Diabetic Retinopathy Clinical Research Network

Intravitreous Anti-VEGF vs. Prompt Vitrectomy for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy (Protocol AB)

Statistical Analysis Plan

NCT 02858076

Document date 27 April 2020

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	Wesley Beaulieu	Michele Melia	17 October 2017	Initial version for Protocol version 1.0.
1.1	Wesley Beaulieu	Michele Melia	12 February 2019	Revisions for consistency across DRCR.net SAPs following DSMC review. Still applies to Protocol version 1.0. Changes made prior to initial data analysis.
1.2	Wesley Beaulieu	Maureen Maguire	27 April 2020	Updated significance threshold for primary outcome from .05 to .049 for consistency with protocol. Added post hoc visual acuity subgroup analysis. Changed measure of treatment group effect for binary outcomes to risk difference instead of odds ratio. Other minor changes and clarifications. Changes were made after the initial analysis. Still applies to Protocol version 1.0.

SIGNATURES	
AUTHOR	
APPROVER	

1.0 Introduction

This document outlines the statistical analysis plan for the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol AB comparing prompt vitrectomy with panretinal photocoagulation (PRP) versus an intravitreous anti-vascular endothelial growth factor (VEGF) regimen for treatment of vitreous hemorrhage from proliferative diabetic retinopathy (PDR) for which intervention is deemed necessary. The anti-VEGF agent used in this trial is aflibercept (Eylea®, Regeneron Pharmaceuticals, Tarrytown, New York, USA).

The primary objective of the protocol is to determine if there is a difference between the two treatment groups in visual acuity area under the curve (AUC) over 24 weeks. Participants will have outcome visits at 4, 12, 24, 36, 52, 68, 84, and 104 weeks. The long-term outcomes (e.g., 2-year visual acuity AUC, other secondary outcomes, safety) are considered equally important as the primary outcome. Therefore, results from this trial will not be published until the 104-week follow-up has closed.

Study eyes will be assigned randomly to the two treatment groups in a 1:1 ratio stratified by site. Participants may have only one study eye enrolled in the randomized trial.

2.0 Efficacy Analysis Plan

2.1 Primary Outcome Analysis

The primary analysis will consist of a treatment group comparison of mean visual acuity AUC from baseline to 24 weeks adjusting for baseline visual acuity and phakic status using a general linear model with robust variance estimation. The primary analysis is an intention-to-treat analysis. All randomized eyes will be included in the primary analysis according to treatment group assignment at randomization. Only baseline and outcome visits (4, 12, 24, 36, 52, 68, 84, and 104 weeks), which are common to both groups, will be used to calculate AUC through the appropriate visit for the primary and secondary outcomes (e.g., 24 weeks for the primary outcome). AUC will be calculated for each participant by the trapezoidal rule using the following formula:

$$AUC = \sum_{i=1}^{n} \left(\frac{V_i + V_{i+1}}{2} \times d \right)$$

Where V_i is the visual acuity measured at the ith visit, d is the number of days between visits i and $i+1$, and n is the number of outcome visits included in the analysis. For example, the primary outcome has $n = 4$ as the analysis will include visits at baseline, 4, 12, and 24 weeks. For presentation, AUC will be divided by the number of days between baseline and the nth visit so that the value shown will have units of letters rather than letter·days (e.g., 168 days for the primary outcome at 24 weeks). This statistic can then be interpreted as the average visual acuity over the time between baseline and the nth visit. If the P value for the test of the treatment effect is less than or equal to .049, then it will be concluded that there is a significant difference in visual acuity AUC between the two groups.

37 Markov chain Monte Carlo (MCMC) multiple imputation will be used to impute missing data.
38 The imputation model will include the visual acuities measured at baseline and at all outcome
39 visits (4, 12, 24, 36, 52, 68, 84, and 104 weeks) along with treatment group and phakic status. If
40 the data are judged to be substantially non-normal, then predictive mean matching with a match
41 set of $k = 5$ may be used for imputation instead of MCMC. Due to the nature of vitreous
42 hemorrhage, there is a higher than usual chance of the data following a non-normal distribution.
43 To limit the influence of extreme data points, visual acuity will be truncated to ± 3 standard
44 deviations based on observed 24-week data (see Section 7.4) prior to the AUC calculation but
45 after imputation. Imputed data implying a nonbiologic value for visual acuity (< 0 or > 100) will
46 be truncated at the closest biologic value (i.e., 0 or 100).

47 A plot showing the mean level of visual acuity by group over time will be constructed using
48 observed data. In general, summary statistics (e.g., within-group means and standard deviations),
49 will be based on observed data while numbers from statistical models (e.g., treatment group
50 differences, confidence intervals, and P values) will be based on imputed data.

51 ### 2.1.1 Sensitivity Analyses

52 A sensitivity analysis including observed data from participants completing the 24-week visit (no
53 imputation of missing data) will be conducted (i.e., complete-case analysis). If the analyses of
54 imputed and observed data differ substantially, then exploratory analyses will be performed to
55 evaluate factors that may have contributed to the differences. An additional sensitivity analysis
56 using observed visual acuity data without truncation or imputation of missing data will also be
57 performed.

58 A sensitivity analyses using nonparametric methods will be conducted using observed data from
59 participants completing the 24-week visit. The primary outcome will be converted to van der
60 Waerden (Normal) scores and analyzed similarly as above with a general linear model adjusting
61 for baseline visual acuity and phakic status.

62 Multiple imputation assumes that data are missing at random (MAR). In the present study, this
63 would mean that whether follow-up visual acuity data are missing or observed may be a function
64 of observed baseline characteristics included in the imputation model (e.g., baseline visual
65 acuity, follow-up visual acuity, treatment group, or phakic status), but not a function of the
66 unobserved follow-up visual acuities that are being imputed. This assumption cannot be tested
67 since these unobserved data are unknown. However, a tipping point analysis will be conducted to
68 adjust the imputed values using a shift parameter and thereby determine how severe the
69 departure from MAR must be to change outcome of the analysis with respect to rejecting or
70 failing to reject the null hypothesis.

71 A shift parameter will be applied to the imputed values in the aflibercept group to determine the
72 tipping point at which the conclusion of the primary hypothesis test changes. That is, if one
73 group is found to be superior, the tipping point will identify the shift parameter necessary to
74 nullify the result. Conversely, if the null hypothesis is not rejected, two tipping points will be
75 identified – one that would make aflibercept superior and one that would make vitrectomy

76   superior. In either case, the tipping point(s) will be evaluated to determine plausibility. If not
77   plausible, then the MAR assumption is likely reasonable. For example, if the tipping point were
78   100 letters, then this would be evidence that the MAR assumption is reasonable for this analysis.

79   ### 2.1.2 Per-Protocol Analysis

80   A per-protocol analysis will be conducted to estimate the treatment effect for each treatment
81   among those who complied with the treatment. This analysis will include observed data (no
82   imputation) from all randomized eyes that complete the 4-, 12-, and 24-week visits except those
83   in the prompt vitrectomy group that never receive vitrectomy and eyes in the aflibercept group
84   that missed at least one injection before the 24-week visit. The intention-to-treat analysis is
85   considered the primary analysis. If the results of the primary and per-protocol analyses differ
86   substantially, then exploratory analyses will be performed to evaluate the factors that may have
87   contributed to the differences. The per-protocol analysis will only be performed if more than
88   10% of randomized participants would be excluded by these criteria.

89   ### 2.1.3 Confounding

90   Imbalances between groups in important covariates are not expected to be of sufficient
91   magnitude to produce confounding in the primary analysis. However, the presence of
92   confounding in the primary analysis will be evaluated in additional regression models using
93   observed data (no imputation) by including baseline participant and study eye covariates
94   including but not limited to the following:

95   - Age
96   - Duration of diabetes
97   - Mean arterial blood pressure
98   - Duration of vitreous hemorrhage
99   - HbA1c
100   - Prior PRP
101   - Prior treatment for diabetic macular edema (DME)

102   Additional variables associated with the outcome will be included in regression models if there is
103   an imbalance in the variables between treatment groups. Imbalance by treatment group will not
104   be judged using statistical testing. Instead, imbalance will be judged by whether the size of the
105   imbalance is clinically important, i.e., whether the imbalance is large enough to have a clinically
106   important effect on the primary outcome.

107   ### 2.1.4 Subgroup Analyses

108   Pre-planned subgroup analyses will repeat the primary analysis while including an interaction
109   term for the baseline subgroup factor by treatment. Only observed data (no imputation) will be
110   used for these analyses. Unless the imputation process is done separately for each treatment
111   group and the subgroup factor is included in the imputation model, the analysis will be biased
112   towards the null hypothesis of no interaction (Sullivan et al., 2016). It is recognized that

113 analyzing only observed data may be biased, but unlike the imputed analysis, it is not
114 automatically biased in the presence of interaction.

115 A significant type III test of the interaction term will be taken as an indication that subgroup
116 effects need to be explored for full interpretation of the trial results. It is recognized that the
117 study is not powered to detect subgroup effects and that lack of significance is not necessarily an
118 indication that subgroup effects do not exist.

119 Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a
120 significant treatment effect. In the absence of a significant treatment effect in the primary
121 analysis, finding a significant treatment effect in a subgroup will be regarded as likely due to
122 chance.

123 Baseline variables to be evaluated for subgroup effects include the following:

124 • History of PRP: yes vs. no

125 • Phakic status: phakic vs. pseudophakic

126 • Age: continuous and < 60 vs ≥ 60 years

127 The above subgroups are considered those of primary interest for which a rationale for a
128 subgroup effect is hypothesized. For each factor, the rationale for performing the analysis is
129 listed in Table 1 below.

130 **Table 1. Subgroup analyses.**

Factor	Rationale
History of PRP	Eyes with prior PRP may have less active disease, which could be impacted differently by treatment. Alternatively, eyes with prior PRP that subsequently have a vitreous hemorrhage could have more severe underlying disease, which could be impacted differently by treatment.
Phakic status	Phakic eyes may have more cataract progression in the vitrectomy group than in the aflibercept group, which would reduce visual acuity.
Age	Eyes from older individuals may have a longer recovery time from surgery and be at a higher risk of cataract, which could be exacerbated in the vitrectomy group.

131 The following subgroup factors will be evaluated in exploratory analyses. The finding of a
132 significant subgroup effect for any of these factors will be interpreted as hypothesis generating
133 only and in need of confirmation from further studies.

134 • Prior DME treatment: yes vs. no

135 • Prior focal/grid laser for DME: yes vs. no

136 • Prior anti-VEGF for DME: yes vs. no

137 • HbA1c: continuous and $< 7.5\%$ vs. $\geq 7.5\%$

138 • Duration of vitreous hemorrhage: below vs. at or above median

139 • Sex: female vs. male

140 • Race/Ethnicity: White vs. Black/African American vs. Hispanic (exclude all other groups
141   due to anticipated small sample size) and White vs. non-White

142 • Baseline visual acuity: 20/32 to 20/800 (78 to 4 letters) vs. worse than 20/800 (< 3 letters)

143   o The subgroup analysis by baseline visual acuity was added after reviewing the
144   data (i.e., post hoc)

145 To increase the accuracy of estimates, subgroups will only be analyzed if there are at least 20
146 eyes in each treatment group for each subgroup. Cutoffs of continuous and ordinal outcomes
147 may be modified to achieve a reasonable number of eyes in each group. Interaction P values will
148 be calculated using the continuous and ordinal variables, where possible, in addition to the
149 categorizations described above.

150 ### 2.1.5 Center Effects

151 The number of study participants per center is expected to be small for many centers. Therefore,
152 center effects will not be included in the statistical model. However, for centers with a large
153 number of study participants (N = 20 in either treatment group), heterogeneity across centers will
154 be explored using random center effects by estimating empirical best linear unbiased predictors
155 along with 95% confidence intervals.

156 ## 2.2 Secondary Outcome Analyses

157 ### 2.2.1 Visual Acuity

158 Additional analyses of visual acuity will use the imputed data sets created for the primary
159 outcome. These analyses are summarized in Table 2. The analysis models will include
160 adjustments for baseline visual acuity and phakic status. Analyses will be conducted at 4, 12, 24,
161 52, and 104 weeks unless otherwise noted. Note that visual acuity AUC at 24 weeks is the
162 primary outcome and not a secondary outcome.

163 For all outcomes analyzed with logistic regression, the percentage of eyes meeting the outcome
164 at the visit will be reported for each treatment group. The treatment group comparison will be
165 summarized with a risk difference and 95% confidence interval (estimated using the delta
166 method, see Localio et al. 2007) and a *P* value. For binary change in visual acuity outcomes,
167 only eyes at risk of the outcome will be included in the analysis. For example, because the
168 minimum visual acuity letter score is 0 letters, only eyes with baseline visual acuity $\geq$ 15 letters
169 will be included in the analysis $\geq$ 15-letter loss. All eyes will be included in the analyses of
170 binary visual acuity letter score (e.g., $\geq$ 69 letters) since visual acuity may increase or decrease
171 following randomization, which makes all eyes at risk for the outcome.

172 **Table 2. Visual Acuity Secondary Outcome Analyses.**

Outcome	Analysis Technique
Visual acuity letter score AUC (104 weeks only)	General linear model
Visual acuity letter score	General linear model
Success proportion: visual acuity $\geq$ 84 letters (~20/20)	Tabulation only
Success proportion: visual acuity $\geq$ 74 letters (~20/32)	Logistic regression
Success proportion: visual acuity $\geq$ 69 letters (~20/40)	Tabulation only
Failure proportion: visual acuity $\leq$ 38 letters (~20/200)	Logistic regression
Failure proportion: visual acuity $\leq$ 8 letters (~20/800)	Tabulation only
Success proportion: visual acuity gain $\geq$ 15 letters [*]	Logistic regression
Success proportion: visual acuity gain $\geq$ 30 letters [*]	Tabulation only
Failure proportion: visual acuity loss $\geq$ 15 letters [*]	Logistic regression
Failure proportion: visual acuity loss $\geq$ 30 letters [*]	Tabulation only

173 [*] These outcomes are considered exploratory because they were added after the protocol was finalized.

174 **2.2.2 PDR and DME**

175 Additional secondary outcomes will be evaluated at 24, 52, and 104 weeks. Analyses will use
176 observed data (no imputation) and adjust for phakic status.

177 **Table 3. Additional Secondary Outcomes.**

Outcome	Analysis Technique
Percentage of eyes with recurrent vitreous hemorrhage on clinical exam at any time during follow-up[*]	Logistic regression
Percentage of eyes with retinal neovascularization on clinical exam (neovascularization of the disc or elsewhere)	Logistic regression
OCT central subfield thickness[†]	General linear model

178 [*]A subgroup analysis similar to what is described in section 2.1.4 will be conducted for this outcome by whether the
179 participant was on anticoagulants or antiplatelet medication at baseline. This outcome will be evaluated through 104
180 weeks only.
181 [†]No adjustment for baseline central subfield thickness because vitreous hemorrhage will prevent obtaining usable
182 OCT scans for many participants.

183 A plot of mean OCT central subfield thickness over time by group will be constructed using
184 observed data.

2.2.3 Workplace Productivity and Activity Impairment Questionnaire

186 Outcomes from the Workplace Productivity and Activity Impairment Questionnaire (WPAIQ)
187 will be compared between treatment groups at 4, 12, 24, 52 and 104 weeks unless otherwise
188 indicated in the bulleted list below. Analyses will be conducted with a general linear model that
189 is adjusted for the baseline level of the score being analyzed and phakic status. Only participants
190 completing the corresponding visit will be included in the analysis. There will be no imputation
191 of missing data. The following outcomes will be evaluated:

192 • Change in Absenteeism score (tabulated without statistical comparison)

193 • Change in Presenteeism score (tabulated without statistical comparison)

194 • Change in Work Productivity Loss score

195 • Change in Work Productivity Loss score AUC (24 and 104 weeks only)

196 • Change in Activity Impairment score

197 • Change in Activity Impairment score AUC (24 and 104 weeks only)

198 WPAIQ AUC scores will be calculated similarly to visual acuity AUC (described in Section 2.1).

199 The Work Productivity Loss score (a composite of the Absenteeism and Presenteeism scores)
200 will be considered the scale of primary interest from the WPAIQ. It is anticipated that the
201 vitrectomy group will be superior to the anti-VEGF group due to a faster recovery of visual
202 acuity. Plots showing the mean levels of the Work Productivity Loss and Activity Impairment
203 scores by treatment group over time will be constructed.

2.3 Exploratory Outcomes

205 The following outcomes were not outlined in the protocol. However, they are considered of
206 interest. These analyses will adjust for baseline phakic status and use observed data only.

207 **Table 4. Exploratory Outcomes.**

Outcome	Analysis Technique
Presence of DME[*]	Logistic regression
Time to initiation of DME treatment through 104 weeks[†]	Cox Proportional Hazards Regression

208 [*]Defined as OCT central subfield thickness ≥ 305 μm for women and ≥ 320 μm for men (Heidelberg Spectralis) or
209 ≥ 290 for women and ≥ 305 for men (Zeiss Cirrus). Evaluated at 24, 52, and 104 weeks for eyes completing the visit.
210 [†]Defined as anti-VEGF injection, corticosteroid injection, administration of focal/grid laser, or vitrectomy for DME.
211 Includes all randomized eyes. The hazard ratio with 95% confidence interval and *P* value will be reported for the
212 full 104-week follow-up. A Kaplan-Meier plot will be constructed and the cumulative probabilities with 95%
213 confidence intervals will be presented for each treatment group at 104 weeks.

214 The ability to obtain an OCT scan may be related to the treatment if the hemorrhage clears more
215 quickly in one arm, potentially introducing bias into the treatment comparison for these two
216 outcomes. Therefore, the proportion of eyes in which an OCT scan cannot be obtained will be
217 tabulated for each group at 24, 52, and 104 weeks.

2.3.1 Development of DME

219 Development of DME in eyes with OCT assessment at baseline with be evaluated as an
220 exploratory outcome over the full 2-year follow-up. Having DME on OCT at baseline is an
221 exclusion criterion for randomization. It is recognized that OCT will be unavailable for many
222 eyes due to dense vitreous hemorrhage at baseline; however, since OCT is obtained prior to
223 randomization, the treatment comparison is still valid. The analysis will adjust for baseline OCT
224 central subfield thickness and phakic status. Therefore, only eyes with available baseline OCT
225 data will be included. Cox proportional hazards regression will be used to estimate the hazard
226 ratio and associated 95% confidence interval for developing DME with vitrectomy versus
227 aflibercept. Data from eyes not developing DME within the 2-year follow-up period will be
228 considered censored on the day of their final completed visit, without regard for interim missed
229 visits. To increase the accuracy of estimates, this analysis will be conducted only if at least 20
230 eyes in each treatment group meet the outcome criteria.

231 A Kaplan-Meier curve showing time-to-development of DME by treatment group will be
232 constructed. Within each treatment group, the Kaplan-Meier estimate of the survival function
233 and 95% confidence interval at the final available time point will be calculated.

3.0 Outcomes within Treatment Groups

235 Within each treatment group, the following outcomes will be tabulated at 24, 52, and 104 weeks
236 (for 24-, 52-, and 104-week completers, respectively), both cumulatively from baseline, and for
237 the intervening periods between those visits. There will be no formal statistical comparisons.

238 • Proportion of eyes undergoing vitrectomy (initial vitrectomy in aflibercept group and
239 repeat vitrectomy in vitrectomy group)

240 • Distribution and mean (standard deviation) number of intravitreous aflibercept injections
241 performed

242 • Proportion of eyes receiving PRP during follow-up

243 For the vitrectomy group, the following components of the surgical treatment will be
244 characterized with data tabulations and descriptive statistics:

245 • Surgery time in minutes

246 • Vitrectomy system gauge

247 • Intraoperative use of anti-VEGF or steroid

248   o Drugs used

249 • Administration of PRP

250   o For those undergoing PRP, also tabulate the average power (mW), exposure time
251   (seconds), total number of spots, estimated number of quadrants treated, estimated
252   total number of burns that had a visible effect on the retina, and if the PRP is
253   considered "complete" as defined by the protocol

254 • Surgical complications (e.g., choroidal detachment, rhegmatogenous retinal detachment,
255   retinal dialysis, retinal tear, etc.)

256 • Use of staining agents to visualize epiretinal proliferation or internal limiting membrane

257   o Agent used

258 • Placement of gas in the eye (C_3F_8, SF_6, or filtered air)

259 • Additional procedure(s) performed during vitrectomy surgery (e.g., cataract extraction,
260   cryopexy, fluid-gas exchange, epiretinal membrane peeling, internal limiting membrane
261   peel, intraocular lens implantation, laser retinopexy, removal of fibrous proliferation,
262   scleral buckle, etc.)

263 **4.0 Economic Analysis**

264 The purpose of the economic analysis is to compare the treatment groups with respect to cost,
265 cost effectiveness, and workplace productivity loss. Resource utilization data will be calculated
266 using the number of clinic visits along with the number and types of diagnostic and therapeutic
267 ocular procedures performed on each group. To capture patient resource utilization, cost data for
268 all diagnostic and therapeutic procedures performed will tabulated to obtain a total cost for eye
269 care services over 2 years of follow-up.

270 To capture the health-related quality-of-life associated with receipt of the two interventions over
271 the course of the trial, two methods will be used. The first method will be to convert the visual
272 acuities from the better-seeing eye over the two years of the trial into Quality-Adjusted Life-
273 Years (QALYs) using the methods of Brown et al (2003). This method has been used widely in
274 prior cost-effectiveness analyses of ophthalmologic interventions. The second method will use
275 the best-corrected visual acuities from the treated eye, regardless of whether it is the better or
276 worse-seeing eye. Resource use, costs, and QALYs will be aggregated over the two years of the
277 trial. The incremental cost-effectiveness ratio (ICER) will calculated by taking the incremental
278 cost of intravitreous aflibercept over vitrectomy and dividing it by the incremental QALYs of
279 aflibercept over vitrectomy. A probabilistic sensitivity analysis will be conducted to better
280 characterize overall uncertainty in the results.

281 **5.0 Safety Analysis**

282 Adverse events will be categorized as study eye, fellow eye, or systemic. A full listing of adverse
283 events will be tabulated by treatment group for systemic, study-eye ocular, and fellow-eye ocular
284 adverse events. An additional tabulation will be made for adverse events possibly related to
285 study treatment.

286 All randomized eyes will be included in the safety analysis and analyzed according to the
287 treatment group they were assigned to at randomization. For the 104-week primary safety
288 analysis, any adverse event that occurred at least once prior to the 104-week visit (or 728 days if
289 the participant did not complete the 104-week visit) will be reported.

290 Due to the different visit schedules among the treatment groups, the mean ratio of adverse events
291 divided by the number of visits will be provided in addition to the number of eyes with an
292 adverse event and the total number of adverse events for each treatment group. This will attempt
293 to account for a potential disproportion of reported adverse events observed in the aflibercept
294 group because of having more visits.

295 **5.1 Study Eye Ocular Adverse Events**

296 The proportion of eyes experiencing each event listed below will be reported for study eyes by
297 treatment group. Proportions will be compared between treatment groups using Barnard's
298 unconditional exact test, considering the number of eyes randomized to each group as fixed.

299 The following ocular adverse events will be assessed:

300 - Endophthalmitis

301 - Any retinal detachment (rhegmatogenous, traction, combined rhegmatogenous and
302   traction, or not otherwise specified)

303   o Rhegmatogenous retinal detachment (tabulated without statistical comparison)

304   o Traction retinal detachment (tabulated without statistical comparison)

305 - Retinal tear

306 - Cataract extraction in eyes phakic at baseline or visually significant cataract on clinical
307   exam as defined on the case report form

308   o Cataract extraction in eyes phakic at baseline (tabulated without statistical
309   comparison)

310   o Visually significant cataract on clinical exam as defined on the case report form
311   (tabulated without statistical comparison)

312 - Ocular inflammation

313 - Intraocular pressure (IOP) elevation (any of the following)

314   o Increase in IOP ≥ 10 mmHg from baseline (at a follow-up visit)

315   o IOP ≥ 30 mmHg (at a follow-up visit)

316   o Initiation of medication to lower IOP that was not in use at baseline

317   o Glaucoma procedure

318 - Neovascular glaucoma

319 • Neovascularization of the iris

5.2 Systemic Adverse Events

The proportion of randomized participants experiencing each event listed below will be reported by treatment group. Proportions will be reported and compared using Barnard's unconditional exact test, considering the number of eyes randomized to each group as fixed. The following serious systemic adverse events will be assessed:

• Primary:
  o Death
  o Serious adverse event (at least one)
  o Hospitalization (at least one)
  o Cardiovascular and cerebrovascular events according to the Antiplatelet Trialists' Collaboration (excerpted from BMJ Jan 8, 1994):
    ▪ Nonfatal myocardial infarction
    ▪ Nonfatal stroke (counted only if symptoms lasted at least 24 hours)
    ▪ Death attributed to cardiac, cerebral, hemorrhagic, embolic, other vascular (does not need to be ischemic in origin), or unknown cause
    ▪ At least one event (nonfatal myocardial infarction, nonfatal stroke, or death attributed to potential vascular or unknown cause)

Note that transient ischemic attack, angina, possible myocardial infarction, and possible stroke are not counted. Nonfatal myocardial infarction and nonfatal stroke require that the patient is alive at the end of the study. If not, then only the death is counted.

• Secondary (tabulated without statistical comparison):
  o Frequency of at least one event per participant in each Medical Dictionary for Regulatory Activities (MedDRA) system organ class

6.0 Additional Tabulations

The following will be tabulated according to treatment group:

• Baseline demographic and clinical characteristics
• Visit completion rate for each outcome visit (4, 12, 24, 36, 52, 68, 84, and 104 weeks)
• Treatment completion

348 **7.0 General Principles for Analysis**

349 **7.1 Analysis Cohort**

350 Unless otherwise stated, all treatment comparison analyses will follow the intention-to-treat
351 principle with all randomized eyes included and each eye analyzed according to the randomized
352 treatment assignment, regardless of treatment actually received.

353 **7.2 Visit Windows for Analysis**

354 For common visits, the analysis windows will be defined according to Table 5. For visits falling
355 in more than 1 window, priority will be given to the 104-, 52-, and 24-week visits. Otherwise, the
356 visit will be assigned to the earlier window (e.g., a visit on day 42 would be assigned as the 4-
357 week visit).

358 **Table 5. Analysis Windows for Outcome Visits**

Visit (Protocol Window)	Target	Analysis Window	
4 (±1) weeks	28 days	14 – 42 days	(4 ± 2 weeks)
12 (±4) weeks	84 days	42 – 126 days	(12 ± 6 weeks)
24 (±4) weeks	168 days	126 – 210 days	(24 ± 6 weeks)
36 (±4) weeks	252 days	210 – 308 days	(36 +8 weeks)
52 (±4) weeks	364 days	308 – 420 days	(52 ± 8 weeks)
68 (±4) weeks	476 days	420 – 532 days	(68 ± 8 weeks)
84 (±4) weeks	588 days	532 – 644 days	(84 ± 8 weeks)
104 (±4) weeks	728 days	644 – 812 days	(104 ± 12 weeks)

359 **7.3 Missing Data**

360 The strategy for handling missing data generally is included with the description of each
361 individual analysis. Where not otherwise specified, only participants with non-missing data are
362 included in the analysis.

363 **7.4 Outliers**

364 To help ensure that statistical outliers do not have undue impact on analyses of continuous visual
365 acuity and OCT central subfield thickness outcomes (including the primary outcome), outcomes
366 will be truncated to ± 3 standard deviations based on the mean and standard deviation at 24
367 weeks for 24-week completers, irrespective of treatment group. Visual acuity letter score, change
368 in visual acuity from baseline, and OCT central subfield thickness will be truncated. Truncation
369 will be performed after imputation of missing data, where applicable (i.e., raw data will be used
370 for imputation). For the primary outcome, AUC will be calculated based on the imputed values
371 after truncation. There will be no truncation of the AUC outcome itself.

7.5 Model Assumptions

All model assumptions, including linearity, normality of residuals, and heteroscedasticity, will be verified. If model assumptions are not reasonably satisfied, then covariates may be categorized or excluded, and a nonparametric approach, robust estimation method, or transformation may be considered. The possibility of using a transformation, robust method, or nonparametric approach is higher than usual in this study due to the nature of the cohort as vitreous hemorrhage severity can vary greatly, potentially leading to atypical (non-Gaussian) distributions of outcome data.

7.6 Type I Error Rate

There is no formal adjustment for multiplicity to compensate for the large number of outcomes being compared. All comparisons are conducted at alpha level 0.05 unless otherwise noted (e.g., the primary outcome is conducted at alpha level 0.049). In some cases, select secondary outcomes have been designated as being of "primary interest" along with a hypothesized direction of effect to place more weight on these outcomes over others.

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