STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF FARICIMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (AVONELLE-X)**
STUDY NUMBER:	GR42691
STUDY NAME:	AVONELLE-X
VERSION NUMBER:	2
ROCHE COMPOUND(S):	Faricimab (RO6867461)
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PLAN PREPARED BY:	[redacted], PhD

STATISTICAL ANALYSIS PLAN APPROVAL

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DATE FINAL:	See electronic date stamp on the last page of this document

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document 01 May 2024 (SAP eMD_v3.0) and 01 Aug 2024 (Ophtha SAP Template_v1.0).

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
2	see electronic date stamp on the last page of this document	Version 3, dated 15 Jul 2022
1	05 September 2022	Version 3, dated 15 Jul 2022

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Key changes to the SAP, along with the rationale(s) for each change, are summarized below.

Section	Description of Change	Rationale for Change
Section 3	GCP non-compliance handling added	To specify the handling of the non-compliance
	PP population removed	Considered not needed by team
	PK/immunogenicity population removed	Per the new ophtha SAP template, define these as subset of safety-evaluable population rather than separate analysis sets and describe in the PK/immunogenicity sections
Section 4.1	Additional details added	Provide more clear details in statistical analysis, e.g., grouping, windowing and Japan extension patients analysis strategy
Section 4.2.1 and 4.2.2	Minor update to definition of treatment emergent AE: from enrollment to first dose of faricimab	Clarify the AE reporting strategy to report the safety profile in AVONELLE-X
Section 4.2.2	Details added	To clearly specify the safety summaries of study eye, fellow eye
Section 4.2.4.1	Subgroup analyses added	To fully understand the safety profiles in relevant subgroups
Section 4.4, 4.4.1 and 4.4.2	Details about exploratory efficacy analyses added	To further clarify the analysis strategy
Section 4.5.1	Specification of treatment duration updated Dose interruption summary added	To specify the analysis detail
Section 4.5.3.1, 4.5.3.2 and 4.5.3.3	Language and structure update	To align with new optha SAP template and to further specify the analysis
Section 4.6.1, 4.6.2, 4.6.3, 4.6.4 **and** 4.6.5	Language and structure update	To align with new ophtha SAP template and to further specify the analysis
Section 4.6.7	Removed “missed visits due to COVID-19” and 2 other safety related bullet points	“missed visits” is not applicable and the other 2 safety related endpoints are described in 4.6.8

Section 4.8	Added	To summarize changes to protocol-defined analyses

Additional minor changes have been made throughout to improve clarity and consistency.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
Ang-2	angiopoietin-2 (protein)
anti-VEGF	anti-vascular endothelial growth factor
APTC	Anti-Platelet Trialists' Collaboration
ATE	arterial thromboembolic event
BCVA	best-corrected visual acuity
BM	Bruch's membrane
CFP	Color Fundus Photograph
CI	confidence interval
CMH	Cochran Mantel-Haenszel
CNV	choroidal neovascularization
COVID-19	Coronavirus Disease
CRC	Central Reading Center
CSR	Clinical Study Report
CST	central subfield thickness
eCRF	electronic Case Report Form
ETDRS	early treatment diabetic retinopathy study
FFA	Fundus Fluorescein Angiography
GCP	Good Clinical Practice
igG1	Immunoglobulin
ICGA	Indocyanine Green Angiography
ILM	internal limiting membrane
IOI	intraocular inflammation
IOP	intraocular pressure
IVT	Intravitreal
IxRS	interactive voice or web-based response system
LLD	low-luminance deficit
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	neovascular Age-related Macular Degeneration
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25

OCT-A	Optical Coherence Tomography-Angiography
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	preferred term
PTI	personalized treatment interval
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
Q16W	every 16 weeks
RPE	retinal pigment epithelium
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD-OCT	Spectral-Domain Optical Coherence Tomography
SFU	safety follow-up
SMQ	standardized MedDRA queries
SOC	System Organ Class
SS-OCT	Swept-Source Optical Coherence Tomography
UWP	Ultra-wide photography
VA	visual acuity
VEGF (-A)	vascular endothelial growth factor (-A)

1. INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is a form of advanced age-related macular degeneration (AMD) that causes rapid and severe visual loss and remains a leading cause of visual impairment in the elderly. In nAMD, choroidal neovascularization (CNV) leaks fluid, lipids, and blood into the outer retina causing severe, irreversible loss of central vision if left untreated.

Treatment of nAMD has been markedly improved by the introduction of biological molecules that target vascular endothelial growth factor (-A) (VEGF-A). The impressive benefit of anti-vascular endothelial growth factor (anti-VEGF) therapies and their ability to restore vision has been widely recognized since the first approval of Lucentis (ranibizumab) in 2006. A key challenge with currently available anti-VEGF treatments is the requirement for long-term frequent administration to maintain vision gains. Real-world data suggest that many patients with nAMD do not receive treatment at the optimal frequency, and this under-treatment in clinical practice is associated with lower visual acuity (VA) gains compared with those observed in controlled clinical trials. Under-treatment of nAMD in clinical practice reflects the burden of frequent therapy on patients, caregivers, and the healthcare system.

Faricimab is a novel humanized bispecific immunoglobulin (igG1) monoclonal antibody that selectively binds to angiopoietin-2 (Ang-2) and VEGF-A. Nonclinical studies have shown that Ang-2 and VEGF-A act in concert to regulate the vasculature and to increase retinal endothelial cell permeability such that simultaneous inhibition of Ang-2 and VEGF-A with faricimab led to a greater reduction in the leakiness and severity of CNV lesions compared with inhibition of either target alone. Furthermore, data from the completed Phase II studies also support the hypothesis that targeting Ang-2 has the potential to extend the durability of effect beyond anti-VEGF therapy alone in nAMD. Data from earlier non-clinical and clinical studies, as well as the clear unmet need for less-frequent dosing in nAMD, supported the evaluation of faricimab in a Phase III program. The Phase III studies TENAYA (GR40306) and LUCERNE (GR40844) were identically designed registrational studies that investigated the efficacy, safety and pharmacokinetics of faricimab given at up to 16 week intervals (Q16W) against aflibercept dosed every 8 weeks (Q8W) as per its global label. The primary analysis of these Phase III studies demonstrated that faricimab given at up to Q16W was non-inferior to aflibercept Q8W. In addition, the majority of faricimab-treated patients ($>$70%) were on an extended dosing regimen (every 12 weeks [Q12W] or Q16W) at Week 48. Comparable efficacy between the 2 treatment arms was maintained through Week 112.

The purpose of this document is to provide details of the planned analyses for inclusion in the clinical study report of the Phase III long term extension (LTE) Study GR42691 (AVONELLE-X). In this Statistical Analysis Plan (SAP), ‘study drug’ refers to faricimab

whereas ‘study treatment’ refers to faricimab or the sham procedure in the masked period. This document will address analysis for efficacy, safety, immunogenicity, biomarkers and pharmacokinetics. Detailed specifications of tables, figures and listings are provided in separate documents.

The analysis plan and the endpoints specified in this document supersede the analysis plan described in the study protocol. Changes to the protocol-planned analyses are described in Section 4.8.

1.1 OBJECTIVES AND ENDPOINTS

This study will evaluate the long term safety and tolerability of intravitreal (IVT) faricimab in patients with nAMD who have completed either of the Phase III (GR40306 or GR40844) studies, also referred to as the parent studies.

Eligible patients who choose to enroll into the LTE study will have monthly, masked, study visits for the first 3 months of the study (Day 1 through to Week 12). Following the masked period, the study will follow an open-label design in which patients will only be required to attend study visits at which faricimab is to be administered. See Section 1.2 for details on the study design.

The primary objective is to evaluate the long-term ocular and systemic safety and tolerability of faricimab on the basis of the incidence and severity of ocular and non-ocular adverse events (AEs).

Additional assessments relating to efficacy, pharmacokinetics, immunogenicity, and biomarkers will be performed.

All efficacy endpoints will be assessed at selected timepoints, including at the 1 and 2 year timepoints in the LTE study.

1.1.1 Primary Objective

The primary objective for this study is to evaluate the long-term ocular and systemic safety and tolerability of faricimab in all participants who have enrolled in this LTE study, regardless of adherence to treatment or to the protocol, on the basis of the following endpoints:

- Incidence and severity of ocular AEs
- Incidence and severity of non-ocular AEs

1.1.2 Exploratory Efficacy Objectives

The exploratory efficacy objective of this study is to assess the long-term efficacy of IVT faricimab for the management of nAMD on the basis of the following endpoints over time:

- Change from baseline in best-corrected visual acuity (BCVA)
- Proportion of patients avoiding loss of ≥15, ≥10 or ≥5 letters in BCVA from baseline
- Proportion of patients gaining ≥15, ≥10, ≥5, or ≥0 letters in BCVA from baseline
- Change from baseline in CST ILM- retinal pigment epithelium (RPE)
  - CST is defined as the distance between ILM and RPE, as measured in μm as assessed by CRC
- Proportion of patients with absence of intraretinal fluid
- Proportion of patients with absence of subretinal fluid
- Proportion of patients with absence of both intraretinal fluid and subretinal fluid
- Proportion of patients with pigment epithelial detachment
- Change from baseline in total area of CNV lesion as assessed by Fundus Fluorescein Angiography (FFA)
- Change from baseline in total area of leakage as assessed by FFA
- Number of faricimab injections received during the LTE study
- Proportion of patients on each treatment interval during the study
- Change from baseline in patient-reported vision-related functioning and quality of life as assessed using the National Eye Institute Visual Functioning Questionnaire 25-item (NEI VFQ-25) composite score, the near activity subscale score, the distance activities subscale score, and driving subscale score

1.1.3 Pharmacokinetic Objectives

The exploratory pharmacokinetic (PK) objective for this study is to assess the PK of faricimab, including in patients who have switched from the Phase III active comparator, as well as explore concentration-effect relationships on the basis of the following endpoints:

- Plasma concentration of faricimab over time
- The correlation between concentration of aqueous humor faricimab and the change in BCVA and other endpoints (e.g., anatomical markers) over time

1.1.4 Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to faricimab on the basis of the following endpoints:

- Presence of anti-drug antibodies (ADAs) at Day 1 of the parent study for the faricimab personalized treatment interval (PTI) arm and Day 1 of this LTE study for the aflibercept Q8W to faricimab PTI arm
- Incidence of ADAs over time during the study from the start of the LTE

1.1.5 Exploratory Biomarker Objectives

The exploratory biomarker objectives for this study are to identify and/or evaluate biomarkers that are predictive of response to faricimab (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing AEs or can lead to improved AEs monitoring or investigation (i.e., safety biomarkers), can provide evidence of faricimab activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology, on the basis of the following endpoints:

- Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., the frequency of faricimab administration) over time. Over time refers to the study period starting from LTE Day 1
- Relationship between low-luminance deficit (LLD) and/or low-luminance BCVA and BCVA or other endpoints (e.g., anatomical markers) at baseline of the LTE study and over time

1.2 STUDY DESIGN

This is a multicenter LTE study designed to evaluate the long-term safety and tolerability of faricimab 6 mg administered by IVT injection at a PTI to participants who enrolled in and completed one of the Phase III studies (GR40306 or GR40844). Participants in the parent studies who discontinued from the study or study treatment prior to completion of the 108-week treatment period are not eligible for enrollment in this extension study.

To be noted, LUCERNE China extension participants will not roll over to AVONELLE-X but may roll over to study NAMTSO-X (YR42837). TENAYA Japan extension participants will be eligible to roll over to AVONELLE-X.

Eligible individuals who consent to participate in this study will be enrolled upon completion of the end-of-study visit in the parent study (i.e., Week 112 visit in Studies GR40306 and GR40844). Individuals will be enrolled into the extension study using the same interactive web-based response system (IxRS) as was used in the parent study.

The end-of-study visit (Week 112) of the parent study and the enrollment visit for this extension study will occur on the same day. All assessments from the parent study end-of-study visit must be completed prior to the LTE study enrollment visit

assessments. Assessments that are required for the Week 112 study visit of the parent study do not need to be repeated as part of Day 1 of the LTE if the visits are done on the same day. If the end-of-study visit of the parent study and enrollment visit for this extension study cannot be completed on the same day, or within 2 business days, the investigator must contact the Sponsor for further discussion prior to scheduling the extension study enrollment visit.

Participants enrolled in this extension study after completion of the parent studies will all follow a single faricimab 6 mg PTI regimen:

- Participants previously randomized to Arm A (faricimab up to Q16W) will begin on their previously calculated faricimab interval at entry to the LTE study
- Participants previously randomized to Arm B (aflibercept Q8W) who have had their last dose of aflibercept at Week 104 of the parent study (see Figure 1) will have a dose of faricimab at Day 1 of the LTE study, and will then be eligible to have their subsequent faricimab dosing based on the PTI algorithm

Participants in this arm who (e.g., because of dose holds/missed visits in the parent study) received their last aflibercept dose at Week 108 of the parent study will have a faricimab dose on Week 4 of the LTE study. These participants will then be eligible to have their subsequent dosing based on the PTI algorithm.

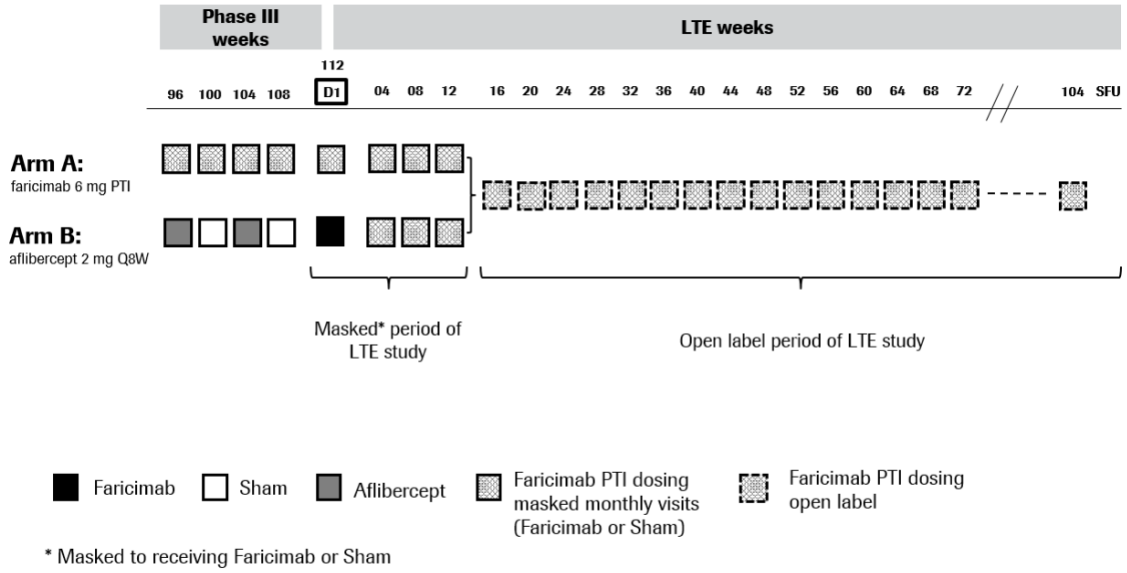
In this extension study, the study eye will be the same as that in the parent studies, GR40306 and GR40844.

Participants will be required to attend monthly study assessment visits between Day 1 and Week 12 (the masked period of the study) in order to preserve masking of a participants's treatment assignment in the parent study. From Week 16 until approximately Week 104, participants will attend study visits at intervals as scheduled by the IxRS system based on the PTI algorithm.

For scheduling purposes during study conduct, annual visits are defined as the scheduled PTI visit that is closest to 52 weeks (occurring between Week 48 and 64 for Year 1) and 104 weeks (occurring between Week 96 and 104 for Year 2) from Day 1. IxRS will advise the site whether the next scheduled visit should be considered the Year 1 or Year 2 visit. If more than one visit meets the criteria of the annual visits, then the earliest eligible visit will be considered Year 1 or Year 2. If the participant is not scheduled to return for a PTI visit between Week 96 and 104, then the participant should return to the site at Week 104 to perform the Year 2 visit. If the earliest scheduled visit is missed, then the next visit within the period should be considered the annual visit.

Participants will also attend a final safety follow-up visit $\geq$28 days and $<$35 days after the actual date of the Year 2 visit or the actual date of the last study treatment, whichever is later. For the study schema, see Figure 1.

Figure 1 Study Schema



LTE= long-term extension; PTI = personalized treatment interval; Q8W = every 8 weeks; SFU = safety follow-up.

Individuals who discontinue study treatment should be encouraged to continue their study participation and attend LTE annual visits (Year 1 and Year 2), as outlined in the schedule of activities. In addition to this, individuals will return to the clinic for an early treatment/study termination visit a minimum of 28 days after receiving the final dose of study drug.

LTE Visit Schedule during the Masked Period

Eligible individuals who choose to enroll into the LTE study will have monthly, masked, study visits for the first 3 months of the study (Day 1 through to Week 12; see Figure 1). and they will receive sham injections at study visits at which they are not scheduled to receive faricimab. During the masked period, participants and physicians will only be masked to the faricimab treatment interval (if faricimab or sham is administered). The BCVA examiner will remain masked for the duration of the LTE study.

LTE Visit Schedule following Masked Period

Following the masked period, the study will follow an open-label design in which participants will only be required to attend study visits at which faricimab is to be administered, at intervals determined according to the PTI algorithm. However, the treatment arm to which participants were assigned in the parent Phase III study will not be disclosed until the final Phase III analysis (Year 2) is reported.

Personalized Treatment Interval Algorithm

An IxRS system will be used to calculate a participant's PTI interval. The PTI uses participant's BCVA and CST data obtained at dosing visits during both the parent study and the LTE to determine the next interval for faricimab dosing. Faricimab dosing intervals can be extended in 4-week increments to a maximum of Q16W, maintained, or reduced to a minimum of every 4 weeks (Q4W) (Q8W in protocol versions 1 and 2) as mentioned below in Table 1

In protocol versions 1 and 2 the PTI algorithm is the same as that used in the Phase III studies. The PTI algorithm in Protocol Version 3 (dated 15 Jul 2022) is based on the algorithm used in the Phase III studies and has been expanded to include Q4W as a possible dosing interval. All participants had been enrolled in the study at the time of version 3 being implemented.

Table 1 Personalized Treatment Interval Algorithm

Dosing Interval	Criteria
Interval extended by 4 weeks (to a maximum of Q16W)	• Stable CST [a] compared with the average of the last two study drug dosing visits, and no increase ≥ 50 µm in CST (compared with the lowest on-study drug dosing visit measurement) and • No decrease ≥ 5 letters in BCVA [b] compared with the average from the last two study drug dosing visits, and no decrease ≥ 10 letters in BCVA [b] compared with the highest on-study drug dosing visit measurement and • No new macular hemorrhage [c]
Interval reduced (to a minimum Q4W) If one of the criteria is met, the interval will be reduced by 4 weeks. If two or more criteria are met or one criterion includes new macular hemorrhage, the interval will be reduced by 8 weeks [d]	• Increase ≥ 50 µm in CST compared with the average from the last two study drug dosing visits or ≥ 75 µm compared with the lowest on-study drug dosing visit measurement or • Decrease ≥ 5 letters in BCVA [b] compared with average of last two study drug dosing visits or decrease ≥ 10 letters in BCVA [b] compared with the highest on-study drug dosing visit measurement or • New macular hemorrhage [c]
Interval maintained	If extension or reduction criteria have not been met

BCVA = best-corrected visual acuity; CST = central subfield thickness; nAMD = neovascular age-related macular degeneration; Q4W = every 4 weeks; Q16W = every 16 weeks.

[a] Where stability is defined as a change of CST of less than 30 mm.

[b] Change in BCVA should be attributable to nAMD disease activity (as determined by investigator).

[c] Refers to macular hemorrhage owing to nAMD activity (as determined by investigator).

[d] Patients whose treatment interval is reduced by 8 weeks from Q16W to Q8W will not be allowed to return to a Q16W interval during the study.

The final analysis will be performed when all participants have either completed the study or have discontinued early from the study, whichever comes later, and all data are in the database and cleaning and verification of critical variables have been completed.

1.2.1 Treatment Assignment and Masking

This is a non-randomized study. After initial written informed consent has been obtained, all procedures and assessments have been completed, and eligibility has been established for an individual, the study site will obtain the participant's study number and treatment assignment from the IxRS. In this extension study, the participant number will be the same as that assigned in the parent studies.

As outlined in Section 3.1 of the protocol, there will be a masked period in the early phase of the LTE study (Day 1 to Week 12). Masked site staff and participants will be informed that the participant will receive faricimab 6 mg IVT injections, and that they will be masked to the faricimab treatment interval only.

During this masked period, participants will be advised that at masked study visits they will either receive faricimab or sham injection. After the Week 12 treatment procedure, the study will follow an open-label design and participants will only be required to attend study visits at which they are scheduled to receive faricimab, and a final safety follow-up visit.

Further details about masked roles during the masked period of the LTE study can be found in Section 4.2.1.1 of the protocol.

1.2.2 Independent Review Facility

Ocular Imaging

The protocol for image acquisition for the LTE study is the same as that used in the parent Phase III studies. All ocular images are obtained by site personnel and imaging systems (including software) that have been certified by the CRC. All ocular images obtained by trained and CRC certified site personnel are to be forwarded to the CRC for independent analysis and storage.

The CRCs provide a masked evaluation of all ocular images including Color Fundus Photograph (CFP), FFA, Spectral-Domain Optical Coherence Tomography (SD-OCT) or Swept-Source Optical Coherence Tomography (SS-OCT), Optical Coherence Tomography-Angiography (OCT-A) and optional Indocyanine Green Angiography (ICGA). Ultra-wide photography (UWP) is only permitted when no other alternative is available and must be discussed with the CRC.

The data resulting from this review of ocular images are forwarded to the Sponsor and additionally, the SD-OCT CST values are forwarded to the IxRS for treatment interval determination.

Anti-Platelet Trialists' Collaboration (APTC)
Potential APTC events that are identified during the study are externally adjudicated on an ongoing basis. A dossier of available information on each case of interest is provided to the external expert adjudicators for their review and assessment.

1.2.3 Data Monitoring

Not Applicable

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

No formal statistical hypothesis will be tested.

2.2 SAMPLE SIZE DETERMINATION

No formal sample size calculations were performed for this LTE study. This study is open to all individuals who complete study treatment and the Week 112 visit in one of the parent studies GR40306 (TENAYA) or GR40844 (LUCERNE).

3. ANALYSIS SETS

The analysis sets for the purposes of analyses are defined in Table 2.

An investigator audit was conducted at one site for non-faricimab Studies GR40550, GR41675, GR40549, and GR44277, where the quality of the source documentation was found to be inadequate. The identified issues included significant delays in responding to monitor queries, insufficient management of AEs, and protocol deviations. Additionally, the records were not an accurate representation of what has been reported in the eCRF.

There was no evidence suggesting a risk to AVONELLE-X data integrity. However, the Sponsor decided as a precautionary measure not to include the data from the participants at GCP non-compliance affected site from the analyses.

Additional details of the GCP breach will be provided in the study CSR.

Table 2 Participant Analysis Sets

Participant Analysis Set	Description
Safety-Evaluable	All eligible enrolled participants who received at least one faricimab treatment during the LTE study (excluding participants from GCP non-compliance affected site).
Efficacy-Evaluable	All eligible participants enrolled into this study (excluding participants from GCP non-compliance affected site).

LTE = long-term extension

Specific data points to be included for each analysis will be described in Section 4.

4. STATISTICAL ANALYSES

Unless otherwise specified, the analyses described in this section are based on participants enrolled in AVONELLE-X, excluding participants from GCP non-compliance affected site.

The analyses timing for final analyses is provided in Section 1.2.

4.1 GENERAL CONSIDERATIONS

The participants in this study consist of individuals enrolled in the global phase of the parent studies (TENAYA [GR40306] and LUCERNE [GR40844]) and the Japan extension of TENAYA (GR40306). The analyses described in this SAP document will be performed on all participants, with global phase and Japan extension phase combined.

Safety analyses will be based on the safety-evaluable population.

Safety summary tables will include all events occurring or worsening on or after the first faricimab treatment during AVONELLE-X. Additional listings will be provided for events that occurred from AVONELLE-X enrollment to the first faricimab dose.

For safety analyses using the parent study group, participants will be grouped according to the actual treatment received in the parent study up to Week 108. If during the parent study by error, a participant receives a combination of different active study drugs (faricimab and aflibercept) in the study eye, the participant's treatment group will be as randomized.

Since efficacy objectives are exploratory, no formal estimand framework is defined. Unless otherwise noted, the exploratory efficacy analyses will be based on the efficacy-evaluable population and will be presented by parent study treatment group and overall (if applicable) for both binary and continuous endpoints. All efficacy endpoints

will be presented at monthly visits until Week 12, as well as at Year 1, Month 18, Year 2 and safety follow-up (SFU) timepoints as applicable. Definition of Year 1, Month 18, Year 2 and SFU is described in Section 4.4.

For exploratory efficacy endpoints, data collected in scheduled and unscheduled visits will be mapped to visits that appear in the schedule of assessments per the protocol using the actual study day of assessment. For any study visit starting from Week 4, if there are multiple values in the same visit window, the value closest to the target study day will be mapped to the visit and used as the analysis value corresponding to that visit. For example: for the visit corresponding to Week 52 (target study Day 364), the assessment within the visit window (349–377 days) which is closest to study Day 364 will be mapped to study visit Week 52 as the analysis value. Additional details of target study day and analysis window for each scheduled visit will be provided in Module 2 of the Data Analysis Plan.

4.2 ANALYSIS TO SUPPORT THE PRIMARY OBJECTIVE

The primary objective is to evaluate the long-term ocular and systemic safety and tolerability of faricimab in all participants who have enrolled in the LTE study, regardless of adherence to treatment or to the protocol.

4.2.1 Endpoint to Support the Primary Objective

The primary safety objective will be evaluated on the safety population on the basis of the incidence and severity of ocular and non-ocular AEs. All verbatim AEs terms will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

Only treatment-emergent AEs will be analyzed. A treatment emergent adverse event is defined as any new AE reported or any worsening of an existing condition on or after the first dose of faricimab in AVONELLE-X and no later than 28 days after study completion/discontinuation. Adverse events with missing onset date will be considered to be treatment emergent. Adverse events with partially missing onset date will also be included as treatment emergent when the month (if it was recorded) and the year occur on or later than the month and year of the start date of the reporting period.

Clinically significant laboratory abnormalities and clinically significant vital sign abnormalities will be reported as AEs and evaluated as part of the AE assessments.

Missing data for safety analyses will not be imputed.

4.2.2 Main Analytical Approach

All verbatim AEs terms will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Non-ocular AEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT). Ocular AEs in the study eye will be tabulated by PT. AE summary tables will be presented overall, and by parent study treatment group.

Frequency tables, including patient incidence rates, will be provided for the adverse events listed below. Ocular AEs will be reported for study eyes. Graphical presentations will be included, as applicable.

- Ocular AEs and serious adverse events (SAEs)
- Ocular AEs by severity
- Non-ocular AEs and SAEs
- Non-ocular AEs by severity
- Adverse events of special interest (AESI) defined as follows:
  - Cases of potential drug-induced liver injury that include elevated alanine aminotransferase or aspartate aminotransferase in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.2.3 of the protocol)
  - Suspected transmission of an infectious agent by the study drug
  - Sight-threatening AEs (see Section 5.2.3 of the protocol for definitions)
- AEs leading to discontinuation of study treatment
- AEs leading to discontinuation from the study
- AEs leading to study treatment interruption
- Treatment related ocular AEs and SAEs as determined by the Investigator
- Non-ocular AEs of arterial thromboembolic event (ATE) and cerebrovascular haemorrhagic AEs
- Externally adjudicated APTC events
- Selected Ocular Events
  - Intraocular inflammation (IOI)
  - Infectious endophthalmitis
  - Retinal vascular occlusion
- Deaths

For the fellow eye, frequency tables including patient incidence rates will be provided for the events listed below:

- Ocular AEs and SAEs in the fellow eye
- Ocular AESIs in the fellow eye (sight-threatening AEs)

Relevant ocular and non ocular AE summaries will be provided for participants with bilateral faricimab use, i.e. participants who received faricimab in both eyes, including AEs that occurred or worsened on or after the 1st day of fellow eye faricimab injection. The planned summaries include AE overview, ocular AE in the study eye, ocular AE in the fellow eye, non-ocular AE, non-ocular ATE.

Relevant ocular and non ocular AE summaries will be provided for participants who were always treated Q8W or more frequent treatment interval, including AEs that occurred or worsened on or after the day of 1st faricimab treatment in the study eye in AVONELLE-X. The planned summaries include AE overview, ocular AE in the study eye, ocular SAE in the study eye, non-ocular AE, non-ocular ATE.

As there is no standardized MedDRA queries (SMQ) encompassing the medical concepts of IOI, infectious endophthalmitis or retinal vascular occlusive disease, the definitions will be assessed based on the review of clinical database PTs or reported AEs from clinical database prior to final database lock, and with subsequent MedDRA version updates, to ensure no event terms are missed.

Listings will be provided for the following groups:

- AEs, SAEs, IOI, RPE tear, and Retinal tear/detachment in the study eye
- AESIs, APTCs, ATEs, AEs lead to Study Treatment Interruption and deaths
- IOI in both study and fellow eye in patients receiving bilateral

For comprehensiveness in safety analysis, a separate AE listing will be provided for participants at GCP non-compliance affected site.

4.2.3 Sensitivity Analysis

Not Applicable

4.2.4 Supplementary Analysis

Not Applicable

4.2.4.1 Subgroup Analyses for Primary Endpoint(s)

The ocular AEs in the study eye, non-ocular AEs and SAEs will be analyzed by the following subgroups:

- Age: <75, ≥75, <85, ≥85
- Gender: female and male
- Race: White, Asian, and Other
- Medical History: renal disease, cardiac disease and vascular disease

4.3 SECONDARY ENDPOINT ANALYSIS

Not Applicable.

4.4 EXPLORATORY ANALYSIS

The exploratory efficacy analyses will be based on the efficacy-evaluable population and will be presented by parent study treatment group and overall (if applicable) for both binary and continuous endpoints. No formal statistical hypothesis will be tested.

For participants randomized to aflibercept in the parent study, baseline is defined as the last value collected before the first faricimab injection in AVONELLE-X. For participants randomized to faricimab in the parent study, baseline is defined as the last value collected at or prior to AVONELLE-X Day 1 prior to any study assessments.

Descriptive summaries for continuous endpoints will include number of observations, arithmetic mean, standard deviation, 95% CI for mean, median, minimum, maximum, first quartile (Q1), and third quartile (Q3). Descriptive summaries for binary endpoints will include frequency and/or percent. The estimates and confidence interval (CIs) will be provided for the mean (for continuous variables) or proportion (for binary variables) for each parent study treatment group. All CIs will be two-sided and at the 95% level. Additional details of the analysis of each exploratory endpoint are given in the sub-sections below.

4.4.1 Continuous Exploratory Endpoints

Change from baseline in BCVA and CST (ILM-RPE)

The change from baseline in BCVA and CST will be summarized descriptively as well as using an Analysis of Covariance (ANCOVA) model with adjustment for parent study stratification factors of baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score as assessed on Day 1 (≥74 letters, 73−55 letters, and ≤54 letters), low-luminance deficit (LLD; < 33 letters and ≥ 33 letters), and region (United States and Canada, Asia, and the rest of the world), parent study treatment arm (faricimab 6mg and aflibercept 2mg) and baseline value (continuous).

The analysis of change from baseline in BCVA and CST will be presented at monthly intervals during the masked period, and at Year 1 (Y1), Month 18 (M18), Year 2 (Y2) and SFU timepoints. The M18 time point has been added as an intermediate time point midway between the annual assessment timepoints for continuity in reporting of BCVA and CST outcomes. The calculation of the analysis value at each of the Y1, M18, Y2 and SFU timepoints will be done at patient level and is as described below.

- Analysis value at Year 1 is calculated as an average of values corresponding to all available visits (one value for each visit, mapped as described in Section 4.1) within the Year 1 visit window i.e., Week 44 to Week 64
- Analysis value at Month 18 is calculated as an average of values corresponding to all available visits (one value for each visit, mapped as described in Section 4.1) within the Month 18 visit window i.e., Week 68 to Week 88

- Analysis value at Year 2 is calculated as an average of values corresponding to all available visits (one value for each visit, mapped as described in Section 4.1) within the Year 2 visit window i.e., Week 92 to Week 104.
- Analysis value at SFU is defined as the value collected 4 weeks after the last study treatment. SFU visit is only defined for patients who completed the study treatment.

This averaging will be done for both the BCVA and CST endpoints. The rationale for using this approach is to reduce bias arising from variability due to multiple assessments of BCVA and CST in the annual visit windows, especially from patients on a shorter PTI.

A sensitivity analysis of change from baseline in BCVA and CST will be performed using the ANCOVA model with adjustment for parent study stratification, parent study treatment arm (faricimab 6 mg, aflibercept 2 mg) and baseline value (continuous). For this analysis, the first data point in the analysis window corresponding to the Year 1, Month 18 and Year 2 timepoints respectively will be used as the response variable as follows:

- Analysis value at Year 1 will be the value corresponding to the earliest visit (one value per visit, mapped as described in Section 4.1) available in the Year 1 visit window – Week 44 to Week 64
- Analysis value at Month 18 will be the value corresponding to the earliest visit (one value per visit, mapped as described in Section 4.1) available in the Month 18 visit window – Week 68 to Week 88
- Analysis value at Year 2 will be the value corresponding to the earliest visit (one value per visit, mapped as described in Section 4.1) available in the Year 2 visit window – Week 92 to Week 104
- Analysis value at SFU is defined as the value collected 4 weeks after the last study treatment. SFU visit is only defined for patients who completed the study treatment.

Non-standard BCVA data (assessed by Early Treatment Diabetic Retinopathy Study [ETDRS] BCVA testing with prior visit refraction, test performed by unmasked certified ETDRS BCVA assessor, or by uncertified experienced ETDRS BCVA assessor, or Snellen data) due to COVID-19 restrictions and collected in the COVID-19 Non-Protocol-Specified Visual Acuity Testing electronic Case Report Form (eCRF) will be excluded from all the analyses. Invalid BCVA will be excluded from the analyses.

Continuous Endpoints by Fluorescein Angiography (FFA)

These endpoints will be analyzed using similar approach to change in BCVA/CST from baseline except that no sensitivity analysis will be performed:

- Change from baseline in total area of CNV lesion as assessed by FFA
- Change from baseline in total area of leakage as assessed by FFA

Change from Baseline in NEI-VFQ 25 Patient Reported Outcome

The change from baseline in NEI-VFQ 25 composite score, the near activity subscale score, the distance activities subscale score, and driving subscale score will be summarized descriptively.

4.4.2 Binary Exploratory Endpoints

Binary endpoints will be summarized using frequency and/or percentage. The proportion of participants in each treatment group will be estimated using the weighted average of the observed proportions over the strata defined by the parent study stratification and parent study treatment arm (faricimab 6 mg and aflibercept 2 mg) using the Cochran Mantel-Haenszel (CMH) weights (Cochran and William 1954; Mantel et al. 1959). Confidence intervals of the proportion of participants in each treatment group will be calculated using the normal approximation to the weighted proportions. All CIs will be two-sided and at the 95% level. No formal statistical hypothesis will be tested so no p–values will be provided.

For the purpose of visit windowing for binary exploratory endpoints, Year 1 is defined as the earliest observed value (between Week 44 and Week 64), Month 18 is defined as the earliest observed value (between Week 68 and Week 88) and Year 2 is defined as the earliest observed value (between Week 92 and Week 104) from baseline of the LTE study. If the earliest scheduled visit is missed, then the next measurement within the period should be considered.

Similar to continuous efficacy endpoints, SFU is defined as the value collected 4 weeks after the last study treatment. SFU visit is only defined for patients who completed the study treatment.

The following binary exploratory endpoints will be summarized descriptively and using CMH method:

- Proportion of patients with absence of intraretinal fluid, as measured in the central subfield (center 1 mm)
- Proportion of patients with absence of subretinal fluid, as measured in the central subfield (center 1 mm)
- Proportion of patients with absence of both intraretinal fluid and subretinal fluid (center 1mm)
- Proportion of patients with pigment epithelial detachment, as measured in the central subfield (center 1 mm)

The following binary exploratory endpoint will be summarized descriptively:

- Proportion of patients on a Q4W, Q8W, Q12W, or Q16W treatment:

- Treatment interval at a given visit is defined as the treatment interval decision followed at that visit. If the visit is not an active dosing visit, treatment interval is defined as the treatment interval the patient is on at that visit
- The last observed PTI in the visit window for Year 1, M18 and Year 2 will be used as the patient's PTI at that window as this is expected to represent the treatment interval at the end of long term faricimab treatment. For a patient with a missed Year 2 visit, the PTI calculated at the visit previous to the scheduled Year 2 visit will be the last calculated PTI for the patient.

4.5 OTHER SAFETY ANALYSES

All the safety analyses will be performed on the safety population and presented overall and by parent study treatment group.

Participants will be grouped according to the actual treatment received in the parent study up to the Week 108.

4.5.1 Extent of Exposure

Exposure to study drug (number of study drug administrations and duration of treatment) will be summarized overall and by parent study treatment group for the study eye in the safety evaluable population.

Duration of treatment is the time from the first faricimab administration to the latter of:

- date of the last dose of study drug or
- date of the last treatment dose hold

The number of dose interruptions along with the reason for interruption and the number of interruptions per patient will be summarized using counts and percentages.

4.5.2 Adverse Events

All the details about AEs analysis are provided in Section 4.2.2.

4.5.3 Additional Safety Assessments

4.5.3.1 Ocular Assessments

Results of the following ocular assessments will be summarized by eye (study vs. fellow) using descriptive summaries and graphical presentations (as applicable):

- Intraocular pressure (IOP)
- Slit lamp examination
- Indirect ophthalmoscopy

Changes from baseline in pre-dose IOP measurements will be summarized overall and by parent study treatment group over time.

Baseline is defined as the first day of faricimab treatment for all participants enrolled in the LTE study.

The presence of IOI and vitreous hemorrhage, as determined on slit lamp examination, will be tabulated by grade (according to grading scales for flares and cells in Appendix 3 of the protocol). The presence of retinal break or detachment as determined from ophthalmoscopy will be tabulated.

4.5.3.2 Laboratory Data

No general summary is planned for laboratory data other than PK, pharmacodynamic (PD) and ADA data.

4.5.3.3 Vital Signs

Vital signs, including measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure will be recorded at Day 1 and final visit only. These data will be used for interpretation of some AEs; no other summaries are planned.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

Summaries of conduct of study will be based on the efficacy-evaluable population and presented overall, and by parent study treatment group.

The number and percentage of participants who enroll (including from which parent study) will be summarized by country and site. Participant disposition (the number of participants enrolled, treated, and completing the study) will be summarized overall and by parent study treatment group. Reasons for premature study withdrawal will be listed and summarized.

The impact of Coronavirus disease (COVID-19) will be assessed by using metrics reported in Section 4.6.6.

Major protocol deviations will be summarized by parent study treatment arm and overall. Participant listings of major protocol deviations may also be provided.

Concurrent ocular procedures, concomitant systemic medications, ocular medications for the study eye, and ocular medications for the fellow eye will be summarized separately overall and by parent study treatment group. The summaries will be based on medications given at or after the first faricimab dose in the LTE study.

4.6.2 Summaries of Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using the efficacy-evaluable population and presented overall and by parent study treatment group. Demographic data (e.g., age, sex, and race/ethnicity) and medical history will

originate from the parent study. Baseline disease characteristics (e.g., baseline BCVA, ocular assessments) will be summarized for AVONELLE-X. Baseline is defined in the same way as the efficacy endpoints.

Descriptive statistics for continuous data will include number of observations, arithmetic mean, SD, median, minimum, and maximum. Descriptive statistics for categorical data will include frequency and/or percent.

4.6.3 Pharmacokinetic Analyses

Pharmacokinetic (PK) analyses will be based on participants who receive faricimab during the LTE study in the safety-evaluable set and have at least one evaluable PK sample. Data on or after the first dose of faricimab treatment in this LTE study will be included in the analyses. The analyses will be summarized by parent study treatment group.

Summaries of plasma faricimab concentrations by visit will be tabulated.

Concentrations of faricimab from the optional collection of aqueous humor may be reported and/or summarized as appropriate. Additional PK/PD and exposure response analyses may be conducted as appropriate. Exploratory PK analyses to evaluate potential relationships between drug exposure and efficacy of the faricimab may be performed, as applicable.

Population PK modeling may be performed, the data of this study may be pooled with data from previous studies. The results will be reported separately from the Clinical Study Report (CSR). Details of the population PK analyses will be described in a Modeling and Simulation Analysis Plan.

4.6.4 Immunogenicity Analyses

The immunogenicity analyses will be based on participants who receive faricimab treatment during the AVONELLE-X and have at least one evaluable ADA sample. The analyses will be summarized overall and by parent study treatment group.

Baseline ADA prevalence will be estimated based on the baseline ADA finding. Baseline is defined as the last available assessment obtained prior to the first faricimab administration in the parent study for patients randomized to faricimab arm in the parent study, and as the last assessment before the first faricimab administration in AVONELLE-X for patients randomized to aflibercept in the parent study.

The immunogenicity incidence will be summarized in participants who receive faricimab treatment during the AVONELLE-X with at least one evaluable post-baseline ADA assessment as follows:

a) **Treatment-induced ADA response:** Participants whose baseline ADA is either negative or missing and who have at least one positive ADA finding after initiation of faricimab treatment.

b) **Treatment-boosted ADA response:** Participants whose baseline ADA is positive and whose ADA titer increases after initiation of faricimab treatment; in this case, the titer of one or more samples collected after faricimab treatment must be at least 4-fold greater than the titer of the baseline visit sample.

c) **Treatment-unaffected ADA response:** Participants whose baseline ADA is positive and whose ADA titer is unchanged after initiation of faricimab treatment; in this case, the titer results of all samples collected after faricimab treatment should be lower than 4-fold of the baseline ADA titer; or all post-baseline results are negative or missing.

The combined rate described in (a) and (b) above will provide the incidence of participants positive for treatment-emergent ADAs. The combined rate described in (a), (b) and (c) above will provide the incidence of participants positive for ADAs.

Participants are considered to be negative for ADAs if they are ADA negative at all-time points. Participants are also considered to be negative for ADAs if they have missing ADA at baseline, and are ADA negative at all post-baseline time points.

Among participants with a treatment-induced ADA response, the following data will be summarized:

1. **Transient treatment-induced ADA response:** Participants with ADA-positive result detected (i) at only one post-baseline sampling time point (excluding last time point) OR (ii) at two or more time points during treatment where the first and last ADA-positive samples are separated by a period of < 16 weeks, irrespective of any negative samples in between.
2. **Persistent treatment-induced ADA response:** Participants with ADA-positive result detected (i) at the last post-baseline sampling time point, OR (ii) at 2 or more time points during treatment where the first and last ADA-positive samples are separated by a period of ≥16 weeks, irrespective of any negative samples in between.
3. Median time to onset of ADA and range of ADA titers. For positive samples with titer result less than the minimum reportable titer, or any positive samples where a titer cannot be obtained, titer values will be imputed as equal to the minimum reportable titer.

A listing of participants with positive serum antibodies to faricimab will be provided.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be explored.

4.6.5 Clinical Outcome Assessment Analyses

Pharmacodynamic (PD) biomarker analyses will be based on participants in the safety-evaluable population and have at least one evaluable biomarker measurement.

Baseline for the analyses is defined as the last non-missing measurement prior to first administration of the study treatment.

Descriptive summaries of aqueous humor free Ang-2 and free VEGF concentration (original and log-transformed), as well as change in this concentration from baseline will be tabulated and plotted by visit and by treatment group.

Additional exploratory biomarker analyses to evaluate potential relationships between drug exposure, free VEGF, free Ang-2, disease severity, and/or efficacy will be performed, as applicable. Results will be reported in a document separate from the CSR.

4.6.6 Analyses for COVID-19

Based on the first reports of COVID-19 infection globally, the Sponsor determined that the window for all analyses of COVID-19 associated events would start from 1 December 2019.

The impact of COVID-19 will be assessed for study conduct and safety events.

4.6.7 Study Conduct Analyses for COVID-19

In order to assess the impact of COVID-19 on study conduct, the following metrics will be recorded:

- BCVA not performed per protocol (non-standard BCVA) due to COVID-19 or related precautions
- Major protocol deviations associated with COVID-19 directly or indirectly

4.6.8 Safety Analyses for COVID-19

Following the MedDRA 23.1 release, a COVID-19 SMQ (narrow) is available.

This SMQ includes terms relevant to COVID-19 infection. Patients with AEs from this COVID-19 SMQ (narrow) will be considered to have a confirmed or suspected COVID-19 infection (Table 3).

For the patients identified from the search as having confirmed or suspected COVID-19 infection, outputs to evaluate safety events will be produced as follows:

- Summary table of confirmed and suspected COVID-19 AEs

In addition to presenting the suspected/confirmed COVID-19 infections, the Sponsor developed a broad search strategy for AEs associated with COVID-19 infection to further

evaluate the confirmed events of COVID-19 and reported AEs that could be considered complications of the disease. This search strategy includes both the AEs of a confirmed or suspected COVID-19 infection and any AEs considered associated with COVID-19. The Sponsor identified associated AEs as those reported ≤7 days before and ≤30 days after any reported AE suggesting a confirmed COVID-19 infection (PTs listed in Table 3). AEs suspected of being caused by COVID-19 as per eCRF will be considered associated with COVID-19 as well.

For the patients identified as having COVID-19 associated AEs, outputs to evaluate these safety events will be produced as follows:

- Summary table and listing of COVID-19 Associated Events: including all of the above confirmed/suspected COVID-19 infections plus AEs suspected of being cause by COVID-19 as per eCRF and, for those patients with confirmed COVID-19 infection or positive polymerase chain reaction test flag, any other AEs occurring within ≤ 7 days before and ≤ 30 days after start date of all the confirmed COVID-19 events in Table 3.
- Summary table of Adverse Events Associated with COVID-19 Resulting in Death
- Summary table of Adverse Events of Duration >30 days occurring after Initial Diagnosis of Confirmed COVID-19 Infection
- Summary table of Adverse Events Associated with COVID-19 Resulting in Death

Table 3 Roche COVID-19 SMQ (narrow) Preferred Terms for Confirmed Cases

Preferred Terms for Confirmed Cases
Asymptomatic COVID-19
Breakthrough COVID-19
Congenital COVID-19
Coronavirus infection
Coronavirus pneumonia
Coronavirus test positive
COVID-19
COVID-19 immunisation
COVID-19 pneumonia
COVID-19 prophylaxis
COVID-19 treatment
Exposure to SARS-CoV-2
Multisystem inflammatory syndrome
Multisystem inflammatory syndrome in adults
Multisystem inflammatory syndrome in children
Occupational exposure to SARS-CoV-2
Post-acute COVID-19 syndrome
SARS-CoV-2 antibody test positive
SARS-CoV-2 carrier
SARS-CoV-2 RNA decreased
SARS-CoV-2 RNA fluctuation
SARS-CoV-2 RNA increased
SARS-CoV-2 sepsis
SARS-CoV-2 test false negative
SARS-CoV-2 test positive
SARS-CoV-2 viraemia
Suspected COVID-19
Thrombosis with thrombocytopenia syndrome
Vaccine derived SARS-CoV-2 infection

COVID-19 = coronavirus Disease 2019; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SMQ = standardized Medical Dictionary for Regulatory Activities (MedDRA) queries

4.7 INTERIM ANALYSES

One set of Interim analyses was conducted. Details of the analyses were described in IA DAP M2 document.

4.8 CHANGES TO PROTOCOL-PLANNED ANALYSES

Per-protocol analysis was removed from the analysis plan as the study intends to reflect the impact of treatment in a real-world setting, where participants may or may not adhere to a clinical study protocol when taking/receiving medication.

The absence of intraretinal cysts was removed since this endpoint is considered as a repetition of IRF.

5. SUPPORTING DOCUMENTATION

This section is not applicable since there is no additional supporting document.

6. REFERENCES

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