CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial #:	761197
Drug Name:	Ranibizumad Port-Delivery System 100 mg/mL
Indication(s):	Treatment of age-related neo-macular degeneration (nAMD)
Applicant:	Genentech, Inc.
Date(s):	Stamp Date: September 16, 2019 PDUFA Date: October 23, 2021 Review Date: September 23, 2021
Review Priority:	Priority
Biometrics Division:	IV
Statistical Reviewer:	Elena Rantou, Ph.D.
Concurring Reviewers:	Guoxing Soon, Ph.D., Team Leader
Medical Division:	Division of Ophthalmology (DO)
Clinical Team:	Wiley Chambers, MD, Medical Officer William Boyd, MD, Team Leader
Project Manager:	Diana Willard

Keywords: Age Related neo-Macular Degeneration, Best Corrected Visual Acuity, Mixed Effects Repeated-Measures Model, ANCOVA.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The purpose of this BLA is to seek approval of ranibizumad Port Delivery System 100 mg/mL (PDS) for the treatment of neovascular age-related macular degeneration (nAMD). This PDS is an innovative intraocular drug delivery system, designed for continuous release and consists of an ocular implant, a customized formulation of ranibizumad (100 mg/mL), as well as, 4 ancillary devices used to fill, insert, refill-exchange, and explant the implant.

One of the implications of nAMD is the vascular endothelial growth factor (VEGF)-A. Currently, there are three approved anti-VEGF agents for the treatment of nAMD:

a. Ranibizumad (Lucentis®), approved on 6/30/2006 (BLA 125156)
b. Aflibercept (Eylea®), approved on 11/18/2011 (BLA 125387)
c. Brolucizumad (Beovu®), approved on 10/7/2019 (BLA 761125)

The PDS drug and its devices will all be marketed together. The description and intended use of all components are summarized below.

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.

Source: Table 2 of Clinical Overview, pg. 14 of 84

The efficacy of Susvimo was evaluated in the pivotal, Phase III randomized, multicenter, open-label, active comparator clinical trial, GR40548, the Phase III long-term, extension, multicenter, open-label, visual-assessor (VA) masked, multiple-cohort, extension study GR40549, and the Phase-II, dose-ranging, randomized, active treatment-controlled, multicenter, ladder main study GX20228. The

safety of Susvimo was the primary objective of the sub-study of GX28228, a Phase-II, non-randomized, uncontrolled, open-label, sub-study.

For study GR40548 (Archway), a total of 418 eligible patients were randomized in a 3:2 ratio and 415 of them received treatment. On the day of randomization visit best-corrected visual acuity (BCVA) score is measured and randomization is stratified by BCVA score (<74 letters vs. ≥74 letters). For each patient one eye is chosen for the study treatment.

Patients assigned to the PDS arm will have the implant surgically inserted on Day 1, will have scheduled safety visits on Days 2 and 7 and will receive implant refills-exchanges at Week 24, Week 48, and Week 72. Patients assigned to the intravitreal injection arm will receive injections starting on Day 1 and Q4W from Day 1 to Week 92.

The primary efficacy endpoint is the change in BCVA score from baseline averaged over Weeks 36 and 40. PDS 100 mg/mL is considered non-inferior to intravitreal treatment if the lower limit of the 95% confidence interval for the treatment difference in the change in BCVA score from baseline averaged over Weeks 36 and 40 is > -4.5 letters. Another primary objective is to show equivalence of the two treatments. This is accomplished when the 95% confidence interval (CI) for the difference in mean change BCVA from baseline averaged over the Weeks 36 and 40 is contained within ±4.5 letters. To control for the overall Type-I error rate, a fixed-sequence testing procedure was used adjusting the one-sided significance level to 0.02485, which leads to a 95.03% confidence coefficient.

In study GR40548 (Archway), the PDS 100 mg/mL group was statistically non-inferior to the ranibizumad intravitreal (RBZ ITV SOC 0.5MG) group with respect to the change from baseline in BCVA averaged over Weeks 36 and 40. The change from baseline in BCVA averaged over Weeks 36 and 40 was lower in the PDS arm compared to the intravitreal arm by 0.33 (95% CI: -1.58 to 0.92). The lower limit of the 95% CI is greater than -4.5 and both limits of the CI are contained within [-4.5, 4.5] indicating that both the non-inferiority and the equivalence criteria for the primary efficacy endpoint have been satisfied.

Similarly, in study GX28228 (Ladder), the PDS 100 mg/mL group was statistically non-inferior to the RBZ ITV SOC 0.5MG (intravitreal) group with respect to the change from baseline in BCVA averaged over Months 9 and 10. As shown in Table 1 the change from baseline in BCVA averaged over Months 9 and 10 was higher in the PDS arm compared to the intravitreal arm by 1.84 (95% CI: -(-1.48, 5.16)). The lower limit of the 95% CI is greater than -4.5 indicating non-inferiority of the PDS to the intravitreal arm.

Table 1: Summary of the change from baseline in BCVA averaged over Weeks 36 and 40 (Efficacy population [b])

	GR40548			GX28228	
PDS 100 mg/mL (N=248)	ITV SOC 0.5MG (N=165)	Difference[a] (95% CI)	PDS 100 mg/mL (N=59)	ITV SOC 0.5MG (N=41)	Difference (95% CI)
0.19 (0.40)	0.52 (0.49)	-0.33 (-1.58,0.92)	4.92 (1.07)	3.08 (1.30)	1.84 (-1.48, 5.16)

[a] Least squares means (SE), differences and CI were based on a MMRM model with baseline as a covariate.
[b] Efficacy population included all randomized patients who received the study treatment.
Source: Reviewer's analysis

The PDS 100 mg/mL treatment arm showed comparable results to the ITV 0.5 MG arm regarding the change from baseline in BCVA based on the results from Study GR40548. Study GX28228 also provided supporting evidence for the same comparison. Based on the pivotal study results, the largest difference between the mean CFB in BCVA between the two arms was observed at Week 4, whereas the smallest difference was observed at Week 36. The summary of the CFB in BCVA at pre-specified timepoints based on 4 week intervals, for both Studies GR40548 and GX28228 is shown in Table 2 below.

Table 2: Summary of the CFB in BCVA over time in Studies GR40548 and GX28228 (Efficacy population [a])

GR40548	**ITV SOC 0.5MG** **N** **Mean (SD)** **Median** **(Min, Max)**	**PDS 100 mg/mL** **N** **Mean (SD)** **Median** **(Min, Max)**	**GX28228**	**ITV SOC 0.5MG** **N** **Mean (SD)** **Median** **(Min, Max)**	**PDS 100 mg/mL** **N** **Mean (SD)** **Median** **(Min, Max)**
Week 4	165 -0.46 (6.05) 0 (-38, 18)	246 -5.35 (10.90) -3 (-85, 18)	**Month 1**	41 2.34 (6.17) 1 (-9, 22)	58 -4.21 (20.1) 0 (-84, 17)
Week 8	165 0.03 (5.27) 0 (-18,18)	248 -2.03 (7.78) -1 (-58, 17)	**Month 2**	41 1.93 (5.37) 0 (-6, 15)	58 -0.35 (15.4) 2 (-83, 16)
Week 12	165 0.43 (5.80) 0 (-28,22)	248 -0.84 (7.45) 0 (-32, 23)	**Month 3**	40 2.65 (7.16) 2 (-19, 19)	58 1.31 (12.7) 2.5 -83 16
Week 16	165 0.15 (6.57) 0 (-29, 19)	248 -0.53 (6.45) 0 (-46, 22)	**Month 4**	41 1.85 (9.23) 0 (-37, 21)	59 2.78 (7.70) 3 (-12, 34)
Week 20	165 0.12 (6.35) 0 (-32, 17)	248 -0.59 (7.51) -1 (-34, 25)	**Month 5**	41 2.88 (8.51) 3 (-30, 19)	58 3.78 (7.46) 4.5 (-13, 36)
Week 24	165 0.68(6.79) 1 (-32, 19)	248 -2.90 (14.98) 0 (-79, 22)	**Month 6**	41 2.59 (8.28) 4 (-27, 19)	58 3.57 (7.26) 3 (-13, 32)
Week 28	165 0.51 (6.80) 0 (-36, 19)	248 -1.24 (11.46) 0 (-74, 23)	**Month 7**	40 3.08 (8.74) 2.5 (-28, 19)	58 3.45 (7.93) 4 (-19, 34)
Week 32	165 0.79 (7.32) 1 (-34, 27)	248 -0.08 (9.35) 0 (-74, 22)	**Month 8**	40 2.82 (9.21) 2 (-29, 23)	57 3.91 (7.56) 3 (-18, 33)
Week 36	165 0.25 (6.71) 0 (-35, 19)	248 0.15 (8.13) 0 (-74, 22)	**Month 9**	37 3.27 (8.99) 3 (-30, 22)	56 4.82 (7.23) 5 (-13, 35)

Week 40	165 0.58(7.04) 0 (-35, 20)	248 -0.35 (10.34) 0 (-74, 22)	**Month 10**	37 1.95 (8.95) 2 (-31, 19)	58 4.98 (7.90) 4.5 (-14, 37)

[a] Efficacy population included all randomized patients who received the study treatment.
Source: Reviewer's analysis

In summary, based on the totality of evidence from Study GR40548 and supporting evidence from Study GX28228, the reviewer concludes that the application provided substantial evidence to support the efficacy of RBZ PD 100MG/ML in patients with age-related neo-macular degeneration (nAMD).

2 INTRODUCTION

2.1 Overview

The applicant submitted this BLA for the use of RBZ PD 100MG/ML (Ranibizumad Port-Delivery System) for the treatment of age-related neo-macular degeneration (nAMD).

The randomized Phase III Study GR40548 was used as the pivotal study to demonstrate non-inferiority and clinical equivalence in the visual outcome of PDS Q24W compared with ranibizumab intravitreal injections Q4W for the treatment of nAMD.

Apart from the pivotal Study GR40548, data from the two other supportive studies GX28228 (Phase II) and GR40549 (Phase III), conducted in patients with nAMD will be used as supporting evidence to support the adequacy of Study GR40548.

Summaries of studies included in the efficacy analysis

Study ID	Design*	Treatment/ Sample Size	Endpoint/Analysis
GR40548	MC, R, OL, AC trial (92 weeks of treatment)	PDS 100 mg/mL Q24W/ 248 Intravitreal ranibizumad injection (0.5 mg) Q4W / 167	Primary: BCVA change at the average of Weeks 36 and 40 (4.5L margin)
GR40549	MC, OL, VA masked, MC extension study	PDS 100 mg/mL Q24W/ 217: -From study GR40548/ 13 -From study GX28228/ 189 -Non-compliant study GX28228/ 4 -Oral antithrombotic therapy substudy of GX28228/ 11	Primary: -Change in BCVA score from baseline over time -Change from baseline in CPT over time -Proportion of patients who undergo additional intravitreal treatment before the 1st, 2nd, 3rd, 4th and 5th refill interval

GX28228	Phase-II, R, MC, dose-ranging, active treatment-controlled	10 mg/mL, 40 mg/mL, and 100 mg/mL arms vs. ITV SOC 0.5MG	Primary: -Time until a patient first requires the implant refill TTFR (protocol criteria) Secondary: -Change in BCVA from baseline at Month 9 -Average change from baseline in BCVA over time -Change in BCVA from baseline over time -Change from Baseline in CFT -Proportion of patients with an improvement of BCVA from baseline of ≥15 letters over time -Time to subsequent implant refills according to protocol criteria

Source Applicant's Summary of Clinical Efficacy, pg. 12 of 106

The focus of this statistical review is primarily on the Archway pivotal study (GR40548). Outcomes from study GX28228 (Ladder) will be used as supporting evidence for efficacy. Outcomes from Study GR40549 will be used as supporting long-term efficacy evidence.

2.2 Data Sources

The primary data source for this review were the clinical study reports (CSR), study protocols including amendments, statistical analysis plans, and the analyses and tabulation datasets. These were provided in an electronic (rolling) submission located at \\CDSESUB1\evsprod\BLA761197\0002\. The primary analysis datasets are located at \\CDSESUB1\evsprod\BLA761197\0002\m5\datasets\.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer found the quality of the submitted data and analysis acceptable.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study Design

The main efficacy support for PDS 100 mg/mL for the treatment of nAMD was the pivotal Phase 3 Study GR40548 (Archway). This was a Phase III, randomized, multiple-center (78 clinical sites), open-label (visual assessor [VA]-masked), active-comparator study. The primary analysis of Study

GR40548 was conducted with a CCOD of 27 March 2020 after all patients had completed Week 40 assessments or discontinued the study early. With a second data cut with a CCOD of 11 September 2020, data were also analyzed for BCVA, and Center Point Thickness (CPT) when all patients had passed their Week 60 scheduled visit date or had discontinued the study early. For all the above analyses, baseline was defined as the last available measurement prior to first study treatment (PDS implant or post-randomization intravitreal injection). A total of 418 patients were randomized in a 3:2 ratio and 415 of them received treatment.

The key inclusion criteria for Study GR40548 were that patients should be of at least 50 years of age, had a diagnosis of nAMD within 9 months prior to the screening visit, had at least 3revious treatment with at least three anti-VEGF injections in study eye within 6 months prior to the screening, have demonstrated response to prior anti-VEGF intravitreal treatment since diagnosis, all macular choroidal neovascularization (CNV) lesions were permitted, and had BCVA of 34 letters or better (20/200 or better approximate Snellen equivalent).

The key exclusion criteria were subfoveal fibrosis, subfoveal atrophy, or subretinal hemorrhage (greater than 1.27 mm2 involving the center of the fovea) in the study eye, as well as, active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.

Study GX28228 was a Phase II, multiple-center (50 clinical sites), dose-ranging, randomized, active treatment–controlled study. This study evaluated the efficacy, safety, and pharmacokinetics of ranibizumab delivered through the implant using 3 ranibizumab formulation arms (10 mg/mL, 40 mg/mL, and 100 mg/mL, refilled on a PRN regimen, compared with the control arm (0.5 mg monthly intravitreal injections of 10 mg/mL ranibizumab in patients with nAMD. The study also evaluated the safety of the PDS. From the 244 patients who were enrolled between 28 September 2015 and 21 August 2018, 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 intravitreal arm, respectively in the main study (excluding 7 patients randomized at a non-compliant site and 12 patients enrolled in the non-randomized OAT sub-study). Similarly, to the Archway study inclusion and exclusion criteria applied to this study.

Study GR40549 is a multiple-center, 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 every 24 weeks to patients who elected to enroll in the extension study from Study GX28228 or Study GR40548 (parent studies).

For clinical efficacy, only the data from 189 patients collected in Study GR40549 were included in the pooled analyses. These 189 patients were from the main Study GX28228 and were subsequently treated in Study GR40549 (5 patients from GR40549 were not included in the analysis). Fifteen patients from Study GR40548 were enrolled into Study GR40549 by September 11, 2020. These patients each had short duration of participation in the study, so their data were not sufficient for inclusion in the efficacy evaluation.

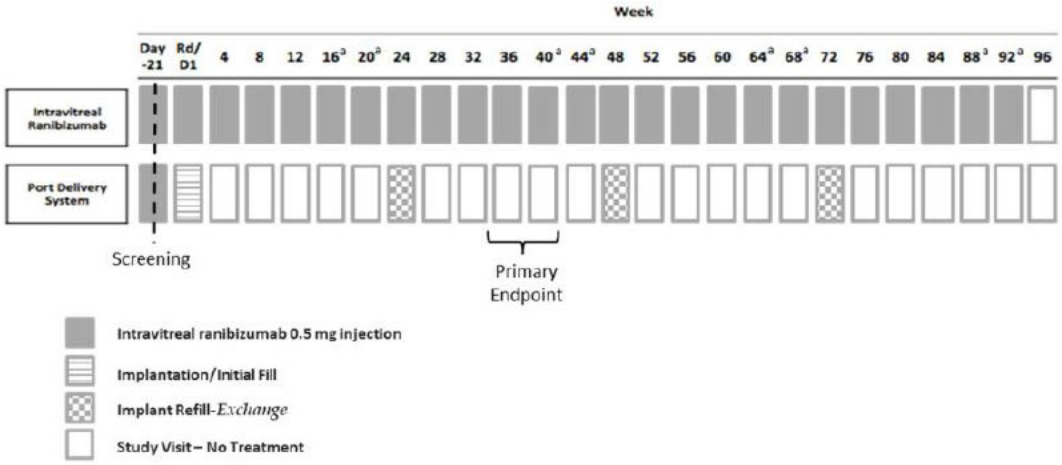
Visual acuity refers to the clarity of vision and rates an examinee's ability to recognize small details with precision. Visual acuity depends on the sharpness of the retinal image within the eye, the health

and functioning of the retina, and the sensitivity of the interpretative faculty of the brain. An eye exam seeks to find the prescription that will provide the best corrected visual performance achievable.

Change in BCVA has been previously used as an endpoint for clinical studies in nAMD. Change from baseline (CFB) in BCVA averaged over Weeks 36 and 40 is the primary efficacy endpoint in Study GR40548, where the BCVA is assessed using the ETDRS charts at a starting distance of 4 meters. The rationale of averaging of 2 measurements from Weeks 36 and 40 was to reduce the variability in BCVA assessment and is considered reasonable if the case that the treatment effect has plateaued.

In Study GR40548, a total of 418 eligible patients were randomized in a 3:2 ratio and 415 of them received treatment. On the day of randomization visit best-corrected visual acuity (BCVA) score was measured and randomization was stratified by BCVA score (<74 letters vs. ≥74 letters). For each patient one eye was chosen as the study eye for treatment.

Patients assigned to the PDS arm had the implant surgically inserted on Day 1, were scheduled for safety visits on Days 2 and 7. They were also scheduled to receive implant refills-exchanges at Week 24, Week 48, and Week 72. Patients assigned to the intravitreal injection (ITV) arm were scheduled to receive injections starting on Day 1 and every 4 weeks (Q4W) from Day 1 to Week 92. This design is presented in the study schema below.



D = day; Rd = randomization.

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

Source: Applicant's Statistical Analysis Plan (SAP), pg. 8 of 61

Efficacy Evaluation

In the Phase III Study GR40548, the primary efficacy endpoint was the change in BCVA score from baseline averaged over Weeks 36 and 40. By Week 36 from enrollment, patients in the PDS arm received at least 2 ranibizumab administrations via the PDS (the initial fill and one refill-exchange)

and patients in the ITV arm received approximately 10 ranibizumab injections, while both arms had received at least 4 anti-VEGF injections prior to enrollment.

Efficacy Variables

The primary efficacy variable in both studies GR40548 and GX28228 was **the CFB in BCVA averaged over Weeks 36 and 40 (Months 9 and 10)**. Change from baseline in BCVA was assessed every 4 weeks, i.e., on Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36 and 40.

The applicant used the CFB in BCVA averaged over Weeks 44 and 48 as a secondary endpoint since this time-point is just prior to a refill-exchange (at Week 48) when the concentration of ranibizumab in the eye is expected to be the lowest.

Other visual function, secondary endpoints are:

- Change from baseline in BCVA score over time: Assessment of BCVA change over a 48-week period allows determination of continuous maintenance of BCVA over an extended period to support the continuous delivery profile of the PDS.
- Proportion of patients with a BCVA score of 38 letters or worse since a BCVA score of 38 letters (Snellen 20/200 equivalent) is the threshold for legal blindness.
- Proportion of patients with a BCVA score of 69 letters or better since a BCVA score of 69 letters (Snellen 20/40 equivalent) can be required to hold a driver's license in some countries such as the US and UK.
- The applicant also evaluated various binary secondary endpoints related to gain of visual function and loss of visual function from baseline to further understand the distribution of BCVA change across patients. These are:

    1. Proportion of patients with loss of visual function or gain of visual function from baseline: Proportion of patients who lose <15, <10 or <5 letters in BCVA score from baseline to the average over Week 36 and Week 40 and

    2. Proportion of patients who gain ≥0, ≥5, and >15 letters in BCVA score from baseline to the average over Week 36 and Week 40 were chosen to further understand the distribution of BCVA change across patients.

In all data analyses in Study GR40548, baseline is defined as the last available measurement prior to first study treatment of either arm.

3.2.2 Statistical Methodology

Primary Efficacy Analysis

The primary objective of the pivotal study was to evaluate the non-inferiority and equivalence in efficacy of ranibizumab PDS Q24W with the 100 mg/mL formulation compared with that of 10 mg/mL (0.5 mg dose) Q4W ITV ranibizumab injections.

The analysis of the primary efficacy endpoint was performed using a mixed-effect model with repeated measures (MMRM) based on all available data up to Week 40. This model included all observed measurements regardless of whether a patient had an intercurrent event and missing assessments were imputed by the MMRM model, assuming a missing at random (MAR) mechanism. The dependent variable in the MMRM model was the CFB in BCVA score at visits on Weeks 4 through 40, whereas the fixed effects were the treatment group, visit, treatment-by-visit interaction, baseline BCVA score (continuous), and the randomization stratification factor of baseline BCVA (<74 letters vs. ≥74 letters). The applicant planned to use an MMRM model with an unstructured covariance, however, a compound symmetry covariance structure was used because of convergence issues.

For the primary efficacy endpoint, the PDS treatment would be considered non-inferior (NI) to the ITV treatment if the lower bound of the two-sided 95.03% CI for the difference of two treatments was greater than − 4.5 letters. For the primary efficacy endpoint, the PDS treatment would be considered clinically equivalent to the ITV treatment if the 95.03% CI for the difference of two treatments was contained within [-4.5, 4.5].

The efficacy population comprised all patients who were randomized and received the study treatment and was used for the primary efficacy analysis.

As a sensitivity analysis, the same MMRM model analysis was performed using the Per-Protocol population. The Per-Protocol population included all patients in the efficacy population who did not have a major protocol deviation.

The applicant also performed supplemental analyses on the primary efficacy endpoint that included:

- Trimmed mean analysis: This analysis was used to assess the difference in BCVA between two treatments, truncating the 20% of patients with the worst outcome, with the assumption that patients have the worst outcome after intercurrent events. An analysis of covariance (ANCOVA) model was used for this analysis.
- Two separate analyses, each using different handling rules for intercurrent events and missing data.

    1. Method 1: assessments after 2 or more supplemental treatments or after prohibited treatments were imputed using the last post-baseline observation prior to such intercurrent event; other missing data were imputed using last post-baseline observation carried forward (LOCF).

2. Method 2: assessments after receipt of 2 or more supplemental or prohibited treatments were excluded and all missing data were implicitly imputed by the MMRM model, assuming a MAR mechanism.

Reviewer's Remark:
For the construction of the 95% CIs in the supplemental analysis the applicant used the randomization reference distribution whereas the reviewer used asymptotic normality. The results were comparable, i.e., had small numerical differences but were in inferential agreement.

Secondary Efficacy Analysis

In the pivotal study GR40548, secondary binary endpoints included the difference of proportion of patients in the two treatments. All such endpoints were estimated using the weighted average of the observed proportions and the differences in observed proportions. Weights were based on the randomization stratification factor of baseline BCVA (<74 letters vs. ≥74 letters) and the Cochran-Mantel-Haenszel weighting approach.

Continuous secondary endpoints, such as the Center Point Thickness (CPT), through week 40 were analyzed following the same MMRM model as in the analysis of the primary efficacy endpoint.

In Study GX28228, a similar MMRM model was used to analyze the CFB in BCVA averaged over Months 9 and 10.

The applicant used the data from Study GR40549 to evaluate the long-term efficacy of the PDS 100 mg/mL treatment. These BCVA data were obtained from patients who enrolled from Studies GX28228 and GR40549.

Type I error control (Plan for multiplicity adjustment)

To control the overall type I error, a fixed sequence testing procedure was be used. If the PDS 100 mg/mL arm is shown to be non-inferior to the intravitreal arm at the one-sided 0.02485 level, then the equivalence test would be conducted using two one-sided 0.02485 tests.

At the time of the primary analysis, it was estimated that 3 interim data reviews would have been conducted by the independent data monitoring committee. All efficacy analyses were performed with a family-wise significance level of 0.0497.

Handling of Missing Data

For the primary efficacy analysis of the pivotal study, missing data will be implicitly imputed by the MMRM model, assuming a MAR mechanism.

For supplemental analysis of the primary efficacy endpoint, the rules for handling missing data are described above (see Primary Efficacy Analysis).

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition

In the pivotal study GR40548, 418 patients were randomized into a 2:1 ratio to the PDS and ITV treatments respectively, that is, 251 patients in the PDS 100 mg/mL arm and 167 patients in the ITV arm. From those, 415 patients were treated and were included in the efficacy population, of whom 248 patients in the PDS 100 mg/mL arm and 167 patients in the ITV arm. A total of 7 patients discontinued by Week 40 and another 2 patients discontinued after Week 40 and by Week 48.

Twenty nine patients were excluded from the Per-Protocol population of whom 19 from the PDS 100 mg/mL arm and 10 patients in the ITV arm.

In Study GX-28228 (Ladder), a total of 244 subjects were enrolled and 225 of them were randomized. From the randomized subjects, 59, 62, 63 and 41 were assigned to treatments PDS 10 mg/mL, PDS 40 mg/mL, PDS 100 mg/mL and ITV 0.5MG respectively, whereas from the assigned subjects 58, 62, 59 and 41 received treatment respectively.

From the total of 220 subjects in the efficacy population, 4 discontinued (ITV injection arm) before Month 10 and therefore a total of 216 subjects (98.18%) completed Month 10. Furthermore, a total of 199 subjects (90.45% of the efficacy population) completed the study.

Disposition information for the pivotal study has been summarized in Figure xxx below.

Table 3: Disposition table for Study GR40548

	RBZ PD 100MG/ML N	RBZ ITV SOC 0.5MG N	Total N
Randomized	251	167	418
Efficacy population*	248	167	415
Discontinued by Week 40	5	2	7
Reason for discontinuation			
Death	2	0	2
Physician's decision	0	1	1
Withdrawal by subject	0	4	4
Discontinued after Week 40 (by Week 48)	2	0	2

Per-Protocol (PP) population	232	157	389
Excluded from PP population	19	10	29
Reason for exclusion			
Protocol 1	14	7	21
Protocol 2	5	3	8

Source: Reviewer's analysis

Demographic Characteristics

The summaries of the demographic characteristics for the efficacy population, i.e., all randomized subjects who received at least one dose of study medication in Studies GR40548 and GX28228 are shown in Figure 1. As shown, the average and median age in both studies is around 75 years, whereas most participants are non-Hispanic and White. On average, participants in Study GR40548 have a higher ETDRS BCVA and a higher Center Point Thickness (CPT), than that in Study GX28228. Furthermore, patients in Study GR40548 had an average of 5 anti-VEGF injections prior to enrolling compared to an average of about 3 anti-VEGF injections prior to enrolling to Study GX28228. Additionally, patients in Study GR40548 had, on average, a higher value for time since first nAMD diagnosis compared to that of patients in Study GX28228.

Within each study, baseline BCVA scores are comparable between the two treatments.

Figure 1: Summary of demographic and baseline disease characteristics in Studies GR40548, GX28228 (Efficacy population)

	Archway		**Ladder**			
Characteristic	PDS 100 mg/mL Q24w (N=248)	Intravitreal Ranibizumab 0.5 mg (N=167)	Ranibizumab 10 mg/mL (N=58)	Ranibizumab 40 mg/mL (N=62)	Ranibizumab 100 mg/mL (N=59)	Intravitreal Ranibizumab 0.5mg (N=41)
Sex, n (%)						
Male	103 (42%)	67 (40%)	22 (38%)	23 (37%)	21 (36%)	13 (32%)
Female	145 (58%)	100 (60%)	36 (62%)	39 (63%)	38 (64%)	28 (68%)
Age, years						
Mean (SD)	75 (8)	75 (8)	74 (8)	76 (8)	75 (8)	72 (9)
Median (min, max)	75 (51, 96)	75 (54, 89)	76 (56, 92)	76 (50, 90)	75 (57, 91)	74 (52, 85)
Age groups (years), n (%)						
≥17 to <65	26 (10%)	17 (10%)	8 (14%)	7 (11%)	9 (15%)	7 (17%)
≥65 to <75	81 (33%)	57 (34%)	15 (26%)	18 (32%)	19 (32%)	16 (39%)
≥75	141 (57%)	80 (48%)	35 (60%)	37 (57%)	31 (53%)	18 (44%)

	Archway		**Ladder**			
Characteristic	PDS 100 mg/mL Q24w (N=248)	Intravitreal Ranibizumab 0.5 mg (N=167)	Ranibizumab 10 mg/mL (N=58)	Ranibizumab 40 mg/mL (N=62)	Ranibizumab 100 mg/mL (N=59)	Intravitreal Ranibizumab 0.5mg (N=41)
Race, n (%)						
White	240 (97%)	161 (96%)	57 (98%)	61 (98%)	56 (95%)	41 (100%)
Asian	1 (0.4%)	0	0	0	2 (3%)	0
Black/African American	3 (1%)	1 (1%)	1 (2%)	0	0	0
Other	4 (2%)	5 (3%)		1 (2%)	1 (2%)	0
Ethnicity, n (%)						
Hispanic	7 (3%)	8 (5%)	3 (5%)	3 (5%)	2 (3%)	1 (2%)
Non-Hispanic	241 (97%)	159 (95%)	55 (95%)	56 (90%)	57 (97%)	39 (95%)
ETDRS BCVA						
Mean (SD)	74 (10)	75 (10)	69 (13)	70 (12)	70 (10)	71 (13)
Median	77	78	72.5	71.5	72	73
Min-Max	35-92	35-94	34-87	34-88	37-85	34-88
>=74	163 (66%)	113 (68%)				
>=66			43 (74%)	43 (69%)	41 (70%)	30 (73%)
Center Point Thickness						
Mean (SD)	177 (55)	177 (49)	194 (73)	182 (73)	183 (69)	185 (62)
Median	169 5	171.0	187.5	171	161	174
Number of anti-VEGF injections prior to first Study Treatment						
Mean (SD)	5.0 (2.1)	5.0 (1 5)	2.7 (1.2)	2.8 (1.2)	3.1 (1.5)	2.9 (1.3)
Median	4.0	4.0	2	2	3	2
Min-Max	3 - 31	4 - 9	2-7	2-6	2-8	2-7
Number of anti-VEGF injections prior to first Study Treatment						
1	0	0	0	0	0	0
2	0	0	37 (64%)	37 (60%)	27 (46%)	23 (56%)
3	1 (0.4%)	0	7 (12%)	8 (13%)	17 (29%)	8 (20%)
4	137 (55.2%)	99 (59 3%)	10 (17%)	10 (16%)	4 (7%)	5 (12%)
5	49 (19.8%)	21 (12.6%)	2 (3%)	4 (7%)	4 (7%)	2 (5%)
6	26 (10.5%)	17 (10 2%)	1 (2%)	3 (5%)	6 (10%)	2 (5%)
7	21 (8.5%)	11 (6.6%)	0	0	0	0
8	7 (2.8%)	13 (7.8%)	0		1 (2%)	0
9	4 (1.6%)	6 (3.6%)				
10	1 (0.4%)					
11	1 (0.4%)					
31	1 (0.4%)					
Time Since First Diagnosis of Neovascular AMD (Months)						
Mean (SD)	5.9 (9.5)	5.3 (2.0)	3.4 (2.0))	3.2 (1.5)	3.9 (2.1)	3.4 (1.8)
Median	4.6	4.5	2.5	2.5	3.0	2.3
Min-Max	3 - 152	3 - 10	1.0-10.5	1.9-7.6	1.9-10.2	1.3-8.6

Source: Applicant's Clinical Study Report, Table 18

3.2.4 Efficacy Results and Conclusions

In this section, results of the primary and secondary efficacy analysis primarily from Study GR40548, as well as, from Study GX28228, are presented and discussed.

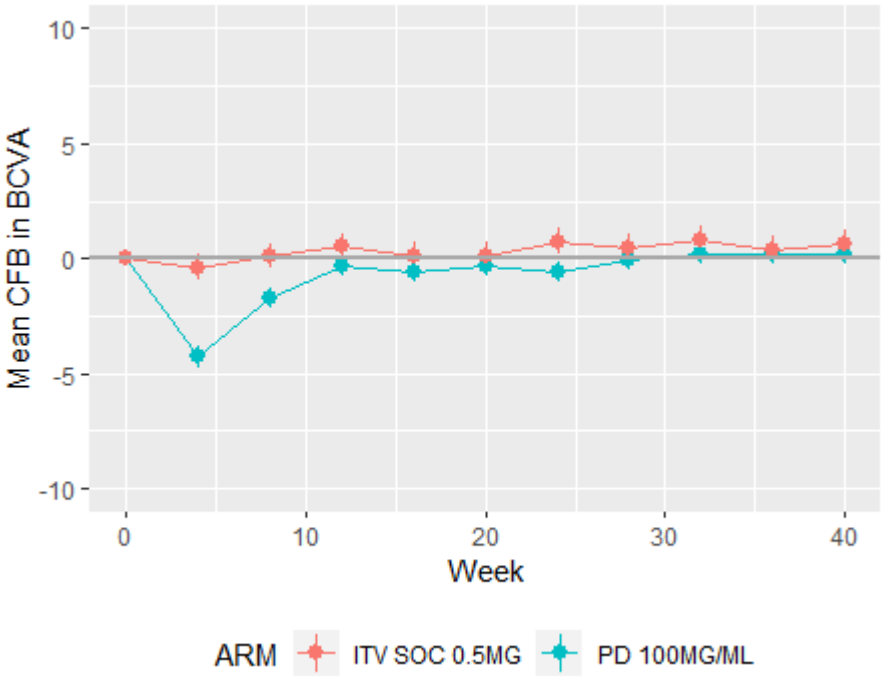
Analysis of Primary Efficacy Endpoint: CFB in BCVA averaged over Weeks 36 and 40

The primary efficacy outcome in the pivotal study was the change from baseline in BCVA (in letters) averaged over Weeks 36 and 40. An increase in the number of letters signals an improvement in visual acuity.

The primary objectives in the pivotal study were demonstration of inferiority and clinical equivalence.

Figure 2 below shows the average CFB in BCVA for all visits starting from baseline through Week 40 for both treatment groups PD 100MG/ML and ITV SOC 0.5MG. A vision loss can be observed for both treatments at Week 4 however, visual acuity improves at later visits.

Figure 2: Average CFB in BCVA per visit, Study GR40548 (Efficacy population)



Treatment comparison in the change from baseline in BCVA averaged over Weeks 36 and was made using a mixed-effects repeated measures (MMRM) model. Table 4 below shows the summary of the CFB in BCVA averaged over Weeks 36 and 40 for the pivotal study GR40548. The table also shows

the CFB in BCVA and the corresponding 95.03% confidence intervals (CIs) separately for Week 36 and Week 40.

Table 4: Summary of CFB in BCVA averaged over Weeks 36 and 40 Study GR40548 (Efficacy population)[b]

	PDS 100 mg/mL (N=248)	**ITV SOC 0.5MG (N=165)**	**Difference[a] (95% CI)**
Week 36	0.18 (0.45) (-0.71, 1.07)	0.38 (0.56) (-0.71,1.48)	-0.10 (0.36) (-0.81,0.61)
Week 40	0.21 (0.46) (-0.69, 1.10)	0.67 (0.56) (-0.43, 1.76)	-0.46 (0.72) (-1.88, 0.95)
Average over Weeks 36 and 40	0.19 (0.40) (-0.60, 0.98)	0.52 (0.49) (-0.441 1.49)	-0.33 **(-1.58,0.92)**

[a] Least squares means (SE), differences and CI were based on a MMRM model with baseline as a continuous covariate.

[b] Efficacy population included all randomized patients who received the study treatment

Source: Reviewer's analysis

The lower bound of the 95.03% CI of the CFB in BCVA averaged over Weeks 36 and 40 is -1.58 (>-4.5) which supports the non-inferiority of the PDS arm to the intravitreal arm. Additionally, the 95.03% CI of the CFB in BCVA averaged over Weeks 36 and 40 is (-1.58, 0.92) which is contained within [-4.5, 4.5] and supports the clinical equivalence of the PDS ant ITV arms.

Table 5 below shows the summary of the CFB in BCVA averaged over Months 9 and 10 for Study GX28228. The table also shows the CFB in BCVA and the corresponding 95.03% confidence intervals (CIs) separately for Month 9 and Month 10.

Table 5: Summary of CFB in BCVA averaged over Months 9 and 10 Study GX28228 (Efficacy population)[b]

	PDS 100 mg/mL (N=59)	**ITV SOC 0.5MG (N=41)**	**Difference[a] (95% CI)**
Month 9	4.92 (1.25) (2.46, 7.39)	3.74 (1.52) (0.74, 6.74)	1.18 (1.97) (-2.71, 5.07)

Month 10	4.92 (1.24) (2.48, 7.36)	2.42 (1.52) (-0.59, 5.42)	2.51 (1.96) (-1.36, 6.38)
Average over Months 9 and 10	4.92 (1.07) (2.82, 7.03)	3.08 (1.30) (0.51, 5.64)	1.84 (-1.48, 5.16)

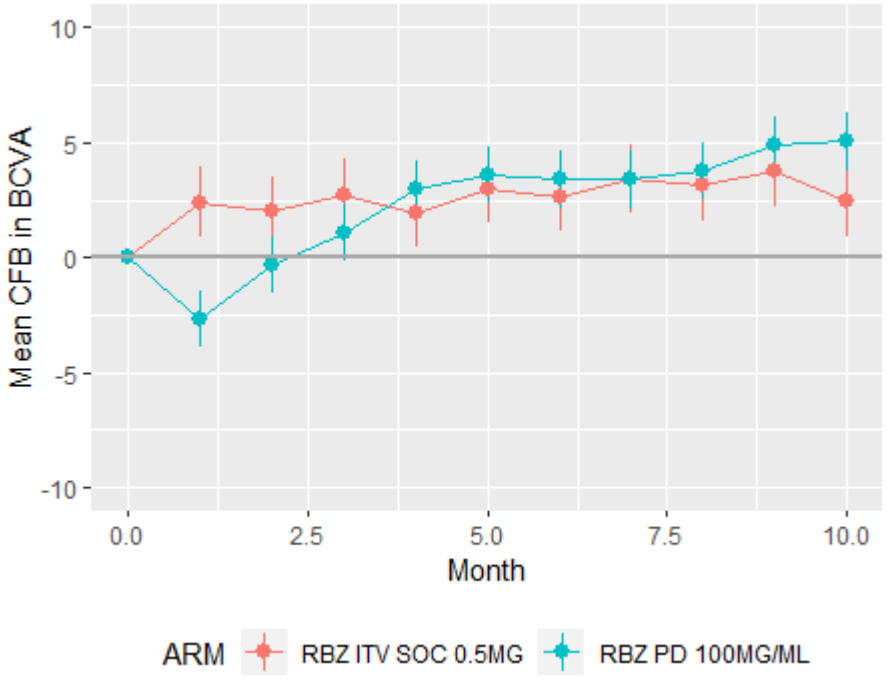
[a] Least squares means (SE), differences and CI were based on a MMRM model with baseline as a continuous covariate.

[b] Efficacy population included all randomized patients who received the study treatment

Source: Reviewer's analysis

The changes of the CFB in BCVA and their comparison between the PDS and intravitreal arms from baseline to Month 10, are also shown in Figure 3 below. We notice that the least square means for two treatment arms get very close in value around Month 4 and remain close until Month 9.

Figure 3: Average CFB in BCVA per visit, Study GX28228 (Efficacy population)



Based on the model, for Study GX28228, patients in the PDS group displayed a statistically non-inferior increase in the CFB in BCVA compared to patients in the ITV group, since the lower bound of the 95% CI is -1.48 (>-4.5).

Sensitivity Analysis of The Primary Efficacy Endpoint

As a sensitivity analysis, the CFB in BCVA averaged over Weeks 36 and 40 was also analyzed using the same MMRM model but using the Per-Protocol population rather than the efficacy population.

Table 6: Summary of CFB in BCVA averaged over Weeks 36 and 40 Study GR40548 (Per-Protocol population)

PDS 100 mg/mL (N=232)	**ITV SOC 0.5MG (N=155)**	**Difference[a] (95% CI)**
0.15 (0.41)	0.55 (0.50)	-0.39 (-1.67, 0.88)

[a] Least squares means (SE), differences and CI were based on a MMRM model with baseline as a continuous covariate.

Source: Reviewer's analysis

Based on the model, in the Per-Protocol population, patients in the PDS group displayed a statistically non-inferior decrease in the CFB in BCVA compared to patients in the ITV group, since the lower bound of the 95% CI is -1.67 (>-4.5).

Supplemental Analysis of The Primary Efficacy Endpoint

The supplemental analysis was performed to determine the difference in BCVA between the PDS and intravitreal treatment arms when patients with the worst outcome are truncated. The analysis of covariance (ANCOVA) model includes the treatment and stratification factor effects as well as, baseline as a continuous covariate. The ANCOVA model is used to estimate the least square means and their standard error, whereas the 95% CIs are estimated using asymptotic normality (Permutt and Li, 2017).

Table 7: Supplemental analysis of **s**ummary of CFB in BCVA averaged over Weeks 36 and 40, Study GR40548

	PDS 100 mg/mL (N=232)	**ITV SOC 0.5MG (N=155)**	**Difference[a] (95% CI)**
Trimmed mean	2.75 (0.28)	3.20 (0.33)	-0.45 (-1.29, 0.39)
Rules for handling missing data after intercurrent events			
1. LOCF	2.73 (0.28)	3.18 (0.33)	-0.45 (-1.29, 0.39)

2. MMRM model, assuming a MAR mechanism	2.75 (0.28)	3.20 (0.33)	-0.45 (-1.29, 0.39)

[a] Least squares means (SE), differences and CI were based on an ANCOVA model.

Source: Reviewer's analysis

It can be noticed from Table 7 that besides the inferential agreement, the numerical outcomes for the primary efficacy endpoint analyses, i.e., the efficacy population analysis, sensitivity, and supplemental analyses, are close. This supports the robustness of the primary efficacy endpoint analysis.

Analysis of Secondary Efficacy Endpoints

For binary secondary efficacy endpoints, Table 9 below shows the proportion of patients in each treatment group as well as, the difference in proportions between the treatment groups. These were estimated using the weighted average of the *observed* proportions and the differences in observed proportions. The weights are defined based on the randomization stratification factor of baseline BCVA (<74 letters vs. ≥74 letters) and using the Cochran-Mantel-Haenszel method.

Table 8: Secondary efficacy endpoints: Adjusted Proportion of Patients with a Change of Visual Acuity from Baseline in the Study Eye through Week 40 (Efficacy population)[a] – Study GR40548

		RBZ PD 100MG/ML N=248	RBZ ITV SOC 0.5MG N=167	Difference[b] (95.03% CI)
Proportion of patients who lose <15 letters of BCVA score from baseline to the average of Weeks 36 and 40	Count, n CMH weighted proportion (%)	240 96.94	158 97.56	0.63 (-2.65, 3.90)
Proportion of patients who lose <10 letters of BCVA score from baseline to the average of Weeks 36 and 40	Count, n CMH weighted proportion	234 95.12	155 95.09	0.03 (-4.24, 4.30)
Proportion of patients who lose <5 letters of BCVA score from baseline to the average of Weeks 36 and 40	Count, n CMH weighted proportion	209 84.96	144 88.34	-3.38 (-10.0, 3.28)
Prop. of patients who gain >=0 letters in BCVA score from baseline to the average over Weeks 36 and 40	Count, n CMH weighted proportion	142 57.76	96 58.89	-1.12 (-10.74, 8.49)
Prop. of patients who	Count, n	51	38	-2.52

gain >=5 letters in BCVA score from baseline to the average over Weeks 36 and 40	CMH weighted proportion	20.77	23.28	(-10.23, 5.20)
Prop. of patients who gain >15 letters in BCVA score from baseline to the average over Weeks 36 and 40	Count, n CMH weighted proportion	4 1.63	2 1.22	0.41 (-1.88. 2.70)

[a] Efficacy population included all randomized patients who received the study treatment.
[b] Weighted proportions and CIs are estimated using the Cochran-Mantel-Haenszel method and the randomization stratification weights.
Source: Reviewer's analysis

The following table shows comparable results between the PDS and ITV arms in terms of visual changes, i.e., visual gain or loss. In other words, the proportions PDS 100 mg/mL Q24W achieved a similar distribution of visual changes compared to monthly ranibizumab; this further demonstrates that both treatments are equally efficacious. For the population enrolled in Study GR40548, who had demonstrated response to anti-VEGF agents, the loss of <10 letters are considered an appropriate threshold to evaluate treatment benefit. This differs from studies in the anti-VEGF naïve population where a loss of <15 letters is a generally accepted endpoint because it is not known whether patients will respond to treatment (Lucentis USPI/SmPC). In Study GR40548, a similar adjusted proportion of patients in the PDS 100 mg/mL arm and the intravitreal arm had a loss of <10 letters, a loss of <5 letters, and a gain of ≥0 letters at the average of Weeks 36 and 40 and from Week 16 through Week 40.

Reviewer's comment
As there is only a small impact of missing values in Study GR40548, the analysis of the binary secondary endpoints is based on all observed data rather than the re-evaluated, after multiple imputation, binary endpoints.

The applicant examined two other binary secondary endpoints based on the rationale that these represent two important vision thresholds:

a. The proportion of patients with a BCVA score of 38 letters or worse at the average of Weeks 36 and 40, since 38 letters (20/200 approximate Snellen equivalent), is the threshold for legal blindness in many countries, and

b. The proportion of patients with a BCVA score of 69 letters or better at the average of Weeks 36 and 40, since 69 letters (20/40 approximate Snellen equivalent), is the threshold required for driving in many countries.

The outcomes of the analysis of these binary endpoints are presented in Table 10.

Table 9: Secondary efficacy endpoints: Proportion of Patients with a BCVA Score of 38 Letters or Worse or 69 Letters or Better at the Average of Weeks 36 and 40

		RBZ PD 100MG/ML N=248	RBZ ITV SOC 0.5MG N=167	Difference (95.03% CI)
Proportion of patients with BCVA score of 38 letters or worse at the average of Weeks 36 and 40	Count, n CMH weighted proportion	3 1.22	3 1.84	-0.61 (-3.10, 1.84)
Proportion of patients with BCVA score of 69 letters or better at the average of Weeks 36 and 40	Count, n CMH weighted proportion	198 80.70	134 82.15	-1.41 (-7.36, 4.54)

At the average of Weeks 36 and 40, a small percentage of 1.22% and 1.84% of the patients in the PDS and ITV arms respectively were below or at the threshold of blindness. Also, At the average of Weeks 36 and 40, 80.7% and 82.15% of the patients were above the threshold required for driving. For both endpoints, the results in the two different arms were comparable.

The change from baseline in center point thickness (CPT) at Week 36 is a secondary endpoint that was used in Study GR40548 to evaluate retinal thickness. A MMRM model with baseline as a continuous covariate was used to estimate the CFB in CPT at Week 36.
A summary of the change from baseline in Center Point Thickness (CPT) at Week 36 is given below in Table 11, below.

Table 10: Summary of the change from baseline in CPT at Week 36 (Efficacy population [b])

PDS 100 mg/mL (N=248)	ITV SOC 0.5MG (N=165)	Difference[a] (95% CI)
5.43 (2.77)	2.54 (3.40)	2.89 (-5.73, 11.52)

[a] Least squares means (SE), differences and CI were based on a MMRM model with baseline as a covariate.
[b] Efficacy population included all randomized patients who received the study treatment.
Source: Reviewer's analysis

Analysis of CFB in CPT over time is given in the Appendix.

3.2.5 Efficacy Conclusion

Based on the totality of evidence in the pivotal study GR40548, the PDS treatment group was shown to be statistically non-inferior to the ITV treatment group in the change from baseline in BCVA averaged over Weeks 36 and 40. The same conclusion was supported by the evidence from Study GX28228. Additionally, given the evidence from Study GR40549, the two treatment groups showed comparable behavior in later time points (until Week 80).

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

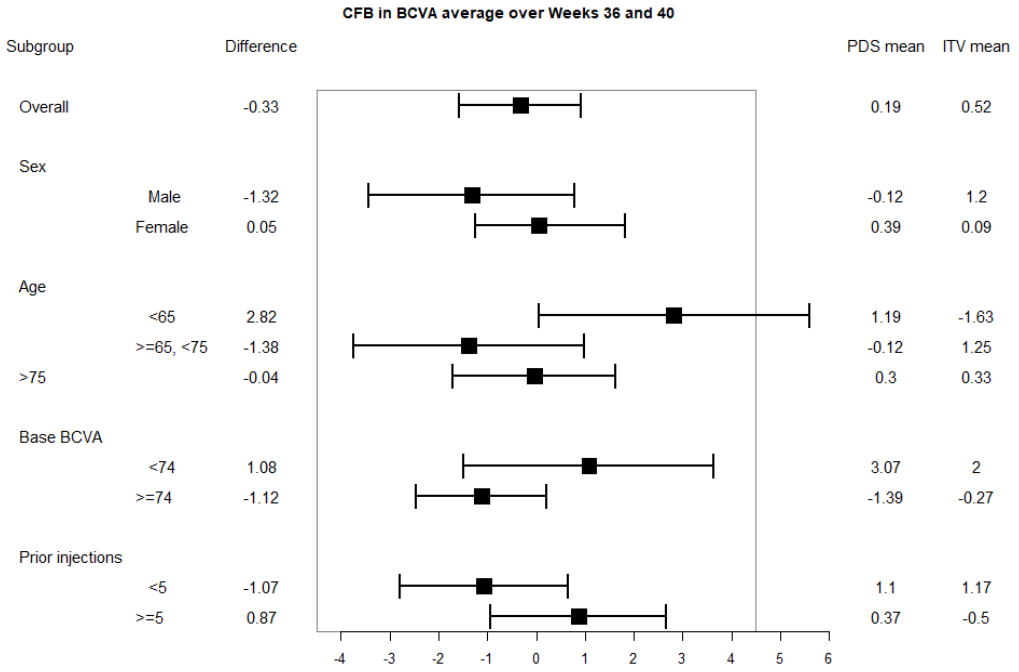
For the pivotal study, the primary efficacy endpoint of CFB in BCVA averaged over Weeks 36 and 40 is evaluated for the following subgroups:

- age (<65 years, 65 to <75 years, ≥75 years),
- sex (male, female),
- number of prior anti-VEGF intravitreal injections (< 5 vs. ≥ 5 prior injections), and
- baseline BCVA score (<74 vs. ≥ 74).

A subgroup analysis for race was not included since the efficacy population consists of 97% White patients.

These subgroup analyses are summarized below in Figure 5. The vertical axes of this forest plot are on (-4.5, 4.5) and mark the non-inferiority (equivalence) limits. Overall, the subgroup analysis findings were consistent with the overall efficacy population analysis for the primary efficacy endpoint.

Figure 4: CFB in BCVA averaged over Weeks 36 and 40 by the subgroups of Sex, Age Group, Baseline BCVA score and prior anti-VEGF injections
(Efficacy population)



[a] Least squares means, differences and CI were based on a MMRM model with baseline as a continuous covariate.

[b] Efficacy population included all randomized patients who received the study treatment

Source: Reviewer's analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues in the submission.

5.2 Collective Evidence

In the pivotal Phase 3 efficacy study, GR40548, the applicant assessed the improvement in BCVA through the CFB in BCVA averaged over Weeks 36 and 40. The findings from the pivotal study showed that this improvement is statistically non-inferior for the PDS arm compared to the intravitreal arm. Findings from the same study also showed that this change is clinically equivalent in the PDS and intravitreal arms. These results showed robustness using the sensitivity and supplemental analyses.

Using the same efficacy endpoint, the non-inferiority of the PDS 100 mg/mL to the ITV SOC 0.5MG arm was also supported from Study GX28228.

Comparability between the visual outcomes of the two treatment arms was also supported by the secondary endpoints in the pivotal study.

5.3 Conclusion and Recommendation

Based on the totality of evidence from Studies GR40548, GX28228 and GR40549, the reviewer concludes that this application provided substantial evidence of efficacy of PDS 100 mg/mL for the treatment of age-related neovascular macular degeneration (nAMD).

Appendix:

1. Change from baseline in BCVA over time, Study GR40549

Table 11: CFB in BCVA over time, Study GR40549

Timepoint		GX28228 RBZ PD 100MG/ML - RBZ ITV SOC 0.5MG (N=29)	GX28228 RBZ PD 100MG/ML – RBZ PD 100MG/ML (N=160)
Week 8	N	29	157
	Mean (SD)	-2.21 (6.22)	-0.63 (5.67)
	Median	-1	-1
	(Min, Max)	(-13, 19)	(-45, 15)
Week 16	N	29	154
	Mean (SD)	-1.69 (6.54)	-0.70 (6.48)
	Median	-2	0
	(Min, Max)	(-10, 25)	(-45, 14)
Week 24	N	29	159
	Mean (SD)	-2.97 (8.04)	-1.64 (8.19)
	Median	-2	-1
	(Min, Max)	(-35, 20)	(-58, 15)
Week 32	N	29	150
	Mean (SD)	-1.38 (5.54)	-0.51 (7.19)
	Median	-1	0
	(Min, Max)	(-10, 19)	(-27, 42)
Week 40	N	28	151
	Mean (SD)	0.11 (5.79)	-0.67 (8.04)
	Median	-0.5	-1
	(Min, Max)	(-9, 22)	(-42, 47)
Week 48	N	29	149

	Mean (SD)	-1.83 (6.88)	-1.20 (8.04)
	Median	-1	-1
	(Min, Max)	(-10, 28)	(-30, 41)
Week 56	N	27	139
	Mean (SD)	-3.37 (5.43)	-2.28 (7.96)
	Median	-3	-1
	(Min, Max)	(-22, 4)	(-30, 41)
Week 64	N	26	136
	Mean (SD)	-1.96 (5.94)	-1.79 (10.11)
	Median	-3	-1
	(Min, Max)	(-10, 20)	(-58, 40)
Week 72	N	28	128
	Mean (SD)	-2.11 (7.44)	-2.23 (9.92)
	Median	-1.5	-1
	(Min, Max)	(-22, 18)	(-35, 59)
Week 80	N	26	119
	Mean (SD)	-4.31 (6.69)	-2.40 (13.13)
	Median	-2.5	-2
	(Min, Max)	(-24, 10)	(-35, 18)
Week 88	N	12	103
	Mean (SD)	-8.42 (8.49)	-2.95 (11.72)
	Median	-6.5	-1
	(Min, Max)	(-27, 0)	(-71, 20)

Source: Reviewer's analysis

Reviewer's note:
The only time points included in Table 11 are those for which there was a substantial number of patients for each treatment arm, so that, the descriptive statistics would be meaningful. Time points with a small number of patients in at least one treatment arm were omitted from this analysis.

2. Change from baseline in CPT over time, Study GR40548

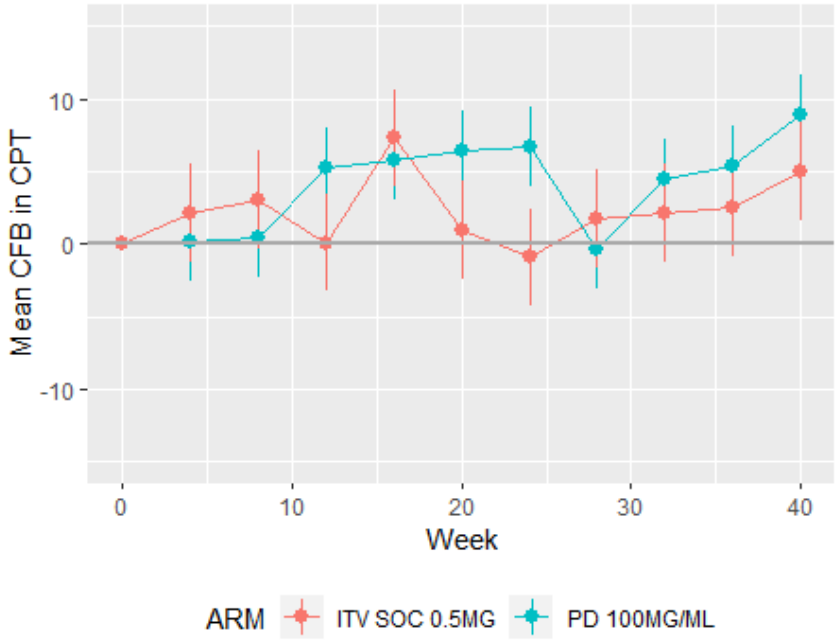
Change from baseline in CPT from Week 4 through Week 40 in the pivotal study has been summarized per time point and treatment arm. The outcomes are shown in Table 12. Additionally, a MMRM model with baseline as covariate has been used to estimate the mean CFB in CPT over the same time interval. The least square means along with their standard error per treatment arm, are shown in Figure 5. A similar behavior between the two treatment arms can be observed, especially at Week 36 which is the secondary endpoint of interest.

Table 12: Summary of the change from baseline in CPT over time (Efficacy population [b])

	ITV SOC 0.5MG N Mean (SD) Median (Min, Max)	PDS 100 mg/mL N Mean (SD) Median (Min, Max)
Week 4	164 1.96 (38.19) 1 (-103, 259)	245 0.44 (29.34) 1 (-135, 241)
Week 8	162 3.10 (39.26) 1 (-108, 255)	247 0.61 (33.13) -1 (-138, 326)
Week 12	161 0.12 (49.26) 0 (-125, 336)	244 5.68 (43.65) 4 (-152, 369)
Week 16	163 6.65 (57.19) 2 (-121, 334)	244 5.35 (53.54) 3 (-170, 560)
Week 20	162 0.82 (42.51) 1 (-131,255)	243 6.72 (44.25) 6 (-162, 320)
Week 24	163 -0.89 (39.17) 2 (-142, 191)	243 7.18 (43. 53) 5 (-163, 196)
Week 28	162 2.35 (42.91) 4 (-129, 262)	241 0.67 (42.50) 1 (-172, 170)
Week 32	162 2.53 (43.70) 4 (-129, 333)	239 4.62 (44.07) 3 (-172, 284)
Week 36	160 2.50 (51.31) 3 (-145, 387)	241 5.44 (44.79) 3 (-171,231)
Week 40	161 4.85 (52.54) 4 (-130, 407)	238 8.75 (54.38) 5 (-179, 425)

Source: Reviewer's analysis

Figure 5: Average CFB in CPT per visit, Study GR40548 (Efficacy population)



Source: Reviewer's analysis

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