Diabetic Retinopathy Clinical Research Network

Prompt Panretinal Photocoagulation Versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy (Protocol S)

Statistical Analysis Plan

Version 1.0

March 4, 2015

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Signature: 
Date: 3-4-15
1.0 Introduction

This document outlines the statistical analysis plan for the DRCR Network study (Protocol S) comparing prompt panretinal photocoagulation (prompt PRP) to intravitreal ranibizumab with deferred panretinal photocoagulation (IVR+deferred PRP) for treatment of proliferative diabetic retinopathy (PDR).

The primary objective of the protocol is to determine whether visual acuity outcomes at 2 years in eyes with PDR that receive ranibizumab with deferred PRP are non-inferior to those in eyes that had the standard therapy, prompt PRP. Secondary objectives include:

- Comparing other visual function outcomes (including Humphrey visual fields and self-reported visual function) in eyes receiving anti-VEGF with deferred PRP to those in eyes receiving prompt PRP.
- Determining percent of eyes not requiring PRP when anti-VEGF is given in the absence of prompt PRP.
- Comparing safety outcomes between treatment groups.
- Comparing associated treatment and follow-up exam costs between treatment groups.

Study eyes are randomly assigned to one of 2 treatment groups: (1) prompt panretinal photocoagulation or (2) intravitreal ranibizumab 0.5 mg with deferred panretinal photocoagulation. Study participants may have one or two eyes. Study participants with two eyes receive prompt PRP in one eye and IVR+deferred PRP in the other eye.

In both treatment groups, intravitreal ranibizumab may be given as needed for diabetic macular edema (DME). To help ensure balance by treatment group on this characteristic, the randomization was stratified as follows:

- Study participants with one study eye were randomly assigned (stratified by site and presence or absence of central-involved DME) with equal probability to one of the treatment groups, prompt PRP or IVR+deferred PRP.
- Study participants with two study eyes (both eyes eligible at the time of randomization), were randomized with equal probability to:
  - Prompt PRP in the eye with greater optical coherence tomography central subfield thickness (OCT CST) and IVR+deferred PRP in the eye with lesser OCT CST
  - IVR+deferred PRP in the eye with greater OCT CST and prompt PRP in the eye with lesser OCT CST

If both eyes had the same OCT CST, the right eye was considered the eye with the greater OCT CST.

Presence of DME for the purpose of randomized treatment assignment was defined as OCT CST ≥ 250 microns on Zeiss Stratus OCT (or equivalent thickness on spectral domain OCT machine). For the purposes of analysis, the randomization stratification variables will be defined as laterality (one eye / two eyes randomized) and continuous OCT CST based on reading center assessment of OCT. Assumptions related to inclusion of OCT CST as a continuous variable in
statistical models will be checked and, if assumptions are not met, transformation or
categorization of OCT CST will be performed.

2.0 Efficacy Analysis Plan

2.1 Primary Outcome Analysis

The primary analysis will consist of a comparison of change in visual acuity in the prompt PRP
group with the change in the ranibizumab+deferred PRP group at the 2-year follow-up visit,
using analysis of covariance to adjust for baseline visual acuity and the randomization
stratification factors (laterality and OCT CST), and generalized estimating equations (GEE) to
account for the correlation within study participants with two study eyes. If the upper limit of
the 2-sided 95% confidence interval on the difference in mean change in visual acuity between
the two groups (prompt PRP group minus IVR+deferred PRP group) lies below 5 letters, the null
hypothesis that IVR+deferred PRP is not non-inferior will be rejected at the 0.025 level. (Note:
the upper limit of the 2-sided 95% confidence interval is equal to the upper limit of the 1-sided
97.5% confidence interval for testing the 1-sided non-inferiority hypothesis.)

The primary analysis will include all randomized eyes, according to the treatment group
assignment at randomization. Missing data and treatment deviations will be handled as follows:

- For study participants who completed the 2-year visit in the analysis window (see section 6.2) and do not receive an alternate treatment for PDR, the 2-year data will be used.
  - Note: this includes any eyes that meet the criteria above regardless of whether or
    not all of the randomized treatments required by the protocol were received (i.e.
    either all required ranibizumab injections for those in the intravitreal ranibizumab
    group or complete PRP for those in the PRP group).
  - This also includes eyes that meet the above criteria and receive ranibizumab or
    focal/grid laser for DME, regardless of frequency of treatment. The primary
    analysis will pool eyes with and without center-involved DME at baseline.
    However, a subgroup analysis based on baseline central-involved DME status will
    be conducted (see section 2.1.4).
  - Alternate treatment for PDR is defined as any treatment other than PRP, anti-
    VEGF, or vitrectomy.

- For study participants who do not complete the 2-year visit and do not receive an
  alternate treatment (as defined above), Markov chain Monte Carlo (MCMC) multiple
  imputation based on treatment group, the randomization stratification factors, and all
  available visual acuity data from assessment visits prior to 2 years (i.e. baseline, 16, 32,
  52, 68, and 84 weeks) will be used to impute 2-year data.

- For all other study participants, i.e. those who receive an alternate treatment for PDR, the
  MCMC multiple imputation method, based on treatment group, randomization
  stratification factors, and only visual acuity data from the assessment visits prior to or the
  day of the administration of the alternate treatment, will be used to impute 2-year data.
  PRP treatment per protocol, intravitreal anti-VEGF, and focal/grid laser are not
  considered alternate treatments.
  - It is assumed that alternate treatments for PDR will tend to make outcomes appear
    more similar between treatments and IVR+deferred PRP more likely to be non-
    inferior. Hence, this missing data strategy is conservative.
All linear model assumptions will be verified, including linearity, normality of residuals, and homoscedasticity. If OCT CST is not approximately linearly related to change in VA, it will be categorized for the primary analysis model and all other models with visual acuity as the outcome. If other model assumptions are not met, a nonparametric analysis, such as rank regression, will be considered.

### 2.1.1 Per-protocol Analyses

Additional per-protocol analyses will be conducted as follows:

- As described for the primary analysis, except the participants who did not complete the 2 year visit within the analysis window, eyes that received alternate treatment, and eyes for which PDR (level 61 or higher) was not confirmed on baseline photographs by the Photograph Reading Center will be excluded from analysis.

- As described for the primary analysis, except the observed 2-year data for the eyes that received alternate treatment will be used for analysis.

The intent-to-treat analysis is considered the primary analysis. If the intent-to-treat and per-protocol analyses yield the same conclusion, the per-protocol analyses will be used to provide supportive evidence that study findings are robust to handling of missing data and eyes with alternate PDR treatment. If the results of the primary and per-protocol analyses differ, exploratory analyses will be performed to evaluate the factors that have contributed to the differences.

### 2.1.2 Test for Superiority

In the event that IVR+deferred PRP is found to be non-inferior to prompt PRP in the primary analysis, IVR+deferred PRP will be tested for superiority to prompt PRP, using the same confidence interval that was constructed for the treatment group difference in mean visual acuity constructed for the primary analysis. The null hypothesis that IVR+deferred PRP is not superior to prompt PRP will be rejected at the 0.025 level if the lower limit of the 2-sided 95% confidence interval on the on the difference in mean change in visual acuity between the two groups (prompt PRP group minus IVR+deferred PRP group) excludes 0.

### 2.1.3 Confounding

Imbalances between groups in important baseline covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated by adding the following baseline covariates to the primary analysis model: age, duration of diabetes, HbA1c, visual acuity, prior treatment for DME, and diabetic retinopathy severity as graded by the Photograph Reading Center. Additional variables that are associated with the outcome will be included if there is an imbalance in the variables between treatment groups. Imbalance by treatment group will not be judged using statistical testing, but will be based on judgment regarding whether the size of the imbalance is clinically important, i.e. large enough that it could have a clinically important effect on visual acuity.

### 2.1.4 Subgroup Analyses

With the exception that multiple imputation for missing outcome data will not be performed, pre-planned subgroup analyses will repeat the primary analysis, including a term for main effect of
the baseline subgroup factor and an interaction term for baseline subgroup factor by treatment. For each subgroup, the estimated mean treatment difference and 2-sided 95% confidence interval will be obtained from the interaction model. A significant (p≤0.05) interaction term will be taken as an indication that subgroup effects need to be explored for full interpretation of the trial results.

It is recognized that the study is not powered to detect subgroup effects and that lack of significance for the subgroup tests of interaction is not necessarily an indication that subgroup effects do not exist.

Baseline factors to be evaluated for possible subgroup effects include:

- Presence of central subfield involved DME, defined as baseline OCT CST≥250 and visual acuity≤78: yes, no
- Visual acuity: 79 letters or better, 78 letters or worse (20/25 or better, 20/32 or worse)
- Central subfield thickness: OCT CST≥250, OCT CST<250
- Prior DME treatment history: yes, no
- Diabetic retinopathy severity (as graded by the Photograph Reading Center): moderate PDR or better (≤ level 65), high-risk PDR or worse (≥ level 71).
  - Eyes without PDR by Photograph Reading Center grading will be included with the moderate PDR or better group. These eyes will be reviewed for clinical evidence of PDR that was not documented on photographs.

Presence of central subfield involved DME with decreased visual acuity is the primary subgroup factor due to its relationship to use of ranibizumab for treatment of DME. It is hypothesized that this subgroup factor will NOT influence treatment effect; the purpose to this subgroup analysis is to provide evidence to support this hypothesis and the combining of the subgroups in the primary analysis. Other subgroup factors will be regarded as secondary. For subgroup factors incorporating OCT CST, i.e. presence of DME and OCT CST, the continuous OCT CST randomization stratification variable will serve as the subgroup factor main effect.

There are no data to suggest that the treatment effect will vary by gender or race/ethnicity. However, both of these factors will be evaluated in exploratory analyses.

The number of study participants per center is small for many centers; therefore center effects will not be included in statistical models. However, for centers with a large number of study participants (N≥20), heterogeneity of treatment effects will be explored by constructing the individual site estimates of treatment effect and 95% confidence intervals.

### 2.2 Secondary Analyses of Visual Acuity

Additional analyses will be conducted on the visual acuity data primarily to aid clinicians and patients in the interpretation of the primary outcome results and to explore treatment group effects at other follow up times. A statistical analysis with a primary purpose of estimating the treatment group difference and 95% confidence interval will be conducted for each of the secondary outcomes. The additional outcomes and the analysis method are tabled below.
Table 1. Additional Analyses of Visual Acuity

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Analysis Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean visual acuity at 2 years</td>
<td>ANCOVA with GEE</td>
</tr>
<tr>
<td>Success Proportion (Improvement ≥ 15 letters) at 2 years</td>
<td>Binomial regression with GEE</td>
</tr>
<tr>
<td>Success Proportion (Improvement ≥ 10 letters) at 2 years</td>
<td>Binomial regression with GEE</td>
</tr>
<tr>
<td>Failure Proportion (Worsening ≥ 15 letters) at 2 years</td>
<td>Binomial regression with GEE</td>
</tr>
<tr>
<td>Failure Proportion (Worsening ≥ 10 letters) at 2 years</td>
<td>Binomial regression with GEE</td>
</tr>
<tr>
<td>Visual Acuity over Two Years</td>
<td>Area under the curve analysis</td>
</tr>
<tr>
<td></td>
<td>Longitudinal analysis</td>
</tr>
</tbody>
</table>

For each outcome, a plot that shows the outcome proportion (or the mean change in visual acuity for AUC and longitudinal analysis) by treatment group over time will be constructed using observed data, with no imputation for missing data.

The treatment groups will be compared using binomial regression adjusting for the same factors as the primary analysis (baseline visual acuity and the randomization stratification factors (laterality and OCT CST)), and using generalized estimating equations (GEE) to account for the correlation within study participants with two study eyes. If the binomial model does not converge, Poisson regression with robust variance estimation [Spiegelman 2005], or a binomial model that is not adjusted for baseline factors will be used. The binary outcomes will be analyzed using the 2 year visual acuity from the MCMC multiple imputed datasets used for the primary analysis with the binary outcome computed from the imputed visual acuity score; hence, all eyes will be included in the analyses. The treatment group difference in proportion and 95% confidence interval will be computed using the analytic model.

Visual acuity over two years will be explored by comparing treatment groups with respect to area under the curve using ANCOVA and by longitudinal analysis with a discrete time linear mixed model to compare specific time points. There will be no imputation of outcome for these analyses. The longitudinal analysis will include visits that were used for imputing the primary outcome, i.e. for participants who do not receive an alternate treatment, all available assessment visits will be included in analysis and for participants who receive alternate treatment only assessment visits up to and including the visit of alternate treatment will be included. The treatment group difference and 2-sided 95% confidence interval will be estimated for each of the time points prior to 2 years (16, 32, 52, 68, and 84 weeks) in the longitudinal analysis, and the same will be done for the 2 year time point in both analyses.
2.3 Treatment Assessment
Distribution of the number of ranibizumab injections from baseline to 1 year, baseline to 2 years, and 1 year to 2 years will be presented. Frequency of focal/grid laser within each group will be tabulated. Distribution of number of ranibizumab injections within the primary subgroups based on central-involved DME will be calculated.

2.4 Analysis of Secondary Outcomes
Secondary outcomes include visual function (Humphrey visual fields, visual function questionnaires), binocular visual acuity, retinal thickness, costs, and diabetic retinopathy outcomes such as vitreous hemorrhage, retinal detachment and diabetic retinopathy severity. Secondary outcomes will be analyzed including adjustment for baseline level of the outcome and randomization stratification factors, and using the last-observation-carried-forward (LOCF) method to impute missing 2-year outcome data, unless otherwise specified.

2.4.1 Visual Function Testing
Humphrey visual field testing (at select sites), NEI VFQ-25, and UAB-LLQ will be performed to assess visual function. It is hypothesized that visual function measures will be worse in the prompt PRP group due to destructive effects of PRP on the peripheral retina. Hence, the usual hypothesis test of no difference between treatment groups will be conducted for all visual function outcomes.

2.4.1.1 Visual Function Questionnaires
A treatment group comparison of mean change in visual function subscale scores from baseline to 2 years (to coincide with the primary visual acuity outcome) will be performed using analysis of covariance with adjustment for baseline level of the subscale and randomization stratification factors. As visual function subscale scores are measured at the study participant level, data from bilateral participants is non-informative with respect to treatment effect because both interventions were received; hence, bilateral participants will not be included in these analyses.

To control for inflation in the type I error rate due to testing of multiple subscales, the following subscales that are hypothesized to be those most likely to differ by treatment group will be considered the primary subscales of interest: driving (NEI VFQ-25 and UAB-LLQ subscales), peripheral vision (NEI VFQ-25 single item and UAB-LLQ subscale), color vision (NEI VFQ-25 and UAB-LLQ single items), and general dim lighting (UAB-LLQ subscale). Evidence of a treatment difference on these scales will be interpreted as definitive evidence of a treatment group difference with respect to the subscale in question. To further control for multiple testing, only p-values less than 0.01 will be considered statistically significant evidence for a treatment difference.

For the primary subscales of interest, binary outcomes for improvement versus no improvement and worsening versus no worsening will be defined based on estimates of minimum clinically important differences for each subscale. Binary outcomes will be compared between treatment groups using binominal regression adjusting for the baseline level of the subscale and the randomization stratification factors. If the binominal model does not converge, Poisson regression
with robust variance estimation [Spiegelman 2005], or a binomial model that is not adjusted for baseline factors will be used.

All other subscales from the NEI-VFQ and UAB-LLQ will be analyzed similarly to the primary subscales; however, statistically significant differences on these subscales will be considered suggestive of treatment group differences rather than definitive.

### 2.4.1.2 Analysis of Visual Field Testing Data

A treatment group comparison of change in total point score, change in relative total point score, and change in mean deviation from baseline to 2 years will be performed using ANCOVA. Bilateral participants will be included in these analyses and GEE will be used to account for correlation in participants with two study eyes. The central (30 degree) and peripheral (30-60 degree) fields will be analyzed separately and combining both fields. When combining fields for the change in mean deviation, the change in mean deviation for each of the fields will be weighted by the number of points in the field to calculate a combined change in mean deviation. Change values will be truncated at ±3 standard deviations from the mean change to ameliorate the impact of outliers on the analysis.

Eyes at sites where visual fields were not performed will not be included in any analyses. Eyes with poor quality baseline fields defined as >33% false positives or >33% fixation losses will be excluded from relevant analyses. As inability to complete visual fields during follow up could be related to treatment, values for missing follow up visual fields will be imputed for eyes that have a valid baseline value using multiple imputation with the MCMC method. The imputation will be based on treatment group, the randomization stratification variables, and visual field data from assessment visits prior to 2 years.

Analyses will be repeated not excluding eyes with poor quality baseline fields in a sensitivity analysis.

### 2.4.2 Binocular Visual Acuity

Binocular visual acuity is a participant-level outcome; hence, bilateral participants will be excluded from analysis. It is expected that binocular visual acuity in unilateral participants will be largely determined by the fellow eye, thus a difference between treatment groups is not expected and will serve as the null hypothesis to be tested. Binocular visual acuity will be compared between treatment groups using ANCOVA.

### 2.4.3 Diabetic Retinopathy Outcomes

The cumulative event rate over 2 years of the following key diabetic retinopathy events of interest will be computed and plotted by treatment group using the Kaplan-Meier method:

- Proportion of eyes with vitrectomy
- Proportion of eyes developing neovascular glaucoma
- Proportion of eyes developing iris neovascularization
- Proportion of eyes with vitreous hemorrhage
- Proportion of eyes with retinal detachment
The treatment groups will be compared using the marginal Cox proportional hazards model to account for correlation between eyes of bilateral participants, with adjustment for randomization stratification factors. Eyes of participants lost to follow up without observing an event will be censored at the time of the last visit. As the IVR+deferred PRP group has more frequent visits, results in this group are likely biased towards more frequent outcomes than in the prompt PRP group. Hence, a finding that the event rate is significantly increased in the IVR+deferred PRP group relative to the prompt group could be due to assessment bias, rather than a true treatment difference. However, a finding that the event rate is significantly higher in the prompt PRP group can be taken as definitive evidence of a difference between treatments.

In addition, the proportion of eyes with the following diabetic retinopathy outcomes at 2 years will be computed, and compared between treatment groups using binomial regression with GEE to account for correlation between eyes, with adjustment for the randomization stratification factors:

- Proportion of eyes with complete regression of neovascularization on fundus photography at 2 years
- Proportion of eyes with 2 step worsening of DR severity on fundus photography at 2 years
- Proportion of eyes with resolution of NV on clinical exam at 2 years

Last observation carried forward will be used to impute an outcome for eyes that did not complete 2 years of follow up. It is recognized that this may underestimate the true proportions with outcome at 2 years; the estimates will be regarded as a minimum.

Within the ranibizumab+deferred PRP group, the exact binomial proportions and 95% confidence intervals with the following outcomes will be estimated:

- Proportion of eyes not requiring PRP by 2 years
- Proportion of eyes improving 2 or more steps in diabetic retinopathy (DR) severity at 2 years based on photograph grading
- Proportion of eyes with DR severity of severe NPDR or better at 2 years based on photograph grading

Within the PRP group, the exact binomial proportions and 95% confidence intervals with the following outcomes will be estimated:

- Proportion of eyes requiring supplemental PRP by 2 years

Eyes lost to follow up prior to 2 years that had not received PRP will be assumed to not have received PRP. Other missing outcomes will not be imputed.

2.4.4 Retinal Thickness

Retinal thickening outcomes will be assessed using OCT central subfield and peripheral field thicknesses and retinal volume. At each assessment visit, the changes in retinal thicknesses and change in retinal volume from baseline will be computed and mean for each treatment group over time will be plotted. Mean change from baseline to 2 years will be compared between
treatment groups using an ANCOVA model, adjusting for baseline level of the outcome, and laterality.

At each assessment visit, the proportion of eyes with OCT central subfield thickness of \( \geq 250 \mu \text{m} \) on Stratus OCT (or standard deviation equivalent for other OCT machines) and at least 25 \( \mu \text{m} \) increase from baseline will be calculated, plotted, and compared between treatment groups using logistic regression adjusting for baseline OCT CST and laterality and using GEE to account for the correlation between two study eyes.

The hypothesis test of no difference between treatment groups will be conducted. Missing 2 year OCT CST will be imputed using LOCF.

### 2.4.5 Development of Center-involved DME

Time to development of center-involved DME, defined as OCT CSF \( \geq 250 \) and visual acuity letter score <79, in eyes without center-involved DME at baseline, will be plotted using the Kaplan-Meier method with the logrank test. Only eyes with baseline OCT CSF < 250 will be included. The marginal Cox model will be used to compare treatment groups accounting for correlation between eyes of bilateral participants, with adjustment for randomization stratification factors. As the IVR+deferred PRP group has more frequent visits, results in this group are likely biased towards finding center-involved DME both earlier and more frequently than in the prompt PRP group. Hence, a finding that the outcome rate is significantly increased in the IVR+deferred PRP group relative to the prompt group could be due to assessment bias. However, a finding that the outcome rate is significantly higher in the prompt PRP group will be taken as definitive evidence of a difference between groups.

### 3.0 Economic Analysis

The purpose of the economic analysis is to compare the treatment groups with respect to cost, cost consequences, and cost utility. For cost, the viewpoint adopted is that of a third party payer. For the cost-consequence and cost-utility analyses, a perspective that includes patient and broader societal issues, particularly focusing on workplace productivity loss, has been adopted. Detailed analysis plans will be developed in consultation with the DRCR.net’s health economic consultants.

### 4.0 Safety Analysis

Adverse events will be categorized as study eye, non-study eye, and systemic. All randomized eyes will be included in the safety analyses.

As the IVR+deferred PRP group has more frequent visits and more injections, results in this group are likely biased towards more frequent outcomes than in the prompt PRP group. Hence, a finding that the outcome proportion is significantly increased in the IVR+deferred PRP group relative to the prompt group could be due to assessment bias. However, a finding that the outcome proportion is significantly higher in the prompt PRP group can be taken as definitive evidence of a difference between groups.
4.1 Ocular adverse events

Ocular events will be tabulated separately for the two treatment groups. For the 2-year primary analyses, any ocular event that occurred at least once prior to the 2 year visit (or 730 days if missing 2 year visit) will be reported. The frequency of the event occurring at least once per eye will be calculated. Eye-level outcomes will be compared between treatment groups using binomial regression models, or Poisson regression with robust variance estimation if the binomial model does not converge, with GEE to account for the potential correlation between two study eyes. For all analyses, the hypothesis test of no difference between treatment groups will be conducted. Due to the large number of outcomes being tested, only p-values less than 0.01 will be considered statistically significant. It is recognized that this does not fully control the type I error rate.

The following adverse events will be assessed:
- Endophthalmitis
- Any retinal detachment
- Rhegmatogenous retinal detachments
- Tractional retinal detachment
- Retinal tears
- Cataract surgery
- Vitreous hemorrhage
- Inflammation (defined as anterior chamber cell, anterior chamber flare, choroiditis, episcleritis, uveitis, or iritis)
- Adverse intraocular pressure events
  - increase of IOP>10 mmHg from baseline
  - IOP>30 mmHg
  - initiation of glaucoma medications,
  - glaucoma procedure
- Neovascularization of the iris

4.2 Systemic adverse events:

Systemic adverse events will be reported in three groups: 1) unilateral participants randomized to PRP, 2) unilateral participants randomized to IVR+PRP, 3) bilateral study participants. For the 2-year primary analyses, any systemic event that occurred at least once prior to the 2 year visit or 730 days from randomization will be reported. The frequency of the event occurring at least once per participant will be calculated. For systemic outcomes, a Fisher’s exact test will be performed including 3 groups (unilateral prompt PRP, unilateral IVR+deferred PRP, and bilateral). If the overall test is statistically significant (p<0.01), then pairwise comparisons between groups will be performed using Fisher’s exact test. For all analyses, the hypothesis test of no difference between treatment groups will be conducted. Due to the large number of outcomes being tested, only p-values less than 0.01 will be considered statistically significant. It is recognized that this does not fully control the type I error rate.
Primary:
- Death
- Serious adverse event (proportion of participants with at least one)
- Hospitalizations (proportion of participants with at least one)
- Cardiovascular/cerebrovascular events according to Antiplatelet Trialists’ Collaboration (excerpted from BMJ Jan 8, 1994):
  - Non-fatal myocardial infarction
  - Non-fatal stroke (counted only if symptoms lasted at least 24 hours)
  - Death of unknown cause
  - Death attributed to cardiac, cerebral, hemorrhagic, embolic, or other vascular cause (does not need to be ischemic in origin)
  Notes: Transient ischemic attacks, angina, and possible MI or stroke are not counted. ‘Nonfatal’ MI or stroke required that the patient was alive at the end of the study. If not, only the death is counted.

Secondary:
- Hypertension
- Frequency of at least one event per participant in each MedDRA system organ class

5.0 Additional Tabulations and Analyses
The following will be tabulated according to treatment group:
- Baseline demographic and clinical characteristics
- Visit completion rate for each visit
- Number of visits per treatment group
- Protocol deviations

5.1 Analysis of Outcomes Through 5 Years
The primary purpose of analyses of outcome data including annual visits from 3 years through 5 years will be to determine trends in outcomes (visual acuity, OCT CST, visual fields, visual function, and safety) over 5 years and whether results at 3, 4, and 5 years are consistent with those at 2 years. Detailed statistical analysis plans will be developed for specific manuscripts on longer term outcomes when the participants are close to reaching 5 years of follow up. It is anticipated that the analytic approach will largely follow that for the 2 year data detailed herein.

6.0 General Principles for Analysis
6.1 Analysis Cohort
Unless otherwise stated, all treatment comparison analyses will follow the intent-to-treat principle with each eye included in the treatment group according to the randomized treatment assignment regardless of treatment actually received.

6.2 Visit Windows for Analysis
For time to event analyses, the windows for analysis are included in the section describing the analysis. For other analyses, including the primary analysis of visual acuity, the analysis windows will be defined as follows:

<table>
<thead>
<tr>
<th>Visit (Protocol Window)</th>
<th>Target</th>
<th>Analysis Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 weeks ± 2 weeks</td>
<td>112 days</td>
<td>84 – 140 days (16 ± 4 weeks)</td>
</tr>
<tr>
<td>32 weeks ± 2 weeks</td>
<td>224 days</td>
<td>196 – 252 days (32 ± 4 weeks)</td>
</tr>
<tr>
<td>52 weeks ± 2 weeks</td>
<td>364 days</td>
<td>308 – 420 days (52 ± 8 weeks)</td>
</tr>
<tr>
<td>68 weeks ± 4 weeks</td>
<td>476 days</td>
<td>434 – 518 days (68 ± 6 weeks)</td>
</tr>
<tr>
<td>84 weeks ± 4 weeks</td>
<td>588 days</td>
<td>546 – 630 days (84 ± 6 weeks)</td>
</tr>
<tr>
<td>104 weeks ± 4 weeks</td>
<td>728 days</td>
<td>644 – 812 days (104 ± 12 weeks)</td>
</tr>
<tr>
<td>120 weeks ± 4 weeks</td>
<td>840 days</td>
<td>798 – 882 days (120 ± 6 weeks)</td>
</tr>
<tr>
<td>136 weeks ± 4 weeks</td>
<td>952 days</td>
<td>910 – 994 days (136 ± 6 weeks)</td>
</tr>
<tr>
<td>156 weeks ± 4 weeks</td>
<td>1092 days</td>
<td>1036 – 1148 days (156 ± 8 weeks)</td>
</tr>
<tr>
<td>208 weeks ± 8 weeks</td>
<td>1456 days</td>
<td>1372 – 1540 days (208 ± 12 weeks)</td>
</tr>
<tr>
<td>260 weeks ± 8 weeks</td>
<td>1820 days</td>
<td>1736 – 1904 days (260 ± 12 weeks)</td>
</tr>
</tbody>
</table>

Study ‘assessment visits’ are the visits required for both treatment groups by protocol and consist of the visits at baseline, 16, 32, 52, 68, 84, 104, 156, 208, and 260 weeks.

6.3 Missing Data

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

6.4 Outliers

To help assure that statistical outliers do not have undue impact on visual acuity and OCT central subfield thickness analyses, changes for these values will be truncated to ±3 standard deviations from the mean change at 2 years.

6.5 Longitudinal Analyses

Longitudinal analyses will be performed using linear mixed models with a random effect for eye to account for correlation between eyes and time treated as a repeated factor. Exploratory data analysis will be used to choose a suitable model for the correlation structure over time. Typically, some type of autoregressive correlation structure, such as autoregressive moving average works well for longitudinal visual acuity and OCT data.

Time will be included in models as a categorical variable in order to ensure a good fit to the time trend without imposing specific assumptions regarding its form.

References