through Week 48			
Total	8 (3.2%)	6 (3.6%)	14 (3.4%)
Adverse event	5 (2.0%)	0	5 (1.2%)
Pregnancy	0	0	0
Death	2 (0.8%)	0	2 (0.5%)
Lack of efficacy	0	0	0
Lost to follow-up	0	0	0
Protocol deviation	0	0	0
Non-compliance with study drug	0	0	0
Withdrawal by subject	0	5 (3.0%)	5 (1.2%)
Study terminated by sponsor	0	0	0
Physician decision	0	1 (0.6%)	1 (0.2%)
Progressive disease	0	0	0
Disease relapse	0	0	0
Symptomatic deterioration	0	0	0
Other	1 (0.4%)	0	1 (0.2%)

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Note: The withdrawal in the PDS 100 mg/mL arm reported as 'other' was due to a damaged implant (no associated AE reported). One of the withdrawals in the intravitreal arm was a patient who experienced a rash that was recorded as leading to withdrawal of treatment while the reason for treatment discontinuation was recorded as "withdrawal by subject"

[Table 1 from Updated CSR]

Four of the patients who discontinued treatment prior to Week 48 (3 discontinuations due to an AE and 1 due to damaged implant) had their implants removed. After Week 48, an additional 3 patients had their implant removed.

Through CCOD, an additional 7 patients in the PDS 100 mg/mL arm withdrew from treatment (3 due to AEs, 2 due to death, 1 due to withdrawal by the subject and 1 listed as other). In the intravitreal arm, 4 patients withdrew from treatment between the Week 48 visit and CCOD (1 due to an AE, 2 due to death and 1 due to withdrawal by subject).

As of CCOD, of the 11 patients in the PDS 100 mg/mL arm who had discontinued treatment for a reason other than death, 2 discontinued the study early and 1 patient who discontinued treatment due to an AE later died.

Conduct of the study

Protocol Amendments

Protocol Version 1 was finalized on 31 May 2018 and was amended on 29 July 2019 (Amendment 1, Version 2), on 18 December 2019 (Amendment 2, Version 3), and on 16 June 2020 (Amendment 3, Version 4). All versions of the protocol are presented.

Key changes incorporated in Protocol Version 2:

- Adjustment made throughout the protocol from "rescue" to "supplemental" injections in order to distinguish between PDS with ranibizumab patients who receive intravitreal ranibizumab 0.5 mg

in the study eye as allowed per protocol Section 5.1.5.3 from PDS patients who receive prohibited anti-VEGF treatment in the study eye that is not covered by protocol Section 5.1.5.3.

- The objective evaluating patient preference per the PDS Patient Preference Questionnaire (PPPQ) was moved from the secondary efficacy objectives to the exploratory patient experience objectives (Section 2).
- The central subfield thickness abbreviation has been updated from CSFT to CST to align with Roche global ophthalmology programs and with the reading center standards.

Key changes incorporated in Protocol Version 3:

- At selected sites, an additional PK sample will be collected from patients in the intravitreal arm 1-5 days after an intravitreal ranibizumab 0.5 mg injection in order to collect a sample near Cmax (Section 3.5.4, Appendix 2)
- The secondary endpoints of proportion of patients who lose < 15 letters in best corrected visual acuity (BCVA) from baseline over week 36 and week 40 and overtime were removed (Section 2, Table 1).

Key changes incorporated in Protocol Version 4:

- Several alternate final study visit scenarios have been provided to allow patients to remain in the study and receive treatment at regular intervals until consenting patients can enroll into an open-label safety extension study per-protocol (Section 3.1, Figure 1, Appendices 1 and 2).
- Schedules of activities and assessment timepoints have been provided for these alternate final study visit scenarios (Appendix 1, Table 3 and Appendix 2, Table 3).

In the initial assessment, it was unclear with which protocol amendment the key secondary endpoints "mean change in BCVA from baseline averaged over Week 36 and Week 40" and "mean change in BCVA from baseline averaged over Week 44 and Week 48" have been introduced into the study protocol. The Applicant clarified with his responses to the D120 LoQ that the key secondary endpoints that had been recommended by the EMA during SA procedure were not included in a protocol amendment, but were introduced as key secondary EP in SAP Version 2.0 (dated 21 Apr 2020).

Visual Acuity Examiners (VAE) Masking

In the study, the visual acuity examiners (VAEs) were to remain masked to study eye, treatment arm, and study visit type. In November 2019, the Sponsor identified that, due to a limitation within the Clinical Trial Management System (CTMS), 144 VAEs at 66 study sites were listed under the category of the Study Coordinator Role, and therefore were inadvertently registered to receive automated emails from the portal used to share study information with site staff (DrugDev). These automated emails were intended to remind Study Coordinators of upcoming patient visits. Within the subject line, information of the patient number, study visit week and type was included, which could indirectly inform the patient's treatment arm and study visit type to the masked VAEs (assigned to 232 patients total).

Immediately upon identification of the issue, the email notifications were discontinued until the roles within the CTMS system were reviewed and updated to accurately reflect user roles. All other automated systems used in the study were also evaluated, to ensure no similar issues had occurred. These CTMS user access checks are now in place and occur monthly.

During general conduct of the trial, sites and VAEs were instructed to self-report in the event a VAE was unmasked. As of CCOD none of the VAEs self-reported having been unmasked due to receiving these automated emails. Other reasons for potential unmasking of VAEs were reported as major protocol deviations.

The Sponsor has met with external consulting bodies including the Executive Advisory Committee (this committee is comprised of scientific experts who play an advisory role for the PDS clinical development program) and the iDMC to discuss this GCP breach. The Roche GCP Council was also consulted, and concurred with the actions taken by the study team. The Executive Advisory Committee and iDMC agreed

that the likelihood of data integrity being affected as a result of this issue is considered to be low. This is recognized. However, to further clarify that there is no critical issue with regard to data integrity resulting from the erroneously sent automated emails, the Applicant was requested to provide a subgroup analysis for all patients with BCVA assessment averaged over Week 36 and Week 40 before and after the stop of the automated emails. The Applicant provided the required analysis according to potential unblinding date. Both before and after the potential unblinding, the confidence intervals of the point estimates were fully contained within the equivalence margins and no hints towards unblinding could be identified.

Baseline data

The randomized study population is overall appropriate to represent the intended indication.

Baseline demographics were generally balanced across treatment groups (see also Primary CSR Table 7). The mean age at randomization was 75.0 years (75.2 years in the PDS 100 mg/mL arm and 74.8 years in the intravitreal arm) and 56.4% were aged ≥75 years (56.9% in the PDS 100 mg/mL arm and 55.7% in the intravitreal arm). The majority of patients were female (59.0% among all patients; 58.5% in the PDS 100 mg/mL arm and 59.9% in the intravitreal arm) and white (96.6% among all patients; 96.8% in the PDS 100 mg/mL arm and 96.4% in the intravitreal arm).

Table 7 Baseline Demographics, Efficacy Population

	PDS with Ranibizumab 100 mg/mL Q24W (N=248)	Intravitreal Ranibizumab 0.5 mg Q4W (N=167)	All Patients (N=415)
Age (years) at Randomization			
n	248	167	415
Mean (SD)	75.2 (8.11)	74.8 (7.63)	75.0 (7.91)
Median	75.0	75.0	75.0
Q1-Q3	70.0 - 81.0	69.0 - 81.0	70.0 - 81.0
Min-Max	51 - 96	54 - 89	51 - 96
Age Group (years)			
n	248	167	415
< 65	26 (10.5%)	17 (10.2%)	43 (10.4%)
65 -< 75	81 (32.7%)	57 (34.1%)	138 (33.3%)
75 -< 85	113 (45.6%)	80 (47.9%)	193 (46.5%)
>= 85	28 (11.3%)	13 (7.8%)	41 (9.9%)
Sex			
n	248	167	415
Male	103 (41.5%)	67 (40.1%)	170 (41.0%)
Female	145 (58.5%)	100 (59.9%)	245 (59.0%)
Ethnicity			
n	248	167	415
Hispanic or Latino	7 (2.8%)	8 (4.8%)	15 (3.6%)
Not Hispanic or Latino	240 (96.8%)	159 (95.2%)	399 (96.1%)
Not Available	1 (0.4%)	0	1 (0.2%)
Race			
n	248	167	415
American Indian or Alaskan Native	1 (0.4%)	2 (1.2%)	3 (0.7%)
Asian	1 (0.4%)	0	1 (0.2%)
Black or African American	3 (1.2%)	1 (0.6%)	4 (1.0%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	240 (96.8%)	161 (96.4%)	401 (96.6%)
Multiple	1 (0.4%)	0	1 (0.2%)
Not Available	2 (0.8%)	3 (1.8%)	5 (1.2%)
Tobacco Use Status			
n	248	167	415
Never used	101 (40.7%)	78 (46.7%)	179 (43.1%)
Previous User	122 (49.2%)	74 (44.3%)	196 (47.2%)
Current User	25 (10.1%)	15 (9.0%)	40 (9.6%)
Weight (kg)			
n	247	163	410
Mean (SD)	81.9 (19.86)	81.4 (21.35)	81.7 (20.44)
Median	80.3	79.0	79.3
Min-Max	40.4 - 162.0	47.0 - 195.5	40.4 - 195.5
BMI (kg/m2)			
n	247	163	410
Mean (SD)	29.0 (6.25)	29.1 (7.44)	29.0 (6.74)
Median	27.8	28.1	28.0
Min-Max	17.1 - 61.3	17.8 - 69.7	17.1 - 69.7

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[Table 7 from Primary CSR]

Baseline ocular characteristics for the study eye were generally balanced across treatment groups. Among all patients, the mean baseline ETDRS BCVA was 74.8 letters (74.4 letters in the PDS 100 mg/mL arm and 75.5 letters in the intravitreal arm), that is an approximate Snellen equivalent of 20/32, and 66.5% of patients had a score of 74 letters or better (65.7% in the PDS 100 mg/mL arm and 67.7% in the intravitreal arm). Mean baseline CPT was 177.0 microns (176.9 microns in the PDS 100 mg/mL arm and 177.2 microns in the intravitreal arm), and the mean baseline CST was 307.9 microns (312.7 microns in the PDS 100 mg/mL arm and 300.9 microns in the intravitreal arm). The mean number of anti-VEGF injections prior to first study treatment in both treatment arms was 5.0. Of note, in the PDS 100 mg/mL arm, 1 patient had received 31 prior injections. Time since first diagnosis of nAMD in this patient was 152 months, in violation of the inclusion criterion requiring diagnosis within 9 months of screening. This was recorded as a major protocol deviation.

Table 8 Baseline Ocular Characteristics of Study Eye, Efficacy Population

	PDS with Ranibizumab 100 mg/mL Q24W (N=248)	Intravitreal Ranibizumab 0.5 mg Q4W (N=167)	All Patients (N=415)
ETDRS BCVA, Letter Score			
N	248	167	415
Mean (SD)	74.4 (10.5)	75.5 (10.3)	74.8 (10.4)
Median	77.0	78.0	77.0
Q1-Q3	71.0 - 81.0	71.0 - 83.0	71.0 - 82.0
Min-Max	35 - 92	35 - 94	35 - 94
< 74	85 (34.3%)	54 (32.3%)	139 (33.5%)
>= 74	163 (65.7%)	113 (67.7%)	276 (66.5%)
<= 38	1 (0.4%)	1 (0.6%)	2 (0.5%)
>38	247 (99.6%)	166 (99.4%)	413 (99.5%)
< 34 Letters	0	0	0
34 - 68 Letters	48 (19.4%)	31 (18.6%)	79 (19.0%)
>= 69 Letters	200 (80.6%)	136 (81.4%)	336 (81.0%)
Lens Status			
N	248	167	415
Phakic	105 (42.3%)	63 (37.7%)	168 (40.5%)
Pseudophakic	143 (57.7%)	104 (62.3%)	247 (59.5%)
Aphakic	0	0	0
Other	0	0	0
Center Point Thickness (um)			
N	248	167	415
Mean (SD)	176.9 (54.8)	177.2 (49.1)	177.0 (52.5)
Median	169.5	171.0	171.0
Q1-Q3	143.0 - 198.5	144.0 - 200.0	143.0 - 199.0
Min-Max	61 - 396	57 - 338	57 - 396
<= 250	226 (91.1%)	150 (89.8%)	376 (90.6%)
> 250	22 (8.9%)	17 (10.2%)	39 (9.4%)
Central Subfield Thickness (um)			
N	248	167	415
Mean (SD)	312.7 (100.9)	300.9 (72.1)	307.9 (90.5)
Median	290.5	282.0	285.0
Q1-Q3	258.0 - 329.5	260.0 - 327.0	258.0 - 329.0
Min-Max	174 - 915	172 - 692	172 - 915
Number of anti-VEGF injections prior to first Study Treatment			
N	248	167	415
Mean (SD)	5.0 (2.1)	5.0 (1.5)	5.0 (1.9)
Median	4.0	4.0	4.0
Q1-Q3	4.0 - 5.0	4.0 - 6.0	4.0 - 6.0
Min-Max	3 - 31	4 - 9	3 - 31
Number of anti-VEGF injections prior to first Study Treatment			
N	248	167	415
3	1 (0.4%) [a]	0	1 (0.2%)
4	137 (55.2%)	99 (59.3%)	236 (56.9%)
5	49 (19.8%)	21 (12.6%)	70 (16.9%)
6	26 (10.5%)	17 (10.2%)	43 (10.4%)
7	21 (8.5%)	11 (6.6%)	32 (7.7%)
8	7 (2.8%)	13 (7.8%)	20 (4.8%)
9	4 (1.6%)	6 (3.6%)	10 (2.4%)
10	1 (0.4%)	0	1 (0.2%)
11	1 (0.4%)	0	1 (0.2%)
31	1 (0.4%)	0	1 (0.2%)
Intraocular Pressure (mmHg)			
N	248	167	415
Mean (SD)	15.1 (3.6)	14.3 (3.1)	14.8 (3.4)
Median	15.0	14.0	15.0
Q1-Q3	13.0 - 17.5	12.0 - 16.0	12.0 - 17.0
Min-Max	5 - 25	8 - 24	5 - 25

Table 8 Baseline Ocular Characteristics of Study Eye, Efficacy Population (cont.)

	PDS with Ranibizumab 100 mg/mL Q24W (N=248)	Intravitreal Ranibizumab 0.5 mg Q4W (N=167)	All Patients (N=415)
Intraocular Pressure Group (mmHg)			
N	248	167	415
<10	14 (5.6%)	6 (3.6%)	20 (4.8%)
10 - 21	225 (90.7%)	158 (94.6%)	383 (92.3%)
>21 - 25	9 (3.6%)	3 (1.8%)	12 (2.9%)
>25	0	0	0
Time Since First Diagnosis of Neovascular AMD (Months)			
N	248	167	415
Mean (SD)	5.9 (9.5)	5.3 (2.0)	5.6 (7.4)
Median	4.6	4.5	4.5
Q1-Q3	3.9 - 6.3	3.7 - 6.5	3.8 - 6.4
Min-Max	3 - 152	3 - 10	3 - 152

ETDRS=Early Treatment Diabetic Retinopathy Study; BCVA=Best Corrected Visual Acuity. Baseline is the last available value taken on or before the day of first study treatment (intravitreal injections or PDS implantation). Center Point Thickness is retinal thickness in the center point of the fovea measured between the internal limiting membrane and the inner third of the retinal pigment epithelium layer. Central Subfield Thickness (CST) is defined as the average thickness of the central 1 mm circle of the ETDRS grid centered on the fovea. CST is measured between the internal limiting membrane and the Bruch's membrane.

[a] One patient had 3 anti-VEGF injections prior to first study treatment instead of the protocol-mandated minimum of 4. This was recorded as a major protocol deviation.

Adapted from t_dm_ocu_stdeye_EP

[Table 8 from Primary CSR]

The ocular medical history of the study eye was comparable between treatment arms. All but 2 patients in the PDS 100 mg/mL arm and all patients in the intravitreal arm reported a history of cataracts (prior cataract surgery or presence of cataract at screening). Overall, 39.3% of patients had a history of dry AMD without geographic atrophy (39.9% in the PDS 100 mg/mL arm and 38.3% in the intravitreal arm).

Table 9 Targeted Ocular Medical History in Study Eye

	PDS with Ranibizumab 100 mg/mL Q24W (N=248)	Intravitreal Ranibizumab 0.5 mg Q4W (N=167)	All Patients (N=415)
Total number of patients with at least one targeted ocular medical history	246 (99.2%)	167 (100%)	413 (99.5%)
CATARACT	246 (99.2%)	167 (100%)	413 (99.5%)
DIABETIC RETINOPATHY	3 (1.2%)	3 (1.8%)	6 (1.4%)
DRY AMD W/O GEOGRAPHIC ATROPHY	99 (39.9%)	64 (38.3%)	163 (39.3%)
GEOGRAPHIC ATROPHY	18 (7.3%)	11 (6.6%)	29 (7.0%)
OPEN ANGLE GLAUCOMA	9 (3.6%)	8 (4.8%)	17 (4.1%)
RETINAL TEAR/HOLE	4 (1.6%)	1 (0.6%)	5 (1.2%)

The denominator is the total number of subjects in the treatment group.

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[Table 9 from Primary CSR]

In the targeted non-ocular medical history, higher numbers of patients had a history of targeted medical history in the PDS 100 mg/mL arm, such as diabetes mellitus (19.4% versus 14.45% in the IVT ranibizumab arm), coronary artery occlusion/ stenosis (11.7% versus 9.0%), and systemic hypertension

(66.5% versus 60.5%). However, this is not considered to be of critical relevance with regard to the study objectives.

With regard to prior targeted ocular therapies and treatments, the median number of IVT ranibizumab injections in the study eye in the 9 months prior to first study treatment was 4.0 in the PDS arm and 4.0 in the IVT arm (mean 3.5 versus 3.8 IVT injections). Eight patients in the PDS arm received an additional ranibizumab injection prior to the first study treatment as permitted by the protocol because the implant procedure was delayed, in 2 cases because of scheduling, 2 due to an AE, and 4 because acetyl salicylic acid or NSAIDs had not been interrupted.

Regarding other anti-VEGF treatments administered in the 9 months prior to first study treatment, aflibercept had been administered to 28 patients (11.3%) in the PDS 100 mg/mL arm and 20 (12.0%) in the intravitreal arm while bevacizumab had been administered to 76 (30.6%) and 51 (30.5%), respectively. An anti-VEGF agent was administered to the fellow eye of 60 patients (24.2%) in the PDS 100 mg/mL arm and 24 (14.4%) in the intravitreal arm in the 9 months prior to first study treatment. The most frequently used anti-VEGF agent in the fellow eye in both treatment arms was ranibizumab (50 patients [20.2%] in the PDS 100 mg/mL arm and 19 [11.4%] in the intravitreal arm).

With regard to prior ocular surgery, cataract surgery in the study eye prior to screening was reported in 143 patients (57.7%) in the PDS 100 mg/mL arm and 104 patients (62.3%) in the intravitreal arm. The only other prior ocular surgery or procedure reported was yttrium-aluminium garnet (YAG) laser capsulotomy (18 patients [7.3%] in the PDS 100 mg/mL arm and 25 patients [15.0%] in the intravitreal arm).

Through Week 40, 26 patients (10.5%) in the PDS 100 mg/mL arm and 4 patients (2.4%) in the intravitreal arm underwent 41 and 4 concomitant ocular procedures, respectively in the study eye (note a patient could undergo more than 1 concomitant ocular procedure). The most frequent types of concomitant ocular procedure were conjunctival repair (11 patients [4.4%] in the PDS 100 mg/mL arm and no patients in the intravitreal arm) and vitrectomy (5 patients [2.0%] in the PDS 100 mg/mL arm and no patients in the intravitreal arm). None of the conjunctival repairs were associated with SAEs and the most frequent indications for this procedure were conjunctival erosion (5 procedures in 4 patients) and conjunctival retraction (3 procedures in 2 patients). None of the vitrectomies were performed to treat vitreous hemorrhage. Through CCOD, an additional 7 procedures were reported in the PDS 100 mg/mL arm (3 cataract extractions, 2 conjunctival repairs, and 2 implant flushes for endophthalmitis).

With regard to concomitant ocular surgeries/ procedures, comparative data through to Week 40 were presented by the Applicant (see Section 4.6.4 in the Primary CSR). For the entire period up to Week 48, only listings were provided (see Section 3.6.3 in the Updated CSR). With his responses to the D120 LoQ, the Applicant presents Week 48 data for concomitant ocular procedures, as requested. Overall, 37 patients (14.9%) in the PDS 100 mg/mL arm and 10 patients (6.0%) in the IVT arm underwent 60 and 11 concomitant ocular procedures, respectively, in the study eye.

Cataract extraction was the most frequent ocular procedure being performed in 4.8% of patients in the PDS arm (n=12) and in 3.6% of patients treated with IVT ranibizumab (n=6). This procedure can be considered expected taking into account the age of the study population as well as the presence of a relevant number of cataracts already at BL.

Conjunctival repair has been performed in the study eye of 5.2% of PDS implant patients (n=13); however, not in any IVT ranibizumab patients. According to the Applicant, this can be explained by poor conjunctival management during peritomy or closure in the context of implant insertion surgery. The Applicant stresses that none of the conjunctival repairs were associated with sight-threatening events, and none were associated with treatment or study discontinuation.

A Pars plana vitrectomy (PPV) has been performed in the study eye of 7 patients having the PDS implant (2.8%); however, not in any IVT ranibizumab patients.

Overall, the imbalances between the treatment arms can be largely attributed to the implant insertion surgery in the PDS arm. This will be discussed further in the context of the benefit/risk evaluation.

Through Week 48, ocular concomitant medication was reported by 184 patients (74.2%) in the PDS 100 mg/mL arm and by 65 (38.9%) in the intravitreal arm. The difference between arms was largely driven by short-term use of ocular medications mandated by the protocol before and/or after implant insertion and/or refill-exchange. The use of self-administered antimicrobial ophthalmic drops was required 4 times within 24 hours before and as per standard of care after PDS implant insertion, and was optional per investigator's discretion prior to the implant refill-exchange procedure but required as per standard of care after the PDS implant refill-exchange procedure. Anti-inflammatory ophthalmic drops were required after implant insertion and implant removal as per standard of care. Topical prednisolone acetate (reported as prednisolone or prednisolone acetate) was reported in 37.5% and 1.8% of patients in the PDS 100 mg/mL and intravitreal arms, respectively; topical oflaxacin in 19.4% and 1.2%, respectively; topical erythromycin in 7.3% and 1.2%, respectively. Concomitant anti-VEGF treatment in the study eye was reported in 9 PDS patients, all of whom also discontinued study treatment early.

Numbers analysed

Analysis populations

Table 2 Overview of Analysis Populations

Analysis Population Reason for Exclusion	PDS with Ranibizumab 100 mg/mL Q24W (N=251)	Intravitreal Ranibizumab 0.5 mg Q4W (N=167)	All Patients (N=418)
All Randomized Population (as Randomized)	251	167	418
Efficacy Population (as Treated)	248	167	415
Randomized and not treated	3	0	3
Per Protocol Population through Week 48 (as Treated)	230	157	387
Randomized and not treated	3	0	3
Inclusion Criteria deviation	2	0	2
Exclusion Criteria deviation	0	0	0
Medication Deviations Prior to Week 48*	4	0	4
Procedural Deviations Prior to Week 48	12	10	22

Efficacy population: All patients who are randomized and receive the study treatment.
Per protocol population: All patients in the efficacy population who do not have a major protocol violation that impact the efficacy evaluation. Patients can meet multiple exclusion criteria. *One patient recieved supplemental treatment due to an error made by the central imaging vendor and was excluded from the population without being counted as a protocol deviation.

[Table 2 from Updated CSR]

The primary analysis has been conducted in a modified ITT population ("Efficacy population")comprising all patients who were randomized and received the treatments, with patients grouped according to the treatment they actually received (patients who received the PDS implant were to be included in the PDS 100 mg/ml arm) Three patients randomized to the PDS 100 mg/mL arm were never treated and thus excluded from the Efficacy population. All patients randomized to the IVT ranibizumab arm were treated as assigned.

In addition, sensitivity analyses have been performed in the Per Protocol population for the primary EP and for the key secondary EP's. The PP population included all patients from the Efficacy population who

did not have a major protocol deviation that impacted the efficacy evaluation. A total of 18 patients in the PDS 100 mg/mL arm and 10 patients in the intravitreal arm were excluded.

Within this context, prior to study unblinding, major protocol deviations were reviewed and a determination of the population for PP analysis was made, based on whether the deviation was expected to impact the planned efficacy assessments.

Through Week 48, the most frequent procedural reason for exclusion from the PP population was VAE performing other study-related tasks or having access to VA scores from previous visits (10/12 procedural reasons in the PDS arm and 7/10 procedural reasons in the IVT arm).

Protocol deviations

Major protocol deviations were defined by the Sponsor (refer to Protocol Deviation Guidance in the CSR). Major protocol deviations were reported in 78 patients [31.5 %] in the PDS 100 mg/mL arm and 42 patients [25.1%] in the IVT arm. The imbalance in rate of major protocol deviations was attributed to medical deviations applicable only to PDS-treated patients (e.g., aspirin/NSAIDs not interrupted per protocol in 14 patients [5.6%] and supplemental treatment administered despite not meeting supplemental treatment criteria in 2 patients [0.8%]).

Overall, the majority of major protocol deviations were procedural in both treatment arms. Within the procedural category, the most frequently reported major protocol deviation through Week 48 was selected missed visits. Importantly, there were no reports of BCVA not performed per protocol specifications.

Other frequently reported major protocol deviations were mandatory blood sample not attempted and SAE/AESI not reported in a timely manner. The VAE performed other study-related tasks or had access to previous scores, potentially leading to unmasking in 10 patients (4.0%) and 7 patients (4.2%), respectively.

From the overall 120 patients who were reported to have major protocol deviations (n=78 in the PDS 100 mg/mL arm and n=42 patients in the IVT ranibizumab arm), only 28 patients (n=18 in the PDS arm and n=10 in the IVT arm) were excluded from the Per Protocol population. With his responses to the D120 LoQ, the Applicant has provided a tabulated summary for all major protocol deviations that were assessed to have an impact on efficacy assessments and the rationale for exclusion from or inclusion into the PP set, as requested. It is clarified that only patients with major protocol deviations likely to have a clinical impact on BCVA at these time-points were excluded, such as: uncertified staff performed BCVA testing, selected missed visits at Wk 44 and 48, VA examiner performed other study-related tasks or assessed previous visit VA scores, patient with long-standing nAMD disease not representing the target population, patient not having received at least 3 anti-VEGF injections prior to the screening visit, patient having received an additional out-of-protocol anti VEGF injection at D7 per investigator´s discretion, and others.

This is considered acceptable, against the background that the sensitivity analyses of the primary and key secondary endpoint (change in BCVA from baseline averaged over Weeks 36 and 40, and over Weeks 44 and 48, respectively) performed in the PP population (i.e. excluding patients with major protocol deviations as detailed above) were consistent with the corresponding primary analyses in the efficacy population.

Number of study treatments received

As of Week 40, patients in the PDS 100 mg/mL arm had received a mean of 2.0 study treatments per patient compared with a mean of 10.7 per patient in the intravitreal arm (Table 5). Study treatments

were initial fill and refill-exchange procedures in the PDS 100 mg/mL arm and IVT injections in the ranibizumab IVT arm.

At Week 48, most patients in the PDS 100 mg/mL arm had received 1 additional treatment (corresponding to the refill-exchange at Week 48), whereas most patients in the IVT arm received 2 additional treatments (Table 5).

Table 5 Overview of Number of Study Treatments in Study GR40548

Time-point	PDS 100 mg/mL (n=248)	Intravitreal Arm (n=167)
Week 40		
Mean (SD) number of treatments[a]	2.0 (0.15)	10.7 (1.26)[b]
Initial fill + refill-exchanges		
1	6 (2.4%)	Not applicable
2	242 (97.6%)	
Week 48		
Mean (SD) number of treatments[a]	2.9 (0.36)	12.6 (1.59)[c]
Initial fill + refill-exchanges		
1	6 (2.4%)	Not applicable
2	9 (3.6%)	
3	233 (94.0%)	

[a]Excludes supplemental treatments. For details on supplemental treatments, see Section 4.1.4.2.7

[b]153 patients (91.6%) with 11 intravitreal injections. [c]144 patients (86.2%) with 13 injections. [d]115 patients (68.8%) with 18-22 injections)

Source: Primary CSR, Report 1100486, Table 16, Update CSR, Report 1104956, t_ex_TW48_SP_UPDCSR

[Table 5 from Clinical Overview]

Overall, the number of treatments received by patients in the PDS arm demonstrated a meaningful reduction in treatment interventions compared with intravitreal injection.

Outcomes and estimation

Primary efficacy results

The pivotal study GR40548 met its primary endpoint - equivalence and non-inferiority have been demonstrated for the PDS 100 mg/mL arm (Q24W) compared to IVT ranibizumab 0.5 mg Q4W (pre-defined margin of ±4.5 letters), as measured by the change from baseline in BCVA at the average of Week 36 and Week 40. The difference in adjusted means between the treatment arms was -0.3 letters (95% CI -1.7, 1.1).

Table 10 Change from Baseline in Best Corrected Visual Acuity in Study Eye Averaged Over Weeks 36 and 40

	PDS 100 mg/mL Arm Adjusted Mean (95.03% CI)	Intravitreal Arm Adjusted Mean (95.03% CI)	Difference in Adjusted Means (95.03% CI)
Primary Analysis (Efficacy Population)			
MMRM method based on Treatment Policy Estimand	0.2 (-0.7, 1.1)	0.5 (-0.6, 1.6)	-0.3 (-1.7, 1.1)
Supplemental Analyses (Efficacy Population)			
Trimmed mean method with ANCOVA	2.8	3.3	-0.5 (-1.4, 0.4)
MMRM method using different rules for measures after intercurrent events: "had > 1 supplemental treatment" and "had prohibited therapy"			
Method 1: Imputed using LOCF	0.1 (-0.9, 1.0)	0.5 (-0.6, 1.6)	-0.5 (-1.9, 1.0)
Method 2: Assessments after 2 or more supplemental treatments or prohibited treatments excluded	0.1 (-0.8, 1.0)	0.5 (-0.6, 1.6)	-0.4 (-1.8, 1.1)
Sensitivity Analysis (Per Protocol Population)			
MMRM method based on treatment policy estimand	0.2 (-0.8, 1.1)	0.6 (-0.6, 1.7)	-0.4 (-1.8, 1.1)

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; MMRM = mixed-effect repeated measures.
Source: t_va_mmrm_SBCVA_OBS_EP, t_va_mmrm_SBCVA_OBS_PPROT, t_va_trim_SBCVAC1_OBS_EP, t_va_mmrm_SBCVAC2_LOCF_EP, t_va_mmrm_SBCVAC2_OBS_EP

[Table 10 from Primary CSR]

Intercurrent Events

A total of 7 patients (2.8%) in the PDS 100 mg/mL arm and no patients in the intravitreal arm experienced at least one intercurrent event through Week 40. The most common intercurrent events were discontinuation of the study due to an AE (5 patients [2.0%] in the PDS 100 mg/mL arm) and receipt of prohibited therapy (4 patients [1.6%] in the PDS 100 mg/mL arm). One patient (0.4%) in the PDS 100 mg/mL arm received more than one supplemental treatment in the study eye prior to Week 40.

Sensitivity analyses for the primary endpoint

The results of the sensitivity analysis in the Per Protocol Population (excluding patients who had major protocol deviations that potentially impacted efficacy outcomes) supported the results of the primary analysis, with an adjusted mean difference in the change from baseline in BCVA of -0.4 letters (95% CI: -1.8, 1.1) at the average of Weeks 36 and 40 (see Table 10 above).

To note, one patient was excluded from the PP Population due to receiving supplemental treatment in error prior to Week 40, which was not classified as a major protocol deviation.

Additional sensitivity analyses among complete cases (i.e. patients having assessments at both Week 36 and Week 40) in the PP Population were performed and supported the results of the primary analysis (see below).

Sensitivity Analyses (Per Protocol Population Among Complete Cases)			
MMRM method based on treatment policy estimand	0.1 (-0.8, 1.1)	0.5 (-0.6, 1.7)	-0.4 (-1.9, 1.1)
ANCOVA method based on treatment policy estimand	0.5	0.8	-0.3 (-1.8, 1.2)

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; MMRM = mixed-effect repeated measures.

Source: Primary CSR, Report 1100486, Table 10; ISE t_va_both_SBCVA_OBSW40_PPROTW40_UPDCSR, ISE t_ancova_SBCVA_OBSW40_PPROTW40_UPDCSR

[From Table 6, Clinical Overview]

Supplementary analyses for the primary endpoint

A trimmed mean analysis was performed by trimming 20% of patients with the worst outcomes from both arms including those who met the "must-be-trimmed criteria" (refer to SAP for details).

Six patients in the PDS 100 mg/mL arm met the "must-be-trimmed" criteria and were considered to have the worst outcomes. After 20% of patients with worst outcomes were trimmed, the adjusted mean change from baseline in BCVA score was similar between the PDS 100 mg/mL arm and the intravitreal arm (2.8 vs. 3.3 letters, respectively), with a difference in adjusted means of -0.5 letters (95% CI: -1.4, 0.4), which was consistent with the results of the primary endpoint analysis.

Two additional supplementary analyses were performed on the primary EP, using the same MMRM model, but different handling rules for two of the intercurrent events.

In Method 1, assessments at any time point either after 2 or more supplemental treatments or after prohibited treatments in the study eye were imputed using the last post-baseline observation prior to such intercurrent event. Using this method, the change in BCVA at the average of Week 36 and Week 40 with the PDS 100 mg/mL Q24W regimen remained non-inferior and equivalent to the intravitreal ranibizumab 0.5 mg Q4W regimen, which was consistent with the results of the primary efficacy endpoint analysis (Table 10).

In Method 2, assessments either after 2 or more supplemental treatments were administered or after prohibited treatments were taken were excluded. Using this method, the change in BCVA at the average of Week 36 and Week 40 with the PDS 100 mg/mL Q24W regimen remained non-inferior and equivalent to the intravitreal ranibizumab 0.5 mg Q4W regimen, which was consistent with the results of the primary efficacy endpoint analysis (Table 10).

Overall, it has to be pointed out that the BCVA changes from baseline in both arms were rather small, which can be attributed to the study population, having already reached a plateau of response at baseline due to the prior anti-VEGF treatments.

Key secondary efficacy endpoints (EMA)

In addition, the key secondary endpoints, which had been requested by EMA, were met: Non-inferiority of the PDS 100 mg/mL Q24W regimen to the IVT ranibizumab 0.5 mg Q4W regimen was also demonstrated when using a NI margin of 3.9 letters for the change from baseline in BCVA at the average of Week 36 and Week 40, as well as at the average of Week 44 and Week 48 (difference in adjusted means of -0.2 [95% CI -1.8, 1.3]). Supplemental analyses and sensitivity analyses further supported the robustness of the findings for this key secondary endpoint. (see Table 4 below).

Table 4 Change from Baseline in Best Corrected Visual Acuity in Study Eye Averaged Over Weeks 44 and 48

	PDS 100 mg/mL Arm Adjusted Mean (95.03% CI)	Intravitreal Arm Adjusted Mean (95.03% CI)	Difference in Adjusted Means (95.03% CI)
Main Analysis (Efficacy Population)			
MMRM method based on Treatment Policy Estimand	0.0 (−1.0, 1.0)	0.2 (−1.0, 1.4)	−0.2 (−1.8, 1.3)
Supplemental Analyses (Efficacy Population)			
Trimmed mean method with ANCOVA	2.6	3.4	−0.8 (−1.9, 0.2)
MMRM method using different rules for measures after intercurrent events: "had > 1 supplemental treatment" and "had prohibited therapy"			
Method 1: Imputed using LOCF	−0.2 (−1.2, 0.9)	0.2 (−1.0, 1.5)	−0.4 (−2.0, 1.2)
Method 2: Assessments after 2 or more supplemental treatments or prohibited treatments excluded	−0.1 (−1.1, 0.9)	0.2 (−1.0, 1.4)	−0.3 (−1.9, 1.3)
Sensitivity Analysis (Per Protocol Population)			
MMRM method based on treatment policy estimand	−0.1 (−1.1, 0.9)	0.6 (−0.6, 1.8)	−0.6 (−2.2, 0.9)

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; MMRM = mixed-effect repeated measures.

Source: t_va_mmrm_SBCVA_OBS_EP_UPDCSR; t_va_trim_SBCVAC1_OBS_EP_UPDCSR; t_va_mmrm_SBCVAC2_LOCF_EP_UPDCSR; t_va_mmrm_SBCVAC2_OBS_EP_UPDCSR; t_va_mmrm_SBCVA_OBS_PPROT_UPDCSR

[Table 4 from Updated CSR]

Although from a formal point of view such analyses could in principle only be considered as exploratory taking into account the narrow CIs and the consistency of the results, they do not reasonably represent a source of concern.

Other secondary efficacy endpoints

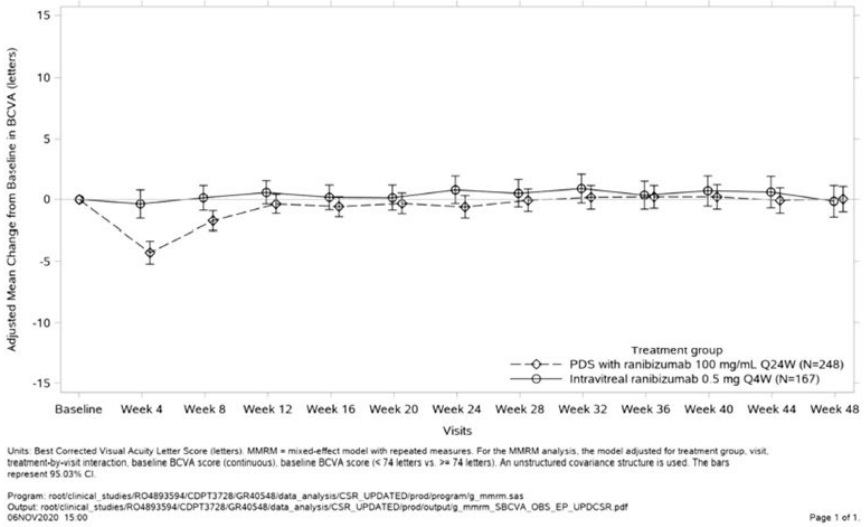
Several other secondary endpoints evaluated the effect of PDS 100 mg/mL Q24W on visual function compared to monthly IVT injections. The results overall supported the outcome of the primary analysis:

Change from baseline in BCVA over time

Through Week 48, the change in BCVA from baseline in the PDS 100 mg/mL arm was generally comparable to the intravitreal arm after Week 8, when PDS 100 mg/mL patients had recovered from surgery and had on average returned to their baseline BCVA score (Figure 3).

The 2 arms were generally similar in the change in BCVA after Week 8, suggesting that most patients had reached a plateau of response at baseline following the prior anti-VEGF treatments.

Figure 3 Adjusted Mean Change in Best Corrected Visual Acuity over Time (Observed Data): MMRM Method

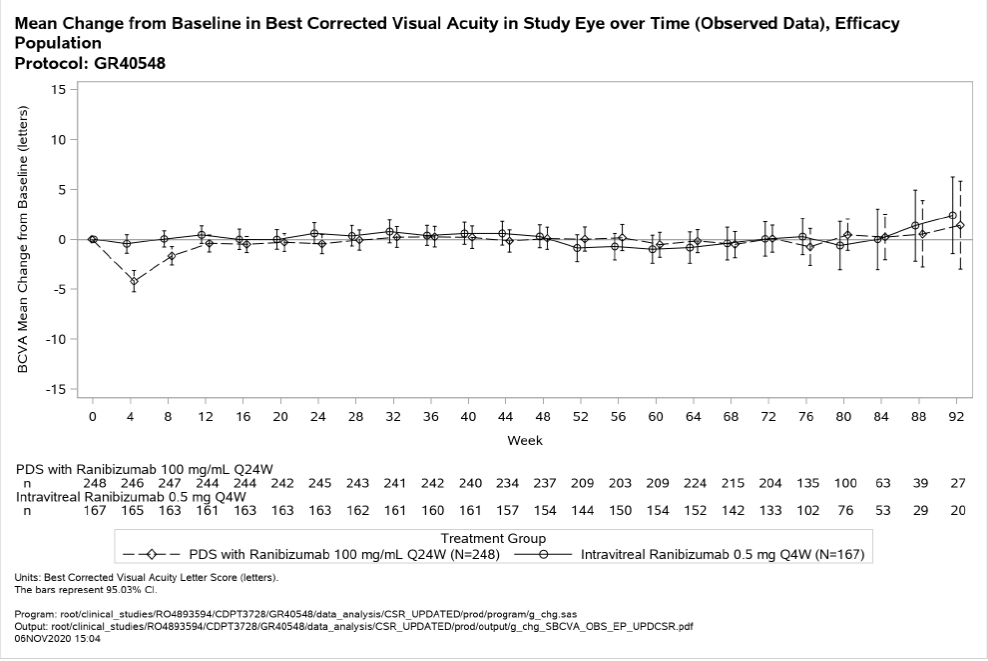


BCVA = best corrected visual acuity; MMRM = mixed-effect repeated measures; PDS = Port Delivery System; Q4W = every 4 weeks; Q24W = every 24 weeks.

[Figure 3 from Updated CSR]

There was a reduction in BCVA in the first 12 weeks in the PDS 100 mg/mL arm. Although this is associated with the implant surgery and after Week 12 there is a visual recovery and BCVA remained stable and generally comparable to the intravitreal arm, this is a limitation for the efficacy and should be balanced in the benefit/risk ratio of the product. In the cases where an explant of the implant was required during clinical development (7 patients as of cut off date Sep 11, 2020), it seems that there was also a reduction in visual acuity, although it is not confirmed for all the cases. (**OC**)

Preliminary data through Week 92 have been submitted with the Updated CSR. However, data past Week 60 are not mature (see Updated CSR).



[Page 231, Updated CSR]

Proportion of patients with a BCVA score ≤38 letters/ ≥69 letters at the average of W36 and W40

A similar adjusted proportion of patients in the PDS 100 mg/mL arm and the intravitreal arm had a BCVA score of 38 letters (20/200 approximate Snellen equivalent) or worse averaged over Weeks 36 and 40, 1.2% (3 patients) in the PDS 100 mg/mL arm versus 1.8% (3 patients) in the Q4W intravitreal arm, corresponding to a difference of -0.6% (95.03% CI: -3.1%, 1.8%) (Table 11).

A similar adjusted proportion of patients in the PDS 100 mg/mL arm and the intravitreal arm had a BCVA score of 69 letters (20/40 approximate Snellen equivalent) or better averaged over Weeks 36 and 40, 80.7% (198 patients) in the PDS 100 mg/mL arm versus 82.1% (134 patients) in the intravitreal arm, corresponding to a difference of -1.4% (95.03% CI: -7.4%, 4.5%) (Table 11).

The treatment group difference for these endpoints over time through Week 40 was small, and the estimates were consistent with those seen at the average of Weeks 36 and 40 (similar adjusted proportion of patients with a BCVA score of 38 letters or worse and 69 letters or better).

Table 11 Proportion of Patients with a Best Corrected Visual Acuity Score of ≤38 letters or ≥69 letters in the Study Eye at the Average of Weeks 36 and 40 (CMH Weighted, Observed Data), Efficacy Population

		PDS with ranibizumab 100 mg/mL (N = 248)	Intravitreal ranibizumab 0.5 mg injections (N = 167)	Difference (95.03% CI)
BCVA Score				
38 letters (20/200 Snellen equivalent) or worse	Proportion: n (%)	3 (1.2%)	3 (1.8%)	-0.6%
	CMH Weighted Estimate	1.2%	1.8%	-0.6%
	(95.03% CI)	(0.0%, 2.6%)	(0.0%, 3.9%)	(-3.1%, 1.8%)
69 letters (20/40 Snellen equivalent) or better	Proportion: n (%)	198 (80.5%)	134 (82.2%)	-1.7%
	CMH Weighted Estimate	80.7%	82.1%	-1.4%
	(95.03% CI)	(76.9%, 84.5%)	(77.5%, 86.7%)	(-7.4%, 4.5%)

BCVA = best corrected visual acuity; CI = confidence interval CMH = Cochran-Mantel-Haenszel; PDS with ranibizumab = Port Delivery System with ranibizumab.

Source: t_cmh_AVAL_SBCVA_OBS_EP

[Table 11 from Primary CSR]

Proportion of patients with loss of VA and gain of VA from baseline at the average of W36 and W40

At the average of Weeks 36 and 40, a similar adjusted proportion of patients in the PDS 100 mg/mL arm and the intravitreal arm had a loss of <10 letters (95.1% [234 patients] vs. 95.1% [155 patients]), a loss of <5 letters (85.0% [209 patients] vs. 88.3% [144 patients]), and a gain of ≥0 letters (57.8% [142 patients] vs. 58.9% [96 patients]; Table 12). The adjusted proportion of patients in the PDS 100 mg/mL arm and intravitreal arm who lost or gained letters in BCVA score from baseline was also similar over time.

Table 12 Adjusted Proportion of Patients with a Change of Visual Function from Baseline in the Study Eye at the Average of Weeks 36 and 40 (CMH Method) (Observed Data), Efficacy Population

		PDS 100 mg/mL (N = 248)	Intravitreal ranibizumab 0.5 mg injections (N = 167)	Difference (95.03% CI)
Loss of Visual Function from Baseline				
<10 letters	Proportion: n (%)	234 (95.1%)	155 (95.1%)	0.0%
	CMH Weighted Estimate (95.03% CI)	95.1% (92.4%, 97.8%)	95.1% (91.8%, 98.4%)	0.0% (-4.2%, 4.3%)
<5 letters	Proportion: n (%)	209 (85.0%)	144 (88.3%)	-3.4%
	CMH Weighted Estimate (95.03% CI)	85.0% (80.5%, 89.4%)	88.3% (83.4%, 93.3%)	-3.4% (-10.0%, 3.3%)
<15 letters[b]	Proportion: n (%)	240 (97.6%)	158 (96.9%)	0.6%
	CMH Weighted Estimate (95.03% CI)	97.6% (95.6%, 99.5%)	96.9% (0.0%, 2.9%)	0.6% (–2.6%, 3.9%)
Gain in Visual Function from Baseline				
≥0 letters	Proportion: n (%)	142 (57.7%)	96 (58.9%)	-1.2%
	CMH Weighted Estimate (95.03% CI)	57.8% (51.8%, 63.7%)	58.9% (51.4%, 66.4%)	-1.1% (-10.7%, 8.4%)
≥5 letters[a]	Proportion: n (%)	51 (20.7%)	38 (23.3%)	-2.6%
	CMH Weighted Estimate (95.03% CI)	20.8% (15.9%, 25.6%)	23.3% (17.3%, 29.3%)	-2.5% (-10.2%, 5.2%)
>15 letters[b]	Proportion: n (%)	4 (1.6%)	2 (1.2%)	0.4%
	CMH Weighted Estimate (95.03% CI)	1.6% (0.1%, 3.2%)	1.2% (0.0%, 2.9%)	0.4% (–1.9%. 2.7%)

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; PDS = Port Delivery System with ranibizumab.
[a] Exploratory efficacy endpoint
[b] Post-hoc exploratory analysis
Source: t_cmh_CHG_SBCVA_OBS_EP, t_cmh_new_CHG_SBCVA_OBS_EP

[Table 12 from Primary CSR]

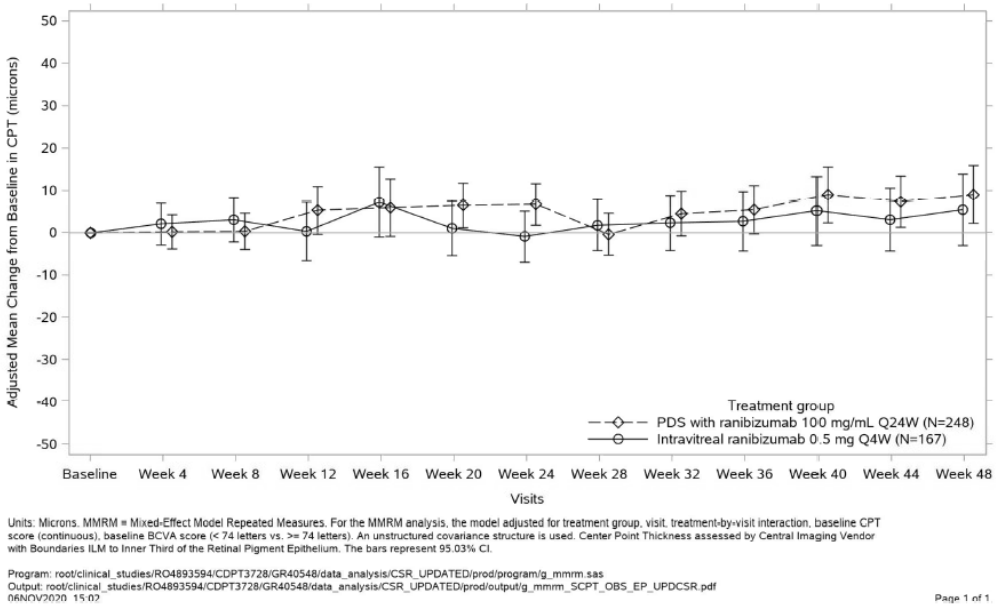
Change from baseline in CPT (center point thickness) at Week 36 (and over time)

CPT change is a surrogate for anatomical response to study treatment and was evaluated at baseline and at Week 36. Mean CPT at baseline was comparable between study arms (176.9 microns in PDS 100 mg/mL arm vs 177.2 microns in IVT arm). The adjusted mean change from baseline at Week 36 was 5.4 microns versus 2.6 microns, corresponding to a difference of 2.8 microns (95% CI: -6.2, 11.9).

The change from baseline in CPT was similar between the two arms over time through Week 48 (Figure 4 below). At Week 48, change from baseline was 9.1 microns for the PDS 100 mg/mL arm and 5.5 microns for the intravitreal arm, corresponding to a difference of 3.6 microns (95% CI: -7.3, 14.5).

A slight increase in CPT in the PDS 100 mg/mL arm leading up to the scheduled refill-exchange followed by a decrease after the refill-exchange was observed over time. According to the Applicant, after each refill-exchange, CPT generally tended to decrease to baseline levels.

Figure 4 Adjusted Mean Change from Baseline in Center Point Thickness in Study Eye through Week 48 (Observed Data): MMRM Method



CPT = central point thickness; MMRM = mixed-effect repeated measures; PDS = Port Delivery System; Q4W = every 4 weeks; Q24W = every 24 weeks.

[Figure 4 from Updated CSR]

Supplemental treatment with IVT ranibizumab in the PDS 100 mg/mL arm

In order to ensure that patients were achieving sufficient vitreous concentrations of ranibizumab to control their disease, the protocol permitted patients in the PDS 100 mg/mL arm to receive supplemental treatment at 8 weeks and/or 4 weeks prior to each scheduled refill-exchange procedure if criteria based on BCVA and CST changes were met. During the first (up to 24 weeks) and second treatment interval (24-48 weeks), 1.6% and 5.4% of patients fulfilled supplemental treatment criteria and received such treatment. No patient who received supplemental treatment in the first treatment interval received additional supplemental treatment in the second treatment interval.

Against the fact that distinctly more patients in the PDS 100 mg/mL arm met the criteria for supplemental treatment with ranibizumab in the second than in the first treatment interval, the Applicant was requested to provide the respective data for the third (48-72 weeks) and fourth (72-96 weeks) treatment interval, as far as available, and to comment on the findings. According to these data, after the first treatment interval the supplemental treatment rate remained consistent and no trend towards increased need for supplemental treatment was observed through Week 96. Regarding the potential specific characteristics of the patients that require supplemental treatment in the PDS arm of Archway study, it seems that the patients with higher CST and CPT values and the ones with intraretinal fluid at baseline are more predisposed to require supplement treatment. As the Applicant mentions, this needs to be further explored and confirmed with ongoing and future studies given the large difference between the sample sizes of the 2 groups (31 vs 217) from Study GR40548.

It is uncertain whether the efficacy of PDS is similar regardless of the anti-VEGF used in the initial boosting period. In study GR40548, about 12% of patients had received aflibercept and 30.5% bevacizumab. The assessment of the response has been conducted under the assumption that all patients received the same initial treatment, but the differential response by previous treatment should be presented. The Applicant has performed and presented analyses of the primary endpoint within subgroups of patients receiving any prior (within 9 months of baseline) aflibercept (n=48), any prior bevacizumab (n=124), and neither aflibercept nor bevacizumab (i.e., ranibizumab only) (n=246). The

data related to aflibercept and bevacizumab are more in favour of PDS and the data for ranibizumab in favour of IVT ranibizumab. As the number of patients for the prior treatments other than ranibizumab are low and all the results are within the equivalence margins, it is acknowledged that there is no evidence of clinically meaningful differences in the primary endpoint between the two treatment groups based on previous treatment.

Exploratory efficacy endpoints

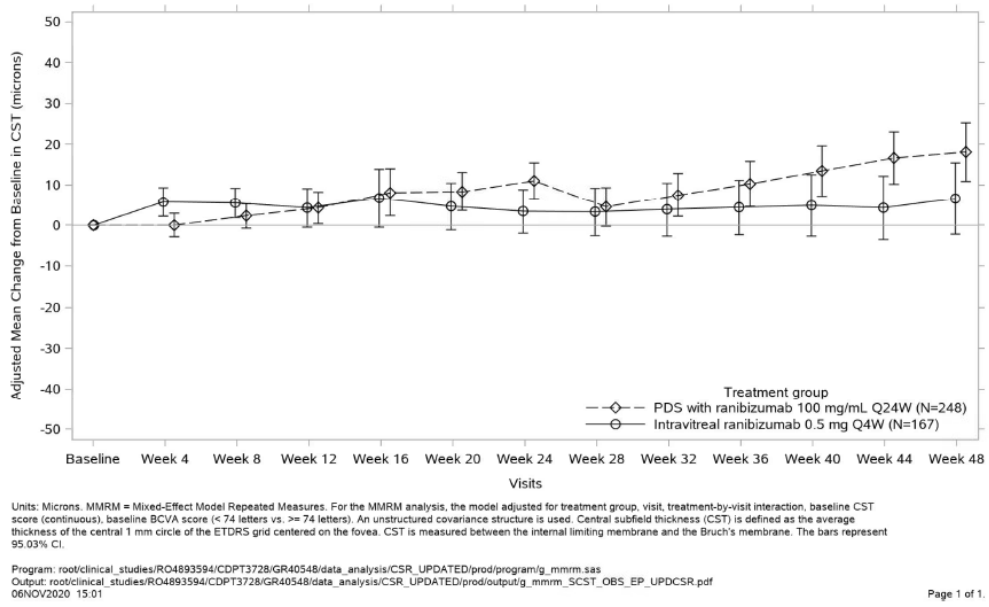
Change from baseline in CST (central subfield thickness) at Week 36 and over time

The adjusted mean change from baseline in CST was similar between the PDS 100 mg/mL arm and the intravitreal arm at Week 36 (10.3 microns vs. 4.4 microns, corresponding to a difference in adjusted means of 5.9 microns [95.03% CI: -2.9, 14.7]).

The adjusted mean change from baseline in CST was overall comparable between the PDS 100 mg/mL arm and the intravitreal arm over time through Week 48 (Figure 5). At Week 48, change from baseline was 18.1 microns for the PDS 100 mg/mL arm and 6.6 microns for the intravitreal arm, corresponding to a difference of 11.5 microns (95% CI: 0.1, 22.9).

A slight increase in CST in the PDS 100 mg/mL arm leading up to the scheduled refill-exchange followed by a decrease after the refill-exchange was observed over time, similar to the observations for CPT. According to the Applicant, after each refill-exchange, CPT generally tended to decrease to baseline levels.

Figure 5 Adjusted Mean Change from Baseline in Center Subfield Thickness in Study Eye through Week 48 (Observed Data): MMRM Method



CST = central subfield thickness; MMRM = mixed-effect repeated measures; PDS = Port Delivery System; Q4W = every 4 weeks; Q24W = every 24 weeks.

[Figure 5 from Updated CSR]

<u>BCVA and CST over time relative to supplemental treatment</u>

A total of 17 patients (6.9%) in the PDS 100 mg/mL arm received supplemental treatment through Week 48. Three of these patients received the first supplemental treatment in error, whereas 14 patients met the supplemental treatment criteria. These patients received supplemental treatment due to the BCVA decrease criteria being met (2 patients), the CST increase criteria being met (7 patients), or the

BCVA/CST combined criteria being met (4 patients). For one patient both CST and BCVA criteria were selected in error. Further query revealed that the patient was only eligible based on the BCVA criterion.

Generally, patients who received supplemental treatment maintained or returned to baseline values in BCVA and CST after receiving the supplemental treatment.

Proportion of patients with a gain of 5 letters in BCVA from baseline over time

At the average of Weeks 36 and 40, a similar adjusted proportion of patients in the PDS 100 mg/mL arm and the intravitreal arm had a gain of ≥5 letters from baseline (20.8% [51 patients] vs. 23.3% [38 patients]).

Ancillary analyses

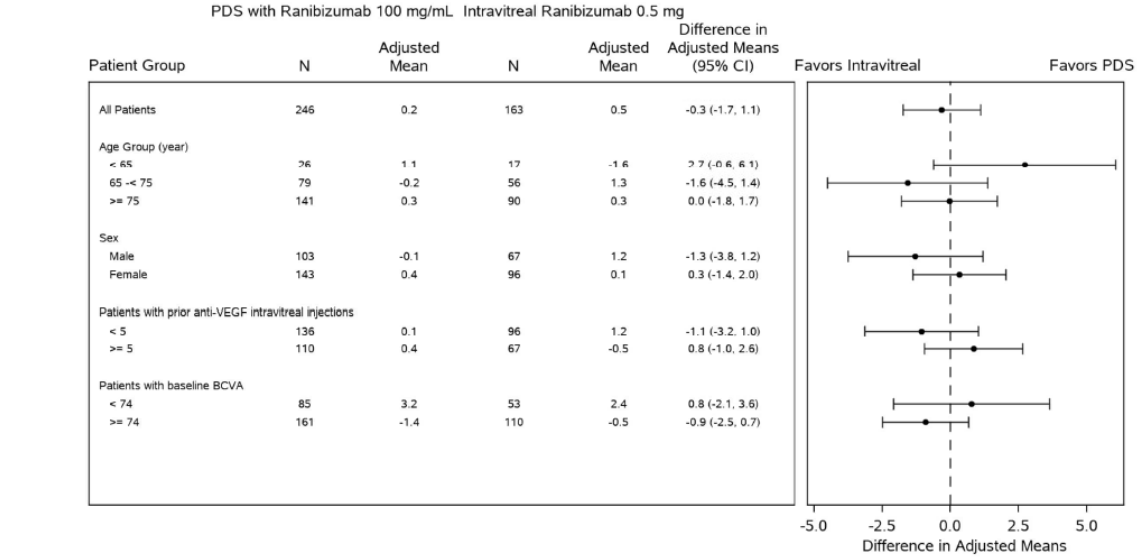
Subgroup analyses

Primary endpoint – Change from baseline in BCVA averaged over Week 36 and Week 40

The differences between the 2 treatment arms in change from baseline in BCVA averaged over Weeks 36 and 40 were similar for age subgroups (<65 years, 65 to <75 years, ≥75 years), sex subgroups (male/female), subgroups of patients with different number of prior anti-VEGF intravitreal injections (<5 vs. ≥5 prior injections), and subgroups according to baseline BCVA score (<74 vs. ≥74).

The subgroup findings were overall consistent with the primary endpoint analysis.

Figure 6 Subgroup Analysis for Change from Baseline in BCVA in Study Eye Averaged over Weeks 36 and 40 (Observed Data): MMRM Method



Units: Best Corrected Visual Acuity Letter Score (letters). MMRM = Mixed-Effect Model Repeated Measures. For the MMRM analysis, the model adjusted for treatment group, visit, treatment-by-visit interaction, baseline BCVA score (continuous), baseline BCVA score (< 74 letters vs. >= 74 letters). Baseline BCVA score (< 74 letters vs. >=74 letters) is excluded from the MODEL statement when BCVA is the subgroup. An unstructured covariance structure is used. 95% CI is a rounding of 95.03% CI. The estimate of the difference between the two groups is using a composite contrast over Weeks 36 and 40.
Program: root/clinical_studies/RO4893594/CDPT3728/GR40548/data_analysis/ADHOC/prod/program/g_sbgr_mmrm_up.sas
Output: root/clinical_studies/RO4893594/CDPT3728/GR40548/data_analysis/ADHOC/prod/output/g_sbgr_mmrm_up_SBCVA_OBS_EP.pdf
05NOV2020 17:35 Page 1 of 1

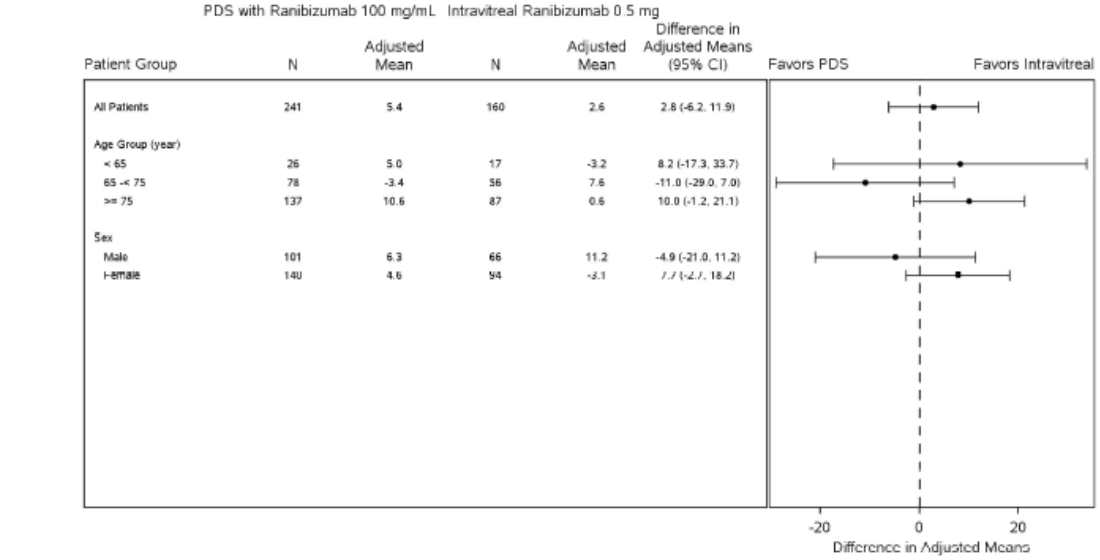
[Figure 6 from Updated CSR]

Secondary endpoint – Change from baseline in CPT at Week 36

For the secondary EP "Change from baseline in CPT at Week 36", subgroup analyses have been performed only for the subgroups age and sex, not for subgroups of patients with different number of prior anti-VEGF intravitreal injections (<5 versus ≥5 prior injections) and for subgroups according to baseline BCVA score (<74 vs. ≥74), as done for the primary EP. The Applicant was requested to provide those additional subgroup analyses, for the sake of clarity and completeness. The requested subgroup

analyses have been provided with the responses to the D120 LoQ. Those additional subgroup findings were overall consistent with the primary analysis in all patients.

Figure 15 Subgroup Analyses for Change from Baseline in Center Point Thickness in the Study Eye at Week 36 (Observed Data): MMRM Method, Efficacy Population



Units: Microns. MMRM = Mixed-Effect Model Repeated Measures. For the MMRM analysis, the model adjusted for treatment group, visit, treatment-by-visit interaction, baseline CPT (continuous), baseline BCVA score (< 74 letters vs. >= 74 letters). An unstructured covariance structure is used. 95% CI is a rounding of 95.03% CI. Center Point Thickness (CPT) Assessed by Central Imaging Vendor with Boundaries ILM to Inner Third of the Retinal Pigment Epithelium.
Program: root/clinical_studies/RO4893594/CDPT3728/GR40548/data_analysis/SREP/prod/program/g_sbgr_mmrm.sas
Output: root/clinical_studies/RO4893594/CDPT3728/GR40548/data_analysis/SREP/prod/output/g_sbgr_mmrm_SCPT_OBS_EP.pdf
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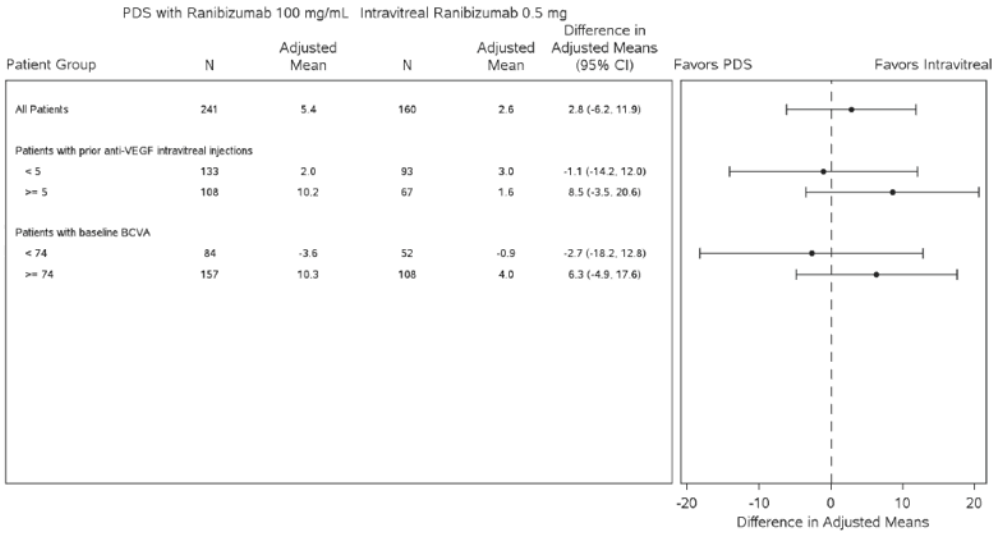
[Figure 15 from Primary CSR]

Figure 1 Study GR40548 Subgroup Analyses for Change from Baseline in CPT in Study Eye at Week 36 (Observed Data): MMRM Method



Units: Microns. MMRM = Mixed-Effect Model Repeated Measures. For the MMRM analysis, the model adjusted for treatment group, visit, treatment-by-visit interaction, baseline CPT (continuous), baseline BCVA score (< 74 letters vs. >= 74 letters). Baseline BCVA score (< 74 letters vs. >=74 letters) is excluded from the MODEL statement when BCVA is the subgroup. An unstructured covariance structure is used. 95% CI is a rounding of 95.03% CI. Center Point Thickness (CPT) Assessed by Central Imaging Vendor with Boundaries ILM to Inner Third of the Retinal Pigment Epithelium.
Program: root/clinical_studies/RO4893594/CDPT3728/GR40548/data_analysis/D120/prod/program/g_sbgr_mmrm.sas
Output: root/clinical_studies/RO4893594/CDPT3728/GR40548/data_analysis/D120/prod/output/g_sbgr_mmrm_SCPT_OBSW40_EP_D120.pdf
25OCT2021 18:37 Page 1 of 1

Post-hoc analyses

Proportion of patients with a gain/ loss of 15 letters in visual function over time

At the average of Weeks 36 and 40, a similar adjusted proportion of patients in the PDS 100 mg/mL arm and the intravitreal arm had a loss of <15 letters (97.6% [240 patients] vs. 96.9% [158 patients], respectively), and a gain of >15 letters (1.6% [4 patients] vs. 1.2% [2 patients], respectively) from baseline

Post-hoc analyses showed that at the average of Weeks 44 and 48, a similar adjusted proportion of patients in the PDS 100 mg/mL arm and the intravitreal arm had a loss of <15 letters (97.5% [238 patients] vs. 96.3% [155 patients], respectively), and a gain of >15 letters (1.6% [4 patients] vs. 1.9% [3 patients], respectively) from baseline.

Impact of COVID-19 on efficacy analyses

As of the CCOD of 27 March 2020 for the primary CSR, there were no missed BCVA assessments from Week 0 through Week 40 due to COVID-19.

With regard to the change from baseline in BCVA averaged over Week 44 and Week 48, there was a low impact of COVID-19. No changes to the SAP were made for the updated CSR with CCOD 11 Sept 2020. The Sponsor will continue to assess the impact of COVID-19 post Week 48, and the SAP may be revised for the final CSR depending on the impact.

There is no concern with regard to the impact of COVID19 on efficacy analyses.

Summary of main efficacy results

The following table summarises the efficacy results from the main study GR40548/ Archway 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: Summary of efficacy for trial GR40548/ Archway

Title: A Phase III, Multicenter, Randomized, Visual Assessor-Masked, Active Comparator Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab in Patients with Neovascular Age-Related Macular Degeneration.		
Study identifier	GR40548, Archway ClinicalTrials.gov Identifier: NCT03677934	
Design	Phase III, Multicenter, Randomized, Visual Assessor-Masked, Active Comparator Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab in Patients with Neovascular Age-Related Macular Degeneration.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	96 weeks (first patient randomized: 12 Sept 2018, last patient randomized: 24 June 2019) 21 days NA
Hypothesis	Non-Inferiority (NI) and Equivalence	
Treatment groups	PDS with ranibizumab 100 mg/mL Q24W	251 patients randomized

	IVT ranibizumab 0.5 mg Q4W		167 patients randomized
Endpoints and definitions	Primary endpoint	Change from baseline (CFB) in BCVA Averaged Over Week 36 (W36) and Week 40 (W40)	CFB in BCVA score at the average of Week 36 and Week 40, assessed using the EDTRS chart (4 m starting distance) with a NI margin of -4.5 letters/ equivalence margin of ± 4.5 letters
	Key secondary endpoint	CFB in BCVA Averaged Over W36 and W40	CFB in BCVA score at the average of Week 36 and Week 40, using the EDTRS chart with a NI margin of -3.9 letters
	Key secondary endpoint	CFB in BCVA Averaged Over W44 and W48	CFB in BCVA score at the average of Week 44 and Week 48, using the EDTRS chart with a NI margin of -3.9 letters
Database lock	The study was ongoing at the time of the initial MAA and database lock had not yet occurred. CCOD is 27 March 2020 for the primary analysis of efficacy data through Week 40, and 11 September 2020 for updated efficacy analyses through Week 48.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy population (mITT; randomized and treated; n=415), Week 40 data		
Descriptive statistics and estimate variability	Treatment group	PDS 100 mg/mL Q24W	IVT ranibizumab 0.5 mg Q4W
	Number of subjects	248	167
	CFB in BCVA Averaged Over W36 and W40, adjusted mean	0.2 letters	0.5 letters
	95.03% CI	(-0.7, 1.1)	(-0.6, 1.6)
Effect estimate per comparison	Primary endpoint: CFB in BCVA Averaged Over W36 and W40 with margin ±4.5	Comparison groups	PDS 100 mg/mL Q24W vs. intravitreal ranibizumab 0.5 mg Q4W
		Difference between groups	0.3 letters
		95.03% CI	(-1.7, 1.1)
		NI Margin = -4.5 EQ Margin = ±4.5	-1.7 > -4.5 -1.7 > -4.5, 1.1 < 4.5
	Key secondary: CFB in BCVA Averaged Over W36 and W40 with margin -3.9	NI Margin = -3.9	-1.7 > -3.9

Notes	MMRM method was used based on treatment policy estimand. Equivalence margins were ± 4.5 letters. Non-inferiority margin was -3.9 letters. Both hypotheses can be rejected.		
Analysis description	**Secondary analysis**		
Analysis population and time point description	Efficacy population (randomized and treated; n=415), Week 48 data		
Descriptive statistics and estimate variability	Treatment group	PDS 100 mg/mL Q24W	IVT ranibizumab 0.5 mg Q4W
	Number of subjects	248	167
	Key secondary: CFB in BCVA Averaged Over W44 and W48, adjusted mean	0.0 letters	0.2 letters
	95.03% CI	(-1.0, 1.0)	(-1.0, 1.4)
Effect estimate per comparison	Key secondary: CFB in BCVA Averaged Over W44 and W48 with margin -3.9	Comparison groups	PDS 100 mg/mL Q24W vs. intravitreal ranibizumab 0.5 mg Q4W
		Difference between groups	-0.2 letters
		95.03% CI	(-1.8, 1.3)
		NI Margin = -3.9	-1.8 > -3.9 -
Analysis description	**Sensitivity analysis for primary EP**		
Analysis population and time point description	Per Protocol (PP) population (all patients from the Efficacy population who do not have a major protocol deviation that impacts efficacy evaluation; n=387), Week 40 data		
Descriptive statistics and estimate variability	Treatment group	PDS 100 mg/mL Q24W	IVT ranibizumab 0.5 mg Q4W
	Number of subjects	230	157
	Primary EP: CFB in BCVA Averaged Over W36 and W40, adjusted mean	0.2 letters	0.6 letters
	95.03% CI	(-0.8, 1.1)	(-0.6, 1.7)
Effect estimate per comparison	Primary EP: CFB in BCVA Averaged Over W36 and W40 with margin ±4.5	Comparison groups	PDS 100 mg/mL Q24W vs. intravitreal ranibizumab 0.5 mg Q4W
		Difference between groups	-0.4 letters
		95.03% CI	(-1.8, 1.1)
		NI Margin = -4.5 EQ Margin = ±4.5	-1.8 > -4.5 -1.8 > -4.5, 1.1 < 4.5

Analysis description	Sensitivity analysis for key secondary EP		
Analysis population and time point description	PP population (all patients from the Efficacy population who do not have a major protocol deviation that impacts efficacy evaluation; n=387), Week 48 data		
Descriptive statistics and estimate variability	Treatment group	PDS 100 mg/mL Q24W	IVT ranibizumab 0.5 mg Q4W
	Number of subjects	230	157
	Key secondary EP: CFB in BCVA Averaged Over W44 and W48, adjusted mean	-0.1 letters	0.6 letters
	95.03% CI	(-1.1, 0.9)	(-0.6, 1.8)
Effect estimate per comparison	Key secondary EP: CFB in BCVA Averaged Over W44 and W48 with margin -3.9	Comparison groups	PDS 100 mg/mL Q24W vs. intravitreal ranibizumab 0.5 mg Q4W
		Difference between groups	-0.6 letters
		95.03% CI	(-2.2, 0.9)
		NI Margin = -3.9	-2.2 > -3.9 -

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

Given the differences in PDS refill-exchange procedure frequency (PRN in Study GX28228 versus Q24W in Study GR40548) and the difference in pre-randomization intravitreal ranibizumab injections (2 in Study GX28288 versus 4 in Study GR40548), the comparative efficacy between the PDS and the monthly intravitreal ranibizumab 0.5 mg arm is described separately for Studies GR40548 and GX28228. No pooled analysis has been performed. This is considered acceptable.

In Study GR40548, changes in BCVA observed in the PDS 100 mg/mL Q24W arm were non-inferior and equivalent to those in the intravitreal ranibizumab 0.5 mg Q4W arm, at the average of 36 and 40 weeks with a difference of -0.3 letters (95.03% CI: -1.7, 1.1), and at the average of weeks 44 and 48 with a difference in adjusted means between the PDS and intravitreal arms of -0.2 letters (95.03% CI: -1.8, 1.3).

In Study GX28228, change in BCVA observed at the average of Month 9 and Month 10 in the PDS 100 mg/mL PRN arm were similar to those in the intravitreal ranibizumab 0.5 mg Q4W arm with a difference of 1.8 letters (95% CI: -1.7, 5.2).

Clinical studies in special populations

N/A

Supportive study

Study GR40549 (Portal) is a multicenter, open-label, VA-masked, multiple-cohort extension study designed with the primary objective of evaluating the long-term safety and tolerability of ranibizumab 100 mg/mL delivered via the PDS administered Q24W to patients who were eligible to enroll in the extension study from Study GX28228 or Study GR40548 (also referred to as "parent studies").

Study No.	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen
GR40549 (Portal) extension study	Phase III, Multicenter, open-label, VA–masked, multiple-cohort extension study (ongoing)	Patients with nAMD who have completed either Phase II Study GX28228 (Ladder) or Phase III Study GR40548 (Archway)	220 patients enrolled [d] -PDS 100 mg/mL Q24W: 217 patients -13 patients from Archway -189 patients from Ladder main study -4 patients from non-compliant Ladder site not included in analyses -11 patients from OATS -3 patients not treated	PDS 100 mg/mL Q24W

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; nAMD = neovascular age-related macular degeneration; PDS = Port Delivery System with ranibizumab; PRN = pro re nata; Q4W = every 4 weeks; Q24W = every 24 weeks; VA = visual assessor; VEGF = vascular endothelial growth factor.

[d] Five patients from the main study of Study GX28228 were not included in the efficacy population in this SCE due to being from a non-compliant site (n = 4) or untreated (n=1) and 11 non-randomized patients from the oral anti-thrombotic (OAT) sub-study were excluded from the analyses in this SCE leaving 189 GR40549 patients in the pooled analysis population; 15 patients enrolled from Study GR40548 (2 not treated) were not included in the efficacy evaluation included in this SCE, due to their short duration of participation in Study GR40549 and therefore limited follow-up data available, as of the CCOD of 11 September 2020.

[Table 1 from Summary of Clinical Efficacy]

Importantly, patients in the parent studies who discontinued from the study or from the study treatment (either the implant or monthly intravitreal ranibizumab 0.5 mg injections) were not eligible for enrollment in this extension study.

Up to approximately 600 patients are planned for enrollment in this extension study after completion of the parent studies.

Study design

At the time of enrolment into the Portal study (ranging from approx. 15 to 38 months from baseline of study GX28228), patients from the GX28228/ Ladder study who already had an implant moved from a PRN regimen to a fixed refill-exchange Q24W regimen, and patients from the IVT arm received the PDS implant at the 100 mg/mL Q24W regimen.

Patients from the GR40548/ Archway study who were enrolled in study GR40549 (n=15) had short duration of participation and therefore limited follow-up in study GR40549 as of the CCOD of 11 September 2020; they were thus excluded from efficacy evaluation.

Interim efficacy data from this ongoing open-label extension study have been submitted with the MAA (CCOD 11 September 2020).

Key Inclusion and Exclusion Criteria

Patients were required to meet the following criteria for study entry:

- Previous enrollment in and completion of Study GX28228 or Study GR40548, without early treatment or study discontinuation in either study (monthly intravitreal ranibizumab 0.5 mg or implant arms)

Patients who met any of the following criteria were excluded from study entry:

- Continuous use of any prohibited medications or treatments

Efficacy Objectives/ Endpoints

Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of ranibizumab delivered via the PDS Q24W with the 100 mg/mL formulation, as assessed by visual acuity	• Change in BCVA score from baseline over time, as assessed using the ETDRS visual acuity chart at a starting distance of 4 meters
• To evaluate the efficacy of ranibizumab, delivered via the PDS Q24W with the 100 mg/mL formulation, as assessed by CPT	• Change from baseline in CPT over time
• To evaluate the proportion of patients who undergo supplemental treatment with intravitreal ranibizumab 0.5 mg	• Proportion of patients who undergo supplemental treatment with intravitreal ranibizumab 0.5 mg before the first, second, third, fourth, and fifth [a] refill interval
Exploratory Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of ranibizumab, delivered via the PDS Q24W with the 100 mg/mL formulation, as assessed by CST	• Change from baseline in CST over time

BCVA = best-corrected visual acuity; CPT = center point thickness; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; PDS = Port Delivery System with ranibizumab; Q24W = every 24 weeks; Q4W = every 4 weeks.

[a] Data for the fourth and fifth refill intervals were not mature at the time of the CCOD and are not included in the SCE.

Note: CPT is defined as the retinal thickness in the center point of the fovea measured between the internal limiting membrane and the inner third of the retinal pigment epithelium layer. CST is defined as the average thickness of the central 1 mm circle of the ETDRS grid centered on the fovea measured between the internal limiting membrane and the Bruch's membrane. CPT and CST were assessed by the central reading center.

[Table 4 from Summary of Clinical Efficacy]

Study Population

For the long-term efficacy analysis, as of the CCOD of 11 September 2020, 220 patients were enrolled in Study GR40549 including 194 patients (189 treated) from the main study of Study GX28228 and 15 patients from Study GR40548. The efficacy population included for evaluation in the SCE includes 189 **patients** enrolled from Study GX28228 (excluding 11 patients in the OAT sub-study of Study GX28228). Five patients from the main Study GX28228 were not included in the efficacy population: 4 patients were enrolled at a non-compliant site and 1 patient was untreated.

Patients enrolled from Study GR40548 had a short duration of participation in Study GR40549 as of the CCOD, and there was limited follow-up on these patients; thus data from these patients were not included in the efficacy evaluation.

Statistical methods

The long-term efficacy of PDS 100 mg/mL was evaluated based upon the visual (BCVA) and anatomical (CPT and CST) outcomes achieved in patients using combined data from Study GX28228 and Study GR40549. Two different baselines were utilized for the endpoints. In the first instance, baseline was defined as measures taken at the first treatment in Study GX28228 and in the second instance baseline was defined as measures taken at first treatment in Study GR40549.

Analysis populations, definition of baseline, and analysis goals are summarized in Table 5.

Table 5 Overview of Populations Used to Evaluate Long-Term Efficacy as of the CCOD of 11 September 2020

Population	Sample Size	Baseline	Goal
Patients who were treated with PDS 100 mg/ml PRN in Study GX28228	n=59	Day 1 of Study GX28228	Evaluate long-term BCVA, CPT, and CST change relative to parent study baseline after being treated with PDS 100 mg/ml PRN in Study GX28228 and then Q24W in Study GR40549
Patients who were treated with monthly intravitreal ranibizumab 0.5 mg in Study GX28228	n=41	Day 1 of Study GX28228	Evaluate long-term BCVA, CPT, and CST change, relative to parent study baseline after being treated with monthly intravitreal ranibizumab 0.5 mg in Study GX28228 and then with PDS 100mg/ml Q24W in Study GR40549
Patients who were treated with monthly intravitreal ranibizumab 0.5 mg in Study GX28228 and subsequently treated with PDS 100 mg/ml Q24W after enrollment in GR40549	n=29	Day 1 of Study GR40549	Evaluate BCVA, CPT, and CST change from the time of receiving PDS 100 mg/ml Q24W in Study GR40549
Patients treated with PDS 100 mg/ml PRN in Study GX28228 and subsequently treated Q24W after enrollment in Study GR40549	n=56	Day 1 of Study GR40549	Evaluate BCVA, CPT, and CST change from the time of switching to PDS 100 mg/mL Q24W in Study GR40549

Note: Results using Study GX28228 baseline data are interim beyond Month 36.
Results using Study GR40549 baseline data are interim beyond Week 72 (approximately 18 months).
Day 1 corresponds to the date of first treatment.
Source: t_pop_SEP2020

[Table 5 from Summary of Clinical Efficacy]

Analyses using First Treatment in Study GX28228 as Baseline

Combined data from Study GX28228 baseline through the CCOD in Study GR40549 were used to evaluate long-term efficacy of PDS 100 mg/mL, based on BCVA, CPT and CST (see Table 5). The data were summarized at each time point (monthly) using descriptive statistics, including point estimates for the means and their associated 95% CI. Last observation carried forward was used for intermittent missing values during Study GR40549 to correct for the difference in visit schedules, and there was no hypothesis testing carried out for any of the endpoints.

The full analysis included data from patients in all arms of the efficacy population of Study GX28228 (see AR Section 3.2) combined with their data after enrollment into Study GR40549 up to the CCOD, if available. However, the analyses presented in this SCE are focused on the PDS 100 mg/ml PRN and the monthly intravitreal ranibizumab 0.5 mg arms in Study GX28228, combined with their data after enrollment into Study GR40549 up to the CCOD (see Table 5).

Analyses using First Treatment in Study GR40549 as Baseline

Data from Study GR40549 baseline through the CCOD were used to evaluate BCVA, CPT and CST (see Table 5). All other analyses are identical to those described above.

While the focus is on the efficacy of the prior monthly intravitreal arm of Study GX28228 who were enrolled and treated in Study GR40549, the analysis includes data from patients of all prior treatment arms in Study GX28228.

Analysis of patients receiving supplemental treatment in the Study GR40549 Efficacy Subpopulation: GX28228

This analysis was not planned in the SCE SAP. The analysis reports the proportions of patients who received supplemental treatment among patients who were assessed at the planned supplemental treatment time points (excluding those who missed the assessment or discontinued treatment prior to the assessment), and is summarized descriptively.

Impact of COVID-19 on data collection, reporting and analysis of efficacy data

The impact of COVID-19 on the efficacy data in Study GR40459 presented herein was low. No changes to the SCE SAP were required as a result of COVID-19. For further details, please refer to the SCE, Section 1.6.3.4.

Long-term efficacy data

As of the CCOD of 11 September 2020, 29 patients from the intravitreal arm of Study GX28228 and 56 patients from the PDS 100 mg/mL arm of Study GX28228 were enrolled into Study GR40549 and provided long-term efficacy data for evaluation (see Table 5 above).

Where baseline is defined as first treatment in Study GX28228, the planned follow-up is complete until Month 36 and data beyond this timepoint presented herein are interim.

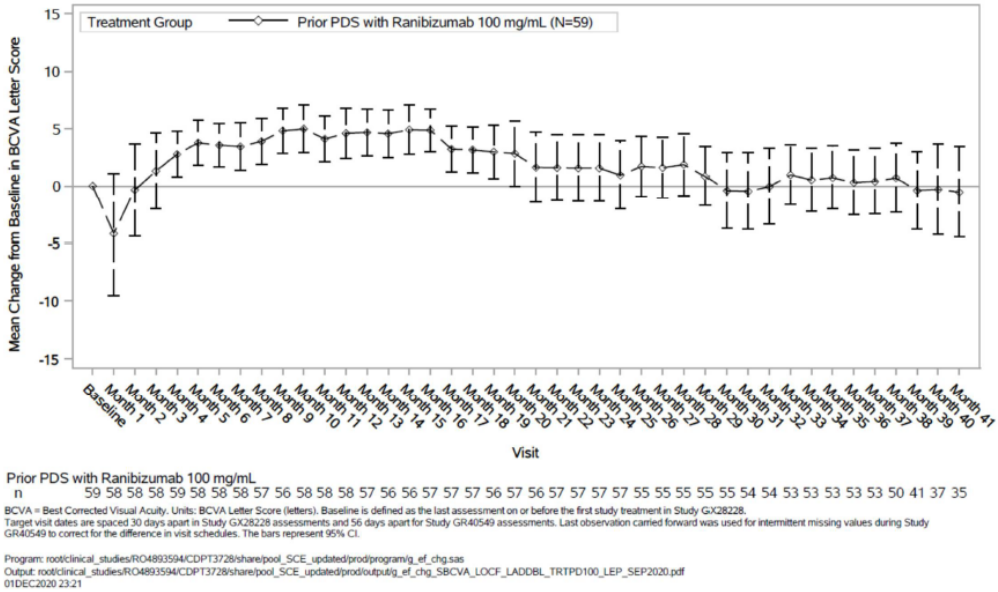
Where baseline is defined as day of first implant or first 100 mg/mL refill-exchange procedure in Study GR40549, the planned follow-up data is complete Week 72 data beyond this timepoint presented herein are interim.

Change in BCVA using First treatment in Study GX28228 as Baseline

Overall, preliminary data from the extension study GR40549/ Portal show that long-term efficacy in patients with the PDS 100 mg/mL (starting with PRN regimen in the Ladder study and then switching to a fixed Q24W regimen in the Portal study) was maintained through month 36, with a trend towards improvement in visual acuity over the first 16 months (Figure 9). Within this context, the Applicant was requested how long the individual patients had been treated in the "parent study" Ladder at baseline of the Portal study, i.e. it should be indicated when they switched to the fixed Q24W regimen. The Applicant clarified with his response to the D120 LoQ that the treatment duration for patients receiving prior PDS 100 mg/mL PRN in study GX28228 was variable and ranged from 14-37 months with a mean treatment duration of 21.7 months before rolling over into study GR40549. In addition, a listing of the timing of individual study treatment has been provided for all patients from the Ladder study who then enrolled in the Portal extension study.

When entering into the Portal extension study, all patients previously treated in the PDS 100 mg/mL PRN arm of Study GX28228 (Ladder) underwent a refill-exchange procedure with 100 mg/mL at study Day 1 of Study GR40549, regardless of when the most recent refill-exchange procedure was in the Ladder study.

Figure 9 Change from Baseline in BCVA in Study Eye Over Time through Month 41 with Baseline as Day 1 of Study GX28228, Patients who Received PDS 100 mg/mL PRN, Study GX28228 Efficacy Population

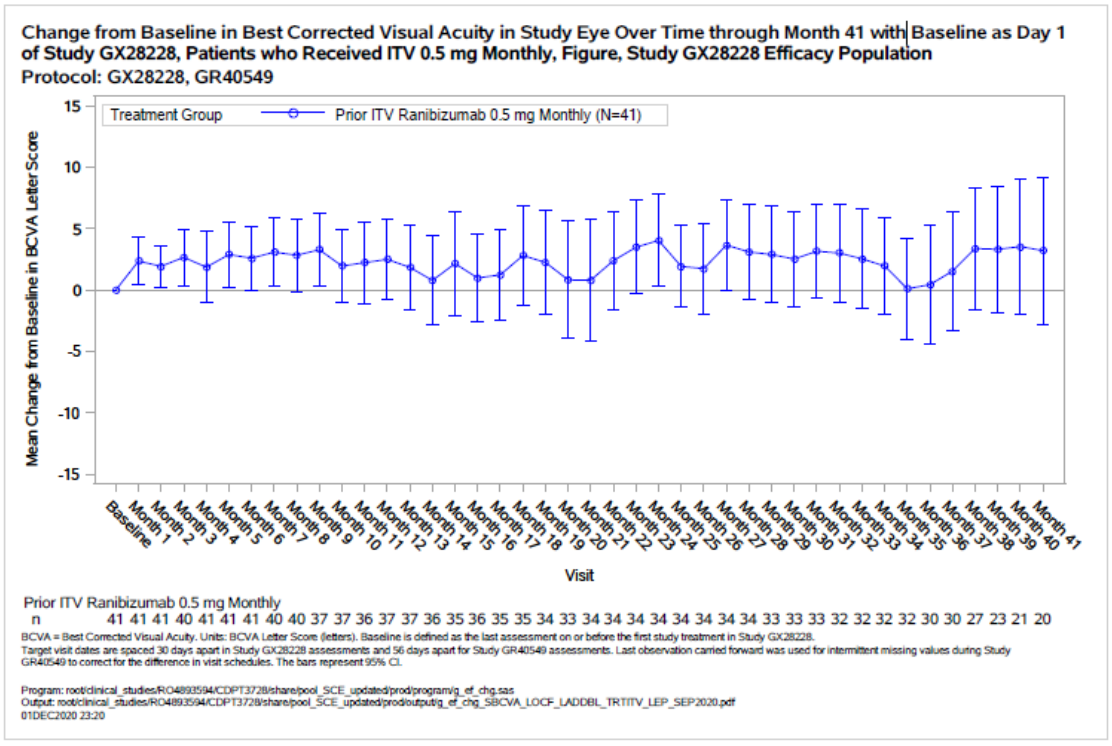


BCVA = best corrected visual acuity; PDS = Port Delivery System

Confidence intervals are included in the figure for characterizing variability around the point estimates and are not adjusted for multiplicity.

[Figure 9 from SCE]

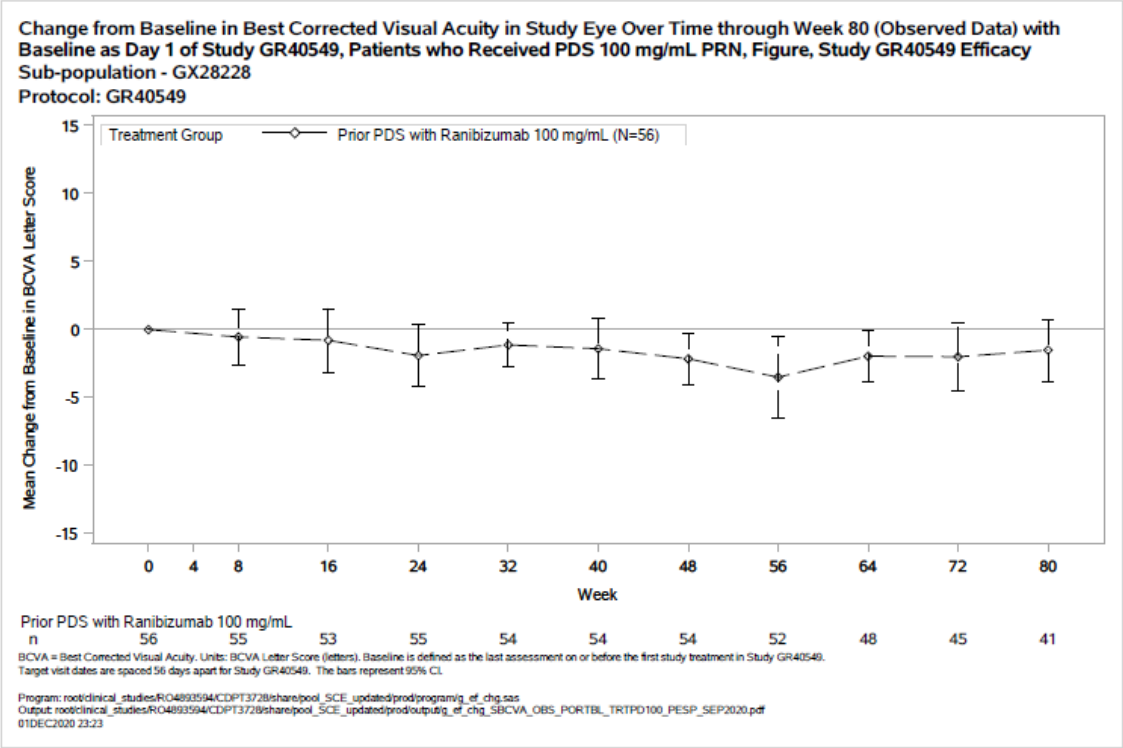
Similarly, patients in the intravitreal ranibizumab 0.5 mg monthly arm in Study GX28228 (including those who enrolled in Study GR40459 and switched to a fixed Q24W regimen), maintained their baseline BCVA through Month 36 from the Study GX28228 baseline.



[Figure from SCE – Supporting Data Presentations]

Change in BCVA using First treatment in Study GR40549 as Baseline

In patients who received PDS 100 mg/mL PRN in Study GX28228, who were enrolled in Study GR40549 and switched to a fixed Q24W regimen, visual outcomes achieved at the end of Study GX28228 were generally sustained during the observed time period within Study GR40549, for an additional 72 weeks from the Study GR40459 baseline.

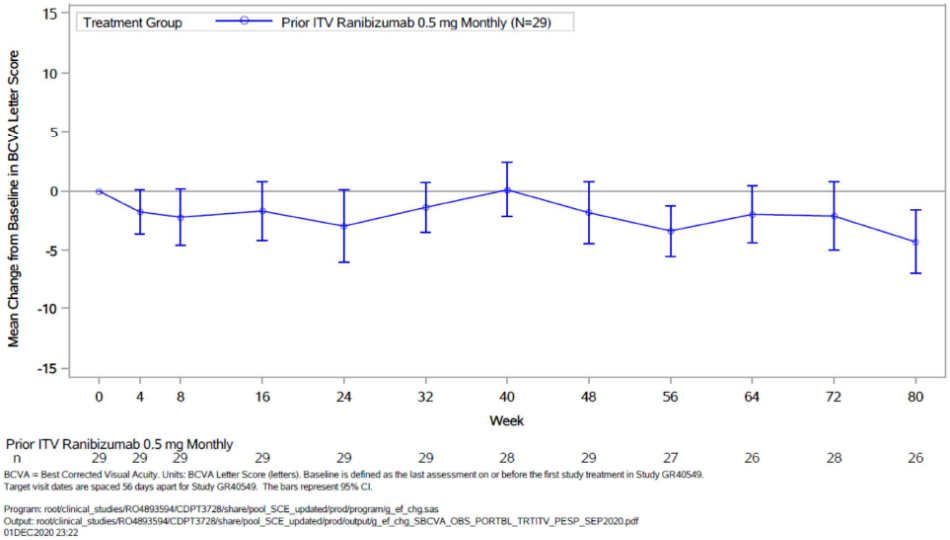


[Figure from SCE – Supporting Data Presentations]

In patients previously treated with monthly IVT ranibizumab 0.5 mg in Study GX28228 who enrolled in Study GR40549 and received PDS 100 mg/mL Q24W, data suggested that visual outcomes achieved at the end of Study GX28228 were generally sustained during the observed time period for an additional 72 weeks from the Study GR40459 baseline (Figure 10).

With regard to the population of patients initially treated with IVT ranibizumab in the Ladder study, then switched to PDS 100 mg/mL Q24W in the Portal study, the Applicant was requested to clarify when exactly the insertion of the PDS implant took place in Study GR40549 – against the background that the "typical" decrease in visual acuity observed after implant insertion was not observed (see Figure 10 compared to Figure 9, where this "drop" in visual acuity is observed). The Applicant clarified with his response to the LoQ that for patients initially treated with IVT ranibizumab in the Ladder study, the PDS was implanted on Day 1 of the Portal extension study. In addition, the Applicant explained that in Figure 10 from the Summary of Clinical Efficacy, the Day 7 BCVA value was not included. This has now been corrected in Figure 1 depicted below. Indeed, when the Day 7 value is included, a decrease from baseline in BCVA over time from the day of implant (Day 1 of Portal study) is observed. It was emphasized by the Applicant that this transient reduction in visual acuity can be attributed to surgical procedures/ post-surgery recovery and is comparable to the post-surgery decrease in BCVA observed in the PDS arm of the Archway study.

Figure 10 Change from Baseline in BCVA in Study Eye Over Time through Week 80 (Observed Data) with Baseline as Day 1 of Study GR40549, Patients who Received ITV Ranibizumab 0.5 mg Monthly, Study GR40549 Efficacy Subpopulation - GX28228

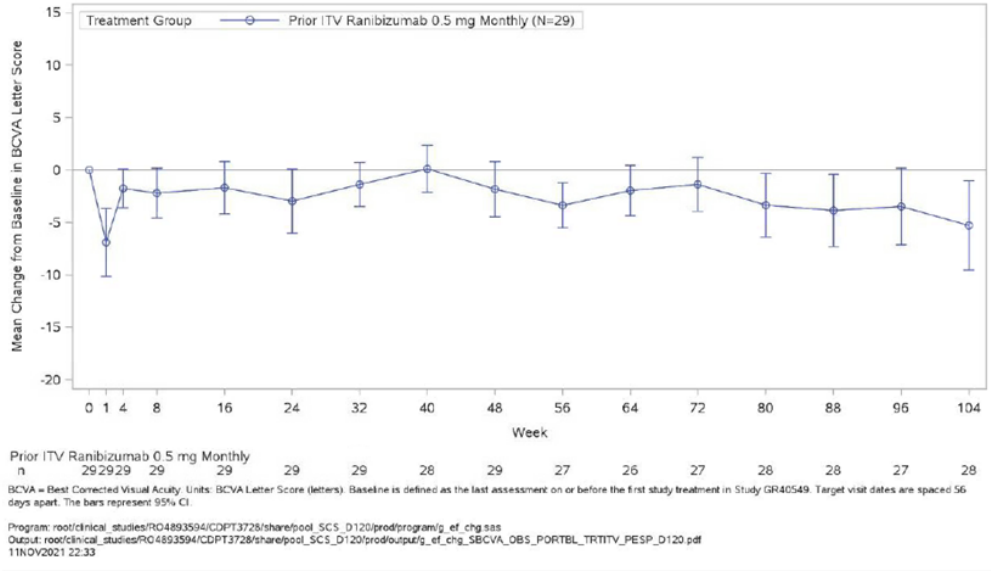


ITV = intravitreal

Note: Confidence intervals are included in the figure for characterizing variability around the point estimates and are not adjusted for multiplicity.

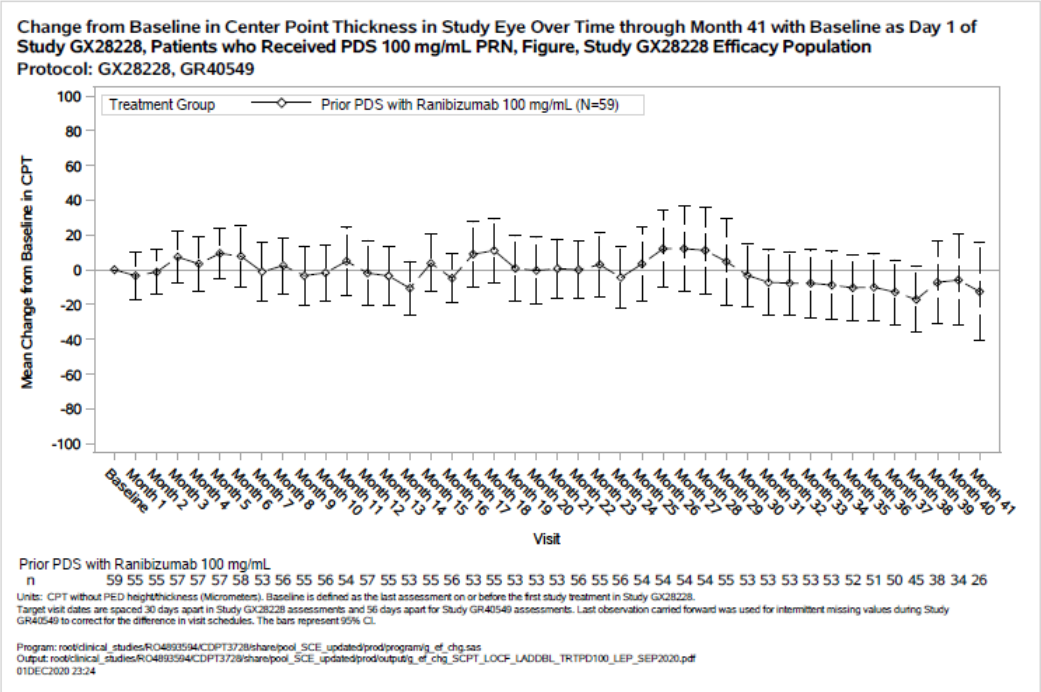
[Figure 10 from SCE]

Figure 1 Change from Baseline in BCVA in Study Eye through Week 104 in Study GR40549 (Baseline Day 1 of Study GR40549): Patients who Received Intravitreal Ranibizumab in Study GX28228, Efficacy Subpopulation as of 12 March 2021



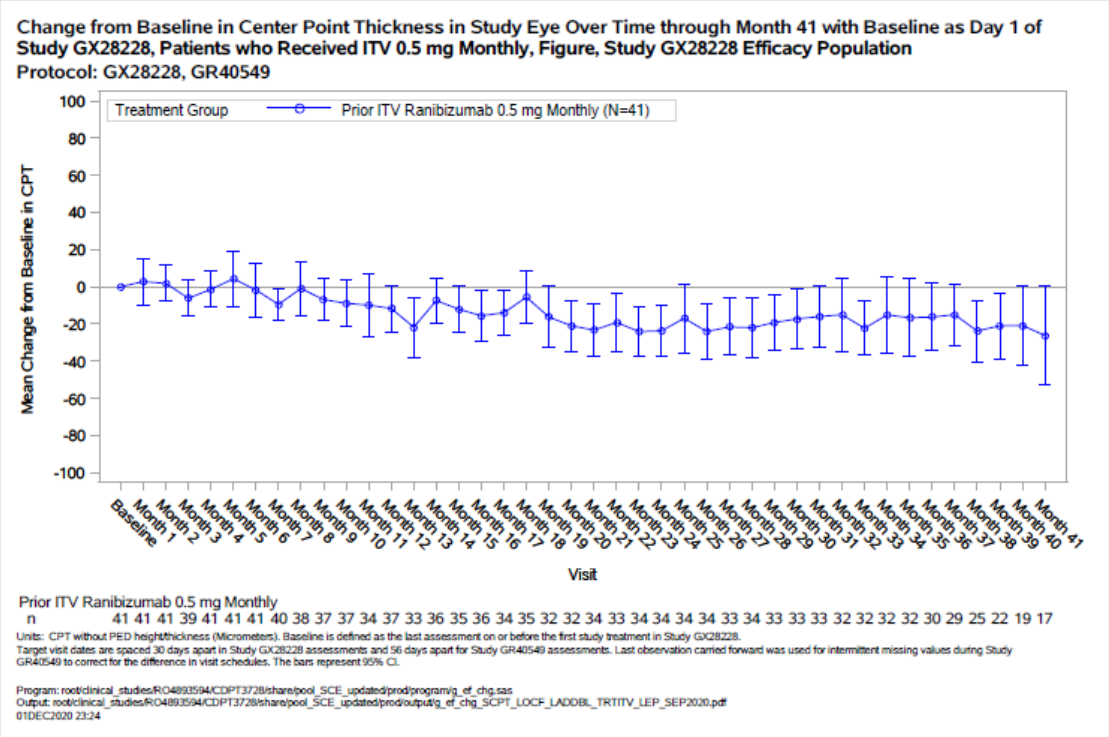
Change in CPT using First Treatment in Study GX28228 as Baseline

Patients in the PDS 100 mg/mL PRN arm of the Efficacy Population in Study GX28228 (including those who enrolled in the extension study GR40459 and switched to a fixed Q24W regimen) maintained their baseline CPT through Month 36 from the Study GX28228 baseline.



[Figure from SCE – Supporting Data Presentations]

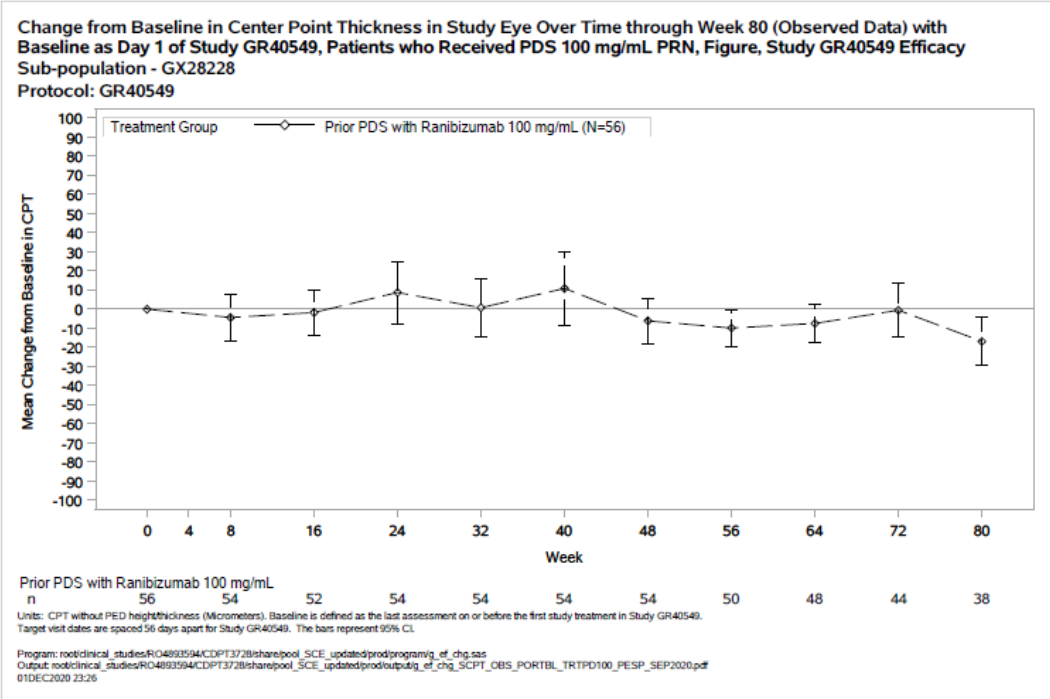
In patients in the intravitreal ranibizumab 0.5 mg monthly arm in Study GX28228 (including those who enrolled in Study GR40459 and switched to a fixed Q24W regimen), baseline CPT remained stable with a trend towards improvement through Month 36 from the Study GX28228 baseline.



[Figure from SCE – Supporting Data Presentations]

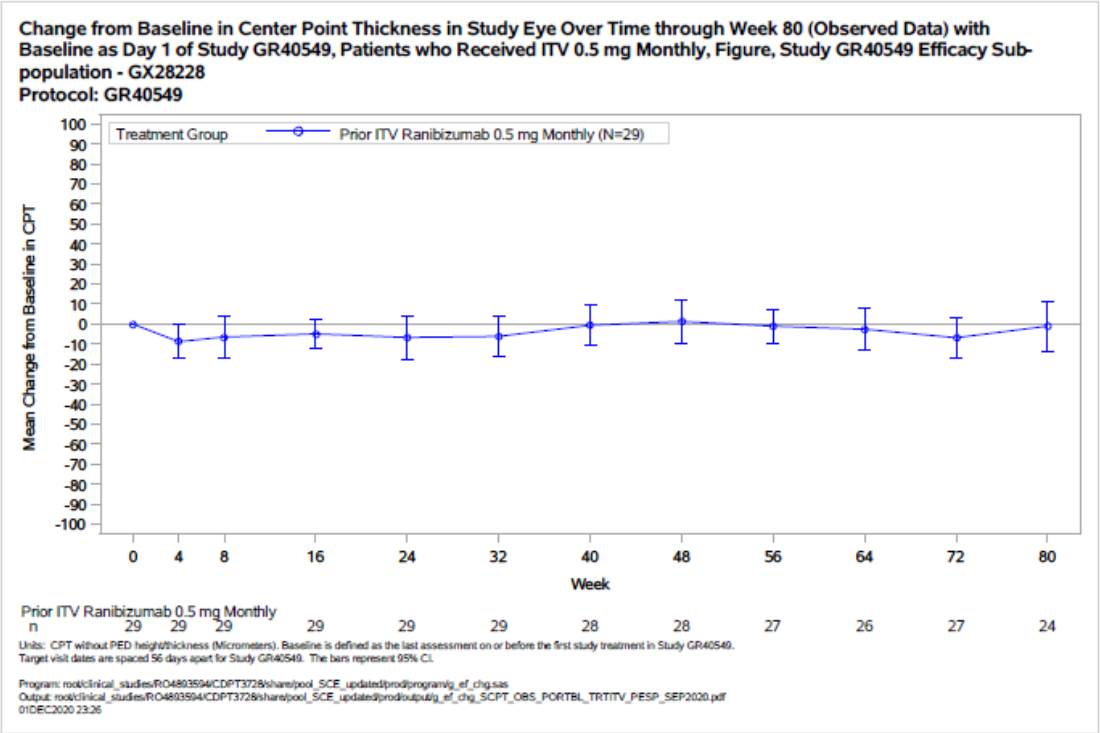
Change in CPT using First Treatment in Study GR40549 as Baseline

In patients who received PDS 100 mg/mL PRN in Study GX28228, who were enrolled in Study GR40549 and switched to a fixed Q24W regimen, the mean CPT achieved at the end of Study GX28228 was maintained during the observed time period within Study GR40549, for an additional 72 weeks from the GR40459 baseline.



[Figure from SCE – Supporting Data Presentations]

In patients previously treated with monthly IVT ranibizumab 0.5 mg in Study GX28228 who were enrolled in Study GR40549 and then received PDS 100 mg/mL Q24W, the mean CPT achieved at the end of Study GX28228 was maintained with a trend towards clinical meaningful anatomical improvement upon enrollment into Study GR40549, according to the Applicant.



[Figure from SCE – Supporting Data Presentations]

Change in CST using First Treatment in Study GX28228 as Baseline

Patients in the PDS 100 mg/mL PRN arm of the Efficacy Population in Study GX28228 (including those who enrolled in the extension study GR40459 and switched to a fixed Q24W regimen) maintained their baseline CST through Month 36 from the Study GX28228 baseline.

In patients in the intravitreal ranibizumab 0.5 mg monthly arm in Study GX28228 (including those who enrolled in Study GR40459 and switched to a fixed Q24W regimen), baseline CST remained stable with a trend towards improvement through Month 36 from the Study GX28228 baseline.

Change in CST using First Treatment in Study GR40549 as Baseline

In patients who received PDS 100 mg/mL PRN in Study GX28228, who were enrolled in Study GR40549 and switched to a fixed Q24W regimen, the mean CPT achieved at the end of Study GX28228 was maintained during the observed time period within Study GR40549, for an additional 72 weeks from the GR40459 baseline.

In patients previously treated with monthly intravitreal ranibizumab 0.5 mg in Study GX28228 who were enrolled in Study GR40549 and received PDS 100 mg/mL Q24W, the mean CPT achieved at the end of Study GX28228 was maintained during the observed time period for an additional 72 weeks from the Study GR40459 baseline.

[Figures see SCE – Supporting Data Presentations]

3.3.5. Discussion on clinical efficacy

With this submission, the Sponsor introduces Susvimo, the port delivery system (PDS) with ranibizumab, an intraocular drug delivery system designed to continuously release the customized formulation of ranibizumab into the eye over time. Susvimo is proposed to be indicated *"in adult patients for the*

treatment of neovascular (wet) age-related macular degeneration (AMD) who have previously responded to at least two intravitreal injections of a vascular endothelial growth factor (VEGF) inhibitor medication".

The indication wording proposed by the Applicant requires further revision. The indication should be restricted to patients who have demonstrated an adequate response to anti-VEGF therapy and a stabilization of the disease's progression. Thus, it is considered mandatory to define responders based on clinical outcome and to incorporate this in the SmPC. Not the number of injections, but rather clinically stable disease, based on ophthalmological judgement, should be a prerequisite for treatment with the PDS. This needs to be reflected in the indication wording, e.g. as follows:

"Susvimo is indicated in adult patients for the treatment of neovascular (wet) age related macular degeneration (AMD) *who have achieved stable disease (see 4.2) after previously responding to intravitreal treatment with a vascular endothelial growth factor (VEGF) inhibitor medication.*"

In addition, in SmPC Section 4.2, „Patient selection", corresponding criteria for stable disease have to be provided. (**MO)**

The clinical dossier of Susvimo comprises efficacy data from three clinical trials.

Study GR40548 (Archway), conducted in patients with wet AMD responsive to anti-VEGF treatment, was considered pivotal for demonstrating therapeutic equivalence in terms of visual acuity and anatomical outcomes between PDS 100 mg/mL Q24W and IVT ranibizumab 0.5 mg Q4W. Supportive efficacy data were derived from the dose-finding study GX28228 (Ladder) and the long-term extension study GR40549 (Portal) in the same patient population.

Generally, the clinical efficacy program is acceptable. The number and design of the studies seem appropriate, taking into account the nature of the submitted medicinal product. PDS 100 mg/mL is an intraocular implant designed to provide localized controlled release of ranibizumab, a well-established treatment for nAMD over an extended period. Therefore, a single pivotal study would be sufficient provided the robustness of the results.

Regulatory interactions took place with the EMA in Sept 2019 (EMA/H/SA/4242/2/2019/III) and FDA.

Design and conduct of pivotal study

Demonstration of equivalence/ non-inferiority on efficacy level is based on one pivotal Phase III study. The **GR40548 (Archway) study** is a randomized, multicenter, open-label (VA-masked), active comparator study comparing efficacy, safety, and PK of the PDS 100 mg/mL Q24W to monthly IVT ranibizumab injection 0.5 mg in patients with nAMD responsive to anti-VEGF treatment. Only patients with a maximum of 9 months since diagnosis who had received at least 4 prior anti-VEGF injections were eligible.

Response to initial anti-VEGF treatment was defined as overall decrease in nAMD disease activity (stable or improved BCVA or decrease in central foveal thickness) from the onset of the intravitreal anti-VEGF treatment.

In total, 418 patients were 3:2 randomized to one of the two treatment arms at 78 centres in the US. Baseline BCVA score was used as a stratification factor (<74 letters versus ≥74 letters). Study duration for participants was 96 weeks.

The Applicant states that the study was conducted in accordance with the ethical principles of the Declaration of Helsinki and were consistent with ICH Guidance and the applicable local regulatory requirements and laws.

With the initial submission, the primary CSR with a clinical cut-off date of 27 March 2020 has been submitted, including data through Week 40. In addition, an updated CSR with a CCOD of 11 September 2020 has been submitted, including data through Week 48. With the responses to the D120 LoQ, the final CSR has been submitted (CCOD 16 July 2021).

Three study amendments to the protocol are reported by the Sponsor.

GR45048 is an open-label study. Patients and study site personnel were not masked with regard to patient assignment because of difficulties of maintaining masking following the surgical procedure. Additional safety visits were planned only to the implant arms, and implant visualisation occurred during ophthalmic examinations. According to the Sponsor, the visual acuity examiners (VAE) were masked to the treatment as best as possible to patient study eye assignment, study visit eye and patient treatment assignment. The VAE had no access to patient's BCVA scores from previous visits, and patients and unmasked personnel were advised not to discuss the study eye assignment.

However, in November 2019, the Sponsor identified that, due to a limitation within the Clinical Trial Management System (CTMS), 144 VAEs at 66 study sites were listed under the category of the Study Coordinator Role, and therefore were inadvertently registered to receive automated emails from the portal used to share study information with site staff. Within the subject line, information of the patient number, study visit week and type was included, which could indirectly inform the patient's treatment arm and study visit type to the masked VAEs (assigned to 232 patients total).

With regard to the issue of potential un-masking of the VAE due to erroneously sent automated emails including information of the patient number, study visit week and type, which could indirectly inform the patient's treatment arm and study visit type to the masked VAE, the Applicant states that dedicated data analyses have been conducted, not suggesting any bias resulting from this GCP breach. However, to further clarify that there is no critical issue with regard to data integrity resulting from the erroneously sent automated emails, the Applicant was requested to provide a subgroup analysis for all patients with BCVA assessment averaged over Week 36 and Week 40 before and after the stop of the automated emails. The Applicant provided the required analysis according to potential unblinding date. Both before and after the potential unblinding, the confidence intervals of the point estimates were fully contained within the equivalence margins and no hints towards unblinding could be identified.

The general study design of the GR40548 study was in line with previous EMA SA. It was agreed by the CHMP that subjects enrolled should have received and been found responsive to prior treatment with anti-VEGFs. The requirement of 3 or more previous IVT injections plus a mandatory boost injection at the screening visit was also supported.

The Applicant has chosen a study population with an initial diagnosis of wet AMD within 9 months prior the screening visit, in order to avoid inclusion of a very advanced patient population. It is endorsed that patients should already have received and been found response to prior anti-VEGF treatment. This increases the likelihood that the patients have reached a stable vision plateau by the time of enrolment. Thus, the selected population is considered adequate to sensitively compare efficacy between the PDS and monthly IVT injections of ranibizumab.

Most baseline demographics and disease characteristics were well balanced over treatment arms. The majority of subjects were White (96.6%). The mean age of patients was approximately 75 years (with 56.4% of patients were equal or older than 75 years of age). Only patients from the USA were included.

The majority of patients (59.0%) were female: 58.5% in the PDS 100 mg/mL arm, 59.9% in the intravitreal arm.

Patients reported a mean course of the condition of 5.6 months (5.9 mth [9.5] for PDS 100 mg/mL ranibizumab and 5.3 [2.0] for intravitreal Ranibizumab 0.5 mg) and a mean (SD) of 5.0 (1.9) anti-VEGF

injections prior to first study treatment. The mean baseline BCVA was 74.8 letters (74.4 letters in the PDS 100 mg/mL arm and 75.5 letters in the IVT arm), and 66.5% presented good visual acuity with a score of 74 or better (65.7% in the PDS 100 mg/mL arm and 67.7% in the intravitreal arm).

Mean baseline CPT was 177.0 microns (176.9 microns in the PDS 100 mg/mL arm and 177.2 microns in the IVT arm), and mean baseline CST was 307.9 microns (312.7 microns in the PDS 100 mg/mL arm and 300.9 microns in the IVT arm).

Regarding the anti-VEGF treatments administered in the 9 months prior to first study treatment, ranibizumab was the most frequently used: 144 patients [58.1%] in the PDS 100 mg/mL arm and 96 patients [57.5%] in the IVT arm received ranibizumab only treatment in the 9 months prior to the first study treatment). Aflibercept had been administered to 28 patients (11.3%) in the PDS 100 mg/mL arm and 20 (12.0%) in the IVT arm while bevacizumab had been administered to 76 (30.6%) and 51 (30.5%), respectively. An anti-VEGF agent was administered to the fellow eye of 60 patients (24.2%) in the PDS 100 mg/mL arm and 24 (14.4%) in the intravitreal arm in the 9 months prior to first study treatment. The most frequently used anti-VEGF agent in the fellow eye in both treatment arms was ranibizumab (50 patients [20.2%] in the PDS 100 mg/mL arm and 19 [11.4%] in the IVT arm).

Only one eye (one implant) was treated. Up to Week 40, 82 patients (33.1%) in the PDS 100 mg/mL arm and 41 patients (24.6%) in the IVT arm received at least one anti-VEGF treatment in the fellow eye.

The sample size calculation for study GR40548 is comprehensible and reproducible, the randomisation scheme is considered acceptable.

From the Phase II dose-finding study GX28228 (Ladder), the PDS 100 mg/ml formulation was chosen for the subsequent pivotal study. Selection of this dose is overall considered acceptable, based on the available efficacy data from study GX28228. However, there remain questions with regard to the chosen Q24W regimen. For further comments on the chosen Q24W regimen, see below.

With regard to study treatment, the comparator for the pivotal study (monthly intravitreal ranibizumab 10 mg/ml) is adequate for the intended purpose of the study. Under non-inferiority hypothesis, the selected monthly treatment regimen provides the maximum ranibizumab available dose, which is a conservative approach from a methodological point of view. Since this was the regimen tested versus sham in the original dossier of Lucentis for the treatment of nAMD, it can be considered also an adequate reference. Whereas monthly dosing of ranibizumab is the approved treatment regimen for nAMD in the United States (where the study was conducted), this is not in line with the EU approved treatment regimen for Lucentis, where less frequent schedules (PRN or treat-and-extend regimens) are recommended.

Endpoints:

The primary efficacy objective was to show equivalence and non-inferiority (NI) of the PDS 100 mg/mL arm compared to the IVT ranibizumab arm, as assessed by visual acuity changes.

The corresponding primary efficacy endpoint was the mean change from baseline in BCVA score averaged over Wks 36 and 40, assessed using the ETDRS visual acuity chart at a starting distance of 4 metres with a pre-specified equivalence/ NI margin of 4.5 letters, in the Efficacy population.

However, during EMA advice the chosen time points were critically reflected. The evaluation of the mean change in BCVA at the time of trough for the PDS (i.e. when the amount of ranibizumab in the implant should be the lowest) just before implant refill was proposed. In addition, the non-inferiority margin of 4.5 letters was considered too wide by SAWP/ CHMP, since a BCVA loss of 5 letters is a criterion for re-treatment and is thus of clinical relevance. This was overall followed by the Sponsor: the mean changes in BCVA from baseline averaged over Week 36 and Week 40 and averaged over Week 44 and Week 48 were evaluated as key secondary endpoints, with a NI margin of 3.9 letters.

Under these circumstances, where the main proof of efficacy relies on a single pivotal study, a primary analysis using a stricter NI margin would have been more reassuring.

In the EMA Scientific Advice, it was also recommended to the Applicant to add secondary endpoints evaluating efficacy at later time points, such as Week 64 and 68, and Week 88 and 92. This was followed by the Applicant. Mean change from BL in BCVA averaged over Wk 60 and Wk 64 was indeed presented as secondary EP in the CSP Version 3 (dated 18 Dec 2019), and mean change from BL in BCVA averaged over Wk 88 and Wk 92 was introduced as key secondary EP in the SAP Version 2.0 (dated 21 Apr 2020). However, since these analyses were not considered mature at the time of MAA submission, they were presented with the responses to the D120 LoQ in the final CSR (Sections 5.2.9 and 5.2.1). Those analyses indicate that there are no hints for loss of efficacy over time for the PDS.

Secondary endpoints were, among others: the change from baseline in BCVA score over time, the proportion of patients with BCVA score of 38 letters or worse/ 69 letters or better at the average over Wk 36 and Wk 40, the change from baseline in CPT at Wk 36 and over time, as a surrogate for anatomical response to study treatment, and the proportion of patients in the PDS 100 mg/mL arm who underwent supplemental treatment with IVT ranibizumab before the respective fixed refill-exchange interval (for the full list of secondary EP's, please refer to AR Section 3.3 "Main study" – "Methods" – "Outcomes/endpoints").

Further issues with regard to statistical methods have to be considered and should be clarified:

The primary estimand is defined so that intercurrent events are treated with treatment policy strategy (regardless whether or not a patient has an intercurrent event). This is questionable in the setting of testing equivalence. Especially intercurrent events like 'more than 1 supplemental treatment', that may have a compensatory effect on the outcome, may lead to an underestimation of treatment differences, which is not endorsed in an equivalence trial. On the contrary, intercurrent events that may have a worsening effect on the outcome are acceptable to be treated by the treatment policy estimand. The Applicant was asked to discuss the treatment policy strategy of the four defined intercurrent events (IE) regarding its sensitivity of detecting differences between the treatments given the observed number of IEs, and to provide sensitivity analyses for more conservative strategies if necessary. The Applicant addressed the issue but methodological questions regarding the imputation remain open and need further clarification. (**LoOI**)

With regard to participant flow, 418 patients were enrolled and randomized. Of these 418 patients, 3 patients randomized to the PDS arm were never treated. The Efficacy population (i.e. randomized and treated) therefore comprised 415 patients (248 in the PDS 100 mg/mL arm and 167 in the IVT arm).

Study completion was overall high. Prior to Week 48, 2 patients in the PDS 100 mg/mL arm and 6 in the IVT arm discontinued the study; thus 99.2% and 96.4%, respectively, were still on study at Week 48. Through Week 48, 94.0% of patients in the PDS 100 mg/mL arm had received an initial fill and 2 refills, while patients in the IVT ranibizumab arm had received a mean of 12.6 treatments out of a possible 13.

The overall time on study was balanced across treatment arms (mean 80.0 weeks in the PDS 100 mg/mL arm and mean 78.5 weeks in the IVT arm through CCOD).

The most common reason for study discontinuation in the PDS 100 mg/mL arm was death (n=5), while the most common reason in the IVT arm was withdrawal by patient (n=6). However, it remains unclear which reasons led to withdrawal by subject. Within this context, the Applicant was requested to provide details for withdrawals by subject since there is an obvious imbalance between the treatment arms (n=7 in the IVT ranibizumab arm vs. n=1 in the PDS arm). However, it was clarified by the Applicant that details on the reason for withdrawals by subject were not requested in the Treatment Discontinuation eCRF, hence they were not documented by the Principal Investigator. Thus, no further details can be

provided regarding the specific reason for the "Withdrawal by Subject". Since this imbalance concerns the IVT ranibizumab comparator arm, this is considered overall negligible and will not be pursued further.

Efficacy data and additional analyses

With this submission, the Applicant provided the results of the primary efficacy analysis for study GR40548 with the primary CSR (CCOD 27 March 2020), including Week 40 data. In addition, an updated CSR (CCOD 11 Sept 2020) has been provided, including Week 48 data.

The primary efficacy population, defined as all patients who received the study treatment and analysed according to the actually received treatment, is acceptable for this equivalence trial, especially as a sensitivity analysis for the PP population, defined as all patients from the primary efficacy population without major protocol deviations, is provided.

The PP population used for the sensitivity analysis excluded a total of 18 patients in the PDS arm and 10 patients in the IVT arm.

Within this context, prior to study unblinding, major protocol deviations were reviewed and a determination of the population for PP analysis was made, based on whether the deviation was expected to impact the planned efficacy assessments.

Up to Week 48, major protocol deviations were reported in 120 patients (28.9%) overall (78 [31.5 %] in the PDS 100 mg/mL arm and 42 [25.1%] in the intravitreal arm). The imbalance in rate of major protocol deviations was driven largely by medical deviations applicable only to PDS-treated patients (for example, aspirin/NSAIDs not interrupted per protocol in 14 patients [5.6%]).

From the overall 120 patients who were reported to have major protocol deviations, only 28 patients (n=18 in the PDS arm and n=10 in the IVT arm) with major protocol deviations likely to have a clinical impact on BCVA at these time-points were excluded, such as: uncertified staff performed BCVA testing, selected missed visits at Wk 44 and 48, VA examiner performed other study-related tasks or assessed previous visit VA scores, patient with long-standing nAMD disease not representing the target population, patient not having received at least 3 anti-VEGF injections prior to the screening visit, patient having received an additional out-of-protocol anti VEGF injection at D7 per investigator´s discretion, and others.

The pivotal study GR40548 met its primary endpoint - equivalence and non-inferiority have been demonstrated for the PDS 100 mg/mL arm (Q24W) compared to IVT ranibizumab 0.5 mg Q4W (pre-defined margin of ±4.5 letters), as measured by the change from baseline in BCVA at the average of Week 36 and Week 40. The difference in adjusted means between the treatment arms was -0.3 letters (95% CI -1.7, 1.1). This was supported by sensitivity analyses in the PP population as well as by supplemental analyses for the primary endpoint (trimmed mean analysis, MMRM model using different rules for measures after intercurrent events), which were consistent with the primary analysis.

Overall, it has to be pointed out that the BCVA changes from baseline in both arms were rather small, which can be attributed to the study population, having already reached a plateau of response at baseline due to the prior anti-VEGF treatments.

In addition, the key secondary endpoints, which had been requested by EMA, were met: Non-inferiority of the PDS 100 mg/mL Q24W regimen to the IVT ranibizumab 0.5 mg Q4W regimen was also demonstrated when using a NI margin of 3.9 letters for the change from baseline in BCVA at the average of Week 36 and Week 40, as well as at the average of Week 44 and Week 48 (difference in adjusted means of -0.2 [95% CI -1.8, 1.3]). Supplemental analyses and sensitivity analyses further supported the robustness of the findings for this key secondary endpoint.

Although from a formal point of view such analyses could in principle only be considered as exploratory taking into account the narrow CIs and the consistency of the results, they do not reasonably represent a source of concern.

Some limitations in efficacy are related with the reduction in BCVA in the first 12 weeks in the PDS 100 mg/mL arm (associated with the implant surgery), and this should be balanced in the benefit/risk ratio of the product. Within this context, the Applicant was requested to explain if there was a reduction in visual acuity in 7 patients (as of cut-off date Sep 11, 2020) where an explant of the implant was required during clinical development. The Applicant has presented the BCVA data (change from baseline) corresponding to the 7 patients who underwent implant removal prior to 11 September 2020 in Study GR40548 as shown in Table 1. The data included changes at last available visit prior to explant, after explant and at last visit. Generally, there was a reduction in visual acuity after the explant that was recovered in the majority of the patients at last visit for the patients that have available data. The Applicant has also informed that 13 additional patients had undergone implant removal through the clinical cut-off of 12 March 2021 (a total of 20 patients with an explant). With the data provided, it seems that for most of the patients, the reduction in visual acuity associated to the implant removal is recovered later. Nevertheless, this reduction in visual acuity associated to the explant has to be taken into account for the overall benefit/risk of the product. The Applicant is requested to inform about the percentage of patients who underwent implant removal in the total PDS population in the last available cut-off date. (**LoOI**)

Several other secondary endpoints evaluated the effect of PDS 100 mg/mL Q24W on visual function compared to monthly IVT injections. The results overall supported the outcome of the primary analysis.

Retinal thickness was evaluated by measuring CPT change as secondary EP, supported by CST change as exploratory endpoint; both representing surrogate endpoints for anatomical response to study treatment. Overall, CPT and CST remained stable over time in both treatment arms, indicating that continuous supply with ranibizumab (either via PDS or via IVT injection) stabilizes retinal thickness.

In the PDS 100 mg/mL arm, a trend towards increase in CPT and CST leading up to the scheduled refill-exchange followed by a decrease after the refill-exchange was observed through Week 76, as stated by the Applicant. After each refill-exchange, CPT and CST generally tended to decrease to baseline levels, according to the Applicant. However, Figure 4 and Figure 5 from the Updated CSR only depict the changes in CPT/ CST through Week 48. For CST, the mean change through Week 92 has been appended (page 262 of Updated CSR). The Applicant was requested to provide updated information through Week 92 also for CPT, preferably as a figure, to substantiate his statement on the decrease of CPT after each refill-exchange. This information has been provided with the responses to the D120 LoQ, as requested. As already observed for CST, a trend towards an increase in CPT at the end of each 24 wks refill-exchange period can be noticed, followed by a CPT decrease immediately after the next refill. However, since the average increase/ change was approx. 10 microns for CPT and approx. 20 microns for CST only, this is overall considered not of clinical relevance; in particular against the background that CPT/CST are both highly sensitive morphological endpoints.

In order to ensure that patients were achieving sufficient vitreous concentrations of ranibizumab to control their disease, the protocol permitted patients in the PDS 100 mg/mL arm to receive supplemental treatment at 8 weeks and/or 4 weeks prior to each scheduled refill-exchange procedure if criteria based on BCVA and CST changes were met. During the first (up to 24 weeks) and second treatment interval (24-48 weeks), 1.6% and 5.4% of patients fulfilled supplemental treatment criteria and received such treatment. No patient who received supplemental treatment in the first treatment interval received additional supplemental treatment in the second treatment interval.

Against the fact that distinctly more patients in the PDS 100 mg/mL arm met the criteria for supplemental treatment with ranibizumab in the second than in the first treatment interval, the Applicant was

requested to provide the respective data for the third (48-72 weeks) and fourth (72-96 weeks) treatment interval, as far as available, and to comment on the findings. In the first and second treatment interval, the corresponding numbers of patients meeting supplemental treatment criteria was 4/246 [1.6%] and 13/241 [5.4%], respectively. During the third and fourth treatment interval, 12/231 patients (5.2%) and 12/225 patients (5.3%) required supplemental treatment. Obviously, after the first treatment interval the supplemental treatment rate remained consistent. No trend towards increased need for supplemental treatment was observed through Week 96.

The number of patients in Archway study that require supplemental treatment (additional injection of ranibizumab 10 mg/ml) in the PDS arm is not high, but not negligible (1.6% in 1st interval [0.4% is the right percentage because some patients received the supplemental treatment in error] and 5.4% in 2nd interval). A discussion on the potential specific characteristics of these patients and/or their predictability and on the potential increase for successive intervals was requested. The Applicant has provided the data for the third (48-72 weeks) and fourth (72-96 weeks) treatment interval, as requested. According to these data, after the first treatment interval the supplemental treatment rate remained consistent and no trend towards increased need for supplemental treatment was observed through Week 96. Regarding the potential specific characteristics of the patients that require supplemental treatment in the PDS arm of Archway study, it seems that the patients with higher CST and CPT values and the ones with intraretinal fluid at baseline are more predisposed to require supplement treatment. As the Applicant mentions, this needs to be further explored and confirmed with ongoing and future studies given the large difference between the sample size of the 2 groups (31 vs 217) from Study GR40548.

The Applicant has performed and presented analyses of the primary endpoint within subgroups of patients receiving any prior (within 9 months of baseline) aflibercept (n=48), any prior bevacizumab (n=124), and neither aflibercept nor bevacizumab (i.e., ranibizumab only) (n=246) and results are shown in Figure 1. The data related to aflibercept and bevacizumab are more in favour of PDS and the data for ranibizumab in favour of IVT ranibizumab. As the number of patients for the prior treatments other than ranibizumab are low and all the results are within the equivalence margins, we are in agreement with the Applicant that there is no evidence of clinically meaningful differences in the primary endpoint between the two treatment groups based on previous treatment.

With regard to the primary EP, the mean change from baseline in BCVA score averaged over Wk 36 and Wk 40, the subgroup analyses for the subgroups age, sex, number of prior anti-VEGF injections and baseline BCVA score were overall consistent with the primary endpoint analysis.

For the secondary EP "Change from baseline in CPT at Week 36", subgroup analyses have been performed only for the subgroups age and sex, not for subgroups of patients with different number of prior anti-VEGF intravitreal injections (<5 versus ≥5 prior injections) and for subgroups according to baseline BCVA score (<74 vs. ≥74), as done for the primary EP. The Applicant was requested to provide those additional subgroup analyses, for the sake of clarity and completeness. The requested subgroup analyses have been provided with the responses to the D120 LoQ. Those additional subgroup findings were overall consistent with the primary analysis in all patients.To note, the number of treatments received by patients in the PDS 100 mg/mL arm was significantly lower compared to the ranibizumab IVT arm. Until Week 40, patients in the PDS arm had received a mean of 2.0 study treatments per patient compared with a mean of 10.7 per patient in the IVT arm. At Week 48, most patients in the PDS 100 mg/mL arm had received 1 additional treatment (corresponding to the refill-exchange at Week 48) while most patients in the intravitreal arm received 2 additional treatments.

This reduction of injections/ treatment visits is considered of clinical relevance for this patient population, since the requirement of frequent anti-VEGF IVT injections and follow-up visits in order to achieve and maintain improved visual acuity poses a burden on patients with nAMD.

However, the potential advantage of reducing the treatment administration from 12 (monthly) to 2 (PDS) would not be so relevant for the T-E regimen, that is mostly used in Europe, where fewer administrations would be needed with respect to the monthly regimen. There are published studies (Fallico M et al, Eur J Ophthalmol 2020; Wykoff CC et al, Am Acad Ophthalmol 2016; Silva R et al, Am Acad Ophthalmol 2017) supporting the non-inferiority of the T-E regimen vs the monthly regimen of anti VEGF therapy (both from the efficacy and the safety point of view). Furthermore, control visits (1-2) between the treatment administration in the Q24W regimen are required, and this implies that the burden for the healthcare system and the patients is not that much reduced.

There is also uncertainty related with the management of nAMD bilateral disease. The Applicant acknowledged that clinical data for bilateral treatment with PDS are not currently available. With his responses to the D120 LoQ, the Applicant has added the following statement in SmPC Section 4.4, consistent with the labelling of other anti-VEGF agents, reflecting the fact there are no available data for bilateral PDS treatment:

Bilateral treatment

The safety and efficacy of Susvimo administered in both eyes has not been studied. In clinical trials, patients with neovascular (wet) age-related macular degeneration (nAMD) in the fellow eye received treatment with an anti-VEGF intravitreal injection.

Supportive studies

As already outlined above, dose response was investigated in the Phase II dose-finding study GX28228 (Ladder), where 3 different doses of the PDS formulation (i.e. 10 mg/mL, 40 mg/mL, and 10 mg/mL) have been evaluated in the PRN regimen compared to monthly IVT ranibizumab 0.5 mg. In this setting, a dose response with regard to efficacy outcomes (visual acuity as well as anatomical changes) was observed across the PDS treatment arms, favouring the PDS 100 mg/ml formulation. Choosing this dose is overall considered adequate, based on the available efficacy data from study GX28228.

However, the rationale for choosing the Q24W refill regimen for further clinical development is not fully understood, based on the fact that in the PDS 100 mg/mL arm, more than 68% of patients proceeded 9 months and more than 59% went even 12 months not meeting the refill criteria. Furthermore, the median time to first implant refill was 15.8 months in the PDS 100 mg/mL arm. For those patients, a Q24W refill interval might bear the risk of overdosing. Within this context, a longer time to refill might have been adequate for further clinical development, also against the background of less frequent burdening refill-exchange procedures. With his responses to the D120 LoQ, the Applicant sets out his reasons for choosing the fixed Q24W refill-exchange regimen for the 100 mg/mL dose in the Archway study.

The Applicant argues that vision deterioration with pro-re-nata (PRN) treatment was seen in Ladder Study PDS 100 mg/mL PRN arm after patients rolled over into Study GR40549 and that the initial BCVA gains were lost at Month 21 post-implantation when the mean BCVA went back to pre-implantation levels, concluding that this loss in BCVA was most likely due to the long-term effect of the initial PRN regimen used in Ladder Study, where a clinically meaningful nAMD worsening had to be observed before receiving a refill-exchange. The justification provided by the Applicant for the risk of overdosing is considered acceptable. However, the appropriateness of the 24W regimen should be balanced against the PDS associated risks in comparison with other regimens. The Applicant is requested to comment on this aspect. (**LoOI**)

In the GX28228 study, a minimum of 2 prior anti-VEGF injections (including ranibizumab, aflibercept or bevacizumab) was required for inclusion in the study (mean of 2.9 injections), in contrast to the Phase

III study, where at least 3 prior injections and one additional ranibizumab IVT injection at screening were required (mean of 5 injections) in order to increase the likelihood for patients to reach a vision plateau prior to randomization. Thus, patients in the Phase II study had most likely not yet reached their vision plateau.

In the supportive extension study GR40549 (Portal), the PDS 100 mg/mL Q24W implant overall maintained visual acuity for up to 36 months both in patients who had been receiving long-term treatment with anti-VEGF injections as well as in patients who switched from the PDS implant refilled PRN.

However, there was a trend towards improvement in visual acuity over the first 16 months observed in patients who switched from the PDS 100 mg/mL PRN to the fixed Q24W regimen. Within this context, the Applicant was requested to clarify how long the individual patients had been treated in the "parent study" Ladder at baseline of the Portal study, i.e. it should be indicated when exactly they switched to the fixed Q24W regimen. The Applicant clarified with his response to the D120 LoQ that the treatment duration for patients receiving prior PDS 100 mg/mL PRN in study GX28228 was variable and ranged from 14-37 months with a mean treatment duration of 21.7 months before rolling over into study GR40549. In addition, a listing of the timing of individual study treatment has been provided for all patients from the Ladder study who then enrolled in the Portal extension study.

When entering into the Portal extension study, all patients previously treated in the PDS 100 mg/mL PRN arm of Study GX28228 (Ladder) underwent a refill-exchange procedure with 100 mg/mL at study Day 1 of Study GR40549, regardless of when the most recent refill-exchange procedure was in the Ladder study.

With regard to the population of patients initially treated with IVT ranibizumab in the Ladder study, who then switched to PDS 100 mg/mL Q24W in the Portal study, the Applicant was requested to clarify when exactly the insertion of the PDS implant took place in Study GR40549 – against the background that the "typical" decrease in visual acuity observed after implant insertion was not observed (see Figure 10 compared to Figure 9, where this "drop" in visual acuity is depicted). The Applicant clarified with his response to the LoQ that for patients initially treated with IVT ranibizumab in the Ladder study, the PDS was implanted on Day 1 of the Portal extension study. In addition, the Applicant explained that in Figure 10 from the Summary of Clinical Efficacy, the Day 7 BCVA value was not included. This has now been corrected in Figure 1 depicted below. Indeed, when the Day 7 value is included, a decrease from baseline in BCVA over time from the day of implant (Day 1 of Portal study) is observed. It was emphasized by the Applicant that this transient reduction in visual acuity can be attributed to surgical procedures/ post-surgery recovery and is comparable to the post-surgery decrease in BCVA observed in the PDS arm of the Archway study.

Extrapolation of efficacy results to a broader nAMD population

The fact that only patients with a new nAMD diagnosis within 9 months prior to screening visit have been allowed to participate in the studies of the clinical program is a limitation for the extrapolation of results to a wider, more advanced/ pretreated nAMD population.

In this respect, the efficacy of PDS in patients chronically treated with other anti-VEGFs is also a matter of uncertainty.

Finally, another consideration for the efficacy is that the complexity of the procedures related with the implant could be greater in real life compared to the well-controlled clinical trial setting, mainly in the first months/years of use. This has to be weighted in the assessment of the benefit/risk profile and the measures to be taken in the different healthcare systems of the countries involved in the authorization of commercialization.

3.3.6. Conclusions on clinical efficacy

In the pivotal efficacy study GR40548 (Archway) in nAMD patients responsive for anti-VEGF treatment, equivalence and non-inferiority have been demonstrated for the PDS 100 mg/mL arm (Q24W) compared to IVT ranibizumab 0.5 mg Q4W with regard to the primary endpoint, the mean change from baseline in BCVA score averaged over Wk 36 and Wk 40, assessed in the Efficacy population ("as treated") with a pre-specified margin of ±4.5 letters. This was supported by sensitivity analyses in the PP population as well as by supplemental analyses for the primary endpoint. In addition, the key secondary endpoints, which had been requested by EMA, were met.

Furthermore, the results for the secondary efficacy visual and anatomical endpoints supported that PDS 100 mg/mL Q24W was similar to the intravitreal ranibizumab 0.5 mg Q4W.

Notably, the number of treatments received by patients in the PDS 100 mg/mL arm was significantly lower compared to the ranibizumab IVT arm. Until Week 40, patients in the PDS arm had received a mean of 2.0 study treatments per patient compared with a mean of 10.7 per patient in the IVT arm (Week 48 data: 2.9 versus 12.6 study treatments). This meaningful reduction of injections/ treatment visits is considered to be clinically relevant for this patient population, since the requirement of frequent anti-VEGF IVT injections and follow-up visits in order to achieve and maintain improved visual acuity poses a burden on patients with nAMD.

Susvimo is proposed to be indicated *"in adult patients for the treatment of neovascular (wet) age-related macular degeneration (AMD) who have previously responded to at least two intravitreal injections of a vascular endothelial growth factor (VEGF) inhibitor medication".*

The indication wording proposed by the Applicant requires further revision. The indication should be restricted to patients who have demonstrated an adequate response to anti-VEGF therapy and a stabilization of the disease's progression. Thus, it is considered mandatory to define responders based on clinical outcome and to incorporate this in the SmPC. Not the number of injections, but rather clinically stable disease, based on ophthalmological judgement, should be a prerequisite for treatment with the PDS. This needs to be reflected in the indication wording, e.g. as follows:

"Susvimo is indicated in adult patients for the treatment of neovascular (wet) age related macular degeneration (AMD) *who have achieved stable disease (see 4.2) after previously responding to intravitreal treatment with a vascular endothelial growth factor (VEGF) inhibitor medication.*"

In addition, in SmPC Section 4.2, „Patient selection", corresponding criteria for stable disease have to be provided. (**MO)**

In the supportive dose-finding study GX28228 (Ladder), the PDS 100 mg/mL implant refilled PRN improved vision in patients with fewer prior anti-VEGF injections (mean of 2.9 injections) – clinical benefit in terms of visual acuity and anatomical changes was comparable to that in the IVT ranibizumab control arm. However, it remains not fully clear why the Applicant chose the Q24W regimen for refill. This might bear the risk of overexposure, as indicated by the results from the Ladder study, as well as the potential burden of too frequent refill-exchange procedures.

In the supportive extension study GR40549 (Portal), the PDS 100 mg/mL Q24W implant overall maintained visual acuity for up to 36 months both in patients who had been receiving long-term treatment with anti-VEGF injections as well as in patients who switched from the PDS implant refilled PRN.

Overall, similar efficacy with regard to visual acuity and anatomical outcomes has been demonstrated for the PDS in patients responsive to anti-VEGF treatment, in conjunction with a reduction in the injection burden for those patients; however, there are several remaining issues including the above mentioned

major objection regarding the indication wording requiring revision, clarification and further data analyses before a final conclusion can be drawn.

Among others, the appropriateness of the Q24W regimen should be balanced against the PDS-associated risks in comparison with other regimens.

3.3.7. Clinical safety

Susvimo, delivered via the PDS, represents a novel way to deliver ranibizumab, with potential benefits for patients (less frequent medical procedures needed), but also potential new risks since the use of the PDS involves surgical implantation (and implant removal if required) as well as 6-monthly refill-exchange procedures.

The safety analyses for Susvimo are based on the following three studies: the pivotal Phase III Study GR40548 (Archway; ongoing), Phase II Study GX28228 (Ladder; includes main study as well as the oral antithrombotic substudy), and Phase III open-label extension Study GR40549 (Portal). One study of the original clinical programme (the pilot Phase I trial Study FH-1.2) using a prototype implant has been excluded from the safety analysis.

The primary analysis for Study GR40548 was conducted with a clinical cut-off date (CCOD) of 27 March 2020 with subsequent interim analysis with a CCOD of 11 September 2020. The safety analyses primarily focus on all safety data collected as of the CCOD of 11 September 2020, which will include the following:

Study GR40548: data from the primary analysis (CCOD 27 March 2020) and additional data collected up to 11 September 2020

Study GR40549: data collected as of 11 September 2020

Study GX28228: data collected through entire study length.

The study designs and the conduct of the three studies ARCHWAY, LADDER and PORTAL are described in detail in Section 3 of this Overview (Clinical efficacy).

Due to differences in the PDS refill-exchange frequency, safety data during the active-controlled treatment period were presented separately for studies GR40548 and GX28228 and were not pooled for comparative safety evaluation.

Data from two pooled safety populations were presented:

1. All PDS 100 mg/ml population, for the characterization of the PDS used in conditions expected for the marketed product. This pool includes all patients who received PDS 100 mg/mL
2. All PDS population, to address safety questions related to device procedures (implantation, refill-exchange and implant removal). This pool includes all patients who received PDS at various ranibizumab dose levels.

A number of patients from study GX28228 were excluded from the pooled safety analyses: 7 patients originally enrolled at one site were excluded due to a serious breach in GCP (these patients were also excluded from the main safety analysis of study GX28228) and a total of 27 PDS patients who were enrolled prior to May 2016 receiving a PDS implant using the instructions for use versions published prior to this date.

No comparison with intravitreal ranibizumab patients has been provided by the Applicant for both pooled safety populations. The results at individual study level are taken into consideration by the assessor for this comparative evaluation.

Patient exposure

Patient exposure to ranibizumab (intravitreal injection)

In the last 15 years, since the first market approval of Lucentis (ranibizumab intravitreal was registered in the US in June 2006 and in the EU in January 2007), the total exposure to ranibizumab has been estimated to be 3.7 million patient-years.

Patient exposure to Susvimo (ranibizumab via PDS)

As of the CCOD, there are approximately 783 patient years of safety data (1.7 years mean follow-up time) in the All PDS 100 mg/mL Population, comprising 443 safety evaluable patients and 10.6% of patients with >3 years of follow-up.

Study GR40548

The mean duration of exposure as of 11 September 2020 was similar between the PDS 100 mg/mL arm (77.9 weeks [range: 2.0–99.3 weeks]) and intravitreal arm (78.5 weeks [range: 2.1–99.3 weeks]).

The mean number of study treatments per patient during the treatment period was 3.8 (from 1 to 5) in the PDS 100 mg/ml group and 19.5 (from 1 to 25) in the intravitreal group.

Of the patients evaluated for supplemental treatment, 4/246 (1.6%) received supplemental treatment during the first treatment interval (at Week 16 or 20), and 13/241 (5.4%) received supplemental treatment during the second treatment interval (at Week 40 or 44).

Study GX28228

Over the entire study, the mean duration of study treatment was 20.95 months (range: 0.26-37.52 months) for patients in the PDS arms and 21.58 months (range: 5.98-37.32 months) for patients in the intravitreal arm.

The mean number of study treatments per patient during the treatment period was 3.3 (from 1 to 16) and 21.9 (from 7 to 38) in the PDS and intravitreal groups, respectively.

Intravitreal supplemental treatment was administered at some point during the study in 6 patients (10.2%) in the PDS 100 mg/ml group.

All PDS 100 mg/mL Population

The majority of patients in the All PDS 100 mg/mL population had >1.5 years of exposure (299/443 [67.5%]) and 4 study treatments per patient (288/443 [65.0%]). 14% (62/443) of patients were treated for at least 2 years. As of 11 September 2020, in the All PDS 100 mg/mL population, the maximum duration of exposure was 222.4 weeks (~4.3 years), and the mean duration of exposure was 92.20 weeks (1.77 years [range: 0.1–222.4 weeks]).

As of 11 September 2020, there is approximately 783 patient years of safety data (N=443, 1.77 years mean follow-up time) in the All PDS 100 mg/mL population.

The All PDS 100 mg/ml safety population included a total of 443 subjects who received unilateral administration of PDS ranibizumab 100 mg/ml. A total of 423 subjects (95.5%) had at least 1 year of follow-up after the PDS was implanted. A total of 62 subjects (14.0%) were followed-up for at least 2 years and 47 subjects (10.6%) for at least 3 years.

Demographics

The median age of patients was 75.2 years (range: 51–96 years), the majority of patients were either in the age group of 65– < 75 years (136/443 [30.7%]) or 75– < 85 years (202/443 [45.6%]), and White (430/443 [97.1%]). There was a higher proportion of women (267/443 [60.3%]) compared to men.

All PDS Population

As of 11 September 2020, the All PDS safety population included a total of 450 subjects who received unilateral administration of PDS ranibizumab 10 mg/ml, 40 mg/ml or 100 mg/ml. A total of 430 subjects (95.6%) had at least 1 year of follow-up after the PDS was implanted. A total of 157 subjects (34.9%) were followed-up for at least 2 years and 138 subjects (30.7%) for at least 3 years.

The maximum duration of exposure as of CCOD was 4 years (12 patients in the All PDS Population had more than 4 years of follow-up). These patients continue to be followed up for safety.

Demographics

In the All PDS population, the patient demographics were similar to the patient population in the PDS 100 mg/mL population.

Table 5 Overall Extent of Exposure as of 11 September 2020, All PDS 100 mg/mL Population

	GR40549 PDS 100 mg/mL patients from GX28228 PDS 10/40 mg/mL (N=96)	GX28228 PDS 100 mg/mL (N=65)	GR40548 PDS 100 mg/mL (N=248)	GR40549 PDS 100 mg/mL Patients from Intravitreal (N=34)	All PDS 100 mg/mL (N=443)
Duration of Study Treatment (Weeks)					
Mean (SD)	86.68 (13.99)	163.27 (36.94)	77.94 (13.26)	75.89 (31.92)	92.20 (36.02)
Median	92.50	167.57	78.21	86.86	83.71
Min - Max	29.4 - 103.3	14.1 - 222.4	2.0 - 104.3	0.1 - 100.6	0.1 - 222.4
Any Exposure	96 (100%)	65 (100%)	248 (100%)	34 (100%)	443 (100%)
>37 days	96 (100%)	65 (100%)	247 (99.6%)	29 (85.3%)	437 (98.6%)
>6 months	96 (100%)	64 (98.5%)	244 (98.4%)	29 (85.3%)	433 (97.7%)
>1 years	92 (95.8%)	63 (96.9%)	239 (96.4%)	29 (85.3%)	423 (95.5%)
>1.5 years	84 (87.5%)	63 (96.9%)	124 (50.0%)	28 (82.4%)	299 (67.5%)
>2 years	0	62 (95.4%)	0	0	62 (14.0%)
>3 years	0	47 (72.3%)	0	0	47 (10.6%)
>4 years	0	4 (6.2%)	0	0	4 (0.9%)
Number of Study Treatment in Study Eye per Patient (PDS initial fill+refill-exchanges)					
Mean (SD)	3.9 (0.6)	6.6 (2.1)	3.8 (0.7)	3.7 (1.2)	4.2 (1.4)
Median	4.0	6.0	4.0	4.0	4.0
Min - Max	2 - 5	1 - 13	1 - 6	1 - 5	1 - 13
1	0	1 (1.5%)	6 (2.4%)	5 (14.7%)	12 (2.7%)
2	5 (5.2%)	0	3 (1.2%)	0	8 (1.8%)
3	7 (7.3%)	1 (1.5%)	42 (16.9%)	0	50 (11.3%)
4	74 (77.1%)	0	189 (76.2%)	25 (73.5%)	288 (65.0%)
5	10 (10.4%)	15 (23.1%)	1 (0.4%)	4 (11.8%)	30 (6.8%)
6	0	21 (32.3%)	7 (2.8%)	0	28 (6.3%)
7	0	13 (20.0%)	0	0	13 (2.9%)
8	0	6 (9.2%)	0	0	6 (1.4%)
9	0	3 (4.6%)	0	0	3 (0.7%)
11	0	2 (3.1%)	0	0	2 (0.5%)
12	0	1 (1.5%)	0	0	1 (0.2%)
13	0	2 (3.1%)	0	0	2 (0.5%)
Number of Supplemental Treatments per Patient					
Mean (SD)	0.2 (0.6)	0.2 (0.6)	0.2 (0.5)	0.0 (0.2)	0.2 (0.5)
Median	0.0	0.0	0.0	0.0	0.0
Min - Max	0 - 4	0 - 3	0 - 3	0 - 1	0 - 4
0	86 (89.6%)	56 (86.2%)	221 (89.1%)	33 (97.1%)	396 (89.4%)
1	6 (6.3%)	6 (9.2%)	17 (6.9%)	1 (2.9%)	30 (6.8%)
2	2 (2.1%)	2 (3.1%)	9 (3.6%)	0	13 (2.9%)
3	1 (1.0%)	1 (1.5%)	1 (0.4%)	0	3 (0.7%)
4	1 (1.0%)	0	0	0	1 (0.2%)

Table 5 Overall Extent of Exposure as of 11 September 2020, All PDS 100 mg/mL Population (cont.)

	GR40549 PDS 100 mg/mL patients from GX28228 PDS 10/40 mg/mL (N=96)	GX28228 PDS 100 mg/mL (N=65)	GR40548 PDS 100 mg/mL (N=248)	GR40549 PDS 100 mg/mL Patients from Intravitreal (N=34)	All PDS 100 mg/mL (N=443)
Number of ranibizumab Treatments per Patient (initial fill, refill-exchanges and supplemental treatments)					
Mean (SD)	4.1 (0.9)	6.8 (2.2)	3.9 (0.8)	3.7 (1.2)	4.4 (1.6)
Median	4.0	6.0	4.0	4.0	4.0
Min - Max	2 - 8	1 - 14	1 - 6	1 - 6	1 - 14
1	0	1 (1.5%)	6 (2.4%)	5 (14.7%)	12 (2.7%)
2	4 (4.2%)	0	2 (0.8%)	0	6 (1.4%)
3	7 (7.3%)	1 (1.5%)	38 (15.3%)	0	46 (10.4%)
4	67 (69.8%)	0	170 (68.5%)	25 (73.5%)	262 (59.1%)
5	15 (15.6%)	13 (20.0%)	17 (6.9%)	3 (8.8%)	48 (10.8%)
6	0	20 (30.8%)	15 (6.0%)	1 (2.9%)	36 (8.1%)
7	2 (2.1%)	13 (20.0%)	0	0	15 (3.4%)
8	1 (1.0%)	8 (12.3%)	0	0	9 (2.0%)
9	0	2 (3.1%)	0	0	2 (0.5%)
10	0	2 (3.1%)	0	0	2 (0.5%)
11	0	1 (1.5%)	0	0	1 (0.2%)
12	0	2 (3.1%)	0	0	2 (0.5%)
13	0	1 (1.5%)	0	0	1 (0.2%)
14	0	1 (1.5%)	0	0	1 (0.2%)

Ranibizumab treatment is based on the actual treatment that patients have received.
The summary only includes Genentech-supplied and commercially available ranibizumab (PDS implantation, PDS refill-exchanges and supplemental intravitreal ranibizumab injection) administered to Study Eye, per the protocol following first dose with PDS 100 mg/mL ranibizumab (either implantation for GX28228 intravitreal to GR40549, GX28228 PDS 100 mg/mL, and GR40548 PDS 100 mg/mL Q24W groups or first PDS refill-exchange with 100 mg/mL ranibizumab for GX28228 10/40 mg/mL to GR40549). Duration of treatment is defined as the time from first dose with PDS 100 mg/mL ranibizumab (either implant or refill-exchange) to treatment end date (as defined in the individual study).
For patients in the GX28228/GR40548 intravitreal to GR40549 group, only exposure data collected as part of the GR40549 is included.

Table 6 Overall Extent of Exposure as of 11 September 2020, All PDS Population

	GX28228 PDS 10/40 mg/mL (N=103)	GX28228 PDS 100 mg/mL (N=65)	GR40548 PDS 100 mg/mL (N=248)	GR40549 PDS 100 mg/mL Patients from Intravitreal (N=34)	All PDS (N=450)
Duration of Study Treatment (Weeks)					
Mean (SD)	168.40 (39.76)	163.27 (36.94)	77.94 (13.26)	75.89 (31.92)	110.82 (50.73)
Median	171.43	167.57	78.21	86.86	86.64
Min - Max	1.1 - 220.4	14.1 - 222.4	2.0 - 104.3	0.1 - 100.6	0.1 - 222.4
Any Exposure	103 (100%)	65 (100%)	248 (100%)	34 (100%)	450 (100%)
>37 days	102 (99.0%)	65 (100%)	247 (99.6%)	29 (85.3%)	443 (98.4%)
>6 months	101 (98.1%)	64 (98.5%)	244 (98.4%)	29 (85.3%)	438 (97.3%)
>1 years	99 (96.1%)	63 (96.9%)	239 (96.4%)	29 (85.3%)	430 (95.6%)
>1.5 years	97 (94.2%)	63 (96.9%)	124 (50.0%)	28 (82.4%)	312 (69.3%)
>2 years	95 (92.2%)	62 (95.4%)	0	0	157 (34.9%)
>3 years	91 (88.3%)	47 (72.3%)	0	0	138 (30.7%)
>4 years	8 (7.8%)	4 (6.2%)	0	0	12 (2.7%)
Number of Study Treatment in Study Eye per Patient (PDS initial fill+refill-exchanges)					
Mean (SD)	6.7 (2.7)	6.6 (2.1)	3.8 (0.7)	3.7 (1.2)	4.9 (2.1)
Median	6.0	6.0	4.0	4.0	4.0
Min - Max	1 - 15	1 - 13	1 - 6	1 - 5	1 - 15
1	3 (2.9%)	1 (1.5%)	6 (2.4%)	5 (14.7%)	15 (3.3%)
2	0	0	3 (1.2%)	0	3 (0.7%)
3	4 (3.9%)	1 (1.5%)	42 (16.9%)	0	47 (10.4%)
4	4 (3.9%)	0	189 (76.2%)	25 (73.5%)	218 (48.4%)
5	29 (28.2%)	15 (23.1%)	1 (0.4%)	4 (11.8%)	49 (10.9%)
6	20 (19.4%)	21 (32.3%)	7 (2.8%)	0	48 (10.7%)
7	11 (10.7%)	13 (20.0%)	0	0	24 (5.3%)
8	10 (9.7%)	6 (9.2%)	0	0	16 (3.6%)
9	6 (5.8%)	3 (4.6%)	0	0	9 (2.0%)
10	4 (3.9%)	0	0	0	4 (0.9%)
11	7 (6.8%)	2 (3.1%)	0	0	9 (2.0%)
12	3 (2.9%)	1 (1.5%)	0	0	4 (0.9%)
13	0	2 (3.1%)	0	0	2 (0.4%)
15	2 (1.9%)	0	0	0	2 (0.4%)
Number of Supplemental Treatments per Patient					
Mean (SD)	0.3 (0.8)	0.2 (0.6)	0.2 (0.5)	0.0 (0.2)	0.2 (0.6)
Median	0.0	0.0	0.0	0.0	0.0
Min - Max	0 - 5	0 - 3	0 - 3	0 - 1	0 - 5
0	83 (80.6%)	56 (86.2%)	221 (89.1%)	33 (97.1%)	393 (87.3%)
1	13 (12.6%)	6 (9.2%)	17 (6.9%)	1 (2.9%)	37 (8.2%)
2	4 (3.9%)	2 (3.1%)	9 (3.6%)	0	15 (3.3%)
3	2 (1.9%)	1 (1.5%)	1 (0.4%)	0	4 (0.9%)
5	1 (1.0%)	0	0	0	1 (0.2%)

Table 6 Overall Extent of Exposure as of 11 September 2020, All PDS Population (cont.)

	GX28228 PDS 10/40 mg/mL (N=103)	GX28228 PDS 100 mg/mL (N=65)	GR40548 PDS 100 mg/mL (N=248)	GR40549 PDS 100 mg/mL Patients from Intravitreal (N=34)	All PDS (N=450)
Number of ranibizumab Treatments per Patient (initial fill, refill-exchanges and supplemental treatments)					
Mean (SD)	7.0 (3.1)	6.8 (2.2)	3.9 (0.8)	3.7 (1.2)	5.0 (2.4)
Median	6.0	6.0	4.0	4.0	4.0
Min - Max	1 - 20	1 - 14	1 - 6	1 - 6	1 - 20
1	3 (2.9%)	1 (1.5%)	6 (2.4%)	5 (14.7%)	15 (3.3%)
2	0	0	2 (0.8%)	0	2 (0.4%)
3	4 (3.9%)	1 (1.5%)	38 (15.3%)	0	43 (9.6%)
4	4 (3.9%)	0	170 (68.5%)	25 (73.5%)	199 (44.2%)
5	27 (26.2%)	13 (20.0%)	17 (6.9%)	3 (8.8%)	60 (13.3%)
6	21 (20.4%)	20 (30.8%)	15 (6.0%)	1 (2.9%)	57 (12.7%)
7	9 (8.7%)	13 (20.0%)	0	0	22 (4.9%)
8	8 (7.8%)	8 (12.3%)	0	0	16 (3.6%)
9	8 (7.8%)	2 (3.1%)	0	0	10 (2.2%)
10	4 (3.9%)	2 (3.1%)	0	0	6 (1.3%)
11	5 (4.9%)	1 (1.5%)	0	0	6 (1.3%)
12	5 (4.9%)	2 (3.1%)	0	0	7 (1.6%)
13	2 (1.9%)	1 (1.5%)	0	0	3 (0.7%)
14	1 (1.0%)	1 (1.5%)	0	0	2 (0.4%)
16	1 (1.0%)	0	0	0	1 (0.2%)
20	1 (1.0%)	0	0	0	1 (0.2%)

Ranibizumab treatment is based on the actual treatment that patients have received.
The summary only includes Genentech-supplied and commercially available ranibizumab administered to Study Eye, per the protocol following PDS implantation (PDS implantation, PDS refill-exchanges and supplemental intravitreal ranibizumab injection). Duration of treatment is defined as the time from first study treatment to treatment end date (as defined in the individual study).
For patients in the GX28228/GR40548 intravitreal to GR40549 group, only exposure data collected as part of the GR40549 is included.

Adverse events

Ocular Safety in Study Eye in the All PDS 100 mg/mL Population and All PDS Population as 11 September 2020

All PDS 100 mg/mL Population

Ocular AEs

As of 11 September 2020, 382 patients (86.2%) in the All PDS 100 mg/mL population experienced at least one ocular AE in the study eye. The ocular AEs in study eye as of 11 September 2020 with the highest incidence (ε10%) by PT were

- conjunctival hemorrhage (238/443 [53.7%]),
- conjunctival hyperemia (98/443 [22.1%]),
- iritis (67/443 [15.1%]), and
- eye pain (53/443 [12.0%]).

The majority of ocular AEs were non-serious and mild or moderate in severity.

Discontinuations due to AEs

Seventeen patients (3.8%) in the All PDS 100 mg/mL population discontinued from study treatment due to an AE. The AEs leading to treatment discontinuation with highest incidence (≥2 patients) by PT were endophthalmitis (5/443 [1.1%]), device dislocation (4/443 [0.9%]), and worsening nAMD (2/443 [0.5%]).

In study GR40548, the rate of subjects withdrawing from study treatment due to AEs was higher in the PDS 100 mg/ml (3.2%) than in the intravitreal arm (1.2%).

Ocular AESI

98 patients (22.1%) in the All PDS 100 mg/mL population experienced at least one ocular AESI in the study eye. The ocular AESIs in study eye with the highest incidence (ε3%) by PT were

- cataract (45/443 [10.2%]),
- vitreous hemorrhage (23/443 [5.2%]),
- conjunctival bleb/conjunctival filtering bleb leak (21/443 [4.7%]),
- and conjunctival erosion (16/443 [3.6%]).

During the post-operative period, 38 patients (11.0%) in the All PDS 100 mg/mL population experienced at least one ocular AESI in the study eye. After the post-operative period, additional ocular AESIs (ε1%) by PT in the study eye were cataract (42/443 [9.5%]), conjunctival bleb/conjunctival filtering bleb leak (9/443 [2.0%]), and endophthalmitis (7/443 [1.6%]).

AR which led to implant removal

During the clinical development, 18 patients underwent implant removal. Of the 18 patients, 12 patients underwent implant removal due to AEs, hereof 8 patients (1.8%) in the All PDS 100 mg/mL population. The AEs that led to implant removal in the study eye were endophthalmitis (n=5), device dislocation (n=3), conjunctival retraction (n=1), endophthalmitis and conjunctival erosion (n=1), rhegmatogenous retinal detachment (n=1) and wound secretion (n=1). All implant removal procedures were well tolerated, and the majority of ocular AEs post-implant removal were mild and recovered/resolved.

All PDS Population

Ocular AEs

The implant insertion surgery and refill-exchange procedures were generally well tolerated. During the post-operative period, 407 patients (90.4%) in the All PDS population experienced at least one ocular AE in the study eye. Of note, the majority of ocular AEs (1048/1874 [55.9%]) in the study eye occurred during the post-operative period. Ocular AEs in study eye during the post-operative period with the highest reported incidence (≥10%) by PT were

- conjunctival hemorrhage (301/450 [66.9%]),
- conjunctival hyperemia (107/450 [23.8%]),
- iritis (77/450 [17.1%]), and
- eye pain (56/450 [12.4%]).

Ocular AESI

As of 11 September 2020, 117 patients (117/450 [26.0%]) in the All PDS population experienced at least one ocular AESI in the study eye. The ocular AESIs in study eye as of 11 September 2020 with the highest incidence (≥3%) by PT were

- cataract (57/450 [12.7%]),
- vitreous hemorrhage (28/450 [6.2%]),
- conjunctival bleb/conjunctival filtering bleb leak (28/450 [6.2%]), and
- conjunctival erosion (17/450 [3.8%]).

During the post-operative period, 48 patients (48/450 [10.7%]) in the All PDS population experienced at least one ocular AESI in study eye. The majority of the mild and moderate ocular AESIs were short in duration (≤90 days) and resolved either spontaneously or with medical intervention. As of 11 September

2020, 30 serious ocular AESIs occurred in 20 patients (20/450 [4.4%]). Eight of the 30 serious AESIs (8/30 [26.7%]) had an onset during post-operative period (prior to or on Day 37). All events resolved (with duration ranging from 1 to 225 days) except for 1 endophthalmitis AESI that was ongoing as of 11 September 2020. Fourteen of these events (14/30 [46.7%]) were considered severe.

Study GR40548

As of 11 September 2020, a higher proportion of patients in the PDS 100 mg/mL arm (162/248 [65.3%]) than in the intravitreal arm (55/167 [32.9%]) experienced mild ocular AEs in the study eye. Overall, a higher percentage of patients in the PDS 100 mg/mL arm experienced ocular AEs compared with patients in the intravitreal arm (96.4% vs. 49.1%).

Study GX28228:

A higher percentage of patients in the PDS arms experienced ocular AEs during the entire study: 92.7% compared with 63.4%, respectively. Over the entire study, 91 patients (91/179 [50.8%]) in the PDS arms and 16 patients (16/41 [39.0%]) in the intravitreal arm experienced at least one mild ocular AE.

Table 35 Safety Summary (Safety Population)

	PDS 10 mg/mL (n=58)		PDS 40 mg/mL (n=62)		PDS 100 mg/mL (n=59)		All PDS Patients (n=179)		Intravitreal Arm (n=41)	
	First 10 months	Entire study	First 10 months	Entire study	First 10 months	Entire study	First 10 months	Entire study	First 10 months	Entire study
All AEs										
Patients with AEs	56 (96.6%)	57 (98.3%)	60 (96.8%)	60 (96.8%)	58 (98.3%)	58 (98.3%)	174 (97.2%)	175 (97.8%)	35 (85.4%)	39 (95.1%)
Total number of AEs	410	572	410	626	438	628	1258	1826	105	226
Ocular AEs: Study Eye										
Patients with ocular AEs in study eye	56 (96.6%)	56 (96.6%)	56 (90.3%)	58 (93.5%)	51 (86.4%)	52 (88.1%)	163 (91.1%)	166 (92.7%)	17 (41.5%)	26 (63.4%)
Total number of ocular AEs	232	292	227	270	214	250	673	812	33	68
Patients with ocular SAEs in study eye	6 (10.3%)	7 (12.1%)	5 (8.1%)	6 (9.7%)	4 (6.8%)	4 (6.8%)	15 (8.4%)	17 (9.5%)	0	0
Total number of ocular SAEs	12	14	12	13	7	7	31	34	0	0
Patients with ocular AEs potentially related to PDS implant or implant procedures by timing[a]										
≤ 1 month	11 (19.0%)	11 (19.0%)	7 (11.3%)	7 (11.3%)	9 (15.3%)	9 (15.3%)	27 (15.1%)	27 (15.1%)	-	-
> 1 month	8 (13.8%)	11 (19.0%)	8 (12.9%)	14 (22.6%)	7 (11.9%)	11 (18.6%)	23 (12.8%)	36 (20.1%)	-	-
Non-ocular AEs										
Patients with non-ocular AEs	40 (69.0%)	46 (79.3%)	43 (69.4%)	52 (83.9%)	47 (79.7%)	52 (88.1%)	130 (72.6%)	150 (83.8%)	27 (65.9%)	36 (87.8%)
Total number of non-ocular AEs	134	207	153	299	186	312	473	818	58	122
Total number of deaths	0	1 (1.7%)	0	2 (3.2%)	0	1 (1.7%)	0	4 (2.2%)	1 (2.4%)	1 (2.4%)
Patients with AEs leading to withdrawal from treatment	2 (3.4%)	2 (3.4%)	2 (3.2%)	3 (4.8%)	1 (1.7%)	1 (1.7%)	5 (2.8%)	6 (3.4%)	0	0

Table 36 Ocular Events in Study Eye Occurring in at Least 5% of All PDS Patients During First 10 Months (Safety Population)

MedDRA System Organ Class Preferred Term	PDS with Ranibizumab 10 mg/mL (N=58)	PDS with Ranibizumab 40 mg/mL (N=62)	PDS with Ranibizumab 100 mg/mL (N=59)	All PDS with Ranibizumab (N=179)	Intravitreal Ranibizumab 0.5 mg Monthly (N=41)
Total number of patients with at least one adverse event	56 (96.6%)	56 (90.3%)	51 (86.4%)	163 (91.1%)	17 (41.5%)
Total number of adverse events	232	227	214	673	33
Eye Disorders					
CONJUNCTIVAL HAEMORRHAGE	40 (69.0%)	43 (69.4%)	35 (59.3%)	118 (65.9%)	5 (12.2%)
CONJUNCTIVAL HYPERAEMIA	17 (29.3%)	13 (21.0%)	13 (22.0%)	43 (24.0%)	0
EYE PAIN	11 (19.0%)	10 (16.1%)	15 (25.4%)	36 (20.1%)	4 (9.8%)
VITREOUS FLOATERS	11 (19.0%)	7 (11.3%)	11 (18.6%)	29 (16.2%)	2 (4.9%)
IRITIS	8 (13.8%)	13 (21.0%)	6 (10.2%)	27 (15.1%)	0
EYE IRRITATION	8 (13.8%)	6 (9.7%)	7 (11.9%)	21 (11.7%)	1 (2.4%)
FOREIGN BODY SENSATION IN EYES	4 (6.9%)	6 (9.7%)	7 (11.9%)	17 (9.5%)	0
VITREOUS HAEMORRHAGE	6 (10.3%)	5 (8.1%)	6 (10.2%)	17 (9.5%)	0
CONJUNCTIVAL OEDEMA	6 (10.3%)	6 (9.7%)	1 (1.7%)	13 (7.3%)	0
VISION BLURRED	5 (8.6%)	1 (1.6%)	5 (8.5%)	11 (6.1%)	2 (4.9%)
DRY EYE	5 (8.6%)	1 (1.6%)	5 (8.5%)	11 (6.1%)	0
CATARACT	0	2 (3.2%)	7 (11.9%)	9 (5.0%)	1 (2.4%)
ANTERIOR CHAMBER CELL	1 (1.7%)	2 (3.2%)	6 (10.2%)	9 (5.0%)	0
CORNEAL OEDEMA	3 (5.2%)	2 (3.2%)	4 (6.8%)	9 (5.0%)	0
EYELID PTOSIS	3 (5.2%)	2 (3.2%)	4 (6.8%)	9 (5.0%)	0
POSTERIOR CAPSULE OPACIFICATION	3 (5.2%)	3 (4.8%)	3 (5.1%)	9 (5.0%)	0

Table 21 Ocular AESIs in the Study Eye during the Post-Operative Period, All PDS Population

MedDRA Preferred Term	GX28228 PDS 10/40 mg/mL (N=103)	GX28228 PDS 100 mg/mL (N=65)	GR40548 PDS 100 mg/mL (N=248)	GR40549 PDS 100 mg/mL Patients from Intravitreal (N=34)	All PDS (N=450)
Total number of patients with at least one adverse event	10 (9.7%)	7 (10.8%)	26 (10.5%)	5 (14.7%)	48 (10.7%)
Sight Threatening	0	1 (1.5%)	2 (0.8%)	0	3 (0.7%)
Overall total number of adverse events	12	11	29	5	57
Cataract*	0	1 (1.5%)	1 (0.4%)	0	2 (0.4%)
Sight Threatening	0	0	0	0	0
Conjunctival Bleb/ Conjunctival Filtering Bleb Leak	6 (5.8%)	1 (1.5%)	11 (4.4%)	1 (2.9%)	19 (4.2%)
Sight Threatening	0	0	0	0	0
Conjunctival erosion	0	1 (1.5%)	1 (0.4%)	0	2 (0.4%)
Sight Threatening	0	0	0	0	0
Conjunctival retraction	0	1 (1.5%)	1 (0.4%)	0	2 (0.4%)
Sight Threatening	0	0	0	0	0
Endophthalmitis	1 (1.0%)	0	0	0	1 (0.2%)
Sight Threatening	0	0	0	0	0
Hyphaema	1 (1.0%)	3 (4.6%)	1 (0.4%)	0	5 (1.1%)
Sight Threatening	0	1 (1.5%)	0	0	1 (0.2%)
Rhegmatogenous retinal detachment	1 (1.0%)	0	1 (0.4%)	0	2 (0.4%)
Sight Threatening	0	0	1 (0.4%)	0	1 (0.2%)
Tractional retinal detachment	0	0	0	0	0
Sight Threatening	0	0	0	0	0
Vitreous haemorrhage	3 (2.9%)	3 (4.6%)	12 (4.8%)	4 (11.8%)	22 (4.9%)
Sight Threatening	0	0	1 (0.4%)	0	1 (0.2%)

Post operative period is defined as 0-37 days after implantation

Non-ocular safety

All PDS 100 mg/ml Population

As of 11 September 2020, 346 patients (346/443 [78.1%]) in the All PDS 100 mg/mL population experienced at least one non-ocular AE. The non-ocular AEs with the highest incidence (≥5% incidence) by PT, were urinary tract infection (47/443 [10.6%]), nasopharyngitis (41/443 [9.3%]), sinusitis (32/443 [7.2%]), bronchitis (24/443 [5.4%]), headache (28/443 [6.3%]), fall (26/443 [5.9%]), pneumonia (23/443 [5.2%]), and hypertension (22/443 [5.0%]). The majority of patients in this safety population experienced mild (24.8%) or moderate (32.3%) non-ocular AEs; 21.0% of patients experienced at least one severe non-ocular AE.

Study GR40548

As of 11 September 2020, 200 patients (200/248 [80.6%]) in the PDS 100 mg/mL arm and 113 patients (113/167 [67.7%]) in the intravitreal arm experienced at least one non-ocular AE.

Through Week 40, 6 patients (2.4%) in the PDS 100 mg/mL arm and 2 patients (1.2%) in the intravitreal arm experienced an Anti-Platelet Trialists Collaboration Event (APTC).

Study GX28228

Over the entire study, the percentage of patients with non-ocular AEs was similar in the PDS arms and in the intravitreal arm with 150 patients (150/179 [83.8 %]) and 36 patients (36/41[87.8%]), respectively, experiencing at least one non-ocular AE. 12 PDS-treated patients (6.7%) experienced APTCs during the study, while no such events were reported in the intravitreal arm.

Studies GX28228 and GR40548

In response to the Day 120 LoQ, the Applicant provided updated data on the frequency of APTC events. Based on a data cutoff of 12 March 2021, APTC events were reviewed in PDS (10/40/100 mg/mL) patients from Studies GR40548 and GX28228 combined; in PDS 100 mg/mL patients from Studies GR40458 and GX28228 combined, and compared with combined intravitreal population (from Studies and GR40548 and GX28228; Table 1). Data from long-term extension Study GR40549 was excluded to better control for variable exposure in PDS and intravitreal patients.

Table 1 Anti-Platelet Trialists Collaboration Events through 12 March 2021 or End of Study; Protocol GX28228, GR40548

	PDS 10/40/100 (N=416)	All PDS 100 (N=313)	All Intravitreal (N=208)
APTC			
Overall	20 (4.8%)	15 (4.8%)	4 (1.9%)
Non-fatal Stroke Adverse Events	11 (2.6%)	9 (2.9%)	2 (1.0%)
Non-fatal Myocardial Infraction Adverse Events	6 (1.4%)	3 (1.0%)	1 (0.5%)
Vascular Death or Deaths of Unknown Cause	4 (1.0%)	4 (1.3%)	2 (1.0%)

Summary includes final data from GX28228 and all data from GR40548 through March 12, 2021. APTCs are defined as non-fatal stroke adverse events or non-fatal myocardial infarction AEs or vascular death (including deaths of unknown cause). Stroke AEs are defined by terms from the conditions associated with central nervous system haemorrhages and cerebrovascular accidents SMP (Narrow), ischaemic cerebrovascular conditions SMQ (Narrow), and haemorrhagic cerebrovascular conditions SMQ (Narrow). Myocardial infarction AEs are defined by terms from the myocardial infarction SMQ (Narrow). For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

In PDS 100 mg/mL patients, overall 4.8% of patients experienced at least one APTC event, compared to 1.9% in the combined intravitreal population. 2.9% of the patients in the All PDS 100 mg/ml group experienced non-fatal stroke AEs, compared to 1.0% in the intravitreal group. 1.0% of the All PDS 100 mg/ml patients experienced non-fatal myocardial infarction AEs, compared to 0.5% in the intravitreal group.

Serious adverse events and deaths

Deaths

All PDS Population

As of 11 September 2020, a total of 11 deaths were reported in the All PDS population. The causes of death in the GX28228 PDS 10/40 mg/mL group were sepsis (1 patient), metabolic acidosis (1 patient), myocardial infarction (1 patient), and anaphylactic shock and cardiac arrest (1 patient; both events in same patient).

The causes of death in the GX28228 PDS 100 mg/mL group were cardiogenic shock, myocardial infarction, and acute respiratory failure (1 patient; all three events in same patient) and pancreatic carcinoma (1 patient). There was 1 death in the intravitreal arm (cause of death, congestive heart failure).

The causes of death in the GR40548 PDS 100 mg/mL group were coronary artery disease (1 patient), death (unexplained death; 1 patient), road traffic accident (1 patient), and acute respiratory failure (1 patient). In the intravitreal arm 2 deaths were reported: non-small lung cancer (1 patient) and cardiac arrest (1 patient). No deaths were considered related to the implant (including implant, implant procedure, or initial fill needle), intravitreal injection procedure, or study drug by the investigator.

Ocular Serious Adverse Events: Study Eye

All PDS 100 mg/mL Population

Twenty-six patients (5.9%) in the All PDS 100 mg/mL population experienced at least one ocular SAE in the study eye. Ocular SAEs with an incidence of (≥0.5%) in study eye, by PT, were

- endophthalmitis (7/443 [1.6%]),
- conjunctival erosion (5/443 [1.1%]),
- device dislocation (4/443 [0.9%]),
- visual acuity reduced (3/443 [0.7%]),
- conjunctival retraction (3/443 [0.7%]), and
- rhegmatogenous retinal detachment and vitreous hemorrhage (2/443 [0.5%] each).

All PDS Population

Thirty-one patients (6.9%) in the All PDS population experienced at least one SAE in the study eye. Ocular SAEs with a reported incidence of (≥0.5%) in the All PDS population in the study eye by PT were

- endophthalmitis (9/450 [2.0%]),
- conjunctival erosion (5/450 [1.1%]),
- device dislocation (4/450 [0.9%]), and
- conjunctival retraction, rhegmatogenous retinal detachment, visual acuity reduced, and vitreous hemorrhage (3/450 [0.7%] each).

Table 16 Ocular Serious Adverse Events in the Study Eye as 11 September 2020, All PDS 100 mg/mL Population

MedDRA System Organ Class MedDRA Preferred Term	GR40549 PDS 100 mg/mL patients from GX28228 PDS 10/40 mg/mL (N=96)	GX28228 PDS 100 mg/mL (N=65)	GR40548 PDS 100 mg/mL (N=248)	GR40549 PDS 100 mg/mL Patients from Intravitreal (N=34)	All PDS 100 mg/mL (N=443)
Total number of patients with at least one adverse event	2 (2.1%)	4 (6.2%)	19 (7.7%)	1 (2.9%)	26 (5.9%)
Total number of adverse events	2	7	29	1	39
Eye disorders					
Total number of patients with at least one adverse event	1 (1.0%)	2 (3.1%)	15 (6.0%)	1 (2.9%)	19 (4.3%)
Total number of adverse events	1	3	19	1	24
Conjunctival erosion	1 (1.0%)	2 (3.1%)	2 (0.8%)	0	5 (1.1%)
Visual acuity reduced	0	0	3 (1.2%)	0	3 (0.7%)
Rhegmatogenous retinal detachment	0	0	2 (0.8%)	0	2 (0.5%)
Vitreous haemorrhage	0	0	2 (0.8%)	0	2 (0.5%)
Cataract cortical	0	0	1 (0.4%)	0	1 (0.2%)
Choroidal detachment	0	0	1 (0.4%)	0	1 (0.2%)
Conjunctival bleb	0	0	1 (0.4%)	0	1 (0.2%)
Corneal disorder	0	0	1 (0.4%)	0	1 (0.2%)
Corneal epithelium defect	0	0	0	1 (2.9%)	1 (0.2%)
Necrotising retinitis	0	0	1 (0.4%)	0	1 (0.2%)
Retinal pigment epithelial tear	0	0	1 (0.4%)	0	1 (0.2%)
Retinal tear	0	0	1 (0.4%)	0	1 (0.2%)
Visual impairment	0	0	1 (0.4%)	0	1 (0.2%)
Infections and infestations					
Total number of patients with at least one adverse event	0	3 (4.6%)	4 (1.6%)	0	7 (1.6%)
Total number of adverse events	0	3	5	0	8
Endophthalmitis	0	3 (4.6%)	4 (1.6%)	0	7 (1.6%)
Product issues					
Total number of patients with at least one adverse event	1 (1.0%)	0	3 (1.2%)	0	4 (0.9%)
Total number of adverse events	1	0	3	0	4
Device dislocation	1 (1.0%)	0	3 (1.2%)	0	4 (0.9%)
Injury, poisoning and procedural complications					
Total number of patients with at least one adverse event	0	1 (1.5%)	2 (0.8%)	0	3 (0.7%)
Total number of adverse events	0	1	2	0	3
Conjunctival retraction	0	1 (1.5%)	2 (0.8%)	0	3 (0.7%)

Investigator text for AEs coded using MedDRA version 23.0. Percentages are based on the N in the column headings. Table summary includes adverse events that started or worsened (for existing condition) on or after the date of PDS 100 mg/mL first dose. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Table 17 Ocular Serious Adverse Events in the Study Eye during the Post-Operative Period as of 11 September 2020, All PDS Population

MedDRA System Organ Class MedDRA Preferred Term	GX28228 PDS 10/40 mg/mL (N=103)	GX28228 PDS 100 mg/mL (N=65)	GR40548 PDS 100 mg/mL (N=248)	GR40549 PDS 100 mg/mL Patients from Intravitreal (N=34)	All PDS (N=450)
Total number of patients with at least one adverse event	2 (1.9%)	1 (1.5%)	8 (3.2%)	1 (2.9%)	12 (2.7%)
Total number of adverse events	2	2	9	1	14
Eye disorders					
Total number of patients with at least one adverse event	0	1 (1.5%)	7 (2.8%)	1 (2.9%)	9 (2.0%)
Total number of adverse events	0	1	8	1	10
Visual acuity reduced	0	0	3 (1.2%)	0	3 (0.7%)
Conjunctival erosion	0	1 (1.5%)	1 (0.4%)	0	2 (0.4%)
Corneal epithelium defect	0	0	0	1 (2.9%)	1 (0.2%)
Retinal tear	0	0	1 (0.4%)	0	1 (0.2%)
Rhegmatogenous retinal detachment	0	0	1 (0.4%)	0	1 (0.2%)
Visual impairment	0	0	1 (0.4%)	0	1 (0.2%)
Vitreous haemorrhage	0	0	1 (0.4%)	0	1 (0.2%)
Injury, poisoning and procedural complications					
Total number of patients with at least one adverse event	1 (1.0%)	1 (1.5%)	1 (0.4%)	0	3 (0.7%)
Total number of adverse events	1	1	1	0	3
Conjunctival retraction	0	1 (1.5%)	1 (0.4%)	0	2 (0.4%)
Conjunctival filtering bleb leak	1 (1.0%)	0	0	0	1 (0.2%)
Infections and infestations					
Total number of patients with at least one adverse event	1 (1.0%)	0	0	0	1 (0.2%)
Total number of adverse events	1	0	0	0	1
Endophthalmitis	1 (1.0%)	0	0	0	1 (0.2%)

After post-operative period is defined as > 37 days after implantation.
Investigator text for AEs coded using MedDRA version 23.0. Percentages are based on the N in the column headings. Table summary includes adverse events that started or worsened (for existing condition) on or after the date of PDS 100 mg/mL first dose. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Study GR40548

As of 11 September 2020, 19 patients (19/248 [7.7%]) in the PDS 100 mg/mL arm reported a total of 29 SAEs vs. 4 patients (4/167 [2.4%]) in the intravitreal arm experienced at least one ocular SAE in the study eye.

In the PDS 100 mg/mL group 4 cases of endophthalmitis, 3 device dislocations, 2 cases of conjunctival retraction, and 19 cases of eye disorders (3 cases of visual acuity reduced, 2 of vitreous haemorrhage, 2 of conjunctival erosion, 2 of rhegmatogenous retinal detachment, 1 retinal tear, 1 cataract cortical, 1 conjunctival bleb, 1 corneal disorder, 1 retinal pigment epithelial tear, 1 choroidal detachment, 1 necrotising retinitis, 1 visual impairment,) were reported. In the intravitreal ranibizumab group, 1 case of endophthalmitis, 1 case of vitreous haemorrhage, 1 case of retinal tear and 1 case of facial bone fracture were reported.

Overall, the reported ocular SAEs suspected by the investigator to be caused by implant (including implant, implant procedure, or initial fill needle) was endophthalmitis, cataract cortical, conjunctival erosion, and device dislocation (1/248 [0.4%] each).

Two patients (1.2%) in the intravitreal arm experienced ocular SAEs of endophthalmitis and retinal tear (1/167 [0.6%] each) suspected by the investigator to be caused by intravitreal injection procedure. One patient in the intravitreal arm experienced an ocular SAE of retinal tear, which was suspected to be caused by ranibizumab (delivered by intravitreal injection).

Table 11 Ocular Serious Adverse Events in Study Eye as of 11 September 2020, Safety Population

MedDRA System Organ Class MedDRA Preferred Term	PDS with Ranibizumab 100 mg/mL Q24W (N=248) Onset after Week 40*	PDS with Ranibizumab 100 mg/mL Q24W (N=248) Overall	Intravitreal Ranibizumab 0.5 mg Q4W (N=167) Onset after Week 40*	Intravitreal Ranibizumab 0.5 mg Q4W (N=167) Overall
Total number of patients with >=1 AE	7 (2.8%)	19 (7.7%)	2 (1.2%)	4 (2.4%)
Overall total number of AEs	9	29	2	4
Eye disorders				
Total number of patients with >=1 AE	5 (2.0%)	15 (6.0%)	1 (0.6%)	2 (1.2%)
Total number of AEs	6	19	1	2
Vitreous haemorrhage	1 (0.4%)	2 (0.8%)	0	1 (0.6%)
Conjunctival erosion	1 (0.4%)	2 (0.8%)	0	0
Retinal tear	0	1 (0.4%)	1 (0.6%)	1 (0.6%)
Visual acuity reduced	0	3 (1.2%)	0	0
Cataract cortical	1 (0.4%)	1 (0.4%)	0	0
Conjunctival bleb	1 (0.4%)	1 (0.4%)	0	0
Corneal disorder	1 (0.4%)	1 (0.4%)	0	0
Retinal pigment epithelial tear	1 (0.4%)	1 (0.4%)	0	0
Rhegmatogenous retinal detachment	0	2 (0.8%)	0	0
Choroidal detachment	0	1 (0.4%)	0	0
Necrotising retinitis	0	1 (0.4%)	0	0
Visual impairment	0	1 (0.4%)	0	0
Infections and infestations				
Total number of patients with >=1 AE	1 (0.4%)	4 (1.6%)	1 (0.6%)	1 (0.6%)
Total number of AEs	1	5	1	1
Endophthalmitis	1 (0.4%)	4 (1.6%)	1 (0.6%)	1 (0.6%)
Product issues				
Total number of patients with >=1 AE	2 (0.8%)	3 (1.2%)	0	0
Total number of AEs	2	3	0	0
Device dislocation	2 (0.8%)	3 (1.2%)	0	0
Injury, poisoning and procedural complications				
Total number of patients with >=1 AE	0	2 (0.8%)	0	1 (0.6%)
AE				
Total number of AEs	0	2	0	1
Conjunctival retraction	0	2 (0.8%)	0	0
Facial bones fracture	0	0	0	1 (0.6%)

Study GX28228

Seventeen patients (17/179 [9.5%]) in the PDS arms experienced 34 ocular SAEs during the entire study while no ocular SAEs were reported in the intravitreal arm.

The most frequently reported ocular SAEs during the first 10 months by preferred term were vitreous hemorrhage (6 patients [3.4%]), conjunctival erosion (3 patients [1.7%]), rhegmatogenous retinal detachment (3 patients [1.7%]), reduced visual acuity (3 patients [1.7%]), and endophthalmitis (3 patients [1.7%]). During the entire study, 3 additional ocular SAEs were reported in the PDS arms (vitreous hemorrhage, retinal hemorrhage and blurred vision), bringing the total number of SAEs to 34 in 17 patients (9.5%).

Table 39 Ocular Serious Adverse Events in Study Eye during the First 10 Months (Safety Population)

MedDRA System Organ Class Preferred Term	PDS with Ranibizumab 10 mg/mL (N=58)	PDS with Ranibizumab 40 mg/mL (N=62)	PDS with Ranibizumab 100 mg/mL (N=59)	All PDS with Ranibizumab (N=179)	Intravitreal Ranibizumab 0.5 mg Monthly (N=41)
Total number of patients with at least one adverse event	6 (10.3%)	5 (8.1%)	4 (6.8%)	15 (8.4%)	0
Total number of adverse events	12	12	7	31	0
Eye Disorders					
Total number of patients with at least one adverse event	5 (8.6%)	4 (6.5%)	3 (5.1%)	12 (6.7%)	0
Total number of adverse events	9	8	5	22	0
VITREOUS HAEMORRHAGE	3 (5.2%)	1 (1.6%)	2 (3.4%)	6 (3.4%)	0
CONJUNCTIVAL EROSION	1 (1.7%)	1 (1.6%)	1 (1.7%)	3 (1.7%)	0
RHEGMATOGENOUS RETINAL DETACHMENT	1 (1.7%)	1 (1.6%)	1 (1.7%)	3 (1.7%)	0
VISUAL ACUITY REDUCED	1 (1.7%)	1 (1.6%)	1 (1.7%)	3 (1.7%)	0
HYPOTONY OF EYE	0	1 (1.6%)	0	1 (0.6%)	0
RETINAL TEAR	0	1 (1.6%)	0	1 (0.6%)	0
RETINOPATHY PROLIFERATIVE	1 (1.7%)	0	0	1 (0.6%)	0
TRACTIONAL RETINAL DETACHMENT	1 (1.7%)	0	0	1 (0.6%)	0
Infections And Infestations					
Total number of patients with at least one adverse event	1 (1.7%)	1 (1.6%)	1 (1.7%)	3 (1.7%)	0
Total number of adverse events	1	1	1	3	0
ENDOPHTHALMITIS	1 (1.7%)	1 (1.6%)	1 (1.7%)	3 (1.7%)	0
Injury, Poisoning And Procedural Complications					
Total number of patients with at least one adverse event	1 (1.7%)	3 (4.8%)	1 (1.7%)	5 (2.8%)	0
Total number of adverse events	1	3	1	5	0
CONJUNCTIVAL RETRACTION	0	1 (1.6%)	1 (1.7%)	2 (1.1%)	0
CONJUNCTIVAL FILTERING BLEB LEAK	0	1 (1.6%)	0	1 (0.6%)	0
HYPHAEMA	1 (1.7%)	0	0	1 (0.6%)	0
WOUND SECRETION	0	1 (1.6%)	0	1 (0.6%)	0
Investigations					
Total number of patients with at least one adverse event	1 (1.7%)	0	0	1 (0.6%)	0
Total number of adverse events	1	0	0	1	0
INTRAOCULAR PRESSURE INCREASED	1 (1.7%)	0	0	1 (0.6%)	0

Ocular Serious Adverse Events: Fellow Eye

All PDS 100mg/mL Population

As of 11 September 2020, 6 patients (1.4%) in the All PDS 100 mg/mL population experienced at least one SAE in the fellow eye. The SAEs in the fellow eye by PT were

- corneal decompensation,
- retinal artery occlusion,
- retinal hemorrhage,
- rhegmatogenous retinal detachment,
- visual acuity reduced, and
- vitreous hemorrhage (1/443 [0.2%] each).

Sight-threatening Adverse Events

All PDS 100 mg/ml Population

As of 11 September 2020, 16 patients (16/443 [3.6%]) experienced at least one sight-threatening AE in the study eye. The sight threatening AEs (≥2 patients) in the study eye as of 11 September 2020 by PT were visual acuity reduced (4/443 [0.9%]), endophthalmitis (3/443 [0.7%]), and device dislocation (2/443 [0.5%]). During the post-operative period, 9 patients (9/347 [2.6%]) in the All PDS 100 mg/mL population experienced at least one sight threatening AE. The most common sight threatening AE (≥2 patients) in the study eye during the pos-operative period as of 11 September 2020 by PT was visual acuity reduced (4/347 [1.2%]).

All PDS Population

As of 11 September 2020, 19 patients (19/450 [4.2%]) experienced at least one sight-threatening AE in the study eye. During the post-operative period, 10 patients (10/450 [2.2%]) in the All PDS population experienced at least one sight threatening AE in the study eye. The most common sight threatening AE (≥2 patients) in the study eye during post-operative period as of 11 September 2020 by PT was visual acuity reduced (5/450 [1.1%]).

Study GR40548

As of 11 September 2020, 11 patients (11/248 [4.4%]) in the PDS 100 mg/mL arm and 4 patients (4/167 [2.4%]) in the intravitreal arm experienced at least one sight-threatening AE in the study eye. All sight-threatening AEs were serious.

Study GX28228

9 patients (7/179 [5.0%]) in the PDS arms and 2 patients (2/41 [4.9%]) in the intravitreal ranibizumab arm experienced at least one sight threatening AE in the study eye during the entire study.

Non-Ocular Safety in the All PDS 100 mg/mL Population as 11 September 2020

98 patients (22.1%) in the PDS 100 mg/mL population experienced at least one (non-fatal) non-ocular SAE. The non-ocular SAEs with the highest reported incidence (≥4 patients) by PT, were

- pneumonia (12/443 [2.7%]),
- urinary tract infection (6/443 [1.4%]),
- osteoarthritis (6/443 [1.4%]), and
- cerebrovascular accident, sepsis and hip fracture (4/443 [0.9%] each).

In the All PDS 100 mg/mL population, two cases of serious COVID-19 were reported. As of 11 September 2020, both cases had resolved, and one patient experienced pneumonia associated with COVID-19.

Non-Ocular safety in studies GR40548 and GX28228

The incidence of non-ocular SAEs was higher in the PDS arms compared to the intravitreal arm (21.8% vs 16.2% in study GR40548 and 20.7% vs 9.8% in study GX28228, respectively).

More patients in the PDS arms compared to the intravitreal arm experienced a SAE of cerebrovascular accident (1.2% vs 0.6% in study GR40548 and 1.7% vs 0 in study GX28228).

Table 12 Safety Summary as of 11 September 2020, All PDS Population

	GX28228 PDS 10/40 mg/mL (N=103)	GX28228 PDS 100 mg/mL (N=65)	GR40548 PDS 100 mg/mL (N=248)	GR40549 PDS 100 mg/mL Patients from Intravitreal (N=34)	All PDS (N=450)
Patients with at least one adverse event	101 (98.1%)	65 (100%)	246 (99.2%)	32 (94.1%)	444 (98.7%)
Overall total number of adverse events	1334	945	1864	181	4324
Ocular Events: Study Eye					
Patients with at least one adverse event	98 (95.1%)	61 (93.8%)	239 (96.4%)	32 (94.1%)	430 (95.6%)
Total number of adverse events	543	329	910	92	1874
Patients with at least one Serious AE	7 (6.8%)	4 (6.2%)	19 (7.7%)	1 (2.9%)	31 (6.9%)
Patients with at least one AE leading to withdrawal from treatment	7 (6.8%)	4 (6.2%)	8 (3.2%)	0	19 (4.2%)
Ocular Events: Fellow Eye					
Patients with at least one adverse event	69 (67.0%)	43 (66.2%)	104 (41.9%)	8 (23.5%)	224 (49.8%)
Total number of adverse events	159	99	171	14	443
Patients with at least one Serious AE	2 (1.9%)	1 (1.5%)	3 (1.2%)	1 (2.9%)	7 (1.6%)
Patients with at least one AE leading to withdrawal from treatment	0	0	0	0	0
Non-Ocular Events					
Patients with at least one adverse event	95 (92.2%)	58 (89.2%)	200 (80.6%)	19 (55.9%)	372 (82.7%)
Total number of adverse events	632	517	783	75	2007
Patients with at least one Serious AE	37 (35.9%)	23 (35.4%)	54 (21.8%)	2 (5.9%)	116 (25.8%)
Patients with at least one AE leading to withdrawal from treatment	2 (1.9%)	0	0	0	2 (0.4%)
Total number of Deaths	4 (3.9%)	2 (3.1%)	5 (2.0%)	0	11 (2.4%)
Adverse Events of Special Interest in Study Eye					
Patients with at least one AE	32 (31.1%)	23 (35.4%)	60 (24.2%)	10 (29.4%)	125 (27.8%)
Total number of AEs	56	43	96	10	205
Patients with Sight Threatening AE	4 (3.9%)	3 (4.6%)	11 (4.4%)	1 (2.9%)	19 (4.2%)
Patients with Ocular AESI	30 (29.1%)	23 (35.4%)	55 (22.2%)	9 (26.5%)	117 (26.0%)
Patients with Serious Ocular AESI	5 (4.9%)	4 (6.2%)	11 (4.4%)	0	20 (4.4%)
Adverse Events of Special Interest in Fellow Eye					
Patients with at least one AE	12 (11.7%)	15 (23.1%)	18 (7.3%)	2 (5.9%)	47 (10.4%)
Total number of AEs	15	15	27	2	59
Patients with Sight Threatening AE	1 (1.0%)	1 (1.5%)	3 (1.2%)	0	5 (1.1%)
Patients with Ocular AESI	11 (10.7%)	15 (23.1%)	16 (6.5%)	2 (5.9%)	44 (9.8%)
Patients with Serious Ocular AESI	0	1 (1.5%)	0	1 (2.9%)	2 (0.4%)

Investigator text for AEs coded using MedDRA version 23.0. Percentages are based on the N in the column headings. Table summary includes adverse events that started or worsened
(for existing condition) on or after the date of PDS implant. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Laboratory findings

Laboratory findings

General chemistry, hematology, and urinalysis laboratory results were collected as part of screening eligibility only. No general summary was generated.

Vital signs, physical findings and other observations related to safety

Vital signs were collected as part of screening eligibility, explant visit, and at study termination visit only. Therefore, vital signs results were reviewed by the Sponsor on an individual patient basis. No aggregate data summaries or shift tables are provided for vital signs. Clinically significant vital sign abnormalities were reported as AEs and evaluated in the adverse event assessments.

Safety in special populations

The incidence of ocular AEs in the study eye was comparable among males and females in the All PDS 100 mg/mL population with 170 males (170/176 [96.6%]) and 257 females (257/267 [96.3%]) who experienced at least one ocular AE as of 11 September 2020. The incidence of ocular AEs in the fellow eye, non-ocular AEs, number of deaths, AESIs in both study eye and fellow eye, and non-ocular AESIs was also comparable among above mentioned age groups and among the males and females.

Pregnancy

The systemic exposure to PDS is low after administration via the PDS implant, but due to its mechanism of action, PDS must be regarded as potentially teratogenic and embryo-/fetotoxic. PDS is not recommended during pregnancy unless the expected benefit outweighs the potential risk to the fetus.

Lactation

It is not known whether PDS is excreted in human breast milk. No studies have been conducted to assess the impact of PDS on milk production or its presence in breast milk.

Because many drugs are excreted in human milk and the potential for absorption and harm to infant growth and development exists, PDS is not recommended during breast-feeding.

MedDRA Terms	**Age <65** **number (percentage)**	**Age 65-74** **number (percentage)**	**Age 75-84** **number (percentage)**	**Age 85+** **number (percentage)**
Total AEs	49 (94.2%)	129 (94.9%)	249 (97.6%)	49 (94.2%)
Serious AEs – Total	2 (3.8%)	10 (7.4%)	14 (5.5%)	2 (3.8%)
- Fatal				
- Hospitalization/prolong existing hospitalization				
- Life-threatening				
- Disability/incapacity				
- Other (medically significant)				
AE leading to drop-out				
Psychiatric disorders				
Nervous system disorders				
Accidents and injuries				
Cardiac disorders				
Vascular disorders				
Cerebrovascular disorders				
Infections and infestations				
Anticholinergic syndrome				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				
<other AE appearing more frequently in older patients>				

Immunological events

The immunogenicity analysis population consisted of all treated patients with at least one ADA assessment. Patients were grouped according to treatment received. The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (post-baseline incidence) were summarized by treatment group.

Study GX28228

ADA

The baseline prevalence and incidence of treatment-emergent ADAs to ranibizumab in PDS treatment arms are provided in Table 3. The baseline prevalence for ADAs to ranibizumab was 6 of 58 patients (10.3%), 3 of 60 patients (5.0%), 3 of 59 patients (5.1%), 12 of 177 patients (6.8%), and 0 of 39 patients (0%), in the PDS 10, 40, 100 mg/mL arms, all PDS arms combined, and the intravitreal arm, respectively. These data may reflect a combination of pre-study immunogenicity elicited by prior anti-VEGF therapy(ies), pre-existing immunoreactivity, and/or the incorporation of an untreated positive rate on the statistical design of the assay cut points.

The mean duration of study treatment was 20.95 months (range, 0.26-37.52 months) for patients in the PDS arms and 21.58 months (range, 5.98-37.32 months) for patients in the intravitreal arm. Incidence of treatment-emergent ADA to ranibizumab over the course of the study was 4 of 58 patients (6.9%), 9 of 62 patients (14.5%), 9 of 59 patients (15.3%), 22 of 179 patients (12.3%), and 6 of 41 patients (14.6%) in the PDS 10, 40, 100 mg/mL arms, all PDS arms combined, and the intravitreal arm, respectively.

NAbs

The baseline prevalence of NAbs and incidence of treatment-emergent NAbs to ranibizumab are provided in (Table 4). The overall baseline prevalence for NAbs to ranibizumab was low, with only one patient (in the PDS 10 mg/mL arm) testing positive out of all 216 baseline-evaluable patients in the study.

Overall, the incidence of treatment-emergent NAb to ranibizumab in Study GX28228 was low: 2 of 58 patients (3.45%), 1 of 62 patients (1.61%), 2 of 59 patients (3.39%), 5 of 179 patients (2.79%), and 0 of 41 patients (0%) in the PDS 10, 40, 100 mg/mL arms, and in all PDS arms combined, and intravitreal arm, respectively.

Study GR40548

ADA

For patients enrolled in Phase III Study GR40548, the median number of intravitreal ranibizumab injections in the study eye prior to first study treatment was 4 injections (Figure 1 in Primary CSR Study GR40548), with a median of 4 injections (Figure 1 in Primary CSR Study GR40548). In addition, 20.2% and 11.4% of patients received at least 1 intravitreal ranibizumab injection in the fellow eye during the 9 months prior to first study treatment.

Despite this prior treatment, the baseline prevalence for ADAs to ranibizumab was low, with 5 of 243 patients (2.1%) and 8 of 162 patients (4.9%) in the PDS 100 mg/mL arm and intravitreal ranibizumab 0.5 mg arm, respectively (Table 5).

The overall mean time on study was 80.0 weeks in the PDS 100 mg/mL arm and 78.5 weeks in the intravitreal arm through the CCOD (11 September 2020 CCOD). Based on this CCOD, incidence of treatment emergent ADA to ranibizumab was 29 of 247 patients (11.7%) and 10 of 165 patients (6.1%) in the PDS 100 mg/mL arm and intravitreal ranibizumab 0.5 mg arm, respectively (Table 5).

Nabs

The baseline prevalence and incidence of treatment-emergent NAbs to ranibizumab are provided in Table 7. The overall baseline prevalence for NAbs to ranibizumab was low, with 1 of 243 patients, and 2 of 162 baseline-evaluable patients in the PDS 100 mg/mL arm and intravitreal arm, respectively.

Overall, the incidence of treatment-emergent NAb to ranibizumab in Study GR40548 was low: 13 of 247 patients (5.3%) in the PDS 100 mg/mL arm, and 4 of 165 patients (2.4%) in the intravitreal arm.

Potential Impact of ADA on Safety

There were no major differences in the ocular or non-ocular adverse event (AE) profiles between ADA-positive patients in PDS 100 mg/mL arm and ADA-positive patients in intravitreal arm (Primary CSR Study GR40548 Section 8.3). However, the low number of patients with a positive ADA response precludes firm conclusions. As immunogenicity to intravitreally administered recombinant therapeutics may result in development of intraocular inflammation, summaries of intraocular inflammation by ADA and NAb status were performed (Table 9).

Table 9 Summary of Intraocular Inflammation in Study Eye by ADA and NAb Status

Study GR40548 (CCOD: 11 Sept 2020)				
	PDS 100 mg/mL Arm (N = 247)		Intravitreal Arm (N = 165)	
	Through 37 days	Day 38 to Day 294	Through 37 days	Day 38 to Day 294
ADA Negative				
# of Patients with intraocular inflammation/ADA Negative patients (%)	49/213 (23.0%)	12/213 (5.6%)	1/149 (0.7%)	0
ADA Positive				
# of Patients with intraocular inflammation/ADA Positive patients (%)	8/34 (23.5%)	1/34 (2.9%)	0	0
NAb Negative				
# of Patients with intraocular inflammation/NAb Negative patients (%)	4/18 (22.2%)	1/18 (5.6%)	0	0
NAb Positive				
# of Patients with intraocular inflammation/NAb Positive patients (%)	3/14 (21.4%)	0	0	0

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies needed due to extremely low systemic exposure after implantation.

Discontinuation due to AES

Type and frequency of discontinuation due to AEs/SAEs has been discussed in subsections "Adverse Events" and "Serious Adverse Events".

Post marketing experience

The PDS has not approved in the US on 22 Oct 2021 and there are limited post-marketing data available to date.

3.3.8. Discussion on clinical safety

The intravitreal use of ranibizumab (Lucentis) is well established and the safety profile of intravitreal injections is well known. Known risks of intravitreal ranibizumab use include increased intraocular pressure, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, and eye irritation.

Susvimo is an innovative drug-device combination for continuous delivery of ranibizumab via an implanted port delivery system (PDS). Due to procedural risks of the surgical implantation as well as of the 6-monthly refill-exchange procedures, and due to potential differences in drug-exposure, the safety profile could substantially differ from the safety profile of conventional intravitreal ranibizumab injections.

The safety analyses for Susvimo are based on the following three studies: the pivotal Phase III Study GR40548 (Archway; PDS 100 mg/mL, refill-exchanged Q24W vs. intravitreal ranibizumab 0.5 mg injections Q4W; ongoing), Phase II dose-finding Study GX28228 (Ladder; PDS 10 mg/mL, refill-exchanged PRN, PDS 40 mg/mL, refill-exchanged PRN, PDS 100 mg/mL, refill-exchanged PRN vs. intravitreal ranibizumab 0.5 mg injections Q4W), and Phase III open-label extension Study GR40549 (Portal; PDS 100 mg/mL, refill-exchanged Q24W; ongoing).

Safety data for pooled safety data analyses were collected through the CCOD of 11 September 2020. For the pooled analyses, 2 populations were defined: For the analysis of ocular AESIs, the All PDS 100 mg/mL Population was analyzed as this population most closely resembles the expected post-marketing conditions. For discussion of specific aspects of PDS-related surgery and procedures, where the ranibizumab dose is not significant (intraocular inflammation, refill exchange, and implant removal), the All PDS Population was analyzed.

Exposure

The safety database comprises a total of n = 450 patients with nAMD. Hereof, 443 patients received the target dose of PDS 100 mg, of which 299 (67.5%) were treated for at least 1.5 years. 288 (65.0%) of patients in the target group received a total of 4 study treatments (implantation plus refill). In the All PDS Population 312 (69.3%) were treated for at least 1.5 years, with 218 patients (48.4%) receiving 4 study treatments. The maximum duration of exposure was ~4.3 years, and the mean duration of exposure was 1.77 years. The comparator group (intravitreal ranibizumab injection, 0.5 mg Q4w) comprises n = 208 patients.

Based on the requirements for drug exposure as specified in ICH E1, the safety database as of 11 September 2020 provided is sufficient. The number of patients treated for at least 1.5 years and of patients receiving at least 4 treatment cycles (implantation + refill) allows for a meaningful assessment.

Overall, the safety data for PDS ranibizumab in the targeted population is considered adequate taking into account that the safety profile of intravitreal ranibizumab for the treatment of nAMD is well established. However, the PDS entails a new pattern of administration of ranibizumab (it continuously releases ranibizumab over the refill interval at steady concentrations) so that the available safety data may be insufficient for addressing new, infrequent, ocular and non-ocular risks. In addition, limited long-term data are available, since only 62 patients (14.0%) in the All PDS 100 mg/ml population had >2 years of exposure. Therefore, long-term safety should be included in the RMP as missing information. In response to the Day 120 LoQ the Applicant agreed to include "long-term safety" as missing information in the RMP.

Demographics

The median age of patients was 75.2 years (range: 51–96 years), the majority of patients were either in the age group of 65– < 75 years (136/443 [30.7%]) or 75– < 85 years (202/443 [45.6%]), and White (430/443 [97.1%]). There was a higher proportion of women (267/443 [60.3%]) compared to men. The safety population is therefore considered representative for the group of patients to be treated in a real world setting.

Adverse events

Ocular Safety in Study Eye

The overall number of ocular AEs in the study eye was significantly higher across all PDS arms compared to the intravitreal control group. Based on safety results from study GR 40548, the overall number of ocular AEs in the study eye was almost twice as high in the PDS 100 mg Arm (96.4%) compared to the Intravitreal Arm (49.1%). The majority of events had an onset before week 40 in the PDS Arm, while events were almost equally distributed (before/after week 40) in the Intravitreal Ranibizumab Arm. From Week 40 through CCOD the incidence of ocular AEs in the study eye were similar in the PDS 100 mg Arm and the Intravitreal Arm.

The greatest imbalance was found for conjunctival haemorrhage, conjunctival hyperaemia, and iritis, which occurred with much higher frequency in the PDS Arm than in the Intravitreal Arm. Nearly all of these cases occurred before week 40 and might hence be attributed to the PDS implantation or to the first refill-exchange procedure.

The same picture was found for study GX28228 (92.7% ocular AEs in the PDS arms vs 63.4% in the intravitreal arm). In the first 10 months, ocular AEs in the study eye were found more than twice as often in the PDS Arms compared with the Intravitreal Arm. The incidence of ocular AEs was similar across all PDS Arms, irrespective of the dose administered. This also contributes to the assumption that the imbalance in ocular AEs between the PDS Arms and the Intravitreal Arm was mainly driven by the implantation and refill procedure itself. Analyses of the number of AEs caused by the implant during the first 10 months revealed that approximately 88 % of patients experienced at least one adverse event caused by the implant. After the postoperative period (up to day 37 after implant insertion), the rates of ocular AEs were similar in the PDS arms and intravitreal arms. While the number of AEs considered caused by implant were in the range of 80-95% across PDS arms, the number of AEs considered caused by refill was in a range of 5.2%-12% (8.4% for the All PDS Population).

Similar to study GR 40548, in study GX28228 the greatest incidence was found for conjunctival haemorrhage, conjunctival hyperemia, eye pain, vitreous floaters, iritis, eye irritation, foreign body sensation in eyes, and vitreous haemorrhage.

The imbalance in ocular AEs has been explained by the Applicant in the context of the ocular surgical procedure performed in the PDS arms. But the differences cannot be totally explained in the context of the ocular surgical procedure because they were also observed beyond the postoperative period. In study GR40548, 38.3% of PDS-treated patients reported at least one ocular AE with onset after 37 days vs 28.7% of intravitreal patients. Similarly, 31.5% vs 26.9% reported AEs at least one ocular AE with onset after Week 40.

It can therefore be concluded that the implantation procedure itself seems to be associated with a relatively high number of typical complications. However, the number of AEs during the refill phase, although more in the range of AEs seen with the conventional intravitreal injection of ranibizumab, was still slightly increased.

In conclusion, the PDS represents a novel way to deliver ranibizumab to the vitreous that involves surgical implantation (and implant removal if required) as well as refill-exchange. The surgical and

medical procedures entail their own inherent risks, which are combined with the risks associated with ranibizumab. The need of training and fulfilment of the procedural requisites appears mandatory from the safety point of view.

As requested in the D120 JAR, the Applicant provided additional analyses on the timely association of AE with implantation and refill procedures. The timely association analysis for studies GR40548 and GX28228 supports the Applicant's statement that differences in the safety profile of ranibizumab administration via PDS compared to the application via intravitreal injections are driven by AEs due to the surgical implantation procedure. These AEs occur with close timely association to the implantation procedure and could therefore be monitored well. On the contrary, the subsequent refill-exchange procedures were not associated with a higher risk of AEs, compared to intravitreal injections, but rather led to a lower AE rate within 9 days after the administration. This appears plausible since the intravitreal injection technique requires a deeper and therefore more traumatic penetration of the eye. In this regard, it must be noted that most EU patients will not be treated monthly, but as per PRN which reduces the number of intravitreal injections needed after month 3. The PRN regimen might therefore have led to a lower AE rate. However, data indicate that nAMD patients treated PRN require on average 6-7 intravitreal injections per year (NEnglJMed, 364;20, May 19, 2011), which is more than three times as many interventions as with the PDS. Moreover, efficacy of such PRN regimen compared to the PDS has not been established and a reduced efficacy with PRN seems possible.

Overall, AEs were not significantly impacting visual acuity and were comparable for both groups, PDS and IVT, with the only exception of one patient that had the irreversible vision loss due to sight-threatening necrotising retinitis.

ADA and NAb were found more often in the PDS arms. However, the clinical relevance of this finding appears neglectable, since no correlation with PK, efficacy and safety was found.

Ocular AESI

As of 11 Sept 2020 cut-off date, in study GR40548, more patients in the PDS 100 mg/ml arm had experienced at least one ocular AESI in the study eye compared to the intravitreal arm (22.2% vs 9.0%). The ocular AESIs in study eye with the highest incidence (≥3%) by PT were cataract (8.1% vs. 4.8%), conjunctival bleb/conjunctival filtering bleb leak (6.9% vs 0), vitreous haemorrhage (6.0% vs 3.6%), conjunctival erosion (2.4% vs 0), conjunctival retraction (2.0% vs. 0) and endophthalmitis (1.6% vs 0.6%), which occurred in a higher proportion of subjects in the PDS 100 mg/ml arm compared to the intravitreal arm.

In the All PDS 100 mg/ml population, 22.1% of patients experienced at least one ocular AESI associated with the PDS implant and procedure, including cataract, vitreous haemorrhage, conjunctival bleb and conjunctival filtering bleb leak, conjunctival erosion, endophthalmitis, conjunctival retraction, hyphema, device dislocation and rhegmatogenous retinal detachment. All the AESIs except cataract and hyphema are covered in sections 4.4 and 4.8 of the SmPC and are included as important identified risks in the RMP. While the Applicant has provided a justification for not including cataract, the reason for not including hyphema has not been provided. The Applicant is asked to clarify this point, since in the All PDS 100 mg/m population 5 patients (1.1%) experienced at least one hyphema AE in the study eye and one of them experienced at least one sight threatening hyphema. The requested justification was provided with the responses to the D120 LoQ. The Applicant adequately justified why hyphema was not included as an important identified risk in the RMP, based on the fact that most of the events were mild or moderate in intensity, occurred in the post-operative period (i.e., up to 37 days after the surgery) and resolved spontaneously within one month. Additionally, the narrative of the patient in study GX28228 who experienced a sight threatening hyphema was provided. This patient presented a moderate

hyphema and increased intraocular pressure (IOP) due to vitreous hemorrhage. The Applicant considers that the clinical assessment of this case is confounded by the multiple concomitant events, as the moderate vitreous hemorrhage may have also contributed to the vision loss that led to the sight-threatening designation of the hyphema event. This justification is considered acceptable.

Ocular Serious Adverse Events

The overall number of ocular SAEs in the study eye is increased across all PDS arms. The majority of events had an onset before week 40 in the PDS Arms.

The highest incidence was found for endophthalmitis, conjunctival erosion, device dislocation, conjunctival retraction, rhegmatogenous retinal detachment, visual acuity reduced, and vitreous hemorrhage. The majority of cases occurred before week 40 and might hence be attributed to the PDS implantation or to the first refill-exchange procedure.

Non-Ocular Adverse Events

More patients experienced APTC in the PDS arms compared to the intravitreal arms in study GX28228 (6.7% vs 0) and study GR40548 (2.4% vs 1.2%). Since the vitreous concentrations are expected to be continuously higher than the minimum concentration after monthly ranibizumab, an increased risk of systemic AEs related to continuous exposure to ranibizumab (absence of through-levels) cannot be excluded and this seems to be the trend in the clinical trials.

The data presented in response to the Day 120 LoQ shows that overall, APTC events were more than twice more frequent in the PDS 100 mg/mL patients from studies GR40548 and GX28228 compared to intravitreal ranibizumab from the same studies. In addition, a theoretical risk of systemic adverse events exists for anti-VEGF drugs administered by intravitreal route, as stated in the SmPC of other intravitreal anti-VEGF medicinal products. This issue should be addressed by adding a warning in section 4.4 of the SmPC, and information about product-class-related adverse reactions in section 4.8 of the SmPC, in line with the Product Information of other anti-VEGF drugs administered by intravitreal route, including Lucentis, Eylea and Beovu. Furthermore, the information in section 4.8 should include the comparative data of All PDS 100 mg/ml versus All intravitreal shown in Table 1 ("Anti-Platelet Trialists Collaboration Events through 12 March 2021 or End of Study; Protocol GX28228, GR40548"). **(LoI)**

Non-Ocular Serious Adverse Events

98 patients (22.1%) in the All PDS 100 mg/mL population experienced at least one other (non-fatal) non-ocular SAE. Non-ocular SAEs with the highest incidence (≥4 patients) by PT were pneumonia, urinary tract infection, osteoarthritis, and cerebrovascular accident, sepsis and hip fracture. Two serious COVID-19 cases had occurred. Both cases had resolved, and 1 pneumonia case was associated with COVID-19. No pattern of non-ocular AEs or association with PDS implantation has been found.

The incidence of non-ocular SAEs was higher in the PDS arms compared to the intravitreal arm (21.8% vs 16.2% in study GR40548 and 20.7% vs 9.8% in study GX28228, respectively). In studies GR40548 and GX28228, more patients in the PDS arms compared to the intravitreal arm experienced a SAE of cerebrovascular accident (1.2% vs 0.6% and 1.7% vs 0, respectively). Since the vitreous concentrations are expected to be continuously higher than the minimum concentration after monthly ranibizumab, an increased risk of systemic SAEs related to continuous exposure to ranibizumab (absence of through-levels) cannot be excluded and this seems to be the trend in the clinical trials.

It can therefore be concluded that non-ocular SAEs were found more often in the PDS arms of the studies (21.4% vs. 17.3%). However, whether there is a causality with differences in the route and mode of administration is not clear yet. A post-marketing observation strategy appears most suitable to further evaluate this finding.

Deaths

As of 11 September 2020, a total of 11 deaths were reported in the All PDS population. The causes of death in the GX28228 PDS 10/40 mg/mL group were sepsis (1 patient), metabolic acidosis (1 patient), myocardial infarction (1 patient), and anaphylactic shock and cardiac arrest (1 patient; both events in same patient).

The causes of death in the GX28228 PDS 100 mg/mL group were cardiogenic shock, myocardial infarction, and acute respiratory failure (1 patient; all three events in same patient) and pancreatic carcinoma (1 patient). There was 1 death in the intravitreal arm (cause of death, congestive heart failure).

The causes of death in the GR40548 PDS 100 mg/mL group were coronary artery disease (1 patient), death (unexplained death; 1 patient), road traffic accident (1 patient), and acute respiratory failure (1 patient). In the intravitreal arm 2 deaths were reported: non-small lung cancer (1 patient) and cardiac arrest (1 patient). No deaths were considered related to the implant (including implant, implant procedure, or initial fill needle), intravitreal injection procedure, or study drug by the investigator.

Laboratory findings and Vital signs

General chemistry, hematology, and urinalysis laboratory results were collected as part of screening eligibility only. No general summary was generated. Vital signs were collected as part of screening eligibility, explant visit, and at study termination visit only. Therefore, vital signs results were reviewed by the Sponsor on an individual patient basis. No aggregate data summaries or shift tables are provided for vital signs.

The systemic exposure of ranibizumab after intravitreal administration is extremely low and no direct effects on laboratory parameters or on vital signs are expected based on current knowledge on ranibizumab's PK/PD and adverse effect profile. The lack of systematic laboratory evaluation and regular measurement of vital signs is therefore acceptable.

Safety in special populations

The Applicant provides safety data for ocular adverse events in the "All PDS 100 mg/mL Population" analysed by specific age groups (<65, 65-74, and ≥75) and gender (female/male). Subgroup analyses by Race/ethnicity were not performed because over 90% of subjects were white with non-Hispanic origin. Data by age strata does not indicate an increase in AEs with age. On the opposite, AESI were found more often in the age strata < 65 years. The Applicant argues that this finding could be due to the low number of participants in this age group, and due to the fact that 96 patients were from the prior 10/40 mg/mL arm of Study GX28228. The adverse events (AEs) reported from the time of implantation with 10/40 mg/mL PDS until the first refill-exchange procedure with 100 mg/mL in Study GR40549 were not included in the analyses because these patients were not receiving PDS 100 mg/mL at that time of AE occurrence. These patients in the 10/40 mg/mL arm of Study GX28228 were older on average than patients in the 100 mg/mL arm of Study GX28228 (76.4 years vs 74.0 years) and the PDS arm of Study GR40548 (76.4 years vs 75.2 years) and this might have biased the analyses. The Applicant also clarifies that ocular AESIs were mainly driven by the occurrence of cataract (both, in the treatment and in the non-treatment eye), which is an ocular AESIs suspected by the Investigator to be caused by implant. As stated above, implant-related procedures that had occurred in the 10/40 mg/mL arm of Study GX28228 prior to receiving 100 mg/mL were not included into the All PDS 100 mg/mL Population safety analyses. These factors in combination might indeed have led to an underreporting of implant-procedure related AEs in the older age strata.

No data have been collected on the safety of Susvimo in pregnancy and during lactation. Due to ranibizumab's mechanism of action, the Applicant states that Susvimo must be regarded as potentially teratogenic and embryo-/fetotoxic. Susvimo may also be excreted in human milk. Respective wording has hence been included into section 4.6, including a statement that the implant may be flushed with saline using a refill needle should the patient become pregnant. This is agreed. The wording regarding pregnancy and breastfeeding in section 4.6 in the SmPC is largely aligned with the approved wording for Lucentis. This is agreed.

The lack of data in pregnant and breastfeeding women is not considered relevant since this product is only intended for use in nAMD patients and elderly patients are the relevant population in this indication. However, this information would be important in case the PDS were to be used in other indications that are already authorised for Lucentis, such as diabetic macular oedema, proliferative diabetic retinopathy or choroidal neovascularisation secondary to pathologic myopia. No clinical studies of PDS ranibizumab in patients with renal or hepatic impairment have been performed. A population pharmacokinetic analyses of nAMD patients with PDS ranibizumab showed that systemic clearance of ranibizumab was slightly lower in renally impaired patients but was not clinically significant. No dose adjustment is considered necessary in patients with hepatic impairment because systemic exposure is negligible; this is supported.

Immunological events

The immunogenicity analysis population consisted of all treated patients with at least one ADA assessment. Patients were grouped according to treatment received. There were no major differences in the ocular or non-ocular adverse event (AE) profiles between ADA-positive patients in PDS 100 mg/mL arm and ADA-positive patients in intravitreal arm, but the incidence of treatment-emergent ADAs and Nabs to ranibizumab administered via the PDS (100 mg/mL) in studies GX28228 and GR40548 was higher than that reported for intravitreal ranibizumab treatment: 15.3% vs 14.6% in study GX28228 and 11.7% vs 6.1% in study GR40548 for treatment-emergent ADAs and 3.39% vs 0% in study GX28228 and 5.3% vs 2.4% in study GR40548 for Nabs. Intraocular inflammation occurred with similar frequency in ADA positive and ADA negative patients. Intraocular inflammation was therefore most likely related to the surgical and treatment procedure itself rather than to an immunogenic reaction. This assumption is also supported by the consistently and significantly higher number of intraocular inflammation in the PDS Arm compared to the Intravitreal Arm, irrespective of ADA status.

Overall, the occurrence of ADAs (including NAbs) to ranibizumab did not result in any clinically meaningful consequences with respect to safety.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies needed due to extremely low systemic exposure after implantation.

Postmarketing data

The PDS has been approved fin the US on 22 Oct 2021. There are limited post-marketing data available to date.

3.3.9. Conclusions on clinical safety

The clinical safety profile of Susvimo in the treatment of nAMD is obtained from n= 443 evaluable patients, hereof 10.6% with >3 years of follow-up. As of CCOD, approximately 783 patients years of safety data (1.7 years mean follow-up time) in the All PDS 100 mg/mL Population is available.

The safety database for PDS ranibizumab in the targeted population is considered adequate considering that the safety profile of intravitreal ranibizumab for the treatment of nAMD is well established. However, the PDS entails a new pattern of administration of ranibizumab (it continuously releases ranibizumab

over the refill interval at steady concentrations) so that the available safety database may be insufficient for addressing new, infrequent, ocular and non-ocular risks. In addition, limited long-term data are available and as requested, long-term safety has been included in the RMP as missing information.

The safety profile of Susvimo mainly resembles the type of adverse events known from intravitreal ranibizumab injections (Lucentis). However, in the controlled study periods, the overall number of ocular AEs/SAEs in the study eye was almost twice as high in the PDS 100 mg Arm (96.4%) compared to the Intravitreal Arm (49.1%). The greatest imbalance was found for conjunctival haemorrhage, conjunctival hyperaemia, and iritis, which occurred with much higher frequency in the PDS Arm than in the Intravitreal Arm. Nearly all of these cases occurred before week 40 and might hence be attributed to the PDS implantation or to the first refill-exchange procedure. The same picture was found for study GX28228. In the first 10 months, ocular AEs in the study eye were found more than twice as often in the PDS Arms compared with the Intravitreal Arm. The incidence of ocular AEs/SAEs was similar across all PDS Arms, irrespective of the dose administered. This contributes to the assumption that the imbalance in ocular AEs between the PDS Arms and the Intravitreal Arm was mainly driven by the implantation and refill procedure itself. Analyses of the number of AEs caused by the implant during the first 10 months revealed that approximately 88 % of patients experienced at least one adverse event caused by implant. After the postoperative period (up to day 37 after implant insertion), the rates of ocular AEs were similar in the PDS arms and intravitreal arms.

While the number of AEs considered caused by implant were in the range of 80-95% across PDS arms, the number of AEs considered caused by refill was in a range of 5.2%-12% (8.4% for the All PDS Population). Similar to study GR 40548, the greatest incidence was found for conjunctival haemorrhage, conjunctival hyperemia, eye pain, vitreous floaters, iritis, eye irritation, foreign body sensation in eyes, and vitreous haemorrhage.

It can therefore be concluded that the implantation procedure itself seems to be associated with a relatively high number of typical complications, while the number of AEs caused by refill might be more in the range of AEs seen with the conventional intravitreal injection of ranibizumab.

Whereas a theoretical risk of systemic adverse events exists for anti-VEGF drugs administered by intravitreal route (as stated in the SmPC of other intravitreal anti-VEGF medicinal products), systemic adverse events and in particular APTC events (defined as non-fatal stroke adverse events, non-fatal myocardial infarction adverse events, or vascular death [including deaths of unknown cause]) were more than twice more frequent in the PDS 100 mg/mL patients compared to intravitreal ranibizumab. Thus, an increased risk of systemic adverse events when treating patients with Susvimo cannot be excluded and should be taken into consideration for the assessment of the overall benefit risk balance and the selection of patients eligible for treatment with Susvimo, albeit it is noticed that systemic exposure seems to be not increased with the PDS compared to monthly intravitreal injections.

In conclusion, available safety data show that a higher proportion of patients in the PDS arms experienced ocular AEs in the study eye compared with patients in the intravitreal arm. This could be understood in the context of the ocular surgical procedure performed in the PDS arms. Differences favouring intravitreal treatment were also observed for non-ocular events. The reason for this imbalance is not clear yet, since the systemic ranibizumab exposure does not appear to be increased with the PDS, and therefore requires further investigation in the context of post-authorisation evaluations. Such PASS should also include the assessment of the safety of bilateral PDS implantation. (**OC**).

Furthermore, a safety memo concerning Susvimo, specifically related to the dislodgement of the septum of the port delivery system observed during clinical trials, was received from the Applicant. The reported septum dislodgement might have a major impact on the benefit/risk of Susvimo in terms of product quality within the implant and/or release of the drug product from the implant, and on clinical efficacy and safety (**Multidisciplinary MO**).

3.3.10. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, device dislocation)
Important potential risks	Implant damage during the PDS procedures
Missing information	Implant removal-related risks Long-term safety

3.3.11. Discussion on safety specification

The AEs listed as important for inclusion in the List of Safety Concerns (Vitreous Hemorrhage, Conjunctival Bleb/Bleb Leak, Conjunctival Erosion, Conjunctival Retraction, Endophthalmitis, Rhegmatogenous Retinal Detachment, Device Dislocation) were observed with significant higher incidence in the PDS Arms compared to the intravitreal ranibizumab arms. All of these AEs require prompt identification and an evaluation of the need of treatment in order to prevent patients from potentially long-term vision impairment.

As requested in the D120 LoQ, long-term safety was included as missing information in the RMP. Moreover, the following should be added as important identified/potential risks: retinal tear, intraocular pressure increase, intraocular inflammation, traumatic cataract.

3.3.12. Conclusions on the safety specification

The proposed safety specifications are considered acceptable. However, due to ongoing unresolved issues the public summary has to be further revised, and additional AEs need to be listed as safety concerns (**OC**).

3.3.13. Pharmacovigilance plan

The applicant proposes routine and additional pharmacovigilance activities to monitor the safety concerns.

The proposed routine pharmacovigilance activity beyond adverse reactions reporting and signal detection is a specific follow-up questionnaire related to the safety concerns.

The applicant describes the purpose of the follow-up questionnaire as to ensure the adequate follow-up of post-marketing case reports and the robust collection of all the appropriate information deemed necessary to further characterize the safety concerns associated with the PDS.

It can be agreed on such a questionnaire aimed at collecting specific device/procedure-related information. The questionnaire is however quite long and will require considerable attention by the medical practitioner but has been somewhat edited by the applicant. Information whether additional surgical correction took place should be added in the questionnaire (OC).

Depending on outcomes of the procedure, additional aspects may need to be addressed here.

Additional pharmacovigilance activities

In addition to the routine pharmacovigilance activities, two post-authorization safety studies are proposed by the applicant:

- A prospective, observational, post marketing surveillance study (GR43341; Villa) to monitor the safety of the PDS in the post-marketing setting, including the evaluation of the important identified risks, the important potential risks and the missing information associated with the PDS. This will allow for relevant safety data to be collected in a prospective manner and will ensure the provision of relevant updates in this RMP.

- A long-term extension study (GR40549; Portal) where patients from the parent studies are being followed up for additional safety data collection. The duration of this study will allow for collection, in Study GR40549, of a total of 5 years of follow-up safety data for patients from Studies GX28228 (Ladder) and GR40548 (Archway), starting with the date of study rollover.

Study GR43341 (Villa)

Study/activity short name and title: Study GR43341 (Villa): A Prospective, Observational, Post-Marketing Surveillance Study to Monitor Safety of PDS in Patients with nAMD
Rationale and study objectives: The purpose of this study is to further monitor the safety of patients treated with PDS in the post-marketing setting, including the evaluation of the important identified risks, important potential risks and the missing information associated with the PDS. This study will prospectively and systematically collect safety data in patients with nAMD treated with PDS in clinical practice. The objective of this study is to evaluate safety and tolerability of the PDS in patients with nAMD in the post-marketing setting, including further characterizing: • The risk of PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, device dislocation) • The risk of implant damage during the PDS procedures • The missing information on implant-removal related risks • The missing information on long term safety
Study design: A single-arm, prospective, multi-center, observational, longitudinal study
Study populations: nAMD patients treated with PDS in the post-marketing setting
Milestones: Final report: Q4 2030

nAMD = neovascular age-related macular degeneration; PDS = Port Delivery System with ranibizumab.

Study GR40549 (Portal)

Study/activity short name and title: Study GR40549 (Portal): A Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of the PDS in Patients with nAMD
Rationale and study objectives: The objective of this study is to evaluate the long-term safety and tolerability of the PDS (100 mg/mL) in patients with nAMD, including further characterizing: ● The risk of PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, device dislocation) ● The risk of implant damage during the PDS procedures ● The missing information on implant-removal related risks ● The missing information on long-term safety
Study design: This is a global, multicenter, open-label, visual assessor-masked, multiple-cohort extension study designed to evaluate the long-term safety and tolerability of ranibizumab 100 mg/mL delivered via the PDS, with refill-exchanges administered Q24W or Q36W to patients who elect to enroll in the extension study from the parent studies.
Study populations: Patients with nAMD who have either completed Phase II Study GX28228 (Ladder), Phase III Study GR40548 (Archway), Phase IIIb Study WR42221 (Velodrome), or completed Week 24 visit in Study WR42221 but were not eligible to be randomized. Patients rolled over from Study GX28228 (Ladder) and Study GR40548 (Archway) are followed up to allow the collection of 5 years of safety data.
Milestones: Clinical Study Report corresponding to the LPLV for the GX28228 (Ladder) and GR40548 (Archway) cohorts in Study GR40549 (Portal): Q1 2027

LPLV = last patient last visit; nAMD = neovascular age-related macular degeneration; PDS = Port Delivery System with ranibizumab.

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Study GR43341, (Villa): A Prospective, Observational, Post-Marketing Surveillance Study to Monitor Safety of	To evaluate safety and tolerability of the PDS in patients with nAMD in postmarketing setting.	· PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal	Final report	Q4 2030

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
PDS In Patients with nAMD		detachment, device dislocation) · Implant damage during the PDS procedures · Implant-removal related risks · Long term safety		
Study GR40549 (Portal): A Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of the PDS in Patients with nAMD	To evaluate the long-term safety and tolerability of the PDS in patients with nAMD	· PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, device dislocation) · Implant damage during the PDS procedures · Implant-removal related risks · Long term safety	Clinical Study Report corresponding to the LPLV for the GX28228 (Ladder) and GR40548 (Archway) cohorts in Study GR40549 (Portal)	Q1 2027

CHMP = Committee for Medicinal Products for Human Use; nAMD = neovascular age-related macular degeneration; LPLV = last patient last visit; NCA = National Competent Authority; PDS = Port Delivery System with ranibizumab; PRAC = Pharmacovigilance Risk Assessment Committee; TBD = to be decided.

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan may be sufficient to identify and characterise the risks of the product.

Nevertheless, while it can be agreed on the need for the proposed follow-up questionnaire (FUQ) related to the safety concerns and aimed at collecting specific device/procedure-related information the questionnaire is quite long and will require considerable attention by the medical practitioner. It has been somewhat edited, but the applicant should look into making it as focussed as possible. Information whether additional surgical correction took place should be added in the questionnaire.

Furthermore, the design of the proposed observational PASS is still not accepted. It is welcomed that the Applicant has initiated discussions with several existing data sources, to be able to collect key safety data for this new application form. The Applicant should put all efforts in proceeding with these

developments. An update should be provided, with preferably a study synopsis. Furthermore, a proper feasibility assessment should be provided, based on at least one or more of relevant existing data sources, and taking the comments in the Day 150 Joint CHMP and PRAC Response Assessment Report into account.

The applicant has added a long-term extension of ongoing clinical trials, as another category three study. This is endorsed.

Plans for post-authorisation efficacy studies

Summary of Post authorisation efficacy development plan

There are no post-authorisation efficacy studies proposed which is endorsed.

3.3.14. Risk minimisation measures

Routine Risk Minimisation Measures

The description of routine risk minimisation measures is agreed.

There may be the need for further update following the final agreed safety specification and product information.

Additional risk minimisation measures

The applicant is proposing a Physician information pack and patient education material as additional risk minimisation measures. Both are regarded as necessary by the PRAC-Rapporteur and have been edited as requested with some minor own changes by the applicant. The initial PDS surgical training program has been altered to become a Physician information pack because "Surgical training" was not and would have been difficult to be defined in the conditions of annex II and this might have led to confusion over the exact practical meaning of "surgical training". The proposed information pack is acceptable in its current form.

Summary of Physician information pack and patient education material by the applicant

Prior to the launch of Susvimo in each Member State, the Marketing Authorization Holder (MAH) must agree about the content and format of the final educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The MAH shall provide information on implant insertion procedure, implant removal procedure and refill-exchange procedure to ophthalmologists experienced in vitreoretinal surgery, with the aim to establish consistency in following the instructions for use and confidence in the surgical procedures associated with Susvimo. The refill-exchange procedure information will also be provided to ophthalmologists who will perform the refill-exchange procedure for Susvimo. The MAH shall also provide patient educational The MAH shall ensure that, following discussions and agreements with the National Competent Authorities in each Member State where Susvimo is marketed, at launch and after launch, all ophthalmological clinics where Susvimo is expected to be used are provided with an up-to-date physician information pack.

Physician Information Pack

Additional Risk Minimization Measure	Physician Information Pack
Objective(s)	To ensure consistency of the surgical procedure and of outcomes in the post-marketing setting, aiming to minimize the: ● Risk of PDS implant and PDS procedure complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, device dislocation) ● Risk of implant damage during the PDS procedures
Rationale for the additional risk-minimization activity	Treatment with the PDS involves a one-time initial surgical implantation procedure. Subsequent procedures are primarily refill-exchange and potential implant removal if required (in rare cases). It is acknowledged that implantation (and implant removal, if required) of the PDS and refill-exchange have their own inherent risks. While the implant and refill-exchange procedures are generally well tolerated, surgical risks exist and surgeon training is crucial for continued safety. Precision on implant and refill-exchange procedures is a critical success factor and strict adherence to the manufacturer's IFU is essential for prevention of the risks of PDS implant and procedure complications and implant damage during the PDS procedures. The physician information pack is aimed to establish consistency in following the IFU and confidence in the surgical procedures associated with PDS, and the ocular implant In addition, ongoing surgical support tailored to physicians performing the PDS procedures will be made available as needed.

Additional Risk Minimization Measure	Physician Information Pack
Target audience and planned distribution path	Ophthalmologists experienced in vitreoretinal surgery who intend to perform the PDS implant insertion procedure, implant removal procedure and refill-exchange procedure and to ophthalmologists who intend to perform the refill-exchange procedure for PDS.
Plans for evaluating the effectiveness of the interventions and criteria for success	How effectiveness will be measured: ● Measuring and tracking the progress of physician information pack, based on the number of surgeons trained ● Evaluation of the reporting rate of the PDS implant and PDS procedures complications, both through routine pharmacovigilance including spontaneous reporting and through the Prospective, Observational, Post-Marketing Surveillance Study to Assess Safety of PDS in Patients with nAMD (Study Study GR43341; Villa) Milestones for reporting: ● Periodically in PBRERs ● The final report of the Prospective, Observational, Post-Marketing Surveillance Study to Assess Safety of PDS in Patients with nAMD (Study Study GR43341; Villa)

IFU = Instructions for Use; PDS = Port Delivery System with ranibizumab;
nAMD = neovascular age-related macular degeneration; PBRER = Periodic Benefit-Risk

Additional Risk Minimization Measure	Physician Information Pack

Evaluation Report.

The physician information pack will contain the following elements (as also reflected in annex II of the PI):

- Physician information
- Instruction video and pictograms on vitreoretinal surgery and performing the port delivery system (PDS) procedures
- Patient guide
- The physician information will include the following key elements:
- Relevant information from the Summary of Product Characteristics
- Sterile techniques to minimize risk of infection
- Techniques for the vitreoretinal surgery and performing the PDS procedures
- Patient monitoring after the vitreoretinal surgery and the PDS procedures
- Key signs and symptoms of vitreoretinal surgery related adverse events
- Management of adverse events related to vitreoretinal surgery and performing the PDS procedures

Patient Educational Materials

Additional Risk Minimization Measure	Patient Educational Materials
Objective(s)	Patient Education Materials will promote awareness of the information contained within the Susvimo Package Leaflet and the PDS manufacturer's IFU, which are intended to inform patients and their caregivers about the risks and potential adverse events, with the objective to minimize the following risks and their impact on the patients: ● Risk of PDS implant and procedure complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, device dislocation) ● Risk of implant damage during the PDS procedures
Rationale for the additional risk-minimization activity	Patient Educational Materials will enable patient and their caregiver to receive education on the key recommendations to be followed during the treatment with Susvimo (i.e., how to prepare for treatment, steps to follow after treatment), with the aim of minimizing the worsening of adverse reactions relevant to the risks of PDS implant and procedure complications and of implant damage. The Patient Educational Materials will instruct patient and/or caregiver on the early recognition of key signs and symptoms both after the initial implant insertion procedure, following each refill-exchange procedure and for the entire duration of the treatment with

Additional Risk Minimization Measure	Patient Educational Materials
	Susvimo. The intent is that the Patient Education Materials will also encourage patient and/or caregiver to seek immediate treatment by contacting the treating physician in a prompt manner, with the aim of optimizing the time to intervention, appropriate management of the adverse reactions, minimizing the risk of vision loss or further worsening of the adverse reaction, and maximizing recovery potential.
Target audience and planned distribution path	Adult patients with nAMD treated with Susvimo via the PDS implant. Planned distribution path TBD.
Plans for evaluating the effectiveness of the interventions and criteria for success	How effectiveness will be measured: • Measuring and tracking the distribution of the Patient Educational Materials • Evaluating patients' comprehension of the key messages and recommendations of the Patient Educational Materials Milestones for reporting: • Periodically in PBRERs

IFU = Instructions for Use; PDS = Port Delivery System with ranibizumab; nAMD = neovascular age-related macular degeneration; PBRER = Periodic Benefit-Risk Evaluation Report; TBD = to be decided.

The patient guide is provided in written and audio format, and will include the following key elements (as also reflected in annex II of the PI):

- Relevant information from the Patient Information Leaflet
- How to prepare for Susvimo treatment
- What are the steps following treatment with Susvimo
- Key signs and symptoms of serious adverse events including endophthalmitis
- When to seek urgent attention from the health care provider

The Applicant argues that key signs and symptoms of serious adverse events "increased intraocular pressure" and "traumatic cataract" do not need to be covered by the educational material. This is not agreed despite them being 'risks not important for inclusion' in the list of safety concerns in the RMP. The applicant is asked to include "key signs and symptoms of serious adverse events" of "increased intraocular pressure" and "traumatic cataract" in the patient guide.

Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
PDS implant and PDS procedure complications (vitreous	**Routine risk minimization measures:** A description of the complications associated with the implant and/or	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, device dislocation)	implant-related procedures and the interventions potentially needed to adequately manage them in Section 4.4 of the SmPC (Special warnings and precautions for use). Vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, device dislocation in Section 4.8 of the SmPC (Undesirable effects). Recommendation for dose (refill-exchange) interruptions in case of adverse events occurrence included in Section 4.2 of the SmPC (Posology and method of administration). Recommendation to perform the implant insertion and refill-exchange procedure under aseptic conditions as per standard of care and to use adequate anesthesia is included in Section 4.2 of the SmPC (Posology and method of administration). Warning to perform the PDS implant insertion or refill-exchange procedures only in patients that do not have ocular infection or severe systemic infection in Section 4.4 of the SmPC (Special warnings and precautions for use). Strict adherence to the manufacturer's IFU in Section 4.4 of the SmPC (Special warnings and precautions for use).	Follow-up questionnaire **Additional pharmacovigilance activities:** Study GR4331 (Villa) Study GR40549 (Portal)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, device dislocation, cont.)	Recommendation to temporarily interrupt antithrombotics prior to the implant insertion procedure in Section 4.4 of the SmPC (Special warnings and precautions for use). Monitoring and care during the treatment with Susvimo, after the implant insertion procedure, and after the refill procedure in Section 2 of the PIL. Vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment and device dislocation in Section 4 of the PIL.	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Pack size Restricted medical prescription Restriction to perform the PDS implant initial fill and implant insertion, and implant removal procedures by an ophthalmologist experienced in vitreoretinal surgery and trained in the PDS procedures, and restriction to perform the implant refill-exchange procedure by an ophthalmologist trained in the PDS refill-exchange procedures in Section 4.2 of the SmPC. **Additional risk minimization measures:** Physician Information Pack Patient Educational Materials	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Implant damage during the PDS procedures	**Routine risk minimization measures:** Recommendation for dose (refill-exchange) interruptions related to adverse events, including observed damage in Section 4.2 of the SmPC (Posology and method of administration). Strict adherence to the manufacturer's IFU in Section 4.4 of the SmPC (Special warnings and precautions for use). Pack size Restricted medical prescription Restriction to perform the PDS implant initial fill and implant insertion, and implant removal procedures by an ophthalmologist experienced in vitreoretinal surgery and trained in the PDS procedures, and restriction to perform the implant refill-exchange procedure by an ophthalmologist trained in the PDS refill-exchange procedures in Section 4.2 of the SmPC. **Additional risk minimization measures:** Physician Information Pack Patient Educational Materials	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire **Additional pharmacovigilance activities:** Study GR4331 (Villa) Study GR40549 (Portal)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Implant removal-related risks	**Routine risk minimization measures:** Monitoring and care after the implant removal procedure in Section 2 of the PIL. Pack size Restricted medical prescription Restriction to perform the PDS implant initial fill and implant insertion, and implant removal procedures by an ophthalmologist experienced in vitreoretinal surgery and trained in the PDS procedures, and restriction to perform the implant refill-exchange procedure by an ophthalmologist trained in the PDS refill-exchange procedures in Section 4.2 of the SmPC. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire **Additional pharmacovigilance activities:** Study GR4331 (Villa) Study GR40549 (Portal)
Long-term safety	**Routine risk minimization measures:** Strict adherence to the manufacturer's IFU in Section 4.4 of the SmPC (Special warnings and precautions for use). Pack size Restricted medical prescription Restriction to perform the PDS implant initial fill and implant insertion, and implant removal procedures by an ophthalmologist experienced in vitreoretinal surgery and trained in the PDS procedures, and restriction to perform the implant refill-exchange procedure by an ophthalmologist trained in the PDS refill-exchange procedures in Section 4.2 of the SmPC. **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** Study GR4331 (Villa) Study GR40549 (Portal)

IFU = Instructions for Use; PDS = Port Delivery System with ranibizumab; PIL = Patient Information Leaflet; SmPC = Summary of Product Characteristics.

Public summary of the RMP

The public summary of the RMP may require revision based on the comments made throughout the report.

PRAC Outcome

Regarding the safety specification, the PRAC advises CHMP to add the following events to the summary of safety concerns:

Important identified risks: rhegmatogenous retinal detachment and retinal tear; intraocular pressure increase; intraocular inflammation

Important potential risks: traumatic cataract

Regarding the pharmacovigilance and risk minimisation plans, the PRAC endorsed the assessment of the Rapporteur. In particular, the concerns regarding the proposed methodology for the observational PASS were shared by the Committee. Furthermore, the PRAC supported the request to detail the specific safety concerns which are to be included in the educational material for both health care professionals and patients.

Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.2 is not yet acceptable. Details are provided in the Rapporteur assessment report and in the list of questions in section 7 of this overview AR.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, device dislocation, cont.)	Recommendation to perform the implant insertion and refill-exchange procedure under aseptic conditions as per standard of care and to use adequate anesthesia is included in Section 4.4 of the SmPC (Special warnings and precautions for use). Recommendation to temporarily interrupt antithrombotics prior to the implant insertion procedure in Section 4.4 of the SmPC (Special warnings and precautions for use). Monitoring and care during the treatment with Susvimo, after the implant insertion procedure, and after the refill procedure in Section 2 of the PIL. Vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment and device dislocation in Section 4 of the PIL. Restricted medical prescription **Additional risk minimization measures:** The PDS Surgical Training Program Patient Educational Materials	

3.4. Pharmacovigilance system

The Rapporteur considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on a fundamentally new administration form, i.e., an intraocularly implanted port delivery system which constantly releases ranibizumab into the eye and requires six-monthly refills, the PRAC Rapporteur is of the opinion that a separate entry in the EURD list for Susvimo is needed, as it cannot follow the already existing entry for ranibizumab. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date. The new EURD list entry will therefore use the {EBD} to determine the forthcoming Data Lock Points.

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

The target indication applied for by the Applicant is for the treatment of adult patients with neovascular (wet) age-related macular degeneration (AMD).

Age-related macular degeneration (AMD) is a chronic, progressive disease of the macula and a leading cause of central vision loss among people over the age of 50 years. nAMD (also known as choroidal neovascularization [CNV] secondary to AMD and wet AMD) is a form of advanced AMD that, if left untreated, causes rapid and severe visual loss, and remains a leading cause of visual impairment in the elderly.

The currently proposed indication for PDS is:

Susvimo is indicated in adult patients for the treatment of neovascular (wet) age-related macular degeneration (AMD) who have previously responded to at least two intravitreal injections of a vascular endothelial growth factor (VEGF) inhibitor medication".

The indication wording proposed by the Applicant requires further revision. The indication should be restricted to patients who have demonstrated an adequate response to anti-VEGF therapy and a stabilization of the disease's progression. Thus, it is considered mandatory to define responders based on clinical outcome and to incorporate this in the SmPC. Not the number of injections, but rather clinically stable disease, based on ophthalmological judgement, should be a prerequisite for treatment with the PDS. This needs to be reflected in the indication wording, e.g. as follows:

"Susvimo is indicated in adult patients for the treatment of neovascular (wet) age related macular degeneration (AMD) *who have achieved stable disease (see 4.2) after previously responding to intravitreal treatment with a vascular endothelial growth factor (VEGF) inhibitor medication.*"

In addition, in SmPC Section 4.2, „Patient selection", corresponding criteria for stable disease have to be provided. (**MO**)

4.1.2. Available therapies and unmet medical need

Until the introduction of anti-VEGF therapy, patients with nAMD were at high risk of severe vision loss and blindness. Verteporfin photodynamic therapy (PDT) was approved in 2001 to limit the proportion of nAMD patients losing <15 letters compared to placebo. However, this treatment was not able to prevent progressive visual loss secondary to nAMD, and the availability of anti-VEGF therapy has markedly

improved visual outcomes and management of nAMD (Brown et al. 2006; Rosenfeld et al. 2006; Heier et al. 2012). Anti-VEGF agents block the pathophysiological functioning of nAMD by preventing abnormal angiogenesis, and limit fluid build-up in the retina, thereby preserving vision (Rosenfield et al. 2006). Three anti-VEGF agents given via intravitreal route are currently approved for the treatment of nAMD (ranibizumab, aflibercept, and brolucizumab).

As a chronic disease, nAMD requires life-long treatment and assessment. Intravitreal anti-VEGF injection therapy is the globally recognized standard of care treatment for nAMD. Ranibizumab was the first anti-VEGF agent proven to be more efficacious in reducing visual loss and blindness compared to other treatments such as PDT and also to improve and maintain vision when using a monthly regimen as in the FVF2587g ANCHOR study (Brown et al. 2009). After 5 injections and a gain of approximately 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, monthly ranibizumab was able to maintain the gained visual acuity throughout the 24-month duration of the study.

An important challenge for anti-VEGF therapy is the requirement for frequent administration of intravitreal injections and monitoring visits (Heier et al. 2012; CATT Research Group 2016). Indeed, many patients are treated with monthly anti-VEGF injections for nAMD control. Less-than-monthly injection regimens are possible for some patients (i.e. PRN or Treat & Extend); however, they still require frequent eye examinations and office visits to achieve the patient's best visual outcomes.

In addition, some fixed less-than-monthly dosing regimens are not as effective as monthly injections, even with regular assessment (Lucentis USPI). For example, patients enrolled in the FVF3192g PIER study had an initial visual gain after 3 monthly loading doses of ranibizumab; however, this gain was not maintained after switching to quarterly dosing, and patients did not experience any visual gain at month 12 or 24 (Regillo et al. 2008; Abraham et al. 2010).

In recent years, Treat & Extend regimens have been used to reduce the treatment burden of anti-VEGF therapy by extending the interval between intravitreal injections. However, recent real-world data studies have indicated that the mean number of injections per year using this regimen is still high. In a meta-analysis of 42 real-world observational studies published between 2007 and 2015, patients receiving Treat & Extend dosing received an average of 6.9 injections per year (Kim et al. 2016). Similarly, a retrospective review of electronic medical records of patients with nAMD in the United States showed after 6, 12, and 24 months of follow-up, patients received means of 5.4, 7.3, and 12.1 injections, respectively (Ciulla et al. 2018).

While accepting that the Treat & Extend regimen still means a relevant number of injections/monitoring for patients, it should be noted that there are several published studies (Fallico M et al, Eur J Ophthalmol 2020; Wykoff CC et al, Am Acad Ophthalmol 2016; Silva R et al, Am Acad Ophthalmol 2017) supporting the non-inferiority of the T-E regimen vs the monthly regimen of anti VEGF therapy (both from the efficacy and the safety point of view).

4.1.3. Main clinical studies

Clinical evidence supporting the marketing authorisation application is primarily based on the ongoing pivotal Phase III clinical study (GR40548/ Archway) investigating the efficacy, safety and pharmacokinetics of the PDS 100 mg/mL Q24W (n=251) compared to IVT ranibizumab 0.5 mg Q4W (n=167) in patients with wet AMD responsive to anti-VEGF with maximum 9 months since diagnosis, having received at least 4 prior anti-VEGF injections (the last one being ranibizumab).

4.2. Favourable effects

The pivotal study GR40548 met its primary endpoint - equivalence and non-inferiority in terms of efficacy have been demonstrated for the PDS 100 mg/mL arm (Q24W) compared to IVT ranibizumab 0.5 mg

Q4W, as measured by the change from baseline in BCVA at the average of Week 36 and Week 40. The difference in adjusted means between the treatment arms was -0.3 letters (95% CI -1.7, 1.1), which fell into the pre-specified margin of ±4.5 letters.

This was supported by sensitivity analyses in the PP population as well as by supplemental analyses for the primary endpoint (trimmed mean analysis, MMRM model using different rules for measures after intercurrent events), which were all consistent with the primary analysis.

In addition, the key secondary endpoints, which had been requested by EMA, were met: Non-inferiority of the PDS 100 mg/mL Q24W regimen to the IVT ranibizumab 0.5 mg Q4W regimen was also demonstrated when using a NI margin of 3.9 letters for the change from baseline in BCVA at the average of Week 36 and Week 40, as well as at the average of Week 44 and Week 48 (difference in adjusted means of -0.2 [95% CI -1.8, 1.3]). Supplemental analyses and sensitivity analyses further supported the robustness of the findings for this key secondary endpoint.

Subgroup analyses for the primary EP, the mean change from baseline in BCVA score averaged over Wk 36 and Wk 40, for the subgroups age, sex, number of prior anti-VEGF injections and baseline BCVA score were overall consistent with the primary endpoint analysis.

In addition, the results for the secondary efficacy visual and anatomical endpoints supported that PDS 100 mg/mL Q24W was similar to the intravitreal ranibizumab 0.5 mg Q4W.

Patients in the PDS arm received considerably fewer treatment interventions than the patients in the intravitreal arm (mean of approximately 2 vs 11 at Week 40). This is of clinical relevance for the target population, since the requirement of frequent anti-VEGF IVT injections and follow-up visits in order to achieve and maintain improved visual acuity poses a burden on patients with nAMD. Thus, the unmet medical need for reduced treatment burden in the nAMD indication is overall acknowledged.

In addition, it has to be kept in mind that although currently used IVT anti-VEGF regimens are highly effective when administered in the controlled clinical trial setting, suboptimal outcomes are observed in clinical practice, due to non-adherence of patients to the currently established treatment regimen requiring numerous treatment visits and injections per year.

Patients with the PDS achieved and maintained improved visual and anatomic outcomes with fewer treatment interventions with the majority of patients (299/443 [67.5%]) in the All PDS 100 mg/mL population with at least 1.5 years of exposure and follow up.

4.3. Uncertainties and limitations about favourable effects

Despite similar efficacy compared to monthly ranibizumab IVT that could be shown in the pivotal trial in terms of primary and secondary endpoints, there are several remaining issues including the proposed indication wording requiring revision, clarification and further data analyses before a final conclusion can be drawn.

Among others, the appropriateness of the Q24W regimen should be balanced against the PDS-associated risks in comparison with other regimens.

With regard to the proposed indication wording, the indication should be restricted to patients who have demonstrated an adequate response to anti-VEGF therapy and a stabilization of the disease's progression. Thus, it is considered mandatory to define responders based on clinical outcome and to incorporate this in the SmPC. Not the number of injections, but rather clinically stable disease, based on ophthalmological judgement, should be a prerequisite for treatment with the PDS. This needs to be reflected in the indication wording, e.g. as follows:

"Susvimo is indicated in adult patients for the treatment of neovascular (wet) age related macular degeneration (AMD) *who have achieved stable disease (see 4.2) after previously responding to intravitreal treatment with a vascular endothelial growth factor (VEGF) inhibitor medication.*"

In addition, in SmPC Section 4.2, „Patient selection", corresponding criteria for stable disease have to be provided. (**MO**)

4.4. Unfavourable effects

The PDS safety profile takes into account not only the known ranibizumab risks applicable to the PDS, but also specific aspects related to the surgical implantation procedure and subsequent procedures (refill-exchanges and implant removal, if medically required).

The unfavourable effects identified for Susvimo 100 mg/mL mainly correspond to the already well known **ocular adverse effects**/ serious adverse effects of intravitreal ranibizumab injections. These include (ordered by frequency): conjunctival haemorrhage (53.7%), conjunctival hyperemia (22.1%), iritis (15.1 %), eye pain (12.0%), cataract (10.2%), vitreous haemorrhage (5.2%), conjunctival bleb/conjunctival filtering bleb leak (4.7%), conjunctival erosion (3.6%), conjunctival retraction (1.6%), endophthalmitis (1.6%), hyphaema (1.1%), rhegmatogeneous retinal detachment (0.7%). An AE exclusively found in the Susvimo treatment group is device dislocation which occurred at a frequency of 0.7% in the ALL PDS 100 mg/mL population.

The incidence of ocular AEs seems to be significantly increased with Susvimo 100 mg/mL compared to conventional intravitreal ranibizumab injections (96.4% vs. 49.1% in study GR40548 and 92.7% vs 63.4% in study GX28228). The greatest imbalance was found for conjunctival haemorrhage, conjunctival hyperaemia, and iritis, which occurred with much higher frequency in the PD Arm than in the Intravitreal Arm. Nearly all of these cases occurred before week 40 and might hence be attributed to the PDS implantation or to the first refill-exchange procedure. In clinical studies, the incidence of ocular AEs was similar across all PDS Arms, irrespective of the dose administered. This also contributes to the assumption that the imbalance in ocular AEs between the PDS Arms and the Intravitreal Arm was mainly driven by the implantation and refill procedure itself. Analyses of the number of AEs caused by the implant during the first 10 months revealed that approximately 88% of patients experienced at least one adverse event caused by the implant. After the postoperative period (up to day 37 after implant insertion), the rates of ocular AEs were similar in the PDS arms and intravitreal arms. While the number of AEs considered caused by implant were in the range of 80-95% across PDS arms, the number of AEs considered caused by refill was in a range of 5.2%-12% (8.4% for the All PDS Population).

It can therefore be assumed that the implantation procedure itself is associated with a relatively high number of typical complications, while the number of AEs caused by refill is in the range of AEs seen with the conventional intravitreal injection of ranibizumab.

Importantly, most AEs were of mild to moderate intensity and well manageable. A total of 24 of 443 patients (5.4%) in the All PDS 100 mg/mL Population experienced at least one serious AR. The highest incidence of ARs (≥1%) by PT were endophthalmitis (1.6%) and conjunctival erosion (1.1%).

In the All PDS 100 mg/ml population, 22.1% of patients experienced at least one ocular AESI associated with the PDS implant and procedure, including cataract, vitreous haemorrhage, conjunctival bleb and conjunctival filtering bleb leak, conjunctival erosion, endophthalmitis, conjunctival retraction, hyphema, device dislocation and rhegmatogenous retinal detachment. In the pivotal study, more patients in the PDS 100 mg/ml arm experienced at least one ocular AESI in the study eye compared to the intravitreal arm (22.2% vs 9.0%).

The most frequent ocular SAEs in the study eye were were endophthalmitis (1.6%), conjunctival erosion (1.1%), device dislocation (0.9%), visual acuity reduced and conjunctival retraction (0.7% each), and rhegmatogenous retinal detachment and vitreous haemorrhage (0.5% each). The incidence of ocular SAEs in the study eye was higher in the PDS arms than in the intravitreal arm: In study GR40548 5.6% (n=14) of patients in the PDS 100 mg/mL group reported a total of 20 SAEs vs. 1.2% (n=2) in intravitreal ranibizumab group. In study GX28228 17 patients (9.5%) in the PDS arms experienced a total of 31 ocular SAEs. No ocular SAEs were reported in the intravitreal arm.

In the All PDS 100 mg/ml population, 16 patients (3.6%) experienced at least one sight threatening AE in the study eye, which included visual acuity reduced, endophthalmitis, device dislocation, hyphaema, corneal disorder, corneal epithelium defect, corneal oedema, necrotising retinitis, retinal pigment epithelial tear, retinal tear, rhegmatogenous retinal detachment, visual impairment and vitreous haemorrhage. More patients in the PDS 100 mg/ml arm reported sight threatening AEs in the study eye compared to the intravitreal arm (6.8% vs 4.9% in Study GX28228; 3.2% vs. 1.2% in Study GR40548).

Eight of 443 patients (1.8%) in the All PDS 100 mg/mL Population experienced at least one AR in the study eye which led to implant removal as of CCOD. The ARs which led to implant removal in the study eye by PT were endophthalmitis (0.9%), device dislocation (0.7%), and conjunctival retraction (0.2%). All implant removal procedures were well tolerated, and the majority of ocular AEs post-implant removal, were mild and resolved.

The rate of non-ocular AEs was comparable between the PDS and intravitreal arm in study GX28228 but it was slightly higher in the PDS arm compared to the intravitreal arm in study GR40548 (80.6% vs 67.7%). 78.1% of patients in the All PDS 100 mg/mL population experienced at least one non-ocular AE. The most frequently reported non-ocular adverse events were pneumonia (2.7%), urinary tract infection (1.4%), osteoarthritis (1.4%) and cerebrovascular accident, sepsis and hip fracture (0.9% each). The majority of patients in this safety population experienced mild or moderate non-ocular AEs; 21.0% of patients experienced at least one severe non-ocular AE. No new non-ocular safety signals were identified compared with intravitreal ranibizumab. More patients experienced Anti-Platelet Trialists Collaboration Events (APTC) in the PDS arms compared to the intravitreal arms in study GX28228 (6.7% vs 0) and study GR40548 (2.4% vs 1.2%). The data presented in response to the Day 120 LoQ shows that overall, APTC events were more than twice more frequent in the PDS 100 mg/mL patients from studies GR40548 and GX28228 compared to intravitreal ranibizumab from the same studies.

In studies GR40548 and GX28228, the incidence of non-ocular SAEs was higher in the PDS arms compared to the intravitreal arm. 22.1% of the patients in the PDS 100 mg/mL population experienced at least one non-ocular SAEs. The non-ocular SAEs in this pooled safety population with the highest reported incidence were pneumonia, urinary tract infection, osteoarthritis and cerebrovascular accident, sepsis and hip fracture.

Overall, the incidence of **treatment-emergent ADAs and Nabs** to ranibizumab administered via the PDS (100 mg/mL) in studies GX28228 and GR40548 was higher than that reported for intravitreal ranibizumab treatment: 15.3% vs 14.6% in study GX28228 and 11.7% vs 6.1% in study GR405483% for treatment-emergent ADAs and 3.4% vs 0% in study GX28228 and 5.3% vs 2.4% in study GR40548 for Nabs. The impact of ADAs and Nabs on PK, efficacy and safety in study GR40548 was only analysed in the Primary Clinical Study Report of study GR40548 (not in the Update CSR). An updated analysis of the impact of ADAs and Nabs on PK, efficacy and safety should be provided. In their responses to D120 LoQ, the Applicant provided the updated end-of-study ADA and NAb incidences from study GR40548. The results show that these incidences were low in both arms and only minor differences were observed between PDS 100 mg/ml and intravitreal ranibizumab (13.4% and 9.1% treatment-emergent ADA in PDS and intravitreal arms, respectively; 6.1% and 2.4% treatment-emergent NAbs, respectively). Updated assessments of potential correlation between ADA status and safety (ocular AEs, non-ocular

AEs, or intraocular inflammation) showed that there does not appear to be a clinically meaningful impact of ADAs, including NAbs, on safety. Despite of this, the Applicant acknowledged the observed numerical difference in ADA incidence in the PDS arm compared to intravitreal arm in Study GR40548 and added Immunogenicity to Sections 4.4 and 4.8 of the SmPC, along with further explanation of Immunogenicity in the Risk Management Plan (RMP) section "Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP".

On 01 March 2022 the Applicant informed EMA about a malfunction of the device (septum dislodgement, septum has dislodged into the implant body) observed in 14 cases. At that time 1,195 implants had been inserted and 4,009 refill exchange procedures had been conducted in patient eyes across all PDS studies. Based on currently available information, cases of septum dislodgement were not associated with safety signals, but further refill-exchange procedures needed to be halted, since normal device functioning was no longer assured.

4.5. Uncertainties and limitations about unfavourable effects

The **safety database** for PDS ranibizumab in the targeted population is considered adequate taking into account that the safety profile of intravitreal ranibizumab for the treatment of nAMD is well established. However, the PDS entails a new pattern of administration of ranibizumab (it continuously releases ranibizumab over the refill interval at steady concentrations) so that the available safety database may be insufficient for addressing new, infrequent, ocular and non-ocular risks. Another important uncertainty about the unfavourable effects of PDS ranibizumab is the lack of long-term safety data, since only 14% of the patients in the All PDS 100 mg/ml population had >2 years of exposure and 10.6% had >3 years of exposure.

The information on the timely association of different types of AEs/SAEs after Susvimo administration, and after intravitreal ranibizumab injection is yet not detailed enough to allow definite conclusions on which AEs can be clearly attributed to the procedure of PDS implantation or to the refill-exchange, and which AEs may be rather caused by the continuous release of ranibizumab via the device. However, this information is key to the understanding of the benefit-risk profile, and hence need to be provided by the Applicant for a more comprehensive assessment of safety data. Consequently, questions have been raised in the LoQ. Moreover, a more detailed elaboration on the non-ocular safety by different age strata needs to be submitted. As requested in the D120 LoQ, the Applicant provided additional analyses on the timely association of AE with implantation and refill procedures. The timely association analysis for studies GR40548 and GX28228 supports the Applicant's statement that differences in the safety profile of ranibizumab administration via PDS compared to the application via intravitreal injections are driven by AEs due to the surgical implantation procedure. On the opposite, the subsequent refill-exchange procedures were not associated with a higher risk of AEs, compared to intravitreal injections

No **comparison with intravitreal ranibizumab patients** has been provided by the Applicant for both pooled safety populations. From the individual studies results a clear trend was observed, intravitreal treatment showing a more favourable safety profile than the PDS 100 mg/ml treatment group. Therefore, a comparative analysis between the safety results of the main pool populations and monthly intravitreal ranibizumab is required to allow a better characterisation of the safety profile of PDS ranibizumab and to adequately define the benefit/risk relationship of the product in the context of alternative (available) methods of administration of ranibizumab. In their responses to the D120 LoQ, the Applicant provided comparative analysis of the pooled PDS 100 mg/ml arms of studies GX28228 and GR40548 and the pooled intravitreal injection arms of these studies.

There remains some uncertainty about the **bilateral administration** of PDS ranibizumab. Since administration of PDS ranibizumab in both eyes has not been studied in clinical trials and pharmacokinetic data and safety data with bilateral PDS implant is missing. The Applicant presented simulations on serum ranibizumab concentrations with bilateral PDS as compared to PDS in one eye and monthly intravitreal ranibizumab injections in the fellow eye. Based on these, serum Cmax and AUC with bilateral PDS is expected to be 66% and 44% lower compared to the Cmax and AUC achieved with PDS in one eye and monthly intravitreal ranibizumab in the fellow eye. Given these predictions hold true, bilateral PDS treatment could be acceptable. However, in the absence of clinical data on bilateral treatment, some uncertainties with regard of the safety and tolerability remain. The evaluation of bilateral treatment is therefore explicitly to be added to the PASS program (**OC**).

There are **ocular events associated with the implant** that have not been reported in this clinical program that are potential risks when more patients are exposed. These potential risks include implant rejection, implant dislocation and migration, implant malfunctioning and consequences of an ocular traumatism. The need of training and fulfilment of the procedural requisites appears mandatory from the safety point of view. A total of 27 patients involved in Study GX28288 were excluded from the pooled safety analyses due to the occurrence of vitreous haemorrhage related to surgical implant technique. Another uncertainty associated with the implant is its durability and whether it will have to be exchanged at some point.

No **interaction studies** with other medicinal products have been performed. However, patients are expected to receive concomitant topical or intravitreal medications in clinical practice. The Applicant should discuss the derived potential risks and propose specific recommendations in the Product Information. In their response to the D120 LoQ, the Applicant adequately addressed this question, providing information on concomitant medications and proposing the inclusion of additional wording in SmPC section 4.5 reflecting this information. This section needs to be modified in order to be in line with other intravitreal anti-VEGF medicinal products. Therefore, the first statement of Section 4.5 should read as follows: No interaction studies have been performed. ~~There are no known interactions of clinical relevance.~~ In addition, the wording of the statement regarding the administration of anti-VEGF agents in the fellow eye should be reviewed for the sake of clarity. Proposed wording: In clinical trials with Susvimo, patients with nAMD in both eyes received anti-VEGF via intravitreal injection in the fellow eye **(LoI)**

Since the vitreous concentrations are expected to be continuously higher than the minimum concentration after monthly ranibizumab, an **increased risk of systemic AEs and SAEs** related to continuous exposure to ranibizumab (absence of through-levels) cannot be excluded and this seems to be the trend in the clinical trials. This issue should be addressed by the Applicant, with a particular focus on the difference in the rate of APTC events and SAEs of cerebrovascular accident between PDS arms and intravitreal arm in studies GX28228 and GR40548, given the link between the use of VEGF inhibitors and the risk of thromboembolic events. While intravitreally injected ranibizumab is cleared from the eye into the circulation with a half-life of 7-9 days [1,2] a prolonged half-life (99 days) has been reported for PDS ranibizumab. The data presented in response to the Day 120 LoQ shows that overall, APTC events were more than twice more frequent in the PDS 100 mg/mL patients from studies GR40548 and GX28228 compared to intravitreal ranibizumab from the same studies. In particular, non-fatal stroke AEs were almost three times more frequent in the PDS 100 mg/mL patients and non-fatal myocardial infarction was twice more frequent in this population. Although these events were not considered by the investigators to be related to PDS treatment, due to pharmacological plausibility, a contributory role of PDS ranibizumab cannot be excluded.

[1] Krohne TU, Liu Z, Holz FG, Meyer CH. Am J Ophtalmol 2012; 154: 682-686
[2] Xu L, Lu T, Tuomi L, Jumbe N, Lu J, Eppler S, et al. Invest Ophtalmol Vis Sci 2013; 54: 1616-24

Another potential risk that is also related to the expected continuous exposure to ranibizumab from the PDS, is the development of **macular atrophy**. Potent, extended neutralization of VEGF, which is a critical neurotrophic factor that has been shown to play a critical role in the development and maintenance of retinal vasculature, may be disruptive to the health of neurovascular cells and there is some evidence that there is an increased risk of macular atrophy with intensive anti-VEGF therapy. Therefore, the expected continuous exposure to ranibizumab from the PDS may increase the risk of development of treatment-emergent macular atrophy. In study GX28228 the macular atrophy assessment showed that there was no evidence that the percentage of patients with macular atrophy or mean change in macular atrophy from baseline was different between the PDS 100 mg/mL arm and the intravitreal arm. However, results of the macular atrophy assessment in studies GR40548 and GR40549 have not been provided. These data should be provided and discussed by the Applicant**.** With their response to the D120 LoQ, the Applicant provided the results of the macular atrophy assessment in studies GR40548 and GR40549, as requested. Based on the presented data, there was no evidence that the percentage of patients with macular atrophy or mean change in macular atrophy area from baseline was different between the PDS 100 mg/mL arm and the monthly intravitreal arm in studies GX28228 and GR40548. Results from study GR40549 show that the proportion of patients with macular atrophy increased from 38.1% at baseline to 51.3% at W96, which is below the macular atrophy increases recently published on the incidence of macular atrophy in nAMD with ranibizumab PRN or Treat and Extend regimens (Gillies et al, 2020; Sadda et al, 2018). Given that the results from studies GX28228 and GR40548 do not allow for a comparison with the most widespread regime in Europe (Treat and Extend strategy) and that study GR40549 had no control arm, no clear conclusions can be drawn regarding the role of Susvimo in the development of macular atrophy.

On 01 March 2022 the Applicant informed EMA about a malfunction of the device (septum dislodgement, septum has dislodged into the implant body) observed in 14 cases. While cases of septum dislodgement seemed to be not associated with safety signals, it is currently unclear whether patients should undergo an explantation procedure or whether the defect device should be retained in the eye. (**B/R MO**)

4.6. Effects Table

Table X. Effects Table for Susvimo (PDS with ranibizumab) for treatment of adult patients with neovascular (wet) AMD (data cut-off 11 Sept 2020)

Effect	Short Description	Unit	Susvimo (PDS 100 mg/mL) Q24W	IVT rani-bizumab (0.5 mg) Q4W	Uncertainties/ Limitations/ Strength of evidence	References
Favourable Effects						
BCVA change over Wk 36 and 40, Equivalence/ NI margin ±4.5 letters (**primary EP**)	Adjusted mean change from BL, assessed using the ETDRS chart (4m) in the Efficacy population (95.03% CI)	Letters	0.2 (-0.7, 1.1)	0.5 (-0.6, 1.6)	- The target population claimed in the label is not consistent with study population in the pivotal trial (nAMD patients responsive to anti-VEGF treatment) - The rationale for choosing the Q24W refill regimen is not fully understood. Results from the GX28228/ Ladder study indicate a risk of overexposure, as well as the potential burden of too frequent refill-exchange procedures - Efficacy data at later time points, such as mean change in BCVA at the average of Week 64 and 68, and Week 88 and 92, are currently missing, in order to substantiate long-term efficacy - There might be a critical issue with regard to data integrity resulting from the GCP breach	Phase III GR40548/ Archway study
	Sensitivity analysis for primary EP in PP population (95.03% CI)	Letters	0.2 (-0.8, 1.1)	0.6 (-0.6, 1.7)		
	Supplemental analyses (Trimmed mean approach, MMRM method)	Letters	Consistent with primary analysis!			
	Subgroup analyses (for age, sex, number of prior anti-VEGF injections, BL BCVA score)	Letters	Consistent with primary analysis!			

Effect	Short Description	Unit	Susvimo (PDS 100 mg/mL) Q24W	IVT rani-bizumab (0.5 mg) Q4W	Uncertainties/ Limitations/ Strength of evidence	References
BCVA change over Wk 36 and 40 in Efficacy population, NI margin -3.9 letters (**key secondary EP**)	Adjusted mean change from BL, assessed using the ETDRS chart (4m) in the Efficacy population (95.03% CI)	Letters	0.2 (-0.7, 1.1)	0.5 (-0.6, 1.6)	(erroneously sent automated emails to VAEs)	
BCVA change over Wk 44 and 48 in Efficacy population, NI margin -3.9 letters (**key secondary EP**)	Adjusted mean change from BL, assessed using the ETDRS chart (4m) in the Efficacy population (95.03% CI)	Letters	0.0 (-1.0, 1.0)	0.2 (-1.0, 1.4)		
	Sensitivity analysis for key secondary EP in PP population (95.03% CI)	Letters	-0.1 (-1.2, 0.9)	0.6 (-0.6, 1.8)		
Change from BL in CPT at Wk 36 (**secondary EP/ surrogate for anatomical response**)	Adjusted mean change from BL, assessed on SD-OCT (95% CI)	Microns	5.4 (-0.3, 11.2)	2.6 (-4.4, 9.7)		

Effect	Short Description	Unit	Susvimo (PDS 100 mg/mL) Q24W	IVT rani-bizumab (0.5 mg) Q4W	Uncertainties/ Limitations/ Strength of evidence	References
Number of study treatments received (W40)	Mean (SD) number of study treatments per patient (Susvimo: initial fill + refill-exchange ; IVT ranibizumab: IVT injections)	Number	2.0 (0.15)	10.7 (1.26)		
Number of study treatments received (W48)	See above	Number	2.9 (0.36)	12.6 (1.59)		
Unfavourable Effects						
Study GX28228						
All AEs	First 10 months Entire study	patients	98.3% 98.3%	85.4% 95.1%		Study GX28228 (Safety Population)
Ocular AEs	First 10 months Entire study	patients	86.4% 88.1%	41.5% 63.4%	Timely association with implantation and refill procedure remains to be defined more precisely	
Ocular SAEs	First 10 months Entire study	patients	6.8% 6.8%	0 0	Timely association with implantation and refill procedure remains to be defined more precisely	

Effect	Short Description	Unit	Susvimo (PDS 100 mg/mL) Q24W	IVT rani-bizumab (0.5 mg) Q4W	Uncertainties/ Limitations/ Strength of evidence	References
Ocular AEs potentially related to PDS implant or implant procedures by timing	≤ 1 month ≥ 1 month	patients	15.3% 18.6%	- -		
Non-ocular AEs	First 10 months Entire study	patients	79.7%	88.1%		
Deaths		patients	1.7%	2.4%		
Study GR40548						
All AEs	After week 40 Entire study	patients	71.0% 99.2%	62.9% 81.4%		Study GR40548 Safety Summary (Safety Population)
Ocular AEs	After week 40 Entire study	patients	31.5% 96.4%	26.9% 49.1%	Timely association with implantation and refill procedure remains to be defined more precisely	
Ocular SAEs	After week 40 Entire study	patients	2.8% 7.7%	1.2% 2.4%	Timely association with implantation and refill procedure remains to be defined more precisely	
Death	First 10 months Entire study	patients	1.2% 2.0%	1.2% 1.8%		

Abbreviations: BCVA = best corrected visual acuity, BL = baseline, CI = confidence interval, CPT = center point thickness, ETDRS = early treatment of diabetic retinopathy study, EP = endpoint, GCP = good clinical practice, MMRM = mixed-effect model with repeated measures, nAMD = neovascular age-related macular degeneration, NI = non-inferiority, PP = per protocol, SD-OCT = spectral domain optical coherence tomography, VAE = visual acuity examiner, VEGF = vascular endothelial growth factor, Wk = Week

Notes:

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

With regard to efficacy, equivalence and non-inferiority have been demonstrated for the PDS 100 mg/mL arm (Q24W) compared to IVT ranibizumab 0.5 mg Q4W, as measured by the change from baseline in BCVA at the average of Week 36 and Week 40.

This was supported by sensitivity analyses in the PP population as well as by supplemental analyses for the primary endpoint, which were all consistent with the primary analysis.

In addition, the key secondary endpoints, which had been requested by EMA, were met: Non-inferiority of the PDS 100 mg/mL Q24W regimen to the IVT ranibizumab 0.5 mg Q4W regimen was also demonstrated when using a NI margin of 3.9 letters for the change from baseline in BCVA at the average of Week 36 and Week 40, as well as at the average of Week 44 and Week 48.

Subgroup analyses for the primary EP for the subgroups age, sex, number of prior anti-VEGF injections and baseline BCVA score were overall consistent with the primary analysis.

The evidence of similar efficacy between the PDS 100 mg/mL Q24W and monthly ranibizumab IVT was considered statistically convincing, and there is good concordance among efficacy endpoints.

Patients in the PDS arm received considerably fewer treatment interventions than the patients in the intravitreal arm (mean of approximately 2 vs 11 at Week 40). This is of clinical relevance for the target population, since the requirement of frequent anti-VEGF IVT injections and follow-up visits in order to achieve and maintain improved visual acuity poses a burden on patients with nAMD. Thus, the unmet medical need for reduced treatment burden in the nAMD indication is overall acknowledged.

In addition, it has to be kept in mind that although currently used IVT anti-VEGF regimens are highly effective when administered in the controlled clinical trial setting, suboptimal outcomes are observed in clinical practice, due to non-adherence of patients to the currently established treatment regime requiring numerous treatment visits and injections per year.

However, there are some remaining issues including the proposed indication wording requiring revision, clarification and further data analyses before a final conclusion can be drawn.

Among others, the appropriateness of the Q24W regimen should be balanced against the PDS-associated risks in comparison with other regimens.

With regard to the proposed indication wording, the indication should be restricted to patients who have demonstrated an adequate response to anti-VEGF therapy and a stabilization of the disease's progression. Thus, it is considered mandatory to define responders based on clinical outcome and to incorporate this in the SmPC. Not the number of injections, but rather clinically stable disease, based on ophthalmological judgement, should be a prerequisite for treatment with the PDS. This needs to be reflected in the indication wording, e.g. as follows:

"Susvimo is indicated in adult patients for the treatment of neovascular (wet) age related macular degeneration (AMD) *who have achieved stable disease (see 4.2) after previously responding to intravitreal treatment with a vascular endothelial growth factor (VEGF) inhibitor medication.*"

In addition, in SmPC Section 4.2, „Patient selection", corresponding criteria for stable disease have to be provided. (**MO**)

Moreover, the PDS implantation itself seems to be associated with a relatively high number of typical complications. The incidence of ocular AEs and ocular SAEs was substantially higher in clinical trials

compared to intravitreal ranibizumab injections. In the controlled study periods, the overall incidence of ocular AEs in the study eye was almost twice as high in the PDS 100 mg Arm (96.4%) compared to the Intravitreal Arm (49.1%). The greatest imbalance was found for conjunctival haemorrhage, conjunctival hyperaemia, and iritis, which occurred with much higher frequency in the PDS Arm than in the Intravitreal Arm. Nearly all of these cases occurred before week 40 and appear to be attributed to the PDS implantation procedure. The same picture was found for study GX28228. In the first 10 months, ocular AEs in the study eye were found more than twice as often in the PDS Arms compared with the Intravitreal Arm. The incidence of ocular AEs was similar across all PDS Arms, irrespective of the dose administered. This also contributes to the assumption that the imbalance in ocular AEs between the PDS Arms and the Intravitreal Arm was mainly driven by the implantation procedure itself. Analyses of the number of AEs caused by implant during the first 10 months revealed that approximately 88 % of patients experienced at least one adverse event caused by implant. After the postoperative period (up to day 37 after implant insertion), the rates of ocular AEs were similar in the PDS arms and intravitreal arms. While the number of AEs considered caused by implant were in the range of 80-95% across PDS arms, the number of AEs considered caused by refill was in a range of 5.2%-12% (8.4% for the All PDS Population). Similar to study GR 40548, the greatest incidence was found for conjunctival haemorrhage, conjunctival hyperemia, eye pain, vitreous floaters, iritis, eye irritation, foreign body sensation in eyes, and vitreous haemorrhage.

These differences in the safety profile have been explained by the Applicant in the context of the ocular surgical procedure performed in the PDS arms. This is acknowledged since the majority of the ocular AEs in the study eye in the PDS arms occurred during the early postoperative period (9 days post-implantation). The vitreous concentrations are expected to be continuously higher than the minimum concentration after monthly ranibizumab. While intravitreally injected ranibizumab is cleared from the eye into the circulation with a half-life of 7-9 days [1],[2] a prolonged half-life (99 days) has been reported for PDS ranibizumab. In these circumstances an increased risk of systemic AEs and SAEs related to continuous exposure to ranibizumab (absence of through-levels) cannot be excluded and this seems to be the trend in the individual clinical trials.

More patients experienced Anti-Platelet Trialists Collaboration Events (APTC) in the PDS arms compared to the intravitreal arms in study GX28228 (6.7% vs 0) and study GR40548 (2.4% vs 1.2%). In studies GR40548 and GX28228, more patients in the PDS arms compared to the intravitreal arm experienced a SAE of cerebrovascular accident (1.2% vs 0.6% and 1.7% vs 0, respectively). The data presented in response to the Day 120 LoQ shows that overall, APTC events were more than twice as frequent in the PDS 100 mg/mL patients from studies GR40548 and GX28228 compared to intravitreal ranibizumab from the same studies.

On 01 March 2022 the Applicant informed EMA about a malfunction of the device (septum dislodgement) observed in 14 cases. The magnitude of impact of these cases on the benefit-risk profile of Susvimo is currently unclear and needs further evaluation (**B/R MO**).

4.7.2. Balance of benefits and risks

The overall efficacy profile of Susvimo could be favourable, but has some limitations.

The potential advantage of this medicinal product is a clinically relevant reduction in treatment burden compared to patients receiving monthly intravitreal ranibizumab injections, while achieving comparable visual and anatomical outcomes.

The pivotal clinical study GR40548 provided evidence on the non-inferior efficacy of PDS ranibizumab 100 mg/ml, in visual function as well as in anatomical parameters, in the treatment of patients with neovascular AMD.

These potential benefits are contrasted by specific safety risks associated by the implantation procedure. However, subsequent refill-exchange procedures seem to have a comparable or even slightly better safety profile compared to conventional intravitreal ranibizumab injections.

The currently proposed indication wording is:

Susvimo is indicated in adult patients for the treatment of neovascular (wet) age-related macular degeneration (AMD) who have previously responded to at least two intravitreal injections of a vascular endothelial growth factor (VEGF) inhibitor medication".

The indication wording proposed by the Applicant requires further revision. The indication should be restricted to patients who have demonstrated an adequate response to anti-VEGF therapy and a stabilization of the disease's progression. Thus, it is considered mandatory to define responders based on clinical outcome and to incorporate this in the SmPC. Not the number of injections, but rather clinically stable disease, based on ophthalmological judgement, should be a prerequisite for treatment with the PDS. This needs to be reflected in the indication wording, e.g. as follows:

"Susvimo is indicated in adult patients for the treatment of neovascular (wet) age related macular degeneration (AMD) *who have achieved stable disease (see 4.2) after previously responding to intravitreal treatment with a vascular endothelial growth factor (VEGF) inhibitor medication.*"

In addition, in SmPC Section 4.2, „Patient selection", corresponding criteria for stable disease have to be provided. (**MO**)

In addition, 14 cases of septum dislodgement of the port delivery system have been reported on 01 March 2022. The impact of this newly identified risk on Susvimo's B/R profile is currently unclear and needs further evaluation (**MO**).

4.7.3. Additional considerations on the benefit-risk balance

N/A

4.8. Conclusions

In accordance with the above evaluation of efficacy and safety, the overall B/R of Susvimo (PDS with ranibizumab), proposed for the treatment of neovascular (wet) age-related macular degeneration (AMD) in adult patients, is currently considered negative.