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

NDA/BLA #:	BLA125387/S-075
Product Name:	Eylea (aflibercept) Injection
Indication(s):	Treatment of Retinopathy Maturity (ROP)
Applicant:	Regeneron Pharmaceuticals, Inc.
Dates:	Date Submitted: 8/11/2022 PDUFA Goal Date: 02/11/2023
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Biometrics Division:	DBIV
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Key words: ROP, Non-Inferiority, anti–vascular endothelial growth factor (VEGF).

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1 EXECUTIVE SUMMARY

This is a statistical review of the supplemental Biologics License Application (sBLA) submitted by Regeneron Pharmaceuticals, Inc. (Applicant) for intravitreal (IVT) aflibercept [EYLEA®, intravitreal aflibercept injection(IAI)]. This sBLA proposes a new indication of treatment of Retinopathy of Prematurity (ROP) for aflibercept which is approved by the FDA for several other retinal/ophthalmological indications. Along with the new indication, the Applicant is seeking pediatric exclusivity.

The primary evidence for this indication comes from three studies [Study 1920, Study 20090, and Study 20275]. Study 1920 was a 52-week, multicenter, randomized, 2-arm, open-label clinical study. The primary objective of this study was to assess the efficacy and safety of aflibercept in comparison to laser through Week 52. Study 20090 was a 24-week randomized, 2-arm, open-label study designed to assess the efficacy and safety of aflibercept in comparison to laser through Week 24. Study 20275 was a safety extension study which enrolled subjects who completed the 24-week follow up period from Study 20090. The objective of this study was to assess the long-term safety outcomes and visual function of participants from 24 weeks through 5 years of age. In this review, for the evaluation of safety and efficacy, the two studies (20090 and 20275) are considered as one continued study and referred to as Study 20090/20275.

In Study 1920, 127 pediatric participants were randomized in a 3:1 ratio to aflibercept (94 participants) and laser (33 participants). Study 20090 randomized 118 participants in a 2:1 ratio to aflibercept (75 participants) and laser (43 participants). Randomization was stratified by baseline ROP status. Note, after completing the 24-week evaluation in Study 20090, 100 of the 118 subjects enrolled in Study 20090 continued into Study 20275.

The primary efficacy endpoint for both studies was the proportion of responders i.e., participants with absence of active ROP (i.e., ROP requiring treatment) and unfavorable structural outcomes (retinal detachment, macular fold, macular dragging, retrolental opacity) at 52 weeks chronological age (CA). The primary efficacy analysis provided the proportion of responders for each treatment arm and the difference in proportions together with a 2-sided 95.1% CI (see Section 3.2.2 for details). Aflibercept was to be declared non-inferior to laser if the CI of the difference lay entirely above the pre-specified non-inferiority margin of -5%. The primary efficacy analysis was conducted based on the full analysis set (FAS) which included all randomized and treated subjects. Missing Week 52 data was imputed using the observed Week 40 data. However, subjects who discontinued the study at or before Week 40, subjects who received rescue or any second treatment modality, and subjects who discontinued the study between Weeks 40 and 52 due to adverse events, were treated as non-responders. Note, the Applicant had a special protocol assessment (SPA) agreement with the Division of Ophthalmology Products (DOP) concerning the statistical analysis plan, including the non-inferiority margin of 5%.

The primary efficacy analysis results are summarized in Table 1. The proportion of responders at Week 52 in the aflibercept arm was 79.6% in Study 1920 and 78.7% in Study 20090/20275.

The corresponding figures for the laser arm were 77.8% and 81.6%, respectively. The treatment difference (95.1% CI) was 1.8% (-15.7%, 19.3%) in Study 1920 and -1.9% (-17.0%, 13.2%) in Study 20090/20275. Because the lower bounds of the 95.1% CI for the treatment differences are lower that -5%, non-inferiority of aflibercept to laser was not established in either of the two studies.

Table 1: Proportion of Patients with Absence of Active ROP and Unfavorable Structural Outcomes at Week 52 of Chronological Age (FAS)

	Treatments		
Study	**Laser**	**Aflibercept**	**Diff (95.1% CI)**
1920	21/27 (77.8%)	74/93 (79.6%)	1.8% (-15.7%, 19.3%)
20090/20275	31/38 (81.6%)	59/75 (78.7%)	-1.9% (-17.0%, 13.2%)

Source: Table 11 of the Applicant's Study Report.

Regarding safety, in Study 1920, the incidence of adverse events (AEs) of any kind was numerically lower in the aflibercept group (74.2%) than the laser group (85.2%) group. Besides, a numerically lower proportion of participants in the aflibercept group reported at least one serious AE (34.4%) compared to participants in the laser group (44.4%). In Study 20090/20275, the incidence of adverse events (AEs) of any kind was comparable between the aflibercept (94.7%) and laser (92.1%) groups, while a numerically lower proportion of participants had a serious AE in the aflibercept group (33.3%) than the laser group (44.7%). In the two studies combined, a total of 4 deaths, all in the aflibercept group, were reported.

In summary, neither of the studies met the pre-specified and SPA agreed non-inferiority criteria. However, in both arms, over 77% of treated subjects achieved absence of active ROP and unfavorable structural outcomes at 52 weeks CA. In addition, based on natural history of the disease, the Applicant assumed a placebo rate of close to zero. If this assumption is clinically justified, it is reasonable to assume that, in a hypothetical match up, aflibercept will have at least a statistically significant treatment difference compared to placebo. Besides, the lower incidence of adverse events including serious adverse events reported in these studies for subjects treated with aflibercept imply a better safety profile than laser. Therefore, the final determination for adding this indication for aflibercept should be made based on a clinical judgment taking the favorable safety outcomes into consideration.

2 INTRODUCTION

This is the statistical review of the supplemental Biologics License Application (sBLA) submitted by Regeneron Pharmaceuticals, Inc, referred to as the Applicant, on August 11, 2022, for 0.4 mg mL aflibercept (EYLEA®, IAI). The proposed indication is for the treatment of Retinopathy of Prematurity (ROP). The primary evidence of efficacy and safety for this sBLA comes from three studies [Study 1920, Study 20090, and Study 20275]. The studies were conducted across multiple sites located globally. Study 1920 enrolled 127 subjects across 39 sites located in Europe, Asia, North America, and South America. Similarly, Study 20090 enrolled 118 subjects across 64 sites located in 27 countries. After completing their 24-weeks of follow up, 100 of the 118 subjects enrolled in Study 20090 were enrolled into Study 20275. For evaluation of safety and efficacy, the two studies are considered as one continued study and referred to in this review as Study 20090/20275.

The Applicant proposes to include findings from Study 1920 and Study 20090/20275 into the "Clinical Studies" (Section 14) of the US Prescribing Information (USPI) to describe the efficacy of 0.4 mg mL aflibercept in the treatment of ROP. This review investigates whether the findings from these studies support the proposed indication and provides recommendations for the USPI to be considered by the Division of Ophthalmology (DOP), if the product is approved.

2.1 Overview

This section provides a brief overview of the class and indication of the studied drug, the history of the drug development and outlines the Applicant's summary of the specific studies reviewed.

2.1.1 Drug Class and Indication

The Applicant is evaluating the efficacy of a single injection of 0.4 mg mL aflibercept for the treatment of ROP. The selected dose corresponds to 20% of the licensed adult dose. Per the Applicant, the efficacy and safety of intravitreal (IVT) aflibercept, an anti-vascular endothelial growth factor (VEGF), in adult patients with retinal/ophthalmological diseases mediated by overexpression of VEGF are well established with a favorable benefit-risk profile.

Per the Applicant, since ROP is also characterized by the pathological development of the retinal vasculature and has been associated with VEGF upregulation, inhibition of VEGF activity by aflibercept can be expected to result in therapeutic benefit in premature infants with treatment requiring ROP.

2.1.2 History of Drug Development

The protocols and the statistical analysis plans for Study 1920 and Study 20090/20275 were reviewed under IND12462. The summary of the relevant interactions between the Applicant and the DOP is provided below:

- On 10/17/2018, the Applicant had a teleconference with the DOP. The objective of the meeting was to gain concurrence from the DOP on Pediatric Written Request (PWR) for a clinical development program for ROP, as well as the eligibility for a 6-month pediatric exclusivity extension upon the fulfillment of the PWR for ROP. The Division informed the Applicant that for supporting the ROP indication and PWR fulfillment, results from two active-controlled (e.g., laser photocoagulation treatment) studies are needed.

- On 04/15/2019, the Applicant submitted the initial protocols for the ROP studies under IND12462.

- On 06/04/2019, the DOP issued PWR for aflibercept for the treatment of ROP based on the 04/15/2019 submission to IND12462. In this request, the Division advised the Applicant to consider the following key study program design elements:

    - Two randomized, open-label, controlled studies.

    - A total of 150 aflibercept-treated ROP patients.

    - Follow up period through 52 weeks of chronological age for the proposed studies.

    - Long-term follow-up (5 years) is needed but will not be a required term in the Pediatric Written Request.

- On 06/21/2019, the Applicant submitted the agreement to the PWR to study aflibercept for the treatment of ROP.

- On 06/27/2019 the Applicant submitted 2 ROP study protocols, as per the PWR requirement, seeking the DOP's agreement.

- On 10/30/2019 the Applicant submitted the statistical analysis plans (SAP) for their study (1920) and the Bayer sponsored study program consisting of 2 study protocols (20090 and 20275), as per PWR requirement, seeking the Division's agreement. After the review of the SAP, the DOP provided the following comments:

    1) We strongly prefer a 2:1 randomization ratio in the study instead of a 3:1 randomization.

    2) In Section 5.5.1.1 of the SAP, you stated that non-inferiority evaluation will be based on one-sided 95% confidence interval of the difference of response rates between the aflibercept group and the laser group. However, the evaluation of non-inferiority should be made based on one-side 97.5% (or two-sided 95%) confidence interval estimate.

3) Per the SAP, the primary efficacy analysis will be based on the FAS population including all randomized subjects who receive any study treatment. However, the FAS definition may not preserve randomization if an imbalance exists in the number of randomized subjects who may not receive any treatment in the two groups as was the case in the RAINBOW study. Therefore, as a sensitivity analysis, we recommend that the primary analysis also be performed based on all randomized subjects.

4) You stated that subjects in both treatment groups may receive rescue treatment based on protocol-defined criteria. We recommend that these subjects remain in the study even after receiving rescue therapy and their efficacy and safety data after rescue be collected. Also, please provide a summary of the number and percentage of subjects who receive rescue medication during the study for each treatment group.

5) In Section 5.5.1.1 of the SAP, you stated the following: "If the patient data are not available at end of study (EOS) visit, then data available from the week 40 of chronological age visit will be carried forward (LOCF) to the end of study (EOS) visit for analysis." For patients that may discontinue the study due to an adverse event between Week 40 and Week 52, we recommend that these patients be considered as non-responders for the primary efficacy variable.

- On 03/05/2020, the Applicant submitted an amendment to the SAP incorporating some of the comments they received in the prior review. They received feedback on the amended SAP on 09/14/2020. In the response, the DOP reiterated that a 2:1 randomization ratio is still recommended and that the non-inferiority assessments in both studies should be made based on one-side 97.5% (or two-sided 95%) confidence interval estimate.

- On 12/15/2020, the Applicant submitted a second SAP amendment and had a teleconference with the DOP regarding the amended SAPs on 02/10/2021. During the meeting, the Division advised the Applicant to submit a special protocol assessment (SPA) for gaining the DOP's agreement that the protocols and associated SAPs are acceptable for filing in accordance with terms of the PWR issued by DOP on 06/04/2019 for EYLEA in the treatment of ROP.

- On 02/18/2021 the Applicant submitted a SPA and received a "No Agreement" letter on 03/30/2021. The following reasons were given for "No Agreement":

    - Appropriate statistical adjustments have not been made for all looks of the data by the Data Monitoring Committee (DMC).

    - Per the protocol "No interim analysis is planned. However, safety assessments will be continuously performed." Statistical adjustments should be made for all looks of the data.

- The DMC charter should be submitted to the IND.

- All confidence intervals should be established based on two-sided 95% confidence interval estimate.

- After establishing the noninferiority of aflibercept to laser in the primary efficacy variable, you state that superiority may be declared if the lower confidence limit lies above 0. To appropriately control the Type I error rate, please clarify if the superiority testing of aflibercept to laser in the primary efficacy variable will be tested before or after the secondary efficacy variables.

- The Week 24 timepoint in the protocol for Study 20090 is too early to evaluate the safety and efficacy of the product. Data from the extension study is needed. We consider the evaluation at Week 52 to be more relevant than Week 24.

- On 04/15/2021, the Applicant responded to the DOP's "No Agreement" letter. The Applicant proposed to include the following aspects of the SAP:

  - Alpha adjustment (0.001) for all looks of the data by the DMC.

  - Confidence intervals to be established based on 2-sided 95% confidence interval analysis as primary analysis.

  - Planned testing hierarchy (following noninferiority tested in the primary efficacy variable) to be clarified.

  - Week 52 chronological age endpoint to be captured in the "FIREFLEYE NEXT (Study 20275)" portion of the FIREFLEYE (Study 20090) and FIREFLEYE NEXT (Study 20275) combination, yielding a single clinical study report (CSR) in support of the PWR fulfillment and a potential sBLA submission.

- On 05/12/2021, the Applicant had a follow-up meeting for SPA. As part of the meeting package, the Applicant submitted the protocols and the statistical analysis plans for the three studies.

- On 06/24/2021, the DOP issued SPA agreement letter to the Applicant. The Division stated that based on the information submitted, we agree that the design and planned analysis of your studies adequately address the objectives necessary to support a regulatory submission.

2.1.3 Studies Reviewed

The Applicant's overall efficacy summary of Studies 1920 and 20090/20275 is presented in Table 2.

Table 2: Efficacy Summaries of 1920 and 20090/20275

Design	Treatment (Sample size)	Endpoint/Analysis	Applicant's findings
1920 [1]MC, RD, OL, PG, AC	▪ Aflibercept (N=93) ▪ Laser (N=27)	**Primary Endpoint**: Proportion of participants with absence of both active ROP and unfavorable structural outcomes at 52 weeks of chronological age based on the investigator's assessment. The statistical analysis was performed using the Cochran-Mantel-Haenszel (CMH) method stratified by baseline ROP status. The 2-sided 95.1% Mantel- Haenszel confidence intervals (CIs) (reflecting an alpha adjustment of 0.001 for the data monitoring committee (DMC) assessments) using normal approximation of the difference of response rates between the aflibercept group and the laser group were calculated. Aflibercept was non-inferior to laser if the CI of the difference lay entirely above -5%. The primary efficacy variable analysis was conducted based on the Full Analysis Set (FAS) which included all randomized participants who received any study intervention.	While non-inferiority of aflibercept to laser could not be established at a significance level of 0.0245 (1-sided) in the primary analysis and the lower bound of the 95.1% CI for treatment difference was below the non-inferiority margin of -5%., a numerically larger proportion of participants in the aflibercept group met the primary endpoint as compared to those in the laser group. The adjusted difference (95.1% CI) was 1.81% (-15.71%, 19.33%) with 79.6% of participants in the aflibercept group and 77.8% in the laser group meeting the primary efficacy endpoint.
20090/20275 [1]MC, RD, OL, PG, AC	▪ Aflibercept (N=75) ▪ Laser (N=38)	**Primary Endpoint**: Proportion of participants with absence of both active ROP and unfavorable structural outcomes at 52 weeks of chronological age based on the investigator's assessment. The statistical analysis was performed using the Cochran-Mantel-Haenszel (CMH) method stratified by baseline ROP status. The 2-sided 95.1% Mantel- Haenszel confidence intervals (CIs) (reflecting an alpha adjustment of 0.001 for the data monitoring committee (DMC) assessments) using normal approximation of the difference of response rates between the aflibercept group and the laser group were calculated. Aflibercept was non-inferior to laser if the CI of the difference lay entirely above -5%. The primary efficacy variable analysis was conducted based on the Full Analysis Set (FAS) which included all randomized participants who received any study intervention.	Non-inferiority of aflibercept to laser could not be established at a significance level of 0.0245 (1 sided) in the primary analysis and the lower bound of the 95.1% CI for treatment difference was below the non-inferiority margin of -5%. The adjusted difference (95.1% CI) was -1.88% (-16.99%, 13.23%) with 78.7% of participants in the aflibercept group and 81.6% in the laser group meeting the primary efficacy endpoint.

Source: Applicant's Study Reports. [1]MC: multicenter, RD: randomized, OL: Open-label, PG: parallel-group, AC: Active-controlled.

2.2 Data Sources

This sBLA application was submitted electronically and includes full study reports as well as standardized datasets using SDTM and ADaM formats that are relevant for the analyses of

studies 1920 and 20090/20275 presented in this review. Datasets and corresponding definition files can be found at the following location:

Study 1920: \\CDSESUB1\evsprod\BLA125387\0702\m5\datasets
Study 20090/20275: \\CDSESUB1\evsprod\BLA125387\0689\m5\datasets

For each study, the following datasets submitted by the Applicant are used in this statistical review:

- adsl.xpt contains the demographic and disposition data
- adoerop.xpt contains the ROP efficacy data
- adae.xpt contains the adverse event data
- advs.xpt contains the vital signs data

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the datasets and analyses conducted by the Applicant are acceptable. The data definition files, and reviewer's guide submitted in the sBLA were sufficiently detailed to facilitate replication of the findings from the Applicant's primary analysis and other major analyses using the submitted datasets.

3.2 Evaluation of Efficacy

This section summarizes the design of studies 1920 and 20090/20275 and the corresponding efficacy results submitted by the Applicant and produced by the reviewer's analyses.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Studies 1920 and 20090/20275 were phase 3, multicenter, randomized, 2-arm, open-label non-inferiority studies. These studies were designed to evaluate the efficacy, safety, and tolerability of intravitreal (IVT) aflibercept versus laser in participants with ROP. Eligible subjects who signed informed consent had to meet the following criteria:

- Gestational age at birth ≤32 weeks or birth weight ≤1500 g
- Treatment-naïve ROP classified according to the international classification of retinopathy of prematurity (ICROP) in at least one eye as:
  - Zone I Stage 1 plus, or 2 plus, or 3 non-plus or 3 plus, or

- Zone II Stage 2 plus or 3 plus, or
- AP-ROP

– Weight at baseline (day of treatment) ≥800 g

3.2.1.1 Randomization and Treatment

Study 1920

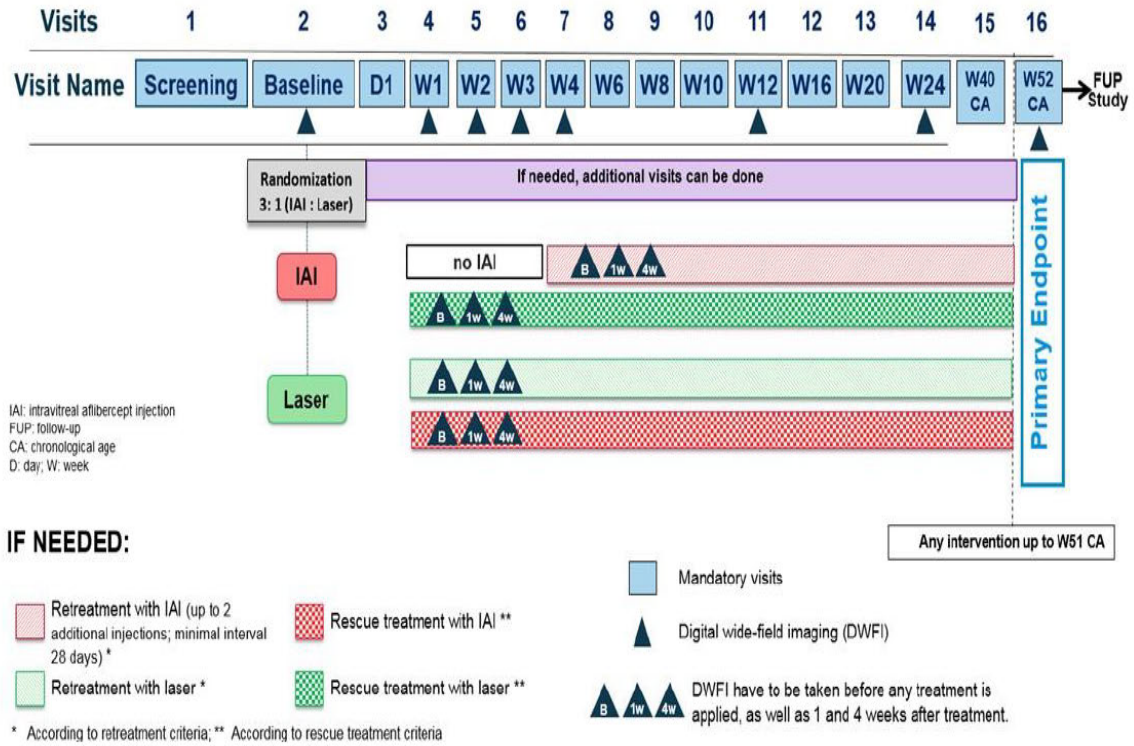
This study used a 3:1 randomization ratio for allocating eligible patients to the two study treatments:

- Aflibercept: 0.4 mg aflibercept administered at baseline (day 1) and if required, each treated eye could receive re-treatment (up to 2 re-treatments in the aflibercept group at least 28 days after the previous injection).

- Laser: laser treatment at baseline in the study eye

Randomization was to be stratified by ROP classification in Zone I, Zone II, or AP-ROP. The total duration of this study was 52-weeks. The study had scheduled visits occurring at Screening, Baseline, Day 1, and Weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 40 and 52 (See Study Design Schema in Figure 1).

Figure 1: Study Design Schema (1920)



Study 20090/20275

This is a combination of two consecutive studies, Study 20090, and Study 20275. Study 20090 was a 24-week phase 3, randomized, multicenter, 2-arm, open-label clinical study. Study 20275 is a phase 3b, multi-center study designed to assess the long-term outcomes of participants previously diagnosed with ROP who were treated in the completed Study 20090.

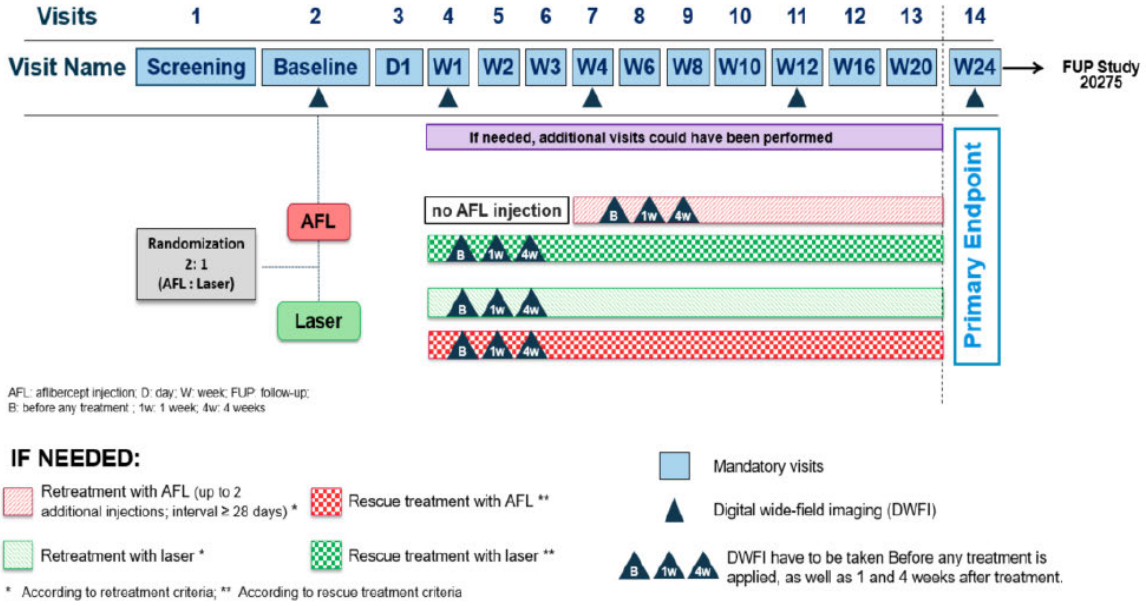
Study 20090 used a 2:1 randomization ratio for allocating eligible patients to the two study treatments:

- Aflibercept: 0.4 mg aflibercept administered at baseline (day 1) and if required, each treated eye could receive re-treatment (up to 2 re-treatments in the aflibercept group at least 28 days after the previous injection).

- Laser: laser treatment at baseline in the study eye

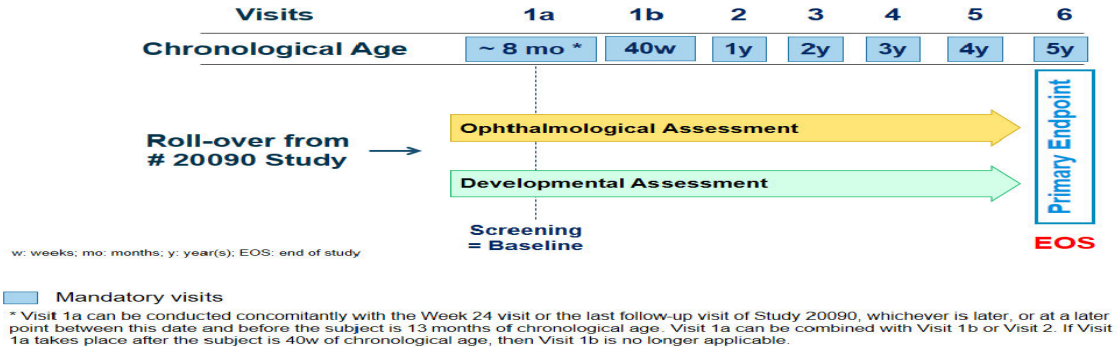
Randomization was to be stratified by Japanese and non-Japanese study sites as well as by ROP classification according to investigator assessment. The total duration of this study was 24-weeks. The study had scheduled visits occurring at Screening, Baseline, Day 1, and Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 (See Study Design Schema).

Figure 2: Study Design Schema (20090)



Note, the extension study, Study 20275, no study intervention is administered. Therefore, the efficacy evaluation at Week 52 in the combination study refers to the evaluation conducted by counting the time from the baseline of Study 20090. The study Schema for this extension study is provided in Figure 3.

Figure 3: Study Design Schema (20275)



3.2.1.2 Rescue Medications

For subjects in the aflibercept arm, rescue treatment with laser was allowed if 1 of the following conditions was met:

- Worsening of ROP compared to the examination before the previous injection during the 27 days following that IVT aflibercept injection, OR
- Presence of ROP requiring treatment after the participant already received a total of 3 aflibercept injections

Similarly, for subjects in the Laser arm, rescue treatment with aflibercept 0.4 mg/0.01 mL was allowed if the fundus examination revealed laser treatment was complete as judged by the investigator and if 1 of the following conditions was met:

- Worsening of ROP compared to the most recent pre-laser examination, OR
- Persistence of ROP requiring treatment

Participants who initiated aflibercept rescue treatment were thereafter managed according to the aflibercept group treatment regimen.

3.2.1.3 Efficacy Endpoints

The primary efficacy endpoint of these studies was the proportion of patients with absence of active ROP and unfavorable structural outcomes at 52 weeks of chronological age (CA) after starting study treatment. Note, in both studies, for the primary efficacy endpoint, the participant was the experimental unit. If both eyes were eligible and treated within 8 weeks from baseline, the success of the primary efficacy endpoint was determined by both eyes. If both eyes were eligible and treated but the second eye was treated after 8 weeks of the initial treatment of the first eye, then the success of the primary endpoint was determined by the first eye only. If only 1 eye was eligible and treated, then the success of the primary endpoint was determined by that eye.

3.2.2 Statistical Methods

This section describes the statistical hypotheses, sample size calculation, analyses populations and the efficacy analyses presented in this review that are performed by the Applicant, as described in the statistical analysis plans (SAPs) for studies 1920 and 20090/20275, as well as independent analyses performed by the statistical reviewer. All statistical analyses are performed at the 0.049 significance level (two-sided).

Reviewer's remark: The Division recommended an alpha adjustment of 0.001 for DMC assessment. Therefore, the alpha of 0.049 (95.1% CI) reflects an adjustment of 0.001.

3.2.2.1 Statistical Hypotheses and Sample Size

Hypothesis

The primary null and alternative hypotheses can be mathematically stated as follows:

$$H_{o1}: P_t - P_c \leq -5\%$$
$$H_{a1}: P_t - P_c > -5\%$$

where Pt, and Pc are the true proportion of participants with absence of active ROP and unfavorable structural outcomes at week 52 CA for the aflibercept group the laser group, respectively. A conclusion that aflibercept is non-inferior to laser is made if the lower bound for the 2-sided 95.1% confidence interval (CI) for the difference in proportions is greater than the pre-specified non-inferiority margin, -5%.

If aflibercept is demonstrated to be non-inferior to laser for the primary endpoint, a hierarchical procedure for testing superiority was to be used for the analysis of the secondary endpoints in the following order:

- Proportion of patients requiring intervention with a second treatment modality from baseline to week 52 CA.

- Proportion of patients with recurrence of ROP through week 52 CA.

Sample Size

In both studies, the Applicant calculates that a sample size of 112 subjects will provide approximately 86% power to demonstrate non-inferiority of an Aflibercept arm versus Laser with a non-inferiority margin of 5%. This calculation assumes that the tests will be conducted at 1-sided alpha level of 0.025; and a 90% response rate for aflibercept and a 66.1% response rate for the Laser arm.

Non-inferiority Margin Derivation

Per the Applicant, the non-inferiority margin of 5% was determined based on the results of the RAINBOW study. Note, the RAINBOW study was a randomized, controlled study evaluating the efficacy and safety of Ranibizumab compared with laser therapy for the treatment of infants born prematurely with ROP. In the RAINBOW study, the success rate for laser was 66.2% (95% CI: 55.0% to 77.4%). Per the Applicant, the success rate for a putative placebo is assumed to be near 0%. Using this assumption, the margin, M1 (also known as statistical margin), is conservatively assumed to be the lower limit of 95% CI for the treatment difference (laser–putative placebo), i.e., 55%. The smaller margin, M2=5% (also known as the clinical margin) was prespecified such that a large fraction of the active control (laser) treatment effect is preserved for treating ROP. The proposed NI margin of 5% is therefore the smaller of M1 and M2 and preserves at least 90.9% of the control treatment effect. The Applicant stated in the statistical analysis plan that, this NI margin is adequate and justified.

3.2.2.2 Analysis Populations

The SAP of the studies defined the following analysis populations:

- The safety analysis set (SAF): included all treated participants who received any amount of study drug.

- The full analysis set (FAS): included all randomized participants who received any study intervention.

- The per protocol set (PPS): included all participants in the FAS who had no validity findings or important deviations.

3.2.2.3 Analysis Methods

Analysis of the Primary Efficacy Endpoint

The primary efficacy analyses in both studies provided the treatment difference (aflibercept minus laser) in the proportion of responders and the corresponding 2-sided 95.1% confidence interval. The confidence intervals were computed using the Cochran–Mantel–Haenszel (CMH) weighted method with the baseline ROP status used as a stratification factor. A responder is a subject with absence of active ROP and unfavorable structural outcomes at 52 weeks of CA after starting study treatment. Note, for participants with both eyes enrolled in the study, both eyes must have met the responder criteria, i.e., the unit of analysis was the subject.

The primary efficacy analysis was conducted based on the FAS population with missing Week 52 data imputed using the observed Week 40 data. However, subjects who discontinued the study at or before Week 40, subjects who received rescue or any second treatment modality, and subjects who discontinued the study between Weeks 40 and 52 due to adverse events, were treated as non-responders. As sensitivity analysis, the Applicant conducted the analysis of the

primary efficacy endpoint on the ITT population (all randomized) and the PP population applying the same missing data handling methods used in the primary efficacy analysis.

Analyses of the Key Secondary Primary Efficacy Endpoints

Recall, if the non-inferiority of the primary endpoint was declared significant, a hierarchical procedure for testing superiority was to be used for the analysis of the secondary endpoints to control the overall alpha error rate at the 0.05 level based on the following order:

- Proportion of patients requiring intervention with a second treatment modality from baseline to week 52 CA.

- Proportion of patients with recurrence of ROP through week 52 CA.

The analysis of the key secondary endpoints was conducted based on the same analysis method used for the primary efficacy endpoint.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

The patient disposition for each study is provided in this section. The summary shows that, in both studies, more subjects in the laser arm discontinued the study compared to the aflibercept arm. The main reason for study discontinuation was withdrawal by the parent/Guardian.

As noted earlier, Study 20090/20275 was a combination of two studies conducted sequentially. Of the 118 subjects enrolled in Study 20090, 104 completed Week 24 and 100 of those entered Study 20275 (Table 4). The percentage of subjects who entered the extension study (20275) was lower in the laser arm (79%) compared to the aflibercept arm (88%).

Table 3: Patient Disposition (Study 1920; ITT)

	Laser (N=33)	**Aflibercept (N=94)**	**Total (N=127)**
All randomized patients	33	94	127
All treated patients	27 (81.8%)	93 (98.9%)	120 (94.5%)
Number of patients who completed study	26 (78.8%)	87 (92.6%)	113 (89.0%)
Number of patients who discontinued from the study	7 (21.2%)	7 (7.4%)	14 (11.0%)
Death	0	1 (1.1%)	1 (0.8%)
Lost To Follow-Up	0	3 (3.2%)	3 (2.4%)
Physician Decision	1 (3.0%)	0	1 (0.8%)
Withdrawal By Parent/Guardian	6 (18.2%)	3 (3.2%)	9 (7.1%)

Source: Table 2 of the Applicant's Study Reports.

Table 4: Patient Disposition (Study 20090/20275; ITT)

	Laser (N=43)	**Aflibercept (N=75)**	**Total (N=118)**
All randomized patients to Study 20090	43	75	118
Number of patients who completed Study 20090	36 (83.7%)	68 (90.7%)	104 (88.1%)

Number of patients who discontinued early in Study 20090	7 (16.3%)	7 (9.3%)	14 (11.9%)
Adverse Event	1 (2.3%)	1 (1.3%)	2 (1.7%)
Death	0	3 (4.0%)	3 (2.5%)
Other	0	1 (1.3%)	1 (0.8%)
Physician Decision	1 (2.3%)	1 (1.3%)	2 (1.7%)
Withdrawal by Parent/Guardian	5 (11.6%)	1 (1.3%)	6 (5.1%)
Number of patients who entered Study 20275	34 (79.1%)	66 (88.0%)	100 (84.7%)
Completed week 52 chronological age visit Number of patients ongoing in Study 20275	34 (79.1%)	66 (88.0%)	100 (84.7%)
Number of patients who discontinued early in Study 20275 (prior to week 52 chronological age visit)	0	0	0

Source: Table 2 of the Applicant's Study Reports.

The summary of subjects included in the different analysis populations is summarized in Table 5 and Table 6. In both studies, more subjects were excluded from the FAS population in the laser arm compared to the aflibercept arm. The main reason subjects were excluded from the FAS population was missed treatments.

Table 5: Number of Subjects Included in the Analyses Populations (All Randomized: Study 1920)

	Laser (N=33)	**Aflibercept (N=94)**	**Total (N=127)**
Patients included in the Safety Analysis Set (SAF), n(%)	27 (81.8%)	93 (98.9%)	120 (94.5%)
Patients excluded from SAF (Not Treated), n(%)	6 (18.2%)	1 (1.1%)	7 (5.5%)
Patients included in the Full Analyses Set (FAS), n(%)	27 (81.8%)	93 (98.9%)	120 (94.5%)
Patients excluded from FAS, n(%)	6 (18.2%)	1 (1.1%)	7 (5.5%)
Patients included in the Per Protocol Set (PPS), n(%)	24 (72.7%)	68 (72.3%)	92 (72.4%)
Patients excluded from PPS, n(%)	9 (27.3%)	26 (27.7%)	35 (27.6%)

Source: Table 3 of the Applicant's Study Reports.

Table 6: Number of Subjects Included in the Analyses Populations (All Randomized: Study 20090/20275)

	Laser (N=43)	**Aflibercept (N=75)**	**Total (N=118)**
All randomized patients	43	75	118
Patients included in the Safety Set (SAF), n(%)	38 (88.4%)	75 (100%)	113 (95.8%)
Patients excluded from SAF (Not Treated), n(%)	5 (11.6%)	0	5 (4.2%)
Patients included in the Full Analysis Set (FAS), n(%)	38 (88.4%)	75 (100%)	113 (95.8%)
Patients excluded from FAS, n(%)	5 (11.6%)	0	5 (4.2%)
Patients included in the Per Protocol Set (PPS), n(%)	35 (81.4%)	66 (88.0%)	101 (85.6%)
Patients excluded from PPS, n(%)	8 (18.6%)	9 (12.0%)	17 (14.4%)

Source: Table 3 of the Applicant's Study Reports.

The summary of subjects who received rescue medication is presented in Table 7. In study 1920, comparable proportion of subjects received rescue medication using the opposite treatment. However, in Study 20090/20275, a higher proportion of subjects the laser group received rescue medication compared to the aflibercept group.

Table 7: Summary of Subjects Who Received Rescue Medications (FAS)

Study	**Laser**	**Aflibercept**
1920	4/27 (14.8%)	13/93 (14.0%)
20090/20275	4/38 (10.5%)	5/75 (6.7%)

Source: Table 14.1.4.3.2 of the Applicant's Study Reports.

In Study 1920, of the 13 subjects in the aflibercept arm who received rescue medication, 11 did so because of worsening of ROP less than 27 Days from the last injection; one because of presence of ROP after 3 aflibercept injection. The reason for rescue use was not specified for one subject. For the laser arm, 2 of the 4 subjects who received rescue medication did so because of persistence of ROP requiring treatment; one had ROP worsening compared to pre-laser treatment and the reason for rescue was not specified for one subject. In Study 20090/20275, all 5 subjects in the aflibercept arm received rescue medication because of worsening of ROP compared to the previous visit. For the laser arm, 2 of the 4 subjects who received rescue medication did so because of persistence of ROP requiring treatment; one had ROP worsening compared to pre-laser treatment and the reason for rescue was not specified for one subject.

3.2.3.2 Demographic and Baseline Characteristics

For Study 1920, there were notable differences between the treatment arms with respect to baseline body weight, race, and gender. Participants in the aflibercept group weighed less than those in the laser group; fewer participants in the aflibercept group identified as white compared to the laser group; more participants in the aflibercept group identified as racially "other" compared to the laser group; and more participants in the aflibercept group were female compared to the laser group. In Study 20090/20275, there was notable difference between the two arms with respect to baseline weight; participants in the aflibercept group weighed more than those in the laser group. Per the Applicant, these observed differences did not impact the safety and efficacy outcomes.

Table 8: Baseline and Demographic Characteristics (Study 1920)

	Laser (N=27)	**Aflibercept (N=93)**	**Total (N=120)**
Chronological Age at Randomization (weeks), n			
Mean (SD)	11.09 (4.338)	9.76 (3.149)	10.06 (3.476)
Median (Min; Max)	11.00 (5.00 : 22.9)	9.90 (4.1 : 19.4)	10.00 (4.1 : 22.9)
Q1 : Q3	6.60 : 13.90	7.40 : 11.60	7.35 : 12.30
Gestational Age at Birth (weeks), n	27	93	120
Mean (SD)	27.06 (2.652)	27.34 (2.753)	27.28 (2.722)
Median (Min; Max)	26.90 (23.1 : 31.9)	27.00 (23.0 : 33.0)	27.00 (23.0 : 33.0)
Q1 : Q3	24.70 : 29.00	25.00 : 30.00	24.95 : 29.30
Post-Menstrual Age at Randomization (weeks) , n	27	93	120
Mean (SD)	38.15 (3.599)	37.11 (2.425)	37.34 (2.751)
Median (Min; Max)	38.30 (32.9 : 50.6)	36.90 (32.6 : 43.6)	37.00 (32.6 : 50.6)
Q1 : Q3	35.40 : 39.90	35.40 : 38.40	35.40 : 38.80
Gestational Age at Birth group, n (%)	27	93	120
<=26 weeks	11 (40.7%)	38 (40.9%)	49 (40.8%)
>26 weeks	16 (59.3%)	55 (59.1%)	71 (59.2%)
Race, n(%)			
White	11 (40.7%)	26 (28.0%)	37 (30.8%)
Black or African American	2 (7.4%)	6 (6.5%)	8 (6.7%)
Asian	13 (48.1%)	44 (47.3%)	57 (47.5%)
American Indian or Alaska Native	0	0	0

Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (3.7%)	12 (12.9%)	13 (10.8%)
Not Reported	0	5 (5.4%)	5 (4.2%)
Sex, n(%)			
Female	10 (37.0%)	52 (55.9%)	62 (51.7%)
Male	17 (63.0%)	41 (44.1%)	58 (48.3%)
Weight at Birth (g), n	27	93	120
Mean (SD)	934.1 (406.61)	991.2 (407.00)	978.3 (405.91)
Median (Min; Max)	798.0 (430 : 1990)	900.0 (476 : 2230)	900.0 (430 : 2230)
Q1:Q3	615.0 : 1122.0	630.0 : 1270.0	630.0 : 1265.0
APGAR score category 1 min after birth, n (%)			
0 - 4	15 (55.6%)	35 (37.6%)	50 (41.7%)
5 - 7	9 (33.3%)	40 (43.0%)	49 (40.8%)
8 - 10	3 (11.1%)	11 (11.8%)	14 (11.7%)
APGAR score category 5 min after birth, n (%)			
0 - 4	6 (22.2%)	8 (8.6%)	14 (11.7%)
5 - 7	9 (33.3%)	35 (37.6%)	44 (36.7%)
8 - 10	7 (25.9%)	30 (32.3%)	37 (30.8%)
O2 supplementation at baseline, n (%)			
Yes	8 (29.6%)	35 (37.6%)	43 (35.8%)
No	19 (70.4%)	58 (62.4%)	77 (64.2%)
History of sepsis, n (%)			
Yes	15 (55.6%)	51 (54.8%)	66 (55.0%)
No	12 (44.4%)	42 (45.2%)	54 (45.0%)
History of necrotizing enterocolitis, n (%)	3 (11.1%)	16 (17.2%)	19 (15.8%)
Yes	24 (88.9%)	77 (82.8%)	101 (84.2%)
No			
History of intraventricular hemorrhage, n(%)			
Yes	8 (29.6%)	35 (37.6%)	43 (35.8%)
No	19 (70.4%)	58 (62.4%)	77 (64.2%)

Source Table 4 of the Applicant's Study Reports

Table 9: Baseline and Demographic Characteristics (Study 20090/20275)

	Laser (N=38)	**Aflibercept (N=75)**	**Total (N=113)**
Chronological Age at Randomization (weeks), n	38	75	113
Mean (SD)	10.17 (2.290)	10.35 (2.781)	10.29 (2.617)
Median (Min; Max)	10.00 (5.9 : 16.1)	10.30 (4.0 : 18.9)	10.00 (4.0 : 18.9)
Q1 : Q3	8.60 : 11.40	9.00 : 12.40	8.90 : 12.00
Gestational Age at Birth (weeks), n	38	75	113
Mean (SD)	25.97 (1.618)	26.48 (2.071)	26.31 (1.938)
Median (Min; Max)	26.00 (23.6 : 31.0)	26.00(23.1 : 31.0)	26.00 (23.1 : 31.0)
Q1 : Q3	24.90 : 27.00	25.00 : 27.40	24.90 : 27.10
Post-Menstrual Age at Randomization (weeks) [a], n	38	75	113
Mean (SD)	36.14 (2.150)	36.82 (2.732)	36.59 (2.562)
Median (Min; Max)	36.00 (32.6 : 43.3)	36.60 (32.1 : 44.6)	36.40 (32.1 : 44.6)
Q1 : Q3	34.70 : 37.10	34.90 : 38.60	34.90 : 38.00
Gestational Age at Birth group, n (%)			
<=26 weeks	22 (57.9%)	38 (50.7%)	60 (53.1%)
>26 weeks	16 (42.1%)	37 (49.3%)	53 (46.9%)
Race, n(%)			
White	28 (73.7%)	55 (73.3%)	83 (73.5%)
Black or African American	0	2 (2.7%)	2 (1.8%)
Asian	9 (23.7%)		17

American Indian or Alaska Native	1 (2.6%)	0	1 (0.9%)
Native Hawaiian or Other Pacific Islander	0	0	0
Multiple	0	1 (1.3%)	1 (0.9%)
Not Reported	0	0	0
Sex, n(%)			
Female	19 (50.0%)	34 (45.3%)	53 (46.9%)
Male	19 (50.0%)	41 (54.7%)	60 (53.1%)
Weight at Birth (g), n			
Mean (SD)	824.6 (230.80)	881.1 (305.63)	862.1 (282.91)
Median (Min; Max)	790.0 (467 : 1500)	820.0 (410 : 1780)	820.0 (410 : 1780)
Q1:Q3	690.0 : 970.0	640.0 : 1060.0	660.0 : 990.0
Baseline weight (g)			
n	38	74	112
Mean (SD)	1850.9 (546.13)	2026.7 (678.93)	1967.0 (639.96)
Median (Min; Max)	1735.5 (898 : 3608)	1851.0 (800 : 3800)	1809.5 (800 : 3800)
Q1 : Q3	1525.0 : 2084.0	1580.0 : 2505.0	1570.0 : 2305.0
APGAR score category 1 min after birth, n (%)			
0 - 4	22 (57.9%)	36 (48.0%)	58 (51.3%)
5 - 7	12 (31.6%)	27 (36.0%)	39 (34.5%)
8 - 10	3 (7.9%)	8 (10.7%)	11 (9.7%)
APGAR score category 5 min after birth, n (%)			
0 - 4	6 (15.8%)	11(14.7%)	17 (15.0%)
5 - 7	19 (50.0%)	32 (42.7%)	51 (45.1%)
8 - 10	9 (23.7%)	27 (36.0%)	36 (31.9%)
O2 supplementation at baseline, n (%)			
Yes	23 (60.5%)	45 (60.0%)	68 (60.2%)
No	15 (39.5%)	30 (40.0%)	45 (39.8%)
History of sepsis, n (%)			
Yes	15 (39.5%)	32 (42.7%)	47 (41.6%)
No	23 (60.5%)	43 (57.3%)	66 (58.4%)
History of necrotizing enterocolitis, n (%)			
Yes	5 (13.2%)	15 (20.0%)	20 (17.7%)
No	33 (86.8%)	60 (80.0%)	93 (82.3%)
History of intraventricular hemorrhage, n(%)			
Yes	16 (42.1%)	19 (25.3%)	35 (31.0%)
No	22 (57.9%)	56 (74.7%)	78 (69.0%)

Source Table 4 of the Applicant's Study Reports

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

Primary Efficacy Analysis

Recall that the primary efficacy endpoint of these studies was the proportion of patients with absence of active ROP and unfavorable structural outcomes at 52 weeks of CA after starting study treatment; and evaluated in the FAS population for the primary analysis. The results are shown in Table 10. For Study 1920, the response rate is 79.6% for aflibercept and 77.8% for laser resulting in a treatment difference of 1.81% with 95.1% CI (-15.7%, 19.3%). For Study 20090/20275, the response rate is 78.7% for aflibercept and 81.6% for laser resulting in a difference of -1.9% with 95.1% CI (-17.0%, 13.2%). Because the lower bounds of the confidence intervals in both studies are all less than the prespecified non-inferiority margin of -

5%, the protocol defined primary efficacy analyses did not established the non-inferiority of aflibercept to laser.

Table 10: Proportion of Patients with Absence of Active ROP and Unfavorable Structural Outcomes at Week 52 of Chronological Age (FAS)

	Treatments		
Study	**Laser**	**Aflibercept**	**Diff (95.1% CI)**
1920	21/27 (77.8%)	74/93 (79.6%)	1.8% (-15.7%, 19.3%)
20090/20275	31/38 (81.6%)	59/75 (78.7%)	-1.9% (-17.0%, 13.2%)

Source: Table 11 of the Applicant's Study Reports.

Reviewer's remark: For Study 1920, of the 19 non-responders in the aflibercept arm, 13 received a rescue medication prior to Week 52, one subject was set as non-responder due to other second treatment, 4 had missing data at Week 52 and hence their responder status was determined based on LOCF (Defined in the SAP), and one subject was a non-responder based on observed data at Week 52. Of the 74 responders, 2 had missing data at Week 52 and hence their status was determined based on their observed outcome at Week 40. The rest were responders based on their observed outcome at Week 52. For the laser arm, 3 of the 6 non-responders received rescue medication prior to Week 52, one was set as a non-responder due to other second treatment, one had missing data at Week 52 and hence LOCF (Defined in the SAP) was used, and one was non-responder based on his/her observed outcome at Week 52. All 21 responders were responders based on their observed outcome at Week 52.

Reviewer's remark: For Study 20090/20275, of the 16 non-responders in the aflibercept arm, 4 received a rescue medication prior to the Week 52 visit, 3 subject was set as non-responder due to other second treatment, and 9 had missing data at Week 52 and hence their responder status was determined based on LOCF (Defined in the SAP), and none were set as non-responder based on his/her observed outcome at Week 52. All 59 responders were responders based on their observed outcome at Week 52. For the laser arm, 3 of the 7 non-responders received rescue medication prior to Week 52, 4 had missing data at Week 52 and hence LOCF (Defined in the SAP) was used, and none were set as non-responder based on his/her observed outcome at Week 52. All 31 responders were responders based on their observed outcome at Week 52.

Breakdown of non-responders by data used

Study	***Data Used***	***Laser***	***Aflibercept***	***Total***
1920	*Observed Case*	*1*	*1*	*2*
	Second Treatment Modality	*4*	*14*	*18*
	LOCF[1]	*1*	*4*	*5*
20090/20275	*Observed Case*	*0*	*0*	*0*
	Second Treatment Modality	*3*	*7*	*10*
	LOCF[1]	*4*	*9*	*13*

Breakdown of responders by data used

Study	***Data Used***	***Laser***	***Aflibercept***	***Total***
1920	*Observed Case*	*21*	*72*	*93*
	LOCF[1]	*0*	*2*	*2*
20090/20275	*Observed Case*	*31*	*59*	*90*
	LOCF[1]	*0*	*0*	*0*

Source Reviewer's Analysis For subjects with data missing at Week 52, the Week 40 data is used to determine the responder status. Subjects who received any second treatment modality were set as non-responders regardless of their observed outcome.

Supplemental Analyses

At Week 52, more subjects in the aflibercept arm had missing data compared to those randomized to the laser arm. Also, compared to the laser arm, a higher percentage of subjects in the aflibercept arm received rescue medications or a second treatment modality. To evaluate the impact of these intercurrent events (treatment discontinuation and receipt of rescue medication) on the efficacy results, both the reviewer and the Applicant conducted additional analyses of the primary efficacy endpoint.

Table 11: Summary of ROP Outcome Observed and Missing at Week 40 and Week 52 (Study 1920)

Week		Laser	Aflibercept	Total
40	Observed data	23	76	99
	Without second treatment modality	19	65	84
	With second treatment modality	4	11	15
	Missing	4	17	21
52	Observed data	26	86	112
	Without second treatment modality	22	73	95
	With second treatment modality	4	13	17
	Missing	1	7	8

Source: Reviewer's Analysis. Second treatment modality includes protocol defined rescue treatment and other interventions.

Table 12: Summary of ROP Outcome Observed and Missing (Study 20090/20275)

Week		Laser	Aflibercept	Total
40	Observed data	20	46	66
	Without second treatment modality	19	40	59
	With second treatment modality	1	6	7
	Missing	18	29	47
52	Observed data	34	66	100
	Without second treatment modality	31	59	90
	With second treatment modality	3	7	10
	Missing	4	9	13

Source: Reviewer's Analysis. Second treatment modality includes protocol defined rescue treatment and other interventions.

A. Applicant's Supplemental Analyses

The Applicant conducted additional analyses of the primary efficacy endpoint. The first analysis was conducted based on the FAS population using observed cases only (excluding subjects with missing data). The Applicant also conducted the analysis of the primary efficacy endpoint based on the ITT and PP populations using the same missing data approach used for the primary efficacy analysis. The analyses results based on the FAS using observed cases only and the PP are consistent with the primary efficacy analysis results in both studies. However, the results based on the ITT population in Study 1920 provided a lower confidence limit for the treatment difference that is great than the non-inferiority margin of -5% (Table 13).

Table 13: Applicant's Sensitivity Analyses for the Primary Efficacy Endpoint

	Treatments		
Approaches	**Laser**	**Aflibercept**	**Difference (95.1% CI)**
	Study 1920		
FAS (OC)	21/26 (80.8%)	72/87 (82.8%)	2.4% (-14.8%, 19.5%)
Per Protocol	19/24 (79.2%)	60/68 (88.2%)	9.1% (-9.1%, 27.3)

ITT	21/33 (63.6%)	74/94 (78.7%)	14.90% (**-3.5%,** 33.3%)
	Study 20090/20275		
FAS (OC)	31/34 (91.2%)	59/66 (89.4%)	-0.45% (-12.3%, 11.3%)
Per Protocol	28/35 (80.0%)	54/66 (81.8%)	3.18% (-12.7%, 19.1%)
ITT	31/43 (72.1%)	59/75 (78.7%)	7.51% (-8.5%, 23.5%)

Source: Table 12 of the Applicant's Study Reports. OC: Observed cases.

Reviewer's remark: For the analysis based on the ITT population, the Applicant set all randomized subjects excluded from the FAS population as non-responders. Therefore, in both arms the responder rate is lower compared to the analysis based on the FAS. However, because there were more subjects who were excluded from the FAS population in the laser arm, this analysis has resulted in slightly lower response rate in this arm compared to aflibercept arm resulting in a treatment difference that is nominally significant based on the 1-sided test for non-inferiority in Study 1920.

B. Reviewer's Supplemental Analyses

Missing Data and Receipt of Second Treatment Modality

a. Multiple imputation approach

For Study 1920, Week 52 primary efficacy data was missing for 6 subjects in the aflibercept arm compared to 1 subject in the laser arm. Similarly, for Study 20090/20275, the primary efficacy outcome was missing for 9 subjects in the aflibercept arm compared to 4 subjects in the laser arm. Consequently, the responder status was determined based on the Week 40 data. To further evaluate the impact of missing data, this reviewer conducted a multiple imputation approach. In this analysis, subjects who received a second treatment modality (rescue or otherwise) are treated as non-responders. This analysis provided results that are consistent with the primary efficacy analysis results (Table 14).

Table 14: Proportion of Patients with Absence of Active ROP and Unfavorable Structural Outcomes at Week 52 of Chronological Age (FAS): Multiple Imputation Approach

	Treatments		
Study	**Laser**	**Aflibercept**	**Diff (95.1% CI)**
1920	80.0%	82.4%	2.6% (-14.9%, 20.1%)
20090/20275	85.7%	83.6%	-1.1% (-15.4%, 13.3%)

Source: Reviewer's Analysis.

b. Analysis using all observed data

Recall, in the primary efficacy analysis, subjects who received a second treatment modality including a rescue medication were treated as non-responders. Note, for some subjects, the data after the receipt of the second treatment modality was collected. This reviewer conducted the analysis of the primary efficacy endpoint by defining responder status based on all observed data regardless of whether the data was collected following a receipt of second treatment modality. For subjects with missing data, their status was set as non-responder. This analysis also provided results that are consistent with the primary efficacy analysis results (Table 15).

Table 15: Proportion of Patients with Absence of Active ROP and Unfavorable Structural Outcomes at Week 52 of Chronological Age (FAS): All Observed Data

Study	Treatments		Diff (95.1% CI)
	Laser	Aflibercept	
1920	24/27 (88.9%)	82/93 (88.2%)	-0.9% (-14.4%, 12.7%)
20090/20275	33/38 (86.8%)	63/75 (84.0%)	-2.0% (-15.5%, 11.6%)

Source: Reviewer's Analysis.

c. Tipping point analysis

Recall, for the primary efficacy analysis, subjects who discontinued the study at or before Week 40, subjects who received rescue or any second treatment modality, and subjects who discontinued the study between Weeks 40 and 52 due to adverse events, were treated as non-responders. To evaluate the impact of setting subjects as treatment non-responders, this reviewer conducted a tipping point type analysis.

Figure 4 and Figure 5 present the estimated lower bounds of the 95.1% CI's when different number of subjects in either arm who were set as non-responders for reasons listed above (primarily rescue medication use) are now considered as responders. For example, for Study 1920, in the top left corner (14, 4), the value 9.0% corresponds to the estimated lower bound of the 95.1% CI if all the 14 subjects in the aflibercept arm and all the 4 subjects in the laser arm who were set as non-responders (due to the reasons listed above) in the primary efficacy analysis are now set as responders.

Reviewer's remark: For Study 1920, of the 19 non-responders in the aflibercept arm, 14 were set as non-responders based on the criteria listed above. Of these, 13 received a rescue medication prior to Week 52. Similarly, for the laser arm, 3 of the 6 non-responders received rescue medication prior to Week 52. For Study 20090/20275, of the 16 non-responders in the aflibercept arm, 7 met one of the criteria prior to Week 52. For the laser arm, 3 of the 7 non-responders met one of the criteria prior to Week 52.

Figure 4: Heatmap of lower bound of CI of treatment difference (Study 1920)

# Subjects whose outcome was changed to responder in the laser arm	#Subjects whose outcome was changed to responder in the aflibercept arm													
	14	13	12	11	10	9	8	7	6	5	4	3	2	1
4	-9.0%	-10.3%	-11.5%	-12.7%	-14.0%	-15.0%	-16.2%	-17.4%	-18.7%	-19.9%	-21.1%	-22.4%	-23.4%	-24.6%
3	-7.1%	-8.4%	-9.6%	-10.9%	-12.1%	-13.1%	-14.4%	-15.6%	-16.8%	-18.0%	-19.2%	-20.4%	-21.4%	-22.6%
2	-5.0%	-6.2%	-7.4%	-8.6%	-9.8%	-10.9%	-12.1%	-13.3%	-14.5%	-15.7%	-16.9%	-18.1%	-19.1%	-20.3%
1	-2.3%	-3.6%	-4.8%	-5.9%	-7.2%	-8.2%	-9.3%	-10.4%	-11.7%	-12.9%	-14.1%	-15.3%	-16.3%	-17.5%

Source Reviewer's Analysis

Figure 5: Heatmap of lower bound of CI of treatment difference (Study 20090/20275)

# Subjects whose outcome was changed to responder in the laser arm	#Subjects whose outcome was changed to responder in the aflibercept arm						
	7	6	5	4	3	2	1
3	-13.6%	-14.9%	-16.2%	-17.9%	-19.5%	-20.8%	-22.1%
2	-11.7%	-12.9%	-14.2%	-15.9%	-17.5%	-18.8%	-20.0%
1	-9.5%	-10.7%	-11.9%	-13.6%	-15.3%	-16.4%	-17.7%

Source Reviewer's Analysis

Determining Different NI Margins

Recall, the NI margin was determined to preserve 90.9% of the effect of laser relative to a putative placebo. The Applicant argues that the NI margin of 5% that preserves 90.9% of the laser effect is rather conservative. Table 16 presents the NI margins (M2) that correspond to different percentages of control treatment effect preserved. As can be seen, both studies would have met the NI criteria if 60% or less of the control treatment effect is to be preserved. Besides, Study 1920 will meet the NI criteria if we preserve 70% or less of the laser effect observed in the RAINBOW study.

Table 16: Summary of NI Margins Under Different Preserved Effects

Percentage preserved (P)	M2
50%	27.5%
60%	22.0%
70%	16.5%
80%	11.0%
90%	5.5%
95%	2.75%

Source Reviewer's Analysis

Also recall, for determination of the NI margin, the Applicant assumed a zero-response rate for a putative placebo arm. To evaluate the effect of this assumption on the NI margin derivation, this reviewer provides possible NI margins that could be determined under four different possible placebo rates (5%, 10%, 15% and 20%). Here, a sample size of 68 subjects was assumed for a hypothetical placebo arm. This sample size matches the sample size for the laser arm in the RAINBOW study.

The results are presented in Table 17. For example, if the putative placebo rate was assumed to be 15%, the statistical margin, M1, which is estimated as the lower bound of the 95% CI for the laser minus placebo would be 37%. If we then preserve 50% of this effect, the clinical NI margin (M2) would be 18.5%, with which, the two studies would have met the non-inferiority criteria.

Table 17: Summary of NI Margins Under Different Assumed Placebo Effect

Hypothetical assumed placebo rate	Laser (Rainbow)	M1	M2 (under different preserved effect)					
			50%	60%	70%	80%	90%	90.9%
0%	66%	55%	27.5%	22%	16.5%	11%	5.5%	5%
5%	66%	49%	24.5%	19.6%	14.7%	9.8%	4.9%	4.4%
10%	66%	42%	21.0%	16.8%	12.6%	8.4%	4.2%	3.8%
15%	66%	37%	18.5%	14.8%	11.1%	7.4%	3.7%	3.4%
20%	66%	31%	15.5%	12.4%	9.3%	6.2%	3.1%	2.8%

Source: Reviewer's analysis

Evaluating the impact of sample size for the laser arm

To evaluate the impact of the relatively smaller sample size in the laser arm on the non-inferiority results, this reviewer generated data from a Bernoulli distribution assuming a success probability of the observed results in this study. For example, for the laser arm in Study 1920, the responder-status for each subject was generated from a Bernoulli distribution with a success probability of 77.8%. Similarly, for the aflibercept arm, the responder-status for each subject was generated from a Bernoulli distribution with a success probability 79.6%. Sample sizes ranging between 35 and 95 were considered. For each sample size, 1000 data sets were generated. From each generated dataset, the treatment difference and the 95.1% CI for the difference was computed.

The summary results presented in Table 18 and
Table 19 show the median difference in response rate and the associated median value for the lower bound of the 95% confidence interval. For example, if the sample size in the laser arm was 55 subjects, and assuming the same rate will be observed, the lower bound of the 95% CI would be -11.84%. Per the simulation results, although the SPA agreed NI criteria would not still be met for the range of sample sizes considered, the results would be slightly better with a larger sample size.

Table 18: Summary of Estimated Differences under Different Sample Sizes (Study 1920)

Assumed sample size	Estimate treatment difference	Lower bound of the 95.1% CI
35	1.7%	-13.7%
45	1.7%	-12.8%
55	1.8%	-11.8%
65	1.7%	-11.0%
75	1.7%	-10.3%
85	1.8%	-10.2%
95	1.6%	-9.9%

Source: Reviewer's analysis

Table 19: Summary of Estimated Differences under Different Sample Sizes (Study 20090/20275)

Assumed sample size	Estimate treatment difference	Lower bound of the 95.1% CI
35	-2.8%	-18.3%
45	-2.6%	-17.1%
55	-2.6%	-16.8%
65	-2.6%	-16.0%
75	-2.6%	-15.5%

Source: Reviewer's analysis

Analysis of Secondary Efficacy Endpoints

Recall, the study had the following key secondary efficacy endpoints which will be tested sequentially if the non-inferiority of aflibercept to laser was established with respect to the primary efficacy endpoint:

– Proportion of patients requiring intervention with a second treatment modality from baseline to week 52 CA.

– Proportion of patients with recurrence of ROP through week 52 CA.

The efficacy summary for the key secondary efficacy endpoints is presented in Table 20 and Table 21. In both studies, there was no noticeable difference in results between the two arms. Note, for both endpoints, the unit of analysis was the subject, i.e., subjects were counted as having the "event" if at least one eye satisfied the criteria.

Table 20: Proportion of Patients Requiring Intervention with Second Treatment Modality from Baseline to Week 52 of CA (FAS)

	Treatments		
Study	**Laser**	**Aflibercept**	**Diff (95.1% CI)**
1920	5/27 (18.5%)	14/93 (15.1%)	-3.7% (-19.9%, 12.5%)
20090/20275	5/38 (13.2%)	10/75 (13.3%)	-0.4% (-13.6%, 12.8%)

Source Table 14 (1920) and Table 15 (20090/20275) the Applicant's Study Reports.

Reviewer's remark: Second treatment modality included any treatment in addition to that assigned to the participant at baseline. This included per-protocol rescue treatment (laser for aflibercept group, aflibercept for laser group), anti-VEGF agents not part of study protocol (e.g., bevacizumab, ranibizumab, commercially available aflibercept not provided as study medication), or any ocular surgery for the management of any retinal pathology secondary to ROP (e.g., victrectomy, scleral buckle for retinal detachments).

Table 21: Proportion Analysis of Patients with Recurrence of ROP through Week 52 of CA (FAS)

	Treatments		
Study	**Laser**	**Aflibercept**	**Diff (95.1% CI)**
1920	8/27 (29.6%)	37/93 (39.8%)	10.1% (-9.8%, 30.0%)
20090/20275	10/38 (26.3%)	23/75 (30.7%)	3.6% (-13.5%, 20.8%)

Source Table 15 (1920) and Table 16 (20090/20275) the Applicant's Study Reports.

3.3 Evaluation of Safety

This section presents treatment exposure and descriptive summaries of the percentages of treatment-emergent adverse events (TEAEs), using MedDRA 24.1 dictionary derived term, from Study 1920 and Study 20090/20275. These summaries are provided for the safety analysis population, which is defined in the SAP as all randomized patients who receive at least 1 dose of study medication. The safety analysis population is comprised of 120 subjects in Study 1920 (laser: 27 subjects; aflibercept: 93 subjects), and 113 subjects in Study 150998-006 (laser: 38 subjects; aflibercept: 75 subjects).

3.3.1 Extent of Treatment Exposure

Study 1920

- Overall, 93 participants in the aflibercept group received treatment in a total of 179 eyes with a total of 214 aflibercept injections. Among the 179 eyes treated, 149 (83.2%) eyes received a single aflibercept injection, and 25 (14.0%) eyes received 2 aflibercept injections (baseline and 1 re-treatment), and 5 (2.8%) eyes received 3 aflibercept injections (baseline and 2 re-treatments). The majority (72.0%) of participants in this group received 2 aflibercept injections due to bilateral injections.

- Among subjects randomized to the laser group, a total of 27 participants (50 eyes) received treatment with laser photocoagulation. Forty-eight of the 50 eyes (96.0%) received a single laser treatment, and 2 eyes (4.0%) received 2 laser treatments (including re-treatment).

Study 20090/20275

- Seventy-five participants in the aflibercept group received a treatment in a total of 146 eyes with a total of 172 aflibercept injections. Among the 146 eyes treated, 120 (82.2%) eyes received a single aflibercept injection, and 26 eyes (17.8%) received 2 aflibercept injections (baseline and 1 re-treatment). The majority (73.3%) of participants in this group received 2 aflibercept injections due to bilateral injections.

- In the laser group, a total of 38 participants (72 eyes) received treatment with laser photocoagulation. Sixty-five of the 72 eyes (90.3%) received a single laser treatment, 5 eyes (6.9%) received 2 laser treatments (including re-treatment) and 2 eyes (2.8%) received 3 laser treatments (including re-treatment).

3.3.2 Adverse Events

The overall adverse event summary for each study separately is presented in Table 22 and Table 24. In both studies, the percentage of subjects who reported at least one adverse event (ocular and non-ocular) was higher in the laser arm compared to the aflibercept arm. The percentage of subjects who reported at least one ocular adverse event in the aflibercept arm was 25.8% and 58.7%, in Study 1920 and Study 20090/20275, respectively. The corresponding figures for the laser group were 44.4% and 60.5%, respectively. A total of 4 subjects, all treated with aflibercept have died in the two studies combined.

In Study 1920, a total of 24 subjects reported eye disorders. Of these, 6 subjects randomized to the aflibercept arm, and 2 subjects randomized to the laser arm had retinal detachment. In addition, 5 subjects randomized to the aflibercept arm had conjunctival haemorrhage while none of the laser treated subjects had this event (Table 23).

In 20090/20275, a total of 43 subjects reported at least one eye disorder. Of these, 4 subjects randomized to the aflibercept arm, and 2 subjects randomized to the laser arm had retinal detachment; 4 subjects randomized to the aflibercept arm had conjunctival haemorrhage while none of the laser treated subjects had this event; 5 subjects each from the two arms reported retinal haemorrhage. In addition, 2 subjects randomized to the aflibercept arm, and 3 subjects randomized to the laser arm had eyelid oedema; 3 subjects randomized to the aflibercept arm,

and 4 subjects randomized to the laser arm reported Infections and infestations; and 3 subjects randomized to the aflibercept arm, and 4 subjects randomized to the laser arm reported conjunctivitis (
Table 25).

Table 22: Overall Summary of Adverse Events (Study 1920)

	Laser (N=27)	Aflibercept (N=93)	Total (N=120)
Number (%) of subjects with any AEs			
Any ocular AE on treated eye	12 (44.4%)	24 (25.8%)	36 (30.0%)
Any ocular AE on non-treated eye	0	1 (1.1%)	1 (0.8%)
Any non-ocular AE	21 (77.8%)	63 (67.7%)	84 (70.0%)
Any AE	23 (85.2%)	69 (74.2%)	92 (76.7%)
Maximum severity for any AE			
Missing	0	0	0
Mild	8 (29.6%)	18 (19.4%)	26 (21.7%)
Moderate	7 (25.9%)	29 (31.2%)	36 (30.0%)
Severe	8 (29.6%)	22 (23.7%)	30 (25.0%)
Any aflibercept-related AE	0	1 (1.1%)	1 (0.8%)
Max. severity for aflibercept-related AE			
Missing	0	0	0
Mild	0	0	0
Moderate	0	0	0
Severe	0	1 (1.1%)	1 (0.8%)
Any photocoagulation-related AE	1 (3.7%)	1 (1.1%)	2 (1.7%)
Max. severity for photocoagulation			
related AE			
Missing	0	0	0
Mild	1 (3.7%)	0	1 (0.8%)
Moderate	0	0	0
Severe	0	1 (1.1%)	1 (0.8%)
Any AE related to study conduct	4 (14.8%)	11 (11.8%)	15 (12.5%)
Any AE leading to discontinuation of study drug	0	0	0
Any SAE	12 (44.4%)	32 (34.4%)	44 (36.7%)
Any aflibercept-related SAE	0	1 (1.1%)	1 (0.8%)
Any photocoagulation-related SAE	0	1 (1.1%)	1 (0.8%)
Any SAE related to study conduct	2 (7.4%)	4 (4.3%)	6 (5.0%)
Any SAE leading to discontinuation of study drug	0	0	0
AE Results in death	0	1 (1.1%)	1 (0.8%)

Source: Table 25 of the study report. AE: Adverse event.

Table 23: Summary of Ocular Treatment-Emergent Adverse Events in the Study Eye(s) per Participant in ≥5% Participants in Either Group (SAF; 1920)

	Laser (N=27)	Aflibercept (N=93)	Total (N=120)
No. of Patients with at Least 1 Such AE, n (%)	7 (25.9%)	17 (18.3%)	24 (20.0%)
Eye disorders	6 (22.2%)	16 (17.2%)	22 (18.3%)
Retinal detachment	2 (7.4%)	6 (6.5%)	8 (6.7%)

Conjunctival haemorrhage	0	5 (5.4%)	5 (4.2%)

Source: Table 27 of the study report. AE: Adverse event.

Table 24: Overall Summary of Adverse Events (Study 20090/20275)

	Laser (N=38)	Aflibercept (N=75)	Total (N=113)
Number (%) of subjects with any adverse events			
Any ocular AE on treated eye	23 (60.5%)	44 (58.7%)	67 (59.3%)
Any ocular AE on non-treated eye	0	2 (2.7%)	2 (1.8%)
Any non-ocular AE	33 (86.8%)	64 (85.3%)	97 (85.8%)
Any AE	35 (92.1%)	71 (94.7%)	106 (93.8%)
Maximum severity for any AE			
Missing	0	0	0
Mild	14 (36.8%)	29 (38.7%)	43 (38.1%)
Moderate	12 (31.6%)	25 (33.3%)	37 (32.7%)
Severe	9 (23.7%)	17 (22.7%)	26 (23.0%)
Any aflibercept-related AE	1 (2.6%)	3 (4.0%)	4 (3.5%)
Maximum severity for aflibercept-related AE			
Missing	0	0	0
Mild	0	2 (2.7%)	2 (1.8%)
Moderate	1 (2.6%)	0	1 (0.9%)
Severe	0	1 (1.3%)	1 (0.9%)
Any photocoagulation-related AE	11 (28.9%)	1 (1.3%)	12 (10.6%)
Maximum severity for photocoagulation-related AE			
Missing	0	0	0
Mild	3 (7.9%)	1 (1.3%)	4 (3.5%)
Moderate	8 (21.1%)	0	8 (7.1%)
Severe	0	0	0
Any AE related to study conduct	7 (18.4%)	8 (10.7%)	15 (13.3%)
Any AE leading to discontinuation of study drug	1 (2.6%)	3 (4.0%)	4 (3.5%)
Any AE related to the injection procedure	0	15 (20.0%)	15 (13.3%)
Any SAE	17 (44.7%)	25 (33.3%)	42 (37.2%)
Any aflibercept-related SAE	1 (2.6%)	1 (1.3%)	2 (1.8%)
Any photocoagulation-related SAE	0	0	0
Any SAE related to study conduct	0	0	0
Any SAE leading to discontinuation of study drug	1 (2.6%)	2 (2.7%)	3 (2.7%)
Any SAE related to the injection procedure	0	1 (1.3%)	1 (0.9%)
AE Results in death	0	3 (4.0%)	3 (2.7%)

Source: Table 26 of the study report. AE: Adverse event.

Table 25: Summary of Ocular Treatment-Emergent Adverse Events in the Study Eye(s) per Participant in ≥5% Participants in Either Group (SAF; 20090/20275)

	Laser (N=38)	Aflibercept (N=75)	Total (N=113)
Number of Patients with at	14 (36.8%)	29 (38.7%)	43 (38.1%)
Least One Such AE, n (%)			
Eye Disorders	10 (26.3%)	20 (26.7%)	30 (26.5%)

Retinal haemorrhage	5 (13.2%)	5 (6.7%)	10 (8.8%)
Retinal detachment	2 (5.3%)	4 (5.3%)	6 (5.3%)
Eyelid oedema	3 (7.9%)	2 (2.7%)	5 (4.4%)
Conjunctival haemorrhage	0	4 (5.3%)	4 (3.5%)
Infections and infestations	4 (10.5%)	3 (4.0%)	7 (6.2%)
Conjunctivitis	4 (10.5%)	3 (4.0%)	7 (6.2%)

Source: Table 28 of the study report. AE: Adverse event.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses for each individual study separately are presented in Figure 6 and Figure 7. The subgroup analyses provided results that were consistent with the Applicant's primary efficacy analyses results. In both studies, for both arms, kids with gestational age>26 weeks had a higher rate of absence of active ROP and unfavorable structural outcomes at 52 weeks of CA after starting study treatment.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are few points that need to be considered when interpreting the findings of this review. These issues are related to the primary analysis population, missing data, and estimands. Firstly, the primary efficacy analysis population, FAS, excluded randomized subjects disproportionately from the laser arm. The decision to exclude subjects was made by guardians or physicians. Further reasons were not provided in the submission.

Secondly, the amount of missing data, i.e., subjects who do not have efficacy measurements reported at the primary analysis time point, i.e., Week 52 CA, is disproportionate between the two arms, with more subjects in the aflibercept arm having missing data. Specifically, approximately 6.4% and 12% subjects in aflibercept arm in Study 1920 and Study 20090/20275, respectively had missing efficacy outcome. The corresponding figures in the laser arm were 3.7% and 10.5%, respectively.

Thirdly, neither the protocol nor the statistical analysis plan clearly specified the treatment difference (estimand) of interest. In the absence of a pre-specified estimand, a possible interpretation of the implied estimand taking the approaches used to deal with intercurrent events into considerations might be attempted. However, this approach should be discouraged as it opens the observed results to conflicting interpretations.

5.2 Collective Evidence

The Applicant's analyses of the primary efficacy endpoint based on the FAS population did not meet the non-inferiority criteria in either of the two studies. However, in the two studies, the percentage of responders was between 77%-80% for subjects treated with aflibercept compared to 78%- 82% for those treated with laser. The incidence of ocular adverse events including serious adverse events was lower in the aflibercept arm compared to the laser arm. The most

frequently reported ocular adverse events in the aflibercept arm were retinal detachment, conjunctival haemorrhage, eyelid oedema, infections and infestations and conjunctivitis.

5.3 Labeling Recommendations

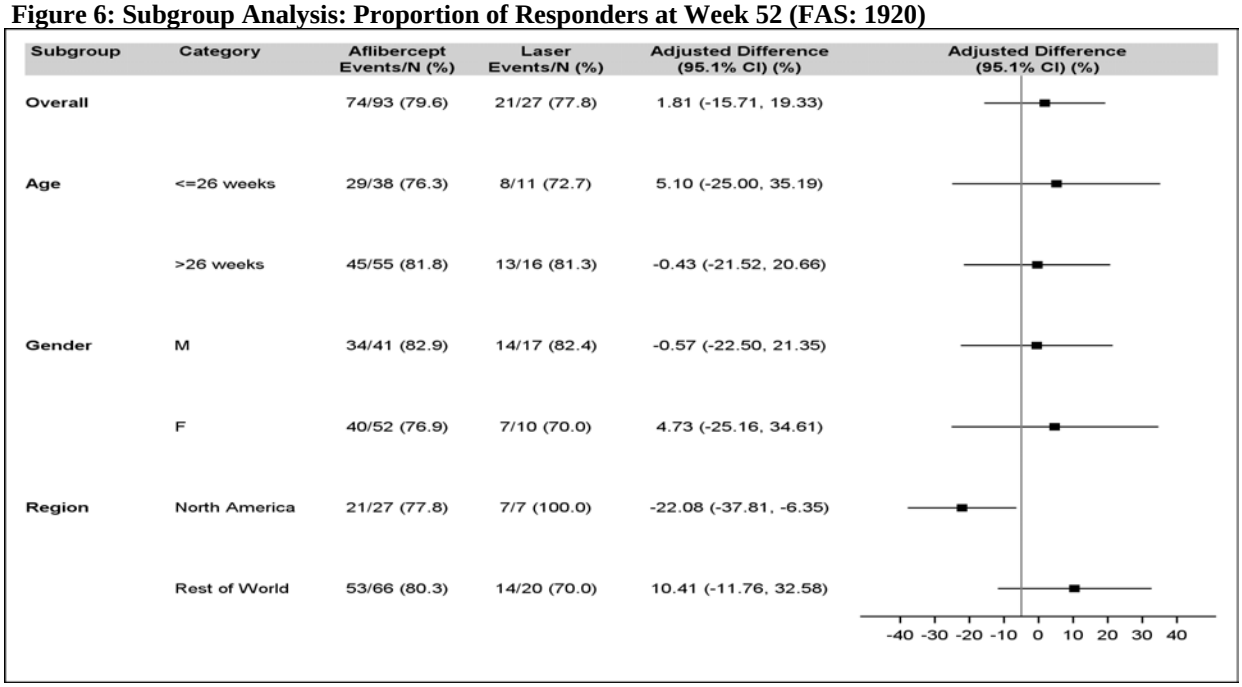
In Section 14 of the draft labeling, the Applicant has included the following for the ROP indication:

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

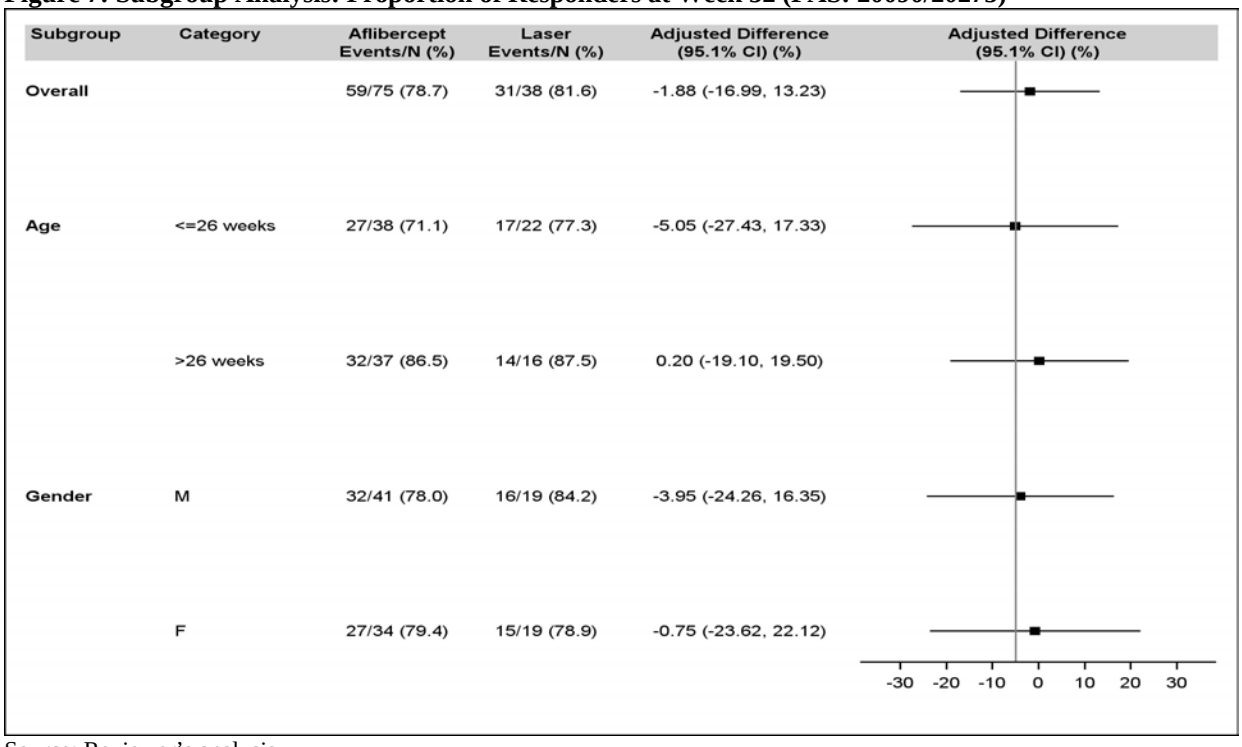
6 Appendix A: Selected Efficacy and Safety Summaries

Figure 6: Subgroup Analysis: Proportion of Responders at Week 52 (FAS: 1920)



Source: Reviewer's analysis

Figure 7: Subgroup Analysis: Proportion of Responders at Week 52 (FAS: 20090/20275)



Source: Reviewer's analysis

Table 26: Exposure Summary (Study 1920)

Summary of Aflibercept Exposure in Study Eye by Treatment Group (SAF)

	Laser (N=27)	Aflibercept (N=93)	Total (N=120)
Number of subjects treated[a]	27	93	120
Number of aflibercept administrations per subject			
0	23 (85.2%)	0	23 (19.2%)
1	0	7 (7.5%)	7 (5.8%)
2	4 (14.8%)	67 (72.0%)	71 (59.2%)
3	0	8 (8.6%)	8 (6.7%)
4	0	8 (8.6%)	8 (6.7%)
5	0	1 (1.1%)	1 (0.8%)
6	0	2 (2.2%)	2 (1.7%)
Number of eyes treated[a, b]	50	179	229
Number of aflibercept administrations (including retreatment) per eye			
0	42 (84.0%)	0	42 (18.3%)
1	8 (16.0%)	149 (83.2%)	157 (68.6%)
2	0	25 (14.0%)	25 (10.9%)
3	0	5 (2.8%)	5 (2.2%)
Number of subjects with eyes treated at baseline	27	93	120
Number of eyes treated at baseline[a, c]	50	176	226
Number of aflibercept administrations (including retreatment) per eye treated at baseline			
0	42 (84.0%)	0	42 (18.6%)
1	8 (16.0%)	147 (83.5%)	155 (68.6%)
2	0	24 (13.6%)	24 (10.6%)
3	0	5 (2.8%)	5 (2.2%)

Patient or eyes treated referred to any study treatment - either with aflibercept or with laser treatment.
Aflibercept administrations for the Laser group were rescue treatments.
[a] This row presents the denominator for calculation of percentages in rows below.
[b] Number of eyes treated included all treated eyes - including also eyes for which treatment started only after the baseline visit.
[c] Number of eyes treated at baseline included all eyes for which treatment started at the baseline visit.
Source: PTT 14.1.4.1.1

Summary of Laser Photocoagulation Exposure in Study Eye by Treatment Group (SAF)

	Laser (N=27)	Aflibercept (N=93)	Total (N=120)
Number of subjects treated[a]	27	93	120
Number of laser treatments per subject			
0	0	80 (86.0%)	80 (66.7%)
1	4 (14.8%)	4 (4.3%)	8 (6.7%)
2	22 (81.5%)	8 (8.6%)	30 (25.0%)
3	0	0	0
4	1 (3.7%)	0	1 (0.8%)
5	0	1 (1.1%)	1 (0.8%)
6	0	0	0
Number of eyes treated[a, b]	50	179	229
Number of laser treatments (including retreatment) per eye			
0	0	158 (88.3%)	158 (69.0%)
1	48 (96.0%)	18 (10.1%)	66 (28.8%)
2	2 (4.0%)	2 (1.1%)	4 (1.7%)
3	0	1 (0.6%)	1 (0.4%)
Number of subjects with eyes treated at baseline	27	93	120
Number of eyes treated at baseline[a, c]	50	176	226
Number of laser treatments (including retreatment) per eye treated at baseline			
0	0	156 (88.6%)	156 (69.0%)
1	48 (96.0%)	17 (9.7%)	65 (28.8%)
2	2 (4.0%)	2 (1.1%)	4 (1.8%)
3	0	1 (0.6%)	1 (0.4%)

Patient or eyes treated referred to any study treatment - either with aflibercept or with laser treatment.
Laser treatment for the Aflibercept group were rescue treatments.
[a]This row presents the denominator for calculation of percentages in rows below.
[b]Number of eyes treated included all treated eyes - including also eyes for which treatment started only after the baseline visit.
[c]Number of eyes treated at baseline included all eyes for which treatment started at the baseline visit.
Source: PTT 14.1.4.2.1

Table 27: Exposure Summary (20090/20275)

Summary of Aflibercept Exposure in Study Eye by Treatment Group (SAF)

	Laser (N=38)	Aflibercept (N=75)	Total (N=113)
Number of subjects treated[a]	38	75	113
Number of aflibercept administrations per subject			
0	34 (89.5%)	0	34 (30.1%)
1	0	4 (5.3%)	4 (3.5%)
2	3 (7.9%)	55 (73.3%)	58 (51.3%)
3	1 (2.6%)	6 (8.0%)	7 (6.2%)
4	0	10 (13.3%)	10 (8.8%)
5	0	0	0
6	0	0	0
Number of eyes treated[a, b]	72	146	218
Number of aflibercept administrations (including retreatment) per eye			
0	64 (88.9%)	0	64 (29.4%)
1	7 (9.7%)	120 (82.2%)	127 (58.3%)
2	1 (1.4%)	26 (17.8%)	27 (12.4%)
3	0	0	0
Number of subjects with eyes treated at baseline	38	75	113
Number of eyes treated at baseline[a,c]	71	144	215
Number of aflibercept administrations (including retreatment) per eye treated at baseline			
0	63 (88.7%)	0	63 (29.3%)
1	7 (9.9%)	118 (81.9%)	125 (58.1%)
2	1 (1.4%)	26 (18.1%)	27 (12.6%)
3	0	0	0

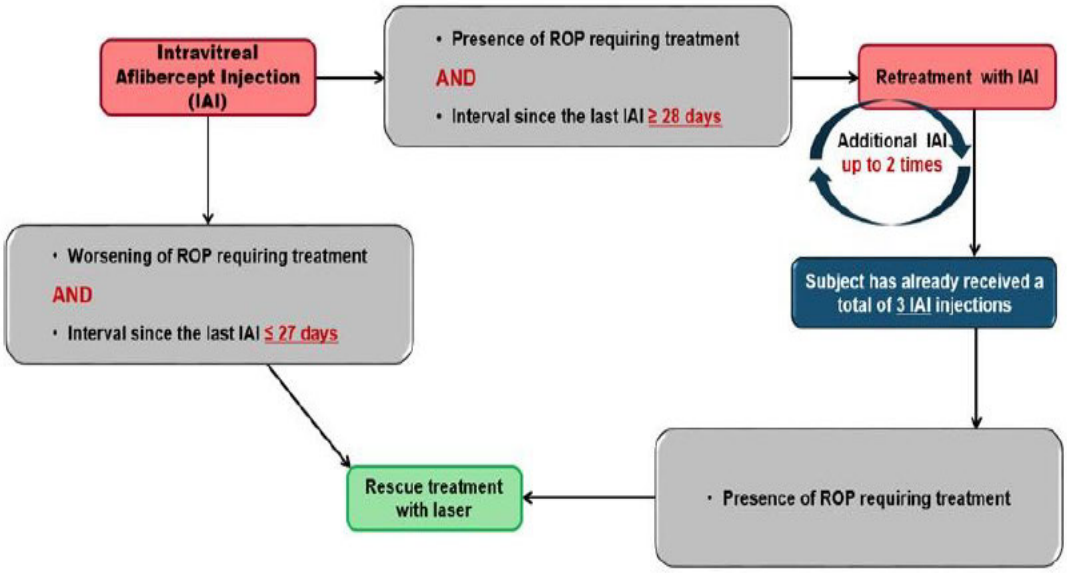
Subject or eyes treated refers to any study treatment – either with aflibercept or with laser treatment.
Aflibercept administrations for the Laser arm are rescue treatments.
[a] This row presents the denominator for calculation of percentages in rows below.
[b] Number of eyes treated includes all treated eyes - including also eyes for which treatment started only after the baseline visit.
[c] Number of eyes treated at baseline includes all eyes for which treatment started at the baseline visit.
Source: PTT 14.1.4.1.1

Summary of Laser Photocoagulation Exposure in Study Eye by Treatment Group (SAF)

	Laser (N=38)	Aflibercept (N=75)	Total (N=113)
Number of subjects treated[a]	38	75	113
Number of laser treatments per subject			
0	0	70 (93.3%)	70 (61.9%)
1	4 (10.5%)	3 (4.0%)	7 (6.2%)
2	30 (78.9%)	2 (2.7%)	32 (28.3%)
3	1 (2.6%)	0	1 (0.9%)
4	2 (5.3%)	0	2 (1.8%)
5	0	0	0
6	1 (2.6%)	0	1 (0.9%)
Number of eyes treated[a, b]	72	146	218
Number of laser treatments (including retreatment) per eye			
0	0	139 (95.2%)	139 (63.8%)
1	65 (90.3%)	7 (4.8%)	72 (33.0%)
2	5 (6.9%)	0	5 (2.3%)
3	2 (2.8%)	0	2 (0.9%)
Number of subjects with eyes treated at baseline	38	75	113
Number of eyes treated at baseline[a,c]	71	144	215
Number of laser treatments (including retreatment) per eye treated at baseline			
0	0	137 (95.1%)	137 (63.7%)
1	64 (90.1%)	7 (4.9%)	71 (33.0%)
2	5 (7.0%)	0	5 (2.3%)
3	2 (2.8%)	0	2 (0.9%)

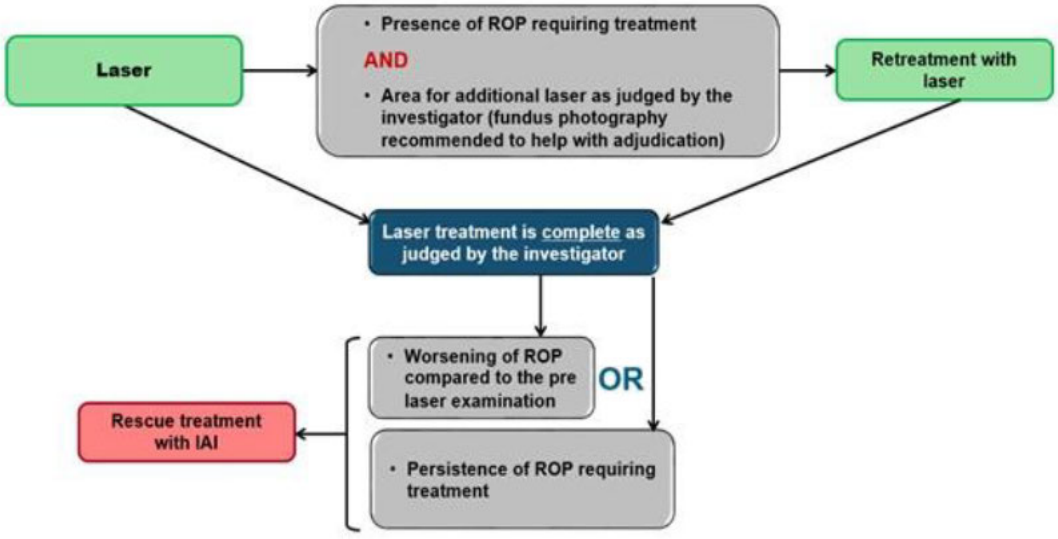
Subject or eyes treated refers to any study intervention – either with aflibercept or with laser treatment.
Laser treatments for the aflibercept arm were rescue treatments.
[a] This row presents the denominator for calculation of percentages in rows below.
[b] Number of eyes treated included all treated eyes - including also eyes for which treatment started only aft baseline visit.
[c] Number of eyes treated at baseline included all eyes for which treatment started at the baseline visit.
Source: PTT 14.1.4.2.1

Figure 8: Aflibercept Treatment, Aflibercept Retreatment, and Rescue Treatment



Once rescue treatment is applied, treatment with the patient's randomized treatment cannot be reinitiated.

Figure 9: Laser Treatment, Laser Retreatment, and Rescue Treatment



Once rescue treatment is applied, treatment with the patient's randomized treatment cannot be reinitiated.

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