NOVARTIS

Clinical Development

CLG561

CCLG561X2201A

A randomized, multi-center, single-masked, sham controlled, proof-of-concept study of intravitreal CLG561 as a monotherapy and in combination with LFG316 in subjects with geographic atrophy

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BCVA	best corrected visual acuity
BLQ	below the limit of quantitation
BPM	beats per minute
CRC	central reading center
CSR	clinical study report
CV	coefficient of variation
DEP	Deviations and Evaluability Plan
EOS	end of study
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	fundus autofluorescence
FCS	Fully conditional specification
FU	follow up
GA	geographic atrophy
GGT	gamma-glutamyl transferase
HIV	human immunodeficiency virus
IOP	intraocular pressure
IRT	interactive response technology
IVT	intravitreal
LLOQ	lower limit of quantification
mmHg	millimeters of mercury
MMRM	mixed-effect model repeated measure
PK	pharmacokinetic(s)
PP analysis set	per protocol analysis set
PPS	Predictive probability of success
RBC	red blood cell(s)

SD-OCT	spectral domain optical coherence tomography
TBL	total bilirubin
ULOQ	upper limit of quantification
WBC	white blood cell(s)

1 Study Objectives and Design

1.1 Study Objectives

Primary Objectives

- To evaluate the safety of 12 (every 28 days) IVT injections of CLG561 as a monotherapy and in combination with LFG316 as compared to sham.
- To evaluate in the study eye the efficacy of 12 (every 28 days) IVT injections of CLG561 as a monotherapy and in combination with LFG316 as compared to sham on the growth of GA lesion size as assessed by FAF based on the change from baseline to Day 337.

Secondary Objectives

- To evaluate the time course of the change in GA lesion size of the active arms as compared to sham as measured by FAF in the study eye.
- To evaluate the time course of the change in BCVA, low luminance visual acuity and low luminance visual acuity deficit up to Day 337 of the active arms as compared to sham in the study eye.
- To evaluate the average change in BCVA, low luminance visual acuity and low luminance visual acuity deficit from baseline to the period Day 281 to Day 337 of the active arms as compared to sham in the study eye.
- To evaluate the time course of the proportion of study eyes losing or gaining ≥15 letters, ≥10 letters, and ≥5 letters in BCVA from baseline up to Day 337 in each of the active arms as compared to sham in the study eye.

To describe:

- The systemic exposure of total CLG561 after IVT administration of CLG561 as a monotherapy up to Day 421.
- The systemic exposure of total CLG561 and total LFG316 after IVT administration of CLG561 in combination with LFG316 up to Day 421.

- To describe the immunogenicity of CLG561 after IVT administration of CLG561 as a monotherapy and the immunogenicity of CLG561 and LFG316 after IVT administration of CLG561 in combination with LFG316 up to Day 421.

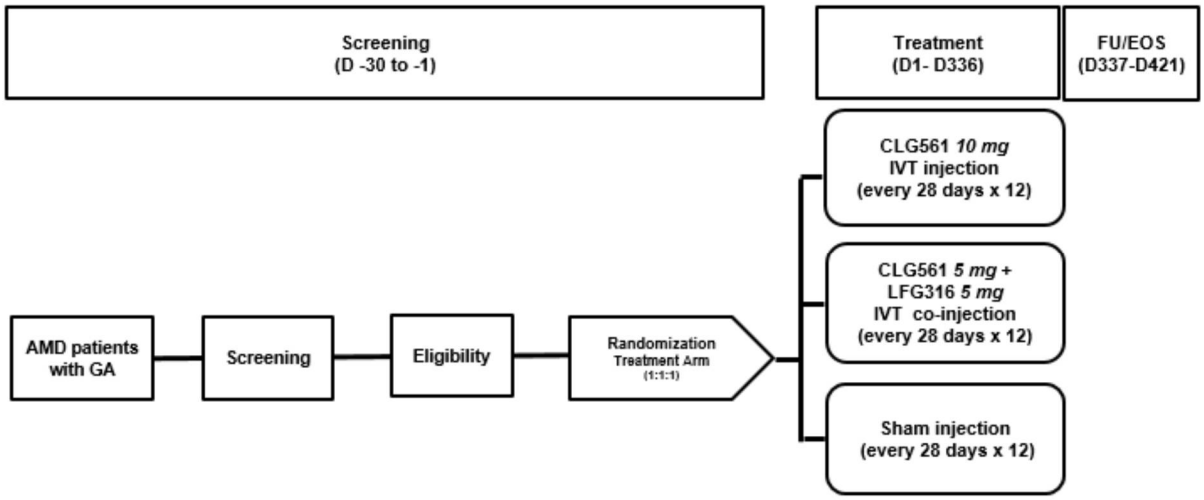
1.2 Study Description

This is a multi-center, randomized, sham-controlled, single masked, proof-of-concept study in geographic atrophy (GA) subjects. On Day -1, subjects will be randomized in a 1:1:1 ratio to receive one of three treatments: CLG561 (10 mg/100 µL), CLG561 (5 mg/50 µL) + LFG316 (5 mg/50 µL) or sham injection. Starting on Day 1, subjects will receive IVT injections from the randomized treatment regimen.

Both eyes must have GA but only one eye must meet the other inclusion/exclusion criteria to be eligible for study participation.

After the initial injection, there will be an additional 12 injections occurring approximately every 28 days. This will result in approximately 336 day treatment period of active drug or sham injection. There will be two follow up visits, occurring approximately 4 weeks and 16 weeks after the last administered injection.

Figure 1.2-1 Study Design



1.3 Randomization

A member of the Randomization Programming group at Alcon who is not part of the study team will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an Interactive Response Technology (IRT) system.

Qualified subjects will be randomized in a 1:1:1 manner through the interactive response technology (IRT) system, at Day -1, to receive either the CLG561 injection, the CLG561 + LFG316 injection or the sham injection on Day 1 and then every 28 days for a total of 336 days to the study eye.

1.4 Masking

This is a single-masked study and the following will be masked to treatment assignment:

- Subjects
- Visual acuity assessor at the study site
- Technicians obtaining images at the study site
- CRC staff

The primary investigator and the sponsor will be unmasked to treatment assignment.

1.5 Interim Analysis

One interim analysis (IA) will be conducted when all subjects complete all of their assessment at the visit following the 6th injection (Day 169).

Purposes of this interim analysis include (Protocol Section 3.5):

- Unmasked assessment of the safety of the treatment arms
- To enroll additional subjects if the treatment arms are not balanced based on the GA lesion phenotype
- Allow a reassessment of the sample-size calculations regarding the assumed lesion growth in the control arm (based on linear growth of the GA lesion)
- Support internal decision making concerning the current clinical study or the Sponsor's clinical development projects in general.

The subject numbers may be augmented up to a maximum of 72 subjects per treatment arm (refer to Section 5.7.1 for more details), or one of the study arms or the entire study may be stopped based on the safety signal.

Preliminary evaluation of the treatment efficacy to slow down GA lesion growth will be performed based on interim data, although the purpose is not to make an efficacy claim.

Additional interim analyses may be conducted based on a safety signal from the study, or if necessary to make internal decisions on the program.

Interim analysis results may be communicated to relevant sponsor teams for information, consulting and/or decision purposes. Further distribution of the interim analyses results can only be made upon sponsor team decision.

For data query and cleaning purposes, a cut-off date will be applied for the interim analysis. All visits which occurred prior to the clinical cut-off date (not limited to day 169) will be used for the IA. Data collected after the cut-off date will not be used for the IA.

2 Baseline and Visit Windows

2.1 Baseline

Baseline will be defined as the last measurement prior to first dose of study drugs. If the baseline visit (Day 1) measurement is missing, the screening values (if available) will be used instead.

2.2 Relative Day

The date of first dose of study drugs will be considered relative Day 1, and the day before the first dose of study drug will be relative Day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

For days on or after the first dose of study drug:
Date of Assessment – Date of First Dose of Study Drug + 1.

For days before the first dose of study drug:
Date of Assessment – Date of First Dose of Study Drug.

2.3 Visit Windows

All nominal visits in the database will be assigned at site per protocol scheduled visit window. For the purpose of statistical analysis, the actual visit numbers and visits will only need to be calculated for the EOS visit of patients who discontinued early. Since the protocol requires the EOS visit to be completed approximately 4 weeks after the last injection, the actual visit number for the EOS visit will be the last injection visit number +1. Otherwise the study visit numbers and visits assigned in the database will be used as is. Unscheduled visit will not be considered for analyses.

3 Analysis Sets

The detailed criteria that qualify a subject for exclusion from each analysis set will be identified in the Deviations and Evaluability Plan (DEP). The final subject evaluability will be determined prior to locking the database. Number of subjects in each analysis set will be summarized, and reasons for exclusion will be listed for subjects who did not qualify.

3.1 Efficacy Analysis Sets

The full analysis set will include all subjects who receive any study treatment and have baseline GA lesion size, and at least one follow-up GA lesion size assessment. The full analysis set will use the treatment as randomized.

The Per Protocol (PP) analysis set will be comprised of all full analysis set subjects who have no critical protocol deviations and have baseline lesion size assessment and the corresponding assessment on Day 337 or Day 253. Critical protocol deviations criteria will be identified in the Deviations and Evaluability Plan (DEP). Protocol deviations will be identified and classified before database lock. The PP analysis set will use the treatment as randomized.

The primary efficacy analysis will be performed using the PP analysis set with treatment as randomized. Sensitivity analyses will be performed on the primary efficacy endpoint using the full analysis set as randomized. If any subjects received a different treatment than the one they were randomized to, additional sensitivity analyses will be performed using full analysis set with the actual treatment most frequently exposed to in the study.

3.2 Safety Analysis Set

The safety analysis set will include all subjects who received any study treatment.
Safety analyses will be conducted using the safety analysis set. Subjects will be analyzed by the actual treatment received. Subjects exposed to an incorrect study treatment for the entire treatment period or a portion of the treatment period will be accounted for under the actual treatment the subject was most frequently exposed to in the study.

3.3 Pharmacokinetics and Immunogenicity Analysis Set

The pharmacokinetic analysis set will include all subjects with available PK data (total LFG316 and total CLG561) or immunogenicity data (anti-LFG316 antibodies and anti-CLG561 antibodies) and no protocol deviations with relevant impact on pharmacokinetic or immunogenicity data. The pharmacokinetics and immunogenicity analysis set will use the treatment as treated.

3.4 Pharmacodynamic Analysis Set

The pharmacodynamic (PD) analysis set will include all subjects with available pharmacodynamic data (total C5, total properdin and serum complement activity measured by Wieslab assay) and no protocol deviations with relevant impact on pharmacodynamic data. The pharmacodynamic analysis set will use the actual treatment.

4 Subject Characteristics and Study Conduct Summaries

Subject characteristics and study conduct summaries will be provided for subject disposition, demographic (age, age group (<75 years, ≥75 years), gender, race, ethnicity), baseline characteristics (BCVA, lesion size, lesion location and lesion type). Ocular and AMD history, family history, and smoking history will be listed. Medical history and prior/concomitant medication will be listed and summarized by treatment groups. Number and percentage will be presented for categorical variables and descriptive statistics including mean, standard deviation, median, minimum and maximum will be presented for continuous variables. Subject disposition and study completion status or reason for early exit will be listed and summarized by treatment group.

5 Efficacy Analysis Strategy

The detailed criteria that exclude certain observed data from analyses due to protocol deviations will be identified in the Deviations and Evaluability Plan (DEP).

5.1 Efficacy Endpoints

Primary Endpoints

The primary endpoint is the change in GA lesion size (mm^2) in the study eye from baseline to Day 337 as measured by FAF.

Each post-screening imaging time point will be reviewed by two FPRC graders (double read). Each Grader will independently complete the assessments. Adjudication will be triggered in the following situations:

- 10% difference between the two graders' area measurements
- Any difference in qualitative assessments

The adjudicator will have the option of selecting either Grader1 or Grader 2's assessments, or providing their own assessment.

The adjudicator assessments will be considered the final assessments for the subject.

When there is no adjudication:

1) If the two graders' area measurements are within 10% of each other (i.e. percentage of absolute difference over the average of the two measurements), the results will be averaged and used for statistical analyses.
2) If only 1 grader result is presented or two graders' results difference are >10%, the assessment will be treated as missing.

Secondary Endpoints

The secondary efficacy endpoints are

- Change in GA lesion size from baseline to Day 85, 169, 253, 337 and 421 as measured by FAF in the study eye
- Change in BCVA, low luminance visual acuity and low luminance visual acuity deficit from baseline by visit up to Day 337 as measured by ETDRS in the study eye.

  Low luminance visual acuity deficit is defined as the difference between BCVA and low luminance visual acuity, i.e.

  Low luminance visual acuity deficit= BCVA- low luminance visual acuity

- Average change in BCVA, low luminance visual acuity and low luminance visual acuity deficit from baseline to the period Day 281 and to Day 337 as measured by ETDRS in the study eye

  The average change is defined by arithmetic mean of change from baseline of all observed time points between Day 281 and Day 337.

- Subject status regarding ≥15 letters, ≥10 letters, and ≥5 letters change from baseline in BCVA by visit up to Day 337 as measured by ETDRS in the study eye

- Serum concentrations of total CLG561 (CLG561 monotherapy) and serum concentrations of total CLG561 and total LFG316 (CLG561/LFG316 combination) by visit up to Day 421

- Serum anti-CLG561 antibodies (CLG561 monotherapy) and serum anti-CLG561 and anti-LFG316 antibodies (sham and CLG561/LFG316 combination) by visit up to Day 421

5.2 Efficacy Hypotheses

Primary Hypotheses

The primary efficacy hypotheses are that the mean change in GA lesion size from baseline at Day 337 in the two active treatment groups (CLG561 and CLG561 + LFG316) separately is lower than in the sham group at Day 337. The null and alternative hypotheses are:

H_{01}: $\mu_{CLG561} \geq \mu_{sham}$ H_{A1}: $\mu_{CLG561} < \mu_{sham}$

H_{02}: $\mu_{CLG561+ LFG316} \geq \mu_{sham}$ H_{A2}: $\mu_{CLG561 + LFG316} < \mu_{sham,}$

where μ_{CLG561}, $\mu_{CLG561+ LFG316}$ and μ_{sham} are the mean change from baseline at Day 337 in the CLG561 monotherapy group, the CLG561 + LFG316 combination group and the sham group, respectively.

Secondary Hypotheses

The secondary efficacy hypotheses for BCVA and low luminance visual acuity are that the mean change from baseline at Day 337 in the two active treatment groups (CLG561 and CLG561 + LFG316) separately is higher than in the sham group at Day 337. The null and alternative hypotheses are:

H_{01}: $v_{CLG561} \leq v_{sham}$ H_{A1}: $v_{CLG561} > v_{sham}$

H_{02}: $v_{CLG561+ LFG316} \leq v_{sham}$ H_{A2}: $v_{CLG561 + LFG316} > v_{sham,}$

where v_{CLG561}, $v_{CLG561+ LFG316}$ and v_{sham} are the mean change from baseline at Day 337 in the CLG561 monotherapy group, the CLG561 + LFG316 combination group and the sham group, respectively.

The secondary efficacy hypotheses for low luminance visual acuity deficit is that the mean change from baseline at Day 337 in the two active treatment groups (CLG561 and CLG561 + LFG316) separately is lower than in the sham group at Day 337.

5.3 Statistical Methods for Efficacy Analyses

5.3.1 Primary efficacy analyses

In the primary efficacy analysis which is based on the PP set, a subject will have in the study a baseline lesion size assessment and a corresponding assessment on Day 337 and/or Day 253. For subjects with missing values of lesion size in the study eye on Day 337, the missing value will be handled by multiple imputations detailed in section 5.5. Multiplicity adjustment based on Hochberg procedure and detailed in section 5.4 will be applied to the primary statistical modeling and all sensitivity analyses. Day 421 GA lesion size will only be summarized descriptively, and will not be included in any statistical modeling.

A basic summary statistics table will be provided for the observed value and change from baseline in study eye GA lesion size at each scheduled time points by treatment. Individual profile plot of GA lesion size and change from baseline will be produced by treatment groups, together with line charts of observed mean change from baseline+/- SD against study days with all treatment groups overlaying.

An ANCOVA model with treatment, baseline lesion location (foveal vs exfoveal), and baseline lesion size, baseline lesion type (unifocal vs multifocal) as covariates will be fit to the change from baseline in study eye GA lesion size at day 337. The least-squares means at the observed mean baseline covariates and associated two-sided 80% confidence intervals for each treatment group and the estimated mean treatment difference, the p-value, and the corresponding two-sided 80% CI will be extracted from the model.

A sensitivity analysis will be performed on the change from baseline in study eye GA lesion using the full analysis set with ANCOVA method.

Another sensitivity analysis of the change from baseline in study eye GA lesion size up to day 337 will be performed using a mixed-effect model repeated measure (MMRM) model with treatment, visit (categorical) and treatment by visit interaction, baseline lesion location, baseline lesion type, and baseline lesion size as fixed effects. Baseline lesion location*visit interaction, baseline lesion type, and baseline lesion size*visit interaction may also be added if adding the interactions provide a better fit statistics (BIC). Unstructured covariance structure will be used for the repeated measures. Unstructured covariance structure will be

used for the repeated measure. If the model fails to converge under unstructured covariance, other covariance structures such as heterogeneous Toeplitz, Ante-dependence , heterogeneous compound symmetry, heterogeneous AR(1), AR(1), and compound symmetry will be used in order until convergence is achieved. The least-squares means at the observed mean baseline covariates and associated two-sided 80% confidence intervals for each treatment group and the estimated mean treatment difference, the one-sided p-value, and the corresponding two-sided 80% CI will be extracted from the model for each time point and summarized in a table. The least-squares mean and associated two-sided 80% confidence will also be plotted against study days with different treatment groups overlaying. Under the assumption of missing at random, no imputations of missing values are needed for the MMRM model and it will be performed on the PP set.

The above analyses (ANCOVA and MMRM) will be also performed for the square root of GA lesion size on the PP set. Square root of baseline lesion size will be used as the covariate instead for these analyses.

In addition, a post-hoc analysis using similar MMRM model will be implemented to day 253 and day 337 lesion size (and square root of lesion size) changes from day 169. Day 169 lesion size will be used as the baseline covariate in the MMRM model. The estimated relative lesion size reduction for 2nd 6 month will be extracted from this analysis and be compared to the primary endpoint's result at 12 month.

An additional sensitivity analysis will be performed on change from baseline in GA lesion size up to day 337 using a linear growth mixed model. The model will include year and treatment*year interaction, and random subject effect on the slope for the year. Possible choices of additional covariate effects are: 1. Treatment, baseline lesion location, baseline lesion type and baseline lesion size as fixed effects, and a random subject effect on the intercept; 2. Baseline lesion location, baseline lesion type and baseline lesion size as fixed effects on the slope for the year (i.e. the interaction of year and listed effects). Inclusion of either or both of these above additional covariate effects will be chosen based on the information criteria fit statistics (BIC). Year is defined as (actual study day-1) divided by 365.25 in order to facilitate report of annual growth rate. Results will be reported in the same fashion as the above MMRM model. In addition, least-squares means and treatment difference at one year will be reported, together with estimate and confidence intervals for the annual growth rate (i.e. the slope for year in the model). The linear growth mixed model will be performed on the PP set.

In order to assess the growth rate change before and after 6 month, a similar piecewise linear growth mixed model will be used for analysis. The model differs from the above model by adding a treatment specific slope change after 6 month (day 169). More specifically, treatment interaction with the spline function (defined as [study day-169]/365.26 for study days greater than 169, 0 otherwise) will be included as additional covariates in the model. Such analysis will be performed on the PP set.

At last, a sensitivity analysis of change in lesion size at day 337 will be analyzed by an ANCOVA model with treatment and baseline lesion size as covariates. Missing day 337 result will be imputed by last observation carried forward (LOCF), i.e. day 253. The analysis will be performed on the PP set.

In order to assess the impact of missing doses, the below sensitivity analyses will be performed, and MMRM model will be used as the statistical models for these analyses.

- Sensitivity analysis 1: Lesion size observed at visits with less than 50% exposure will be dropped from analysis. Percent of exposure is defined as number of actual doses taken divided by number of scheduled doses per protocol prior to the visit*100.
- Sensitivity analysis 2: Lesion size after 2 or more missed doses (consecutive or within 6 months) will be dropped from analysis.
- Sensitivity analysis 3: The lesion size occurred after 1 or more missed doses in the local dosing window (i.e. any of 3 doses between last scheduled lesion assessment and the current lesion assessment) will be dropped from analysis.

5.3.2 Secondary Efficacy Analyses

Secondary efficacy analyses will be performed on full analysis data sets and per protocol analysis set. There will be no imputation or multiplicity adjustment for all secondary efficacy analyses. Day 421 measurements of all secondary endpoints will only be summarized descriptively, and will not be included in any statistical modeling.

Secondary efficacy endpoints (BCVA, low luminance visual acuity, and low luminance visual acuity deficit for the study eye) will be analyzed by basic summary tables, individual profile plots, line charts and the MMRM model in a similar fashion as the primary endpoint.

Linear growth model will not be used for these endpoints. The number and percentage of patients gaining/losing ≥15 letters, ≥10 letters, and ≥5 letters in study eye BCVA will be presented for each time point by treatment group. The average change in study eye BCVA,

low luminance visual acuity, and low luminance visual acuity deficit of Day 281, Day 309 and Day 337 will be calculated and summarized by treatment group.

5.4 Multiplicity Strategy

With two primary hypotheses to be tested, the Hochberg step-up procedure for multiplicity adjustment will be applied as follows:

p[1], p[2] are the 2 ordered one-sided p values, p[1]<p[2]. α=0.2

Step 1. If p[2] < α, reject both null hypothesis H0[1] and H0[2] and stop; otherwise accept H0[2] and go to Step 2.

Step 2. If p[1] < α/2, reject H0[1] otherwise accept H0[1].

There will be no multiplicity adjustment for any other endpoints.

5.5 Treatment of Missing Values

Missing values will be handled by multiple imputation methods. For the primary efficacy analysis ANCOVA model on the PP set, a subject will have a baseline lesion size and a corresponding lesion size on Day 337 and/or Day 253. For subjects with missing lesion size on Day 337, the missing value will be treated as missing at random and imputed based on a regression model including covariates such as observed lesion sizes at previous time points (day 253 and baseline minimally), baseline lesion location, baseline lesion type and other covariates when applicable. The imputation can be performed either within each treatment groups, or when within treatment groups is not feasible, combing all treatment groups together with treatment group as additional covariate in the imputation model. Monotone regression model can be used if all covariates in the imputation model are available or follows a monotone missing pattern. Fully conditional specification (FCS) method (Brand 1999; van Buuren 2007) with regression model can be used if arbitrary missing pattern is present. For the sensitivity analysis of GA lesion size by ANCOVA model on the full analysis set, the imputation can be done similarly.

Following recommendation of Bodner (2008) and Royston et al. (2011), the number of imputations should be similar to the percentage of cases that are incomplete, with 5 as minimum. For example, 20% of the cases in your data set have missing data, 20 imputed data sets will be generated. PROC MI may be used to generate imputed data sets. These imputed data sets will then be analyzed with the primary ANCOVA model under SAS PROC MIANALYZE.

There will be no imputation of other missing endpoints.

5.6 Subgroup Analyses and Effect of Baseline Factors

The following subgroups will be analyzed for the primary efficacy endpoint using similar MMRM approach as described in Section 5.3.3:

- Age category (<75 years and ≥75 years)
- Gender (male and female)
- Baseline BCVA categories (<60 letters, 60-73 letters, ≥73 letters)
- Baseline lesion location (Foveal, Extrafoveal)

  The MMRM model used within each lesion location will be same as one as described in Section 5.3.3, except that baseline lesion location will not be used as a covariate.

- Baseline lesion type (unifocal vs multi-focal)

  The MMRM model used within each lesion location will be same as one as described in Section 5.3.3, except that baseline lesion type will not be used as a covariate.

- Genetic subgroups (ARMS/HTRA1=2 and ARMS2/HTRA1 + CFH ≥ 3)

5.7 Interim Analyses for Efficacy

Interim analyses will be performed on the interim per protocol analysis set, defined as subjects who belong to full analyses datasets and do not have major protocol deviations that could impact the efficacy assessment. Examples of such major protocol deviations include deviations to inclusion/exclusion criteria.

For the per protocol analysis, at the time of lesion size assessment, if the patient in either CLG561 arm or the combo arm had 50% or more injections required by the protocol, the

lesion size will be treated as analyzable, otherwise the lesion size will be excluded. Such criteria will not apply to the sham arm. Additional sensitivity analyses may be performed by relaxing this exposure requirement.

Aforementioned analyses in Section 5.3 and the above criteria will be performed in the following endpoints: GA lesion size, BCVA, Low luminance visual acuity, and low luminance visual acuity deficit.as a preliminary evaluation of efficacy:

Observed values, as well as change from baseline for the study eye and fellow eye will be included for the interim efficacy analyses.

Since there will be a significant amount of unobserved data at day 337 for the ANCOVA analysis at the time of the IA, MMRM model will be used as the primary analysis for interim analysis. Under missing at random (MAR) assumption, MMRM does not require imputation. The detailed set of outputs will be specified in the output shell document.

5.7.1 Sample Size Reassessment

The protocol sample size calculation assumed an average natural disease progression of 2.0mm^2 per year and a standard deviation of 1.2mm^2 for the change from baseline at 12 month for the study population. One key objective of the IA is to verify these assumptions using the interim data and reassess the sample size calculation. On the other hand, the preliminary efficacy evaluation based on unmasked interim data, e.g. treatment difference at Day 169, may also inform the effect size assumption and sample size re-assessment.

The sample size for the study as per protocol may be augmented up to a maximum of 72 subjects per treatment arm.

5.7.1.1 Sham arm growth rate assessment

Sham arm growth rate and standard deviation at Day 169 will be analyzed using descriptive statistics. These observed Day 169 results will then be extrapolated to Day 337 based on linear assumption, which will be used to assess whether the current sample size is adequate. The linear growth of GA lesion size in sham treated patients is well established and supported by previous GATE and GAP studies for GA.

5.7.1.2 Effect size evaluation and sample size re-assessment

Given the uncertainty in the effect size at Day 337 in this very first study of efficacy in humans, the effect size for each active arm and variance of change in lesion size at day 337 will be estimated from the interim observed data.

At the IA, all patients will have the opportunity to complete their Day 169 visit, but fewer patients will have the opportunity to reach later visits. For example, around half of the patients are expected to reach their Day 253 visits, yet only up to 30 patients are expected to have reached their planned Day 337 visit. Therefore the effect size at Day 337 will be estimated or extrapolated using the Day 169 data as well as other already observed data.

Extrapolation to Day 337 will be based on growth trajectory models suggested by the interim data. Although the linearity assumption in the sham arm is plausible based on historical data, growth trajectories in the CLG+LFG combo and CLG mono-therapy arms are unknown. Therefore various models including random effect linear growth model and more flexible (nonlinear) models such as random-effect quadratic growth model and random-effect power model, as well as MMRM will be fitted. Lack of fit statistics, information criteria (BIC), or external validation may be considered for final model selection.

The data available at interim analysis will be used to check if the growth of GA size follows a linear pattern and based on this analysis the sample size may be revised.

6 Safety Analysis Strategy

6.1 Safety Assessments

The safety assessments are:

- Extent of exposure
- Adverse events
- Best Corrected Visual Acuity (letters read)
- Low Luminance Visual Acuity
- Biomicroscopy Findings/Slit Lamp Examinations (lens, aqueous flare, aqueous cell, corneal edema, corneal haze, corneal staining)
- Intraocular pressure

- Dilated Fundus Examination (retinal hemorrhage, vitreal hemorrhage, vitreal cells, retinal tear/detachment)
- Vital signs (body temperature, pulse rate and blood pressure)
- Laboratory Results (hematology, blood chemistry, urinalysis)

6.2 Safety Hypotheses

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of adverse events and safety assessments listed in Section 6.1.

6.3 Statistical Methods for Safety Analyses

Analysis set for all safety analyses is the safety analysis set as defined in Section 3.2. All safety analyses will also be performed by eye specific safety endpoints by eye (study eye versus fellow eye) as well.

6.3.1 Extent of Exposure

Duration of exposure to each treatment is defined as the last day of exposure to each treatment minus the first day of exposure plus 1. Duration of exposure will be summarized as a continuous measure (N, mean, median, standard deviation, minimum and maximum).

Total number of injections and percent of compliance will also be summarized descriptively.

6.3.2 Adverse Events

For treatment-emergent AEs, defined as events that occur after exposure to first treatment, descriptive summaries (frequency and percentages) for specific AEs will be presented by system organ class and preferred term. Ocular events for study eye, ocular adverse events for fellow eye, and non-ocular events will be summarized separately. In addition to an overall presentation of all AEs, reports will be generated for special classes of AEs such as drug related/procedure related AEs, serious AEs and AEs leading to discontinuation. Presentation of ocular AEs will be by eye (study eye versus fellow eye). These reports will be supported by individual subject's listings, as necessary. For pre-treatment AEs, only individual subject listings will be provided. An additional listing will be provided for those subjects who had adverse events after exiting the study.

6.3.3 Best Corrected Visual Acuity (BCVA)

Visual acuity will be measured based on the procedures developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) and the results will be reported in letters read correctly.

Visual acuity assessment will be conducted in both eyes at Day -1, Day 1, Day 2, Day 8, Day 15, Day 29, Day 30, Day 57, Day 85, Day 113, Day 141, Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, Day 337 and Day 421.

Worst change from baseline across all post-baseline visits will be summarized.

6.3.4 Low Luminance Visual Acuity

Visual acuity will be measured based on the procedures developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) and the results will be reported in letters read correctly.

Visual acuity assessment will be conducted in both eyes at Day 1, Day 2, Day 29, Day 57, Day 85, Day 113, Day 141, Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, Day 337 and Day 421.

Worst change from baseline across all post-baseline visits will be summarized.

6.3.5 Biomicroscopy Findings/Slit Lamp Examination

A slit-lamp examination will be performed on Day -1, Day 1, Day 2, Day 8, Day 15, Day 29, Day 30, Day 57, Day 85, Day 113, Day 141, Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, Day 337 and Day 421 to evaluate the anterior segment of the eye, including lens, aqueous reaction (flare and cells), corneal edema and corneal haze. Ocular signs will be captured for the below:

- Lens
- Aqueous flare
- Aqueous inflammatory cell
- Corneal Epithelial Edema
- Corneal Stromal Haze

Slit lamp examination data will be listed for all subjects.

6.3.6 Intraocular Pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg and rounded to the nearest whole mmHg. IOP measurements will be conducted on Day -1, Day 1, Day 2, Day 8, Day 15, Day 29, Day 30, Day 57, Day 85, Day 113, Day 141, Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, Day 337 and Day 421.

Intraocular pressure data will be listed for all subjects by treatment, subject and visit/time. Observed values and change from baseline will be presented descriptively (N, mean, median, standard deviation, minimum and maximum) at each study visit (pre-injection and 30 minutes post injection) by treatment group for study eyes).

Worst change from baseline across all post-baseline visits will be summarized.

6.3.7 Dilated Fundus Examination

The dilated fundus examination will be performed on Day -1, Day 1, Day 2, Day 8, Day 15, Day 29, Day 30, Day 57, Day 85, Day 113, Day 141, Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, Day 337 and Day 421. The dilated fundus examination will be performed to evaluate the health of the retinal or vitreal hemorrhage, vitreous hemorrhage density, vitreal cells and retinal tear/detachment. Below fundus examination parameters will be captured:

- Retinal Hemorrhage (Macular)
- Retinal Hemorrhage (Non-Macular)
- Vitreal Hemorrhage
- Vitreous hemorrhage density
- Vitreal cells
- Retinal tear/detachment

All dilated fundus examination data will be listed by treatment, subject and visit/time. For each fundus parameter, a shift table showing fundus parameter grade at baseline relative to the grade at all post-baseline visits (pre-injection) will be presented by treatment group for study eyes

6.3.8 Vital Signs

Vital signs measurements including pulse rate, body temperature and diastolic and systolic blood pressures will be performed at Screening, Day 29, Day 57, Day 85, Day 113, Day 141, Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, Day 337 and Day 421.

All vital signs data will be listed by treatment, subject and visit/time.

6.3.9 Laboratory Results

Clinical laboratory evaluations consist of hematology, blood chemistry and urinalysis. Evaluations will be performed at Day -1, Day 337 and Day 421. A listing will be provided which lists all abnormal values for each clinical laboratory parameter.

6.3.9.1 Hematology (Complete Blood Count)

The following hematology parameters will be collected: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute and percentage of neutrophils, lymphocytes, monocytes, eosinophils and basophils) and quantitative platelet count.

A subject listing will be provided which contains data for each hematology parameter.

6.3.9.2 Blood Chemistry

The following blood chemistry parameters will be collected: sodium, potassium, creatinine, urea, chloride, albumin, calcium, alkaline phosphatase, total bilirubin (TBL), GGT, AST and ALT.

A subject listing will be provided which contains data for each blood chemistry parameter.

6.3.9.3 Urinalysis

The following urinalysis parameters will be collected: leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/hemoglobin and microscopic examination (WBC, RBC and casts).

A subject listing will be provided which contains data for each urinalysis parameter.

7 Pharmacokinetic Analysis Strategy

The PK endpoints include ocular and serum concentration of CLG561 and LFG316 based on samples collected at the protocol-specified timepoints.

The pharmacokinetic analyst will generate and provide a SAS data set based on the pharmacokinetic concentration data. Using this data set, Biostatistics will provide a listing of ocular and serum concentration of CLG561 and LFG316 by treatment, subject, and visit/sampling time of post dose. Biostatistics will also provide descriptive summary statistics by treatment and visit/sampling time point (post dose elapsed time), including the frequency (n, %) of concentrations below the lower limit of quantification (<LLOQ). <LLOQ will be treated as zero for calculation of descriptive statistics when necessary.

7.1 Pharmacokinetic Endpoints

- Serum concentration of total CLG561 and total LFG316
- Ocular concentrations of CLG561 after IVT administration of CLG561 as a monotherapy and ocular concentrations of CLG561 and LFG316 after IVT administration of CLG561 in combination with LFG316

7.2 Pharmacokinetic Hypotheses

There are no formal PK hypotheses in this study.

7.3 Statistical Methods

Ocular (aqueous humor) and serum concentration will be listed by treatment, subject and visit/time. Descriptive summaries of ocular and serum concentration (including geometric means, coefficient of variation, median, minimum and maximum) will be presented by treatment and study day. Geometric means will be calculated by taking the exponential of the arithmetic mean of the log-transformed parameter values.

For the purpose of calculating descriptive statistics for serum analyte concentrations, all post-dose serum concentrations below the limit of quantification (BLQ) will be replaced by zero.

A listing of individual subject's ocular (aqueous humor) and plasma concentration values for the active treatment groups by time will be presented. Corresponding PK parameters (AUC/Cmax) will also be presented.

Each of the PK parameters (AUCtau, Cmax) will be listed by subject and visit and summarized by subject and visit. Descriptive statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum.

9 Sample Size and Power Calculations

A sample size of 30 PP evaluable subjects per treatment arm will allow identification of a treatment difference of 0.67 mm^2 in lesion size change from baseline to Day 337 (representing a 33% reduction in lesion growth rate, assuming an average natural disease progression of 2.0 mm^2 per year) at a one-sided alpha level of 0.1 with a power of 80% assuming a standard deviation of 1.2 mm^2.

In anticipation of a drop-out /protocol deviation rate of 20%, a total sample size of 114 randomized subjects (38 subjects/arm) is planned for the current study to ensure sufficient study completers for the above described PP analysis. Depending on ongoing monitoring of the drop-out/protocol deviations rate the need for additional recruitment will be assessed to ensure 90 PP evaluable subjects are available for the Day 337 analysis.

10 References

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