STATISTICAL ANALYSIS PLAN

Version 2.0

09-Apr-2025

An Open-Label Extension (OLE) Phase 3 Trial to Assess the Safety of Intravitreal Administration of Avacincaptad Pegol (Complement C5 Inhibitor) in Patients with Geographic Atrophy Who Previously Completed Phase 3 Study ISEE2008 (GATHER2)

ISN/Protocol: ISEE2009

IND: 77902

EudraCT: 2024-515185-13-00

Sponsor:

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Version History

SAP Version History Summary

The changes from the prior approved SAP that impact analyses are listed with the rationale in the table below.

SAP Version	Approval Date	SAP Section(s)	Change	Rationale
1.0	25-Oct-2024		Not Applicable	Original Version
2.0	See the signature page	3.1	Low Luminance Deficits (LLD) and Geographic Atrophy (GA) area will be summarized over Full Analysis Set.	LLD is considered as a variable of interest. Adding LLD and GA area is for completeness of the description.
		4.2.3	Baseline LLD is added as a variable to be summarized for visual acuity.	LLD is considered as a variable of interest.
		4.2.3	List of baseline Fundus Autofluorescence (FAF) measurements to be summarized were added.	For clarification of the baseline FAF measurements to be summarized.
		4.2.3	"Fluorescein angiography (FA) imaging assessment" is removed from baseline characteristics to be summarized	This variable at baseline was not collected per protocol.
		4.4	"Positive" is added to the definition of "Total Positive" in Table 1.	"Positive" was previously missing in the definition of "ADA Total Positive".
		4.4	Swimmer plot for ADA total positive participants' experience of ocular TEAE is removed.	Analysis with limited add-on value due to anticipated small number of ADA total positive participants.
		4.5	Pre-injection IOP and post-injection IOP definitions are updated.	For clarification in the definition of pre-injection IOP and post-injection IOP.
		4.5	Mean of pre-injection IOP change from baseline and post-injection IOP change from pre-injection will be plotted instead of pre-injection IOP and post-injection.	To support visualization of the IOP related analysis with more interests.

SAP Version	Approval Date	SAP Section(s)	Change	Rationale
		4.5	LLD will be summarized by visit over Full Analysis Set.	LLD is considered as a variable of interest.
		4.5	A subtitle is added for Geographic Atrophy Area	The subtitle was previously missing.
		4.6.1	Change the category name of "systemic" TEAE to "non-ocular" TEAE for the additional TEAE overview table.	Consider "non-ocular" is a more appropriate name comparing to "systemic". There is no change in the derivation/interpretation.
		4.6.1	Serious non-ocular TEAEs, Serious Study drug related non-ocular TEAEs, and Serious injection procedure related non-ocular TEAEs will be summarized by SOC and PT.	These TEAEs are of interest.
		4.6.1	TEAEs with frequency of ≥ 2% in any cohort, Ocular TEAE with frequency of ≥ 2% in any cohort, and Non-ocular TEAE with frequency of ≥ 2% in any cohort will be summarized by PT.	The TEAEs with frequency of ≥ 2% are considered as common and of interest.
		4.6.1	Variables in the listings are updated.	For clarification without any change in meaning.
		4.6.2	"Macular oedema/cysts" is added as an AESI.	Alignment at ACP project level.
		4.6.2	Point out AESI are TEAEs on study eye.	For clarification and align with protocol.
		4.10.1	Additional Rules for OE/IOP Analysis Flags except those in the Analysis Visit Month 18 are updated.	For clarification and including unpaired IOPs into the summary at each analysis visit.
		Throughout SAP	Corrected topographic errors and edits without changing contents.	To improve clarity and correct errors.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains technical and detailed elaboration of the principal features of the analysis described in the protocol and includes procedures for executing the statistical analysis to fulfil the objectives of the study.

The final SAP will be approved prior to database lock.

If there are any changes from the planned analyses in the final version of the SAP that impact the statistical analyses, then it will be documented in the Clinical Study Report.

1.1 Objective and Endpoints

The objectives of this trial are to assess long-term safety of avacincaptad pegol intravitreal administration for patients with geographic atrophy (GA) who completed Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment (either avacincaptad pegol or Sham).

The endpoints include below:

- Primary Endpoint
  - Adverse events (AEs),
- Secondary Endpoints
  - Immunogenicity,
  - Pharmacokinetics,
- Exploratory Endpoints
  - Ophthalmic variables
    - best corrected visual acuity (BCVA),
    - low luminance visual acuity (LLVA),
    - intraocular pressure (IOP),
    - ophthalmic examination (OE).

1.2 Study Design

This is a Phase 3, Open-label Extension study to evaluate the long-term safety of avacincaptad pegol (ACP). Approximately 280 patients who completed Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment (either ACP or Sham) and consent to participate will be administered monthly ACP 2 mg from Month 1 through Month 17 (maximum seventeen total doses).

All patients will have a final follow up visit at Month 18 or if the study is terminated early, Month 18 final follow up procedures will be followed. Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the Institutional Review Board/Ethics Committee, or at the discretion of Astellas.

Details of the schedule of clinical assessments are available in the protocol.

1.3 Randomization

This is an open-label study and no randomization applied.

2 STATISTICAL HYPOTHESES

No statistical hypotheses will be tested.

3 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

3.1 Full Analysis Set

The Full Analysis Set (FAS) consists of all enrolled participants. The FAS will be used for the patient disposition, summary of demographics and other baseline characteristics, and analyses of GA area, BCVA, LLVA and LLD in this study ISEE2009.

3.2 Safety Analysis Set

The Safety Analysis Set (SAF) consists of all treated participants, i.e., those received at least one administration of study drug.

The SAF will be used for the analysis of safety endpoints. When all enrolled participants have been treated, the SAF is identical to FAS.

3.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PKAS) consists of all treated participants with at least one valid plasma concentrations result. Additional participants may be excluded from the PKAS at the discretion of the pharmocokineticist.

The PKAS will be used for PK analysis.

3.4 Anti-drug Antibody (ADA) Analysis Set

The ADA analysis set (ADAAS) consists of all treated participants with at least one valid ADA result.

The ADAAS will be used for immunogenicity analysis.

4 STATISTICAL ANALYSES

4.1 General Considerations

Continuous data will be summarized descriptively including the number of participants (n), mean, standard deviation (SD), median, minimum, Q1, Q3 and maximum. Categorical data will be summarized descriptively by frequencies and percentages. Percentages by categories will be based on the number of participants with no missing data, i.e., the percentages for the non-missing categories will add up to 100%. Participants with missing data are generally not included unless otherwise specified. When needed, the category of ‘Missing’ is created and the number of participants with missing data is presented.

All data summarization and analyses will be performed using SAS® Version 9.4 or higher on Red Hat Enterprise Linux. Specifications for table, figures, and data listing formats can be found in the Tables Listings Figures (TLF) specifications.

Summaries will be presented for the following cohorts unless otherwise specified:

- ACP EM to ACP EM, including all participants who received ACP every month (EM) through the Month 24 visit in the parent study ISEE2008 and enrolled in this study,
- ACP EM/EOM to ACP EM, including all participants who received ACP EM through the Month 11 visit and then randomized to ACP at Month 12 and administered ACP every other month (EOM) at Months 13, 15, 17, 19, 21, 23 in the parent study ISEE2008 and enrolled in this study,
- ACP to ACP EM, including all participants who received ACP EM through the Month 11 visit and then ACP EM or EOM through the Month 24 visit in the parent study ISEE2008 and enrolled in this study, which is the combination of the above two cohorts,
- Sham to ACP EM, including all participants who received Sham through the Month 23 visit in the parent study ISEE2008 and enrolled in this study,
- Total, including all participants who enrolled in this study regardless of the study drug and frequency they previously received in the parent study ISEE2008.

Baseline values will be defined as the last available value prior to the first administration of study drug in this study ISEE2009, unless otherwise specified.

4.2 Study Participants

Participant disposition, protocol deviations, demographics and other baseline characteristics and previous and concomitant medications will be summarized descriptively and listed for the FAS. Extent of exposure analysis will be based on the SAF.

4.2.1 Participant Disposition

Disposition of participants will be summarized for the FAS. Number and percentage of participants who complete or prematurely discontinue from the treatment or study will be summarized by cohort. For discontinuation, the primary reason reported by the investigator will be summarized by cohort.

4.2.2 Protocol Deviations

All protocol deviations will be assessed and identified prior to database lock to determine whether they are major or minor by the sponsor. The final list of major protocol deviations will be provided prior to the database lock.

The major protocol deviations will be summarized by cohort for the FAS. In the summary table, participants deviating from a criterion more than once will be counted once for the corresponding criterion. Any participants who have more than one major protocol deviation will be counted once in the overall summary. The details will be provided in a participant listing.

4.2.3 Demographic and Other Baseline Characteristics

Demographics will be summarized descriptively by cohort for the FAS. The variables to be summarized include but not limited to:

- Sex,
- Age, Age Categories (50 to <65, 65 to 74, 75 to 84, ≥85), European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) age categories (<65, ≥65 to <85, ≥85),
- Race,
- Ethnicity.

Other baseline characteristics of SE will be summarized descriptively by cohort in separate tables. These baseline characteristics include the followings:

- Visual acuity, including but not limited to BCVA (Early Treatment Disbetic Retinopathy Study [ETDRS] letters), LLVA (ETDRS Letters) and LLD,
- Ophthalmic exam (OE), including but not limited to motility, lids/lacrimal/lashes, conjunctiva/sclera, cornea, anterior chamber activity, cells, iris, pupils, lens status, vitreous haze, vitreous hemorrhage, posterior vitreous detachment, optic nerve, macula, retinal vessels, and peripheral retina,
- Tonometry,
- Fundus Autofluorescence (FAF) imaging measurements, including but not limited to localization of hypo FAF, multifocal geographic atrophy, temporal peripapillary atrophy, area of geographic atrophy and size of geographic atrophy.

A listing of demographic and other baseline characteristics will be provided.

Prior ocular history is defined as all ocular events prior to the first administration of the study drug in this study, including the prior ocular history events of the parent study ISEE2008. The prior ocular history is coded in Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by System Organ Class (SOC) and Preferred Term (PT), by cohort, for Study Eye (SE) and Fellow Eye (FE) separately. A listing of prior ocular history will also be provided.

Medical history (excluding ocular history) is defined as all non-ocular medical events prior to the first administration of the study drug in this study, including the non-ocular medical history events of the parent study ISEE2008. The medical history (excluding ocular history) is coded by MedDRA, and will be summarized by SOC and PT, by cohort. A listing of medical history will also be provided.

Prior surgeries/procedures are defined as all surgeries/procedures prior to the first administration of the study drug in this study, including any prior or concomitant surgeries/procedures recorded in the parent study ISEE2008. The prior surgeries/procedures are coded by MedDRA, and will be summarized by SOC and PT, by cohort. A listing of prior surgeries/procedures will also be provided.

4.2.4 Previous and Concomitant Medications

Previous medications are defined as any medications that participants started prior to the first administration of the study drug in this study, including the medications that started before and during the parent study ISEE2008.

Concomitant medications are defined as any medications that participants took after the first administration of the study drug in this study and through the last follow-up visit in this study. Medications that started prior to and continued after first administration of study drug in this study will be counted in both previous and concomitant medications.

Previous and concomitant medications will be summarized separately by therapeutic subgroup (anatomical therapeutic chemical (ATC) 2nd level), chemical subgroup (ATC 4th level), preferred world health organization (WHO) name (active ingredients for combination drugs) and cohort for the FAS. Participants taking the same medication multiple times will be counted once per medication. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

4.2.5 Extent of Exposure

The following variables of exposure will be descriptively summarized by cohort for the SAF:

- Treatment duration (months) defined as (last injection date – first injection date + 31)/30.4375,
- Total number of injections received.

4.3 Primary Endpoint(s) Analysis

The primary endpoint is AEs. Analysis on AE will be described in Section 4.6.

4.4 Secondary Endpoint(s) Analysis

The secondary endpoints include immunogenicity and pharmacokinetics. All the assessments will be mapped to an analysis visit. The mapping rule is provided in Table 4.

Immunogenicity

ADA status (either positive or negative) will be evaluated by ADA against ACP, ADA against aptamer and ADA against Polyethylene glycol (PEG) for each ADA sample.

The following ADA incidences will be summarized over the ADAAS in total. A listing of ADA results will also be provided. Baseline value is the last available value prior to the first administration of study drug in this study ISEE2009.

Table 1 Definition of the ADA Incidences

ADA Incidence	Definition
Baseline and at least one post-baseline status	Number of participants with valid baseline and at least one post-baseline ADA results
Baseline negative	Number of participants with a negative ADA status at baseline
Post-baseline positive, who were negative at baseline	Number of participants with a negative baseline and at least one positive post-baseline ADA status
Baseline positive	Number of participants with a positive ADA status at baseline
Post-baseline positive	Number of participants with at least one post-baseline positive ADA status
Treatment boosted positive	Number of participants with an at least one post-baseline ADA increase from a positive baseline [a]
Total Positive	Total number of participants who are either with a negative baseline and at least one post-baseline positive ADA status, OR treatment boosted positive
Total Negative	Total number of participants who are not total positive
[a] For participants with positive baseline ADA status, a post-baseline titer value that is ≥ 4 times higher than the baseline is considered as treatment-boosted ADA.	

A plot of plasma concentrations vs. analysis visits (months) will be created. Plasma concentrations of participants who are ADA total positive will be highlighted to explore the effect of ADA on PK of participants.

Pharmacokinetics

Plasma concentrations will be summarized descriptively for the PKAS in total at each analysis visit, using mean, SD, median, minimum, maximum, geometric mean, and coefficient of variation (CV).

Additional exploratory analysis may be performed after analysis of the data.

4.5 Exploratory Endpoint(s) Analysis

The exploratory endpoints are ophthalmic findings. All the assessments will be mapped to a scheduled visit. The mapping rule is provided in Table 2 for BCVA, OE and IOP and Table 3 for LLVA.

Best Corrected Visual Acuity (BCVA)

The score and the change from baseline of BCVA (ETDRS letters) at each analysis visit will be summarized descriptively by cohort for the FAS.

Low Luminance Visual Acuity (LLVA)

The score and the change from baseline of LLVA (ETDRS letters) at each analysis visit will be summarized descriptively by cohort for the FAS.

Low Luminance Deficits (LLD)

The score and the change from baseline of LLD (ETDRS letters) at each analysis visit will be summarized descriptively by cohort for the FAS, where LLD is calculated by the difference of BCVA and LLVA at a same visit.

Intraocular Pressure (IOP)

Baseline IOP is the pre-injection IOP value before the first study drug administration in this study.

Pre-injection IOP is defined as the last IOP value before an injection on a visit with injection (whether ACP or other treatment) or the last IOP value on a visit without an injection.

Post-injection IOP is defined as the IOP value after one injection that is closest in time to the protocol-specified post-injection timepoint (but at least 30 minutes post-injection).

Pre-injection and post-injection IOPs at each analysis visit will be summarized descriptively by cohort for the SAF with in one table. The number and percentage of participants in categories of pre-injection IOP value ($\leq$ 21 mmHg, 22-29 mmHg, 30-34 mmHg, $\geq$ 35 mmHg) will be summarized at each analysis visit for each cohort.

The change from baseline of pre-injection IOPs will be summarized at each analysis visit for each cohort.

Change of IOP at each analysis visit is the difference between the post-injection and pre-injection IOPs. Change of IOP at each analysis visit will also be summarized descriptively for each cohort. The number and percentage of participants in categories of change of IOP ($\leq$0 mmHg, 1-5 mmHg, 6-10 mmHg, >10 mmHg) will be summarized at each analysis visit for each cohort.

The number and percentage of participants who experienced the following events will be summarized for each cohort. The events are:

- Either pre-injection or post-injection IOP $\geq$ 35 mmHg,
- Had a paracentesis and
- Received IOP-lowering medications.

The number and percentage of injections with the following events will be summarized for each cohort. The events are:

- Either pre-injection or post-injection IOP $\geq$ 35 mmHg,
- Had a paracentesis.

Mean of pre-injection IOPs change from baseline and post-injection IOPs change from pre-injection will be plotted over time separately.

Ophthalmic Examination (OE)

The following OE variables will be analyzed for the SAF by a shift table (Normal/Abnormal/Missing) from Baseline to Month 18/End of Study (Early Withdrawal):

- Motility,
- Lids/Lacrimal/Lashes,
- Conjunctiva/Sclera,
- Cornea,
- Iris,
- Pupils,

- Posterior Vitreous Detachment,
- Optic Nerve,
- Macula,
- Retinal Vessels.

Participants with a change in lens status (aphakic, pseudo-phakic, phakic; if phakic, nuclear/PSC/cortical 0, 1, 2, 3, 4) will be listed for SE and FE.

Geographic Atrophy Area

Change from baseline in Geographic Atrophy Area of SE will be summarized descriptively at each analysis visit for each cohort.

4.6 Safety Analyses

All safety analyses will be performed on the SAF. Missing values of safety data will not be imputed, and safety summaries will be based on observed cases. ACP treated FE will not be considered as a second SE.

4.6.1 Adverse Events

All AEs will be coded in MedDRA. AE analysis will be based on the SAF.

A treatment-emergent adverse event (TEAE) is defined as an AE starting after the first administration of the study drug in this study until 30 days after the last administration of the study drug or until the last follow-up visit required by the protocol, whichever comes later.

An overview table to report the number and percentage of participants and number of events will include but not limited to the following:

- TEAEs,
- Drug related TEAEs,
- Serious TEAEs,
- Serious drug related TEAEs,
- TEAEs leading to withdrawal of study drug,
- Drug-related TEAEs leading to withdrawal of study drug,
- Severe TEAEs,
- TEAEs leading to death,
- Drug related TEAEs leading to death,
- Deaths.

An additional overview of TEAEs will be provided which displays the overall summary of TEAEs by three categories (SE, FE, and non-ocular).

The number and percentage of participants with TEAEs, as classified by SOC and PT will be summarized for each cohort. Summaries will be provided for the following:

- TEAEs,
- TEAEs with frequency of ≥ 5% in any cohort,
- TEAEs with frequency of ≥ 2% in any cohort,
- Non-serious TEAEs with frequency of ≥ 5% in any cohort,
- Study drug related TEAEs,

- Injection procedure related TEAEs,
- Serious TEAEs,
- Serious study drug related TEAEs,
- Serious injection procedure related TEAEs,
- TEAEs leading to withdrawal of study drug,
- Study drug related TEAEs leading to withdrawal of study drug,
- Injection procedure related TEAEs leading to withdrawal of study drug,
- TEAEs leading to death,
- Study drug related TEAEs leading to death,
- Injection procedure related TEAEs leading to death.

Ocular TEAEs have been defined as TEAEs linked to the "Eye Disorders" SOC or the "Intraocular Pressure Increased" PT.

The number and percentage of participants with ocular TEAEs or non-ocular TEAEs, as classified by SOC and PT, will be summarized for each cohort. Summaries will be provided for those including but not limited to the following:

- Ocular TEAEs by SE and FE,
- Ocular TEAEs with frequency of ≥ 2% in any cohort (by PT),
- Non-ocular TEAEs with frequency of ≥ 2% in any cohort (by PT),
- Study drug related Ocular TEAEs (SE),
- Injection procedure related Ocular TEAEs (SE),
- TEAEs with high level term of cataract conditions by SE and FE,
- Serious ocular TEAEs (SE),
- Serious study drug related ocular TEAEs (SE),
- Serious injection procedure related ocular TEAEs (SE),
- Serious non-ocular TEAEs,
- Serious Study drug related non-ocular TEAEs,
- Serious injection procedure related non-ocular TEAEs,
- Ocular TEAEs (SE) leading to withdrawal of study drug,
- Non-ocular TEAEs leading to withdrawal of study drug,
- Study drug related non-ocular TEAEs leading to withdrawal of study drug,
- Injection procedure related non-ocular TEAEs leading to withdrawal of study drug,
- Ocular TEAEs (FE) on and after the initiation of the ACP treatment on FE,
- Ocular TEAEs (FE) on and after the initiation of the Syfovre treatment on FE.

The number and percentage of participants with TEAEs, as classified by SOC and PT will be summarized by severity for each cohort. If a participant has multiple TEAEs with the same SOC or PT, but with differing severity, then the participant will be counted once with the worst severity grade. If severity is missing of the event, the participant will be counted under missing severity. Summaries will be provided for the following:

- TEAEs,
- Study drug related TEAEs,
- Injection procedure related TEAEs,

- Ocular TEAEs (SE),
- Study drug related ocular TEAEs (SE),
- Injection procedure related ocular TEAEs (SE).

All AEs, including non-TEAEs, serious AEs, AEs leading to withdrawal of study drug and AEs leading to death will be listed.

The listings will include the subject identifier, age, sex, verbatim term, SOC, PT, eye (N/A / OD / OS / OU), serious (yes/no), date of onset, relative study day of onset, onset timing, duration of the event (or continuing), severity (mild/moderate/severe), causality (relationship to study drug/injection procedure), action taken (study drug permanently discontinued: yes/no), treatment required (yes/no), and outcome (resolved/not resolved/fatal).

4.6.2 Adverse Events of Special Interest

The AESIs will include the following:

- Endophthalmitis,
- Ischemic optic neuropathy,
- Intraocular inflammation; any case of uveitis, retinal vasculitis, or retinal occlusive vasculitis,
- IOP ≥ 30 mmHg at 30 minutes post injection deemed clinically significant by Investigator,
- Transient loss of light perception immediately after injection,
- Elevation of IOP post-injection requiring surgical/procedural intervention (i.e., paracentesis),
- BCVA decrease ≥30 letters from ISEE2009 Month 1 Visit,
- Choroidal neovascularization (exudative or nonexudative),
- Macular oedema/cysts.

AESIs are TEAEs on SE. Both the AESI electronic case report form (eCRF) data and statistical programs will be used to identify AESI events. And the identification rules will be prespecified and documented in the TLF specifications.

The number and percentage of participants with AESIs within each AESI category will be summarized for each cohort. A listing will also be provided.

4.7 Subgroup Analyses

There will be no subgroup analyses.

4.8 Interim Analysis

There will be no interim analysis.

4.9 Sample Size Determination

Approximately 280 participants will be enrolled. This was based on the number of currently enrolled patients in study ISEE2008 (GATHER2) who completed study ISEE2008 through the Month 24 visit.

4.10 Additional Conventions

4.10.1 Analysis Windows

Study Day for analysis windows will be calculated as: Date of visit/assessment – first dose of study drug in this study + 1.

The assignment of analysis visit will be consistent across all by-visit analysis datasets, and will follow the respective step-by-step algorithm:

- All assessment visits will be windowed, per the below tables, regardless of SE/FE, scheduled/unscheduled status, injection date, or pre/post-injection status.
- Baseline derivations will follow the definitions as stated in Section 4.1.

An analysis flag will be created for each record by following rules.

- **General Rules for Analysis Flags**
  - Scheduled visits falling into their respective analysis window will be prioritized over unscheduled visits.
  - If multiple observations still exist, the observation closest to the scheduled day will be selected for the analysis visit.
  - If there are two observations that have the same distance from the scheduled day, the value that is after the scheduled day will be selected for the analysis visit.
  - If more than one observation (excluding OE/IOP observation) is made on the same day, an average value for continuous measurement, or the worst value for categorical measurement, will be used for the analysis visit.
  - Any additional rules will be prespecified and documented in the TLF specifications.
- **Additional Rules for OE/IOP Analysis Flags except those in the Analysis Visit Month 18**
  - The OE/IOP records on a visit falling into its respective analysis window and with at least one SE ACP pre-injection and one SE ACP post-injection records will be firstly selected.
  - If there are no OE/IOP records satisfying the first rule, the records on a visit (whether scheduled or unscheduled) and with at least one SE ACP pre-injection and on SE ACP post-injection records will be selected.
  - If there is no OE/IOP records satisfying the above two rules, the records will be selected from a visit day (whether scheduled or unscheduled) that contain at least one pre-injection or one post-injection record to separately summarize the pre-injection and post-injection IOPs.
  - The closest OE/IOP observation to the target time will be selected for analysis.
  - If both Tonopen and Goldmann measurement are recorded available at the same time per CRF, the Goldmann measurement will be prioritized.

Listings will include all scheduled, unscheduled, and early withdrawal data.

The definitions of analysis visit by different assessment frequency are described in the table below.

Table 2 Analysis Visit for Monthly Assessments

Analysis Visits	Scheduled Day in Protocol [a] (Study Day)	Analysis Windows [b] (Study Day)
Month 1 (Baseline)	1	≤1
Month 2	30	2-45
Month 3	61	46-75
Month 4	91	76-106
Month 5	122	107-136
Month 6	152	137-166
Month 7	183	167-197
Month 8	213	198-227
Month 9	244	228-258
Month 10	274	259-288
Month 11	304	289-319
Month 12	335	320-349
Month 13	365	350-379
Month 14	396	380-410
Month 15	426	411-440
Month 16	457	441-471
Month 17	487	472-501
Month 18	517	≥502

[a] Calculated as: 30.4375 × (Month Number-1) and rounded to integer.

[b] Lower bound are calculated as:

- Scheduled Day – (Day Difference between Current and Previous Scheduled Visits)/2 and rounded to integer since Month 2.

Upper bound is calculated as:

- Lower Bound for Subsequent visit – 1 since Month 2.

Table 3 Analysis Visit for Half-yearly Assessments

Analysis Visits	Scheduled Day in Protocol [a] (Study Day)	Analysis Windows for FA and OE (FE) [b, c] (Study Day)	Analysis Windows for Other Assessments except FA and OE (FE) [b] (Study Day)
Month 1 (Baseline)	1	Not Applicable	≤1
Month 6 [d]	152	Not Applicable	2-243
Month 12 [e]	335	2-425	244-425
Month 18	517	≥ 426	≥ 426

FA: Fluorescein Angiography; FE: Fellow Eye; OE: Ophthalmic Examination.

[a] Calculated as: 30.4375 × (Month Number-1) and rounded to integer.

[b] Lower bounds are calculated as:

- Scheduled Day – (Upper bound – Scheduled Day) and rounded to integer at Month 6,
- Scheduled Day – (Day Difference between Current and Previous Scheduled Visits)/2 and rounded to integer after Month 6.

Upper bound is calculated as:

- Lower Bound for Subsequent Visit –1, after Month 1.

[c] There is no FA planned before Month 12. Lower bound at Month 12 is calculated as:

Scheduled Day – (Day Difference between Current and Previous Scheduled Visits)/2 and rounded to integer.

[d] The assessments mapped to Month 6 and occurred before Day 62 will not be selected for analysis.

[e] The assessments mapped to Month 12 and occurred before Day 168 will not be selected for analysis.

Table 4 Analysis Visits for Immunogenicity and PK Assessments

Analysis Visits	Scheduled Day in Protocol (Study Day) [a]	Analysis Windows [b] (Study Day)
Month 1 (Baseline)	1	≤1
Month 2	30	2-60
Month 4	91	61-136
Month 7	183	137-273
Month 13	365	274-440
Month 18	517	≥441

[a] Calculated as: 30.4375 × (Month Number-1), rounded to integer.

[b] Lower bounds are calculated as:

- Scheduled Day – (Day Difference between Current and Previous Scheduled Visits)/2 and rounded to integer after Month 2.

Upper bounds are calculated as:

- Lower Bound for Subsequent Visit –1 since Month 2.

4.10.2 Imputation Rules for Incomplete Dates

Assumptions for missing or partially missing dates for important variables will be made to allow inclusion of appropriate data records in the analyses. In general, the assumptions about the missing or partially missing dates, when needed, are made conservatively to avoid overestimation of treatment effect and underestimation of adverse effects.

If a medication date or time is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered both as a prior and a concomitant medication.

If the partial AE onset date information does not indicate whether the AE started prior to treatment or after treatment, the AE will be classified as after the start of treatment.

In case of missing or partial start and stop dates for concomitant medications, the following rules will be used:

- If the start date is missing or partial:
  - If the month is missing, use January.
  - If the day is missing, use the first day of the month under consideration.
  - If the year is missing, use year of the informed consent date.
  - If the entire date is missing, use informed consent date.
- If the stop date is missing or partial:
  - If the month is missing, use December.
  - If the day is missing, use the last day of the month under consideration.
  - If the year or the entire date is missing, set the stop date to December 31st, 2099.
- If the imputed start date is after the stop date, then the imputed start date will be 1 day prior to the stop date.
- For AEs, a missing or incomplete onset date will be imputed according to the following conventions.
- If an onset date is missing, the imputed onset date will be the date of first dose of study drug.
- If only the year is known for the AE onset date, the imputed onset date will be the latest of the following non-missing dates:
  - Date of first dose of study drug, and
  - January 1 of the year of AE onset date.
- If only the month and year is known for the onset date, set the surrogate onset date to the first day of that month and then apply the following rules.
- If the month and year of the onset date is prior to the month and year of the first dose of study drug, then the surrogate onset date will be the imputed onset date.
- If the month and year of the onset date is on or after the month and year of the first dose of study drug, then the imputed onset date will be the latest of the following non-missing dates:

  - Date of first dose of study drug, and
  - Surrogate onset date.
- If the imputed onset date is after the adverse event end date, the imputed onset date will be the same as the adverse event end date.

5 SUPPORTING DOCUMENTATION

5.1 Appendix 1 List of Abbreviations

Abbreviations	Description of abbreviations
ACP	Avacincaptad Pegol
ADA	Anti-drug Antibody
ADAAS	Anti-drug Antibody analysis set
AE	Adverse Event
AESI	Adverse Event of Special Interest
BCVA	Best Corrected Visual Acuity
EM	Every Month
EOM	Every Other Month
ETDRS	Early Treatment Disbetic Retinopathy Study
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
eCRF	Electronic Case Report Form
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence
FAS	Full Analysis Set
FE	Fellow Eye
GA	Geographic Atrophy
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IOP	Intraocular Pressure
LLD	Low Luminance Deficits
LLVA	low luminance best correct visual acuity
MedDRA	Medical Dictionary for Regulatory Activities
OD	Right Eye
OE	Ophthalmic Examination
OS	Left Eye
OU	Both Eyes
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PEG	Polyethylene Glycol
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SE	Study Eye
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TLF	Tables Listings Figures

6 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

7 SIGNATURE

(E-signatures are attached at the end of document)