Official Title: A Multicenter, Open-Label Extension Study to Evaluate The Long-Term Safety and Tolerability of Faricimab in Patients with Diabetic Macular Edema

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STATISTICAL ANALYSIS PLAN

STUDY TITLE:	A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF FARICIMAB IN PATIENTS WITH DIABETIC MACULAR EDEMA
STUDY NUMBER:	GR41987
STUDY NAME:	RHONE-X
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PLAN PREPARED BY:	[redacted]

STATISTICAL ANALYSIS PLAN APPROVAL

SPONSOR: **LEGAL REGISTERED ADDRESS:**	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
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 V2.0.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	see electronic date stamp on the last page of this document	Version 3, dated 13 Dec 2021
2	see electronic date stamp on the last page of this document	Version 3, dated 13 Dec 2021

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This Statistical Analysis Plan (SAP) has been amended to incorporate the following changes:

Section	Description of Change
3	Removed definition of per protocol population
3	Re-defined safety evaluable population
4.1	Restructured section for better clarity and consistency
4.4	Added additional details of the analyses of exploratory endpoints.
4.6	Added additional details of immunogenicity 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
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
CI	confidence interval
COVID-19	Coronavirus Disease
CRC	Central Reading Center
CRF	Case Report Form
CSR	Clinical Study Report
CST	central subfield thickness
eCRF	electronic Case Report Form
DME	diabetic macular edema
DR	Diabetic Retinopathy
DRSS	Diabetic Retinopathy Severity Scale
ET	Early Termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FFA	Fundus Fluorescein Angiography
ILM	internal limiting membrane
IRF	Intra-retinal Fluid
IOI	intraocular inflammation
IOP	intraocular pressure
IVT	intravitreal
IxRS	interactive voice or web-based response system
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25
OCT	Optical Coherence Tomography
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
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD-OCT	Spectral-Domain Optical Coherence Tomography
SMQ	standardized MedDRA queries
SS-OCT	Swept-Source Optical Coherence Tomography
UWP	Ultra-wide photography
VA	visual acuity
VEGF (-A)	vascular endothelial growth factor (-A)

1. INTRODUCTION

Diabetic macular edema (DME), a complication of diabetic retinopathy (DR), can develop at any stage of the underlying disease of retinal microvasculature. DME occurs with increasing frequency as the underlying DR worsens from non-proliferative DR to proliferative DR (PDR). DME is the most common cause of moderate and severe visual impairment in patients with DR and affects approximately 14% of patients with diabetes. On a molecular level, DME is a result of a vascular endothelial growth factor–A (VEGF-A)–mediated increase in vessel permeability and loss of pericytes. VEGF also upregulates a homeostatic factor, angiopoietin-2 (Ang-2), counteracting vessel stabilization. In summary, both Ang-2 and VEGF-A are recognized as key factors mediating diabetic eye disease pathogenesis. The development of anti-VEGF pharmacotherapy in the past decade has led to dramatic improvements in visual outcomes for patients with DME. Despite these advancements, a significant proportion of patients do not experience clinically meaningful improvements in vision in the real world. The current standard of care for administration of anti-VEGF injections requires patients to undergo frequent clinical examinations and intravitreal (IVT) injections imposing a significant burden on patients, caregivers, and treating physicians. In addition, anti-VEGF monotherapy does not fully address other pathways, including inflammation and pericyte destabilization, that contribute to worsening of diabetic eye disease. Consequently, patients on anti-VEGF monotherapy may not be gaining as much vision as they could. Taken together, new treatments that target additional pathways could address the above unmet medical needs by improving visual acuity (VA) outcomes and reducing the burden of IVT injections in DME.

Faricimab is a humanized full-length bispecific immunoglobulin 1 antibody that selectively neutralizes Ang-2 and VEGF-A. The Ang-2 binding and the VEGF binding variable regions of faricimab bind to Ang-2 and VEGF independently and simultaneously with high affinity. Based on this novel mechanism of action of faricimab, and existing evidence of upregulated concentrations of both Ang-2 and VEGF in the vitreous in patients with DR, it is hypothesized that faricimab may lead to stabilization of the pathological ocular vasculature and to improve visual and anatomical outcomes in DME and DR compared with anti-VEGF monotherapies. The available Phase I and II efficacy and safety data showed a benefit–risk profile that supports further assessment of the efficacy, durability, and safety of faricimab compared with anti-VEGF IVT monotherapy in a Phase III setting. The Phase 3 studies YOSEMITE (GR40349) and RHINE (GR40398) were identically designed registrational studies that investigated the efficacy, safety and pharmacokinetics of faricimab given at Q8W intervals or with a PTI regimen compared with aflibercept monotherapy in patients with DME. The primary analysis of these Phase III studies demonstrated that patients treated with faricimab Q8W or PTI had a non-inferior mean change from baseline in BCVA at Week 48/52/56 compared with patients treated with aflibercept Q8W. The mean change in BCVA from baseline

was comparable over time across faricimab Q8W, faricimab PTI, and aflibercept Q8W arms through Week 100. In addition, the majority of faricimab-treated patients (>70%) were on an extended dosing regimen (every 12 weeks [Q12W] or Q16W) at Week 52.

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 GR41987 (RHONE-X). In this Statistical Analysis Plan, 'study drug' refers to faricimab whereas 'study treatment' refers to faricimab or the sham procedure in the masked period.

The analysis plan and the endpoints specified in this document supersede the analysis plan described in the study protocol. This document will address analysis for efficacy, safety, immunogenicity, biomarkers and pharmacokinetics. Detailed specifications of tables, figures and listings are provided in separate documents.

1.1 OBJECTIVES AND ENDPOINTS

This study will evaluate the long term safety and tolerability of intravitreal (IVT) faricimab in patients with DME who have completed either of the Phase III (GR40349 or GR40398) 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 4 months of the study (Day 1 through to Week 16). 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, at intervals determined according to the Personalized Treatment Interval (PTI) algorithm. 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.

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 patients 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 adverse events
- Incidence and severity of non-ocular adverse events

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 diabetic eye disease in all patients who have enrolled in this LTE study on the basis of the following endpoints:

- Change from baseline in best-corrected visual acuity (BCVA) over time as measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a starting distance of 4 meters
- Change from baseline in central subfield thickness (CST) over time
  - CST is defined as the distance between ILM and BM, as measured in µm as assessed by Central Reading Center (CRC). CST for Cirrus spectral-domain optical coherence tomography (SD-OCT) or Topcon SD-OCT were standardized to Spectralis SD-OCT by the central reading center.
- Proportion of patients with absence of intraretinal fluid over time
- Proportion of patients with absence of subretinal fluid over time
- Proportion of patients with absence of both intraretinal fluid and subretinal fluid over time
- Proportion of patients with absence of DME over time
  - Absence of DME is defined as achieving a CST of <325 microns
- Proportion of patients on a Q4W, Q8W, Q12W, or Q16W treatment during the study:
  - 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
- Proportion of patients with:
  - $\geq$2-step DRS improvement from baseline on the ETDRS DRSS over time
  - $\geq$3-step DRS improvement from baseline on the ETDRS DRSS over time
- Proportion of patients with:
  - $\geq$2-step DRS worsening from baseline on the ETDRS DRSS over time
  - $\geq$3-step DRS worsening from baseline on the ETDRS DRSS over time
- Proportion of patients who develop new PDR over time
- Change from baseline in patient-reported vision-related functioning and quality of life over time 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 pharmacokinetics 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 from the start of the LTE study
- The correlation between concentration of aqueous humor faricimab and the change in BCVA and other endpoints (e.g., anatomical markers) over time from the start of the LTE study

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 baseline
- Incidence of ADAs during the study from the start of the LTE.

See Section 4.6.4 for the definition of baseline for immunogenicity analyses.

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 adverse events or can lead to improved adverse event 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

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 patients who enrolled in and completed one of the Phase III studies (GR40349 or GR40398). Patients in the parent studies who discontinued from the study or study treatment prior to completion of the 96-week treatment period are not eligible for enrollment in this extension study.

Eligible patients 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 100 visit in Studies GR40349 and GR40398). Patients 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 100) 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 100 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.

Total 1479 patients have been enrolled in this extension study after completion of the parent studies and will all follow a single faricimab 6 mg PTI regimen.

- Patients previously randomized to Arm A (faricimab Q8W) who have had their last dose of faricimab at Week 92 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.

  Patients in this arm who (e.g., because of dose holds/missed visits in the parent study) received a faricimab dose at Week 96 in the parent study, will not receive a faricimab dose on Day 1 of the LTE study. Instead, these patients will be dosed 8 weeks after the final dose in the parent study (i.e., at Week 4 of the LTE study) and will then be eligible to have their subsequent dosing interval extended, reduced, or maintained on the basis of the PTI algorithm.
- Patients previously randomized to Arm B (faricimab PTI up to Q16W) will continue their previously assigned treatment interval and will then be eligible to have their subsequent faricimab dosing based on the PTI algorithm.
- Patients previously randomized to Arm C (aflibercept Q8W) who have had their last dose of aflibercept at Week 96 of the parent study (see Figure 1) will have a dose of faricimab at Week 4 of the LTE study, and will then be eligible to have their subsequent faricimab dosing based on the PTI algorithm. Patients in this arm who (e.g., because of dose holds/missed visits in the parent study) received their last aflibercept dose at Week 92 of the parent study will have a faricimab dose on Day 1 of the LTE study. These patients will then be eligible to have their subsequent dosing based on the PTI algorithm.

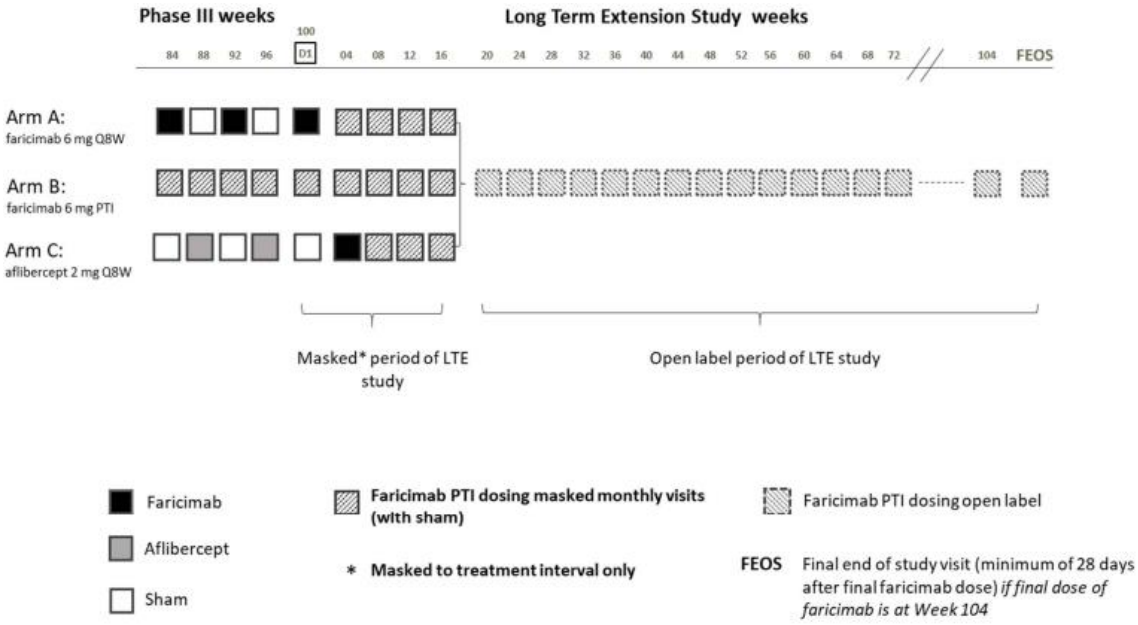
In this extension study, the study eye will be the same as that in the parent studies, GR40349 and GR40398.

Patients will be required to attend monthly study assessment visits between Day 1 and Week 16 (the masked period of the study) in order to preserve masking of a patient's treatment assignment in the parent study. From Week 20 until approximately Week 104, patients will attend study visits at intervals as scheduled by the IxRS system based on the PTI algorithm.

Annual visits are defined as the scheduled PTI visit that is earliest (between Week 48 and Week 64) relative to 52 weeks (for Year 1) and earliest (between Week 96 and Week 104) relative to 104 weeks (for Year 2) from Day 1. If, due to the patient's faricimab PTI, there are multiple options for Year 1 or Year 2 visits, IxRS will advise the site that the earliest scheduled visit between Week 48 and Week 64 should be considered the Year 1 visit and that the earliest scheduled visit between Weeks 96 and 104 should be considered the Year 2 visit. If the earliest scheduled visit is missed, then the next visit within the period should be considered the annual visit.

Patients who undertake their Year 2 visit at Week 96 or Week 100 but are on a PTI that requires them to return at Week 100 and/or Week 104 should also attend these scheduled study visits and attend their Final End of Study visit (FEOS) 28-35 days after their final dose of study treatment. For the study schema, see Figure 1. Figure 1 has FEOS shaded to represent dosing but there is no dosing at this visit.

Figure 1 Study Schema



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

Patients who discontinue study treatment will 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, patients will return to the clinic for an unscheduled visit a minimum of 28 days after receiving the final dose of study drug.

LTE Visit Schedule during the Masked Period

Eligible patients who choose to enroll into the LTE study will have monthly, masked, study visits for the first 4 months of the study (Day 1 through to Week 16; 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, patients and physicians will only be masked to the faricimab treatment interval (if faricimab or sham is administered).

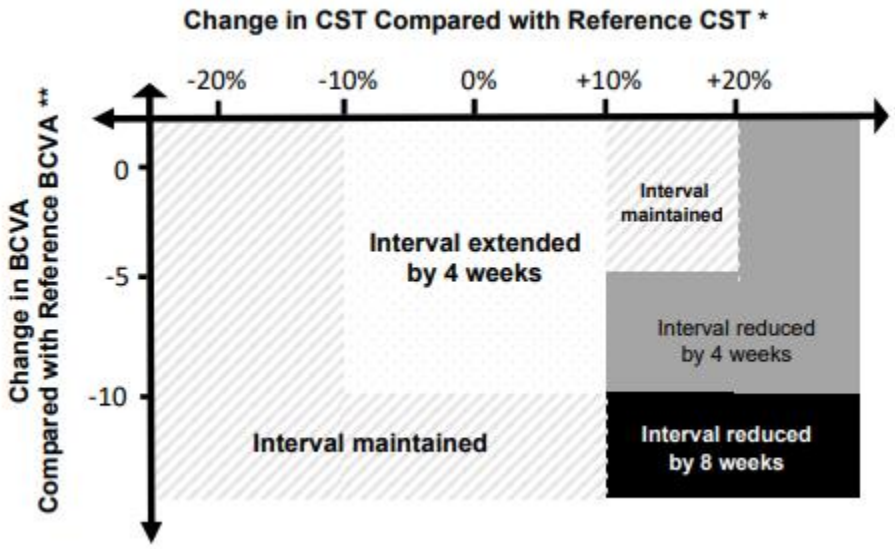
LTE Visit Schedule following Masked Period

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, at intervals determined according to the PTI algorithm. However, the treatment arm to which patients 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 patient's PTI interval. The PTI algorithm is the same as that used in the Phase III studies. The PTI uses patient'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 intervals can be extended in 4-week increments to a maximum of Q16W, maintained, or reduced to a minimum of Q4W as mentioned below in Figure 2.

Figure 2 Algorithm for IxRS-Determined Personalized Treatment Interval Study Drug Dosing Intervals



BCVA = Best Corrected Visual Acuity; CST = Central Subfield Thickness; IxRS = Interactive voice or web-based Response System.

The final analysis will be performed when all patients have either completed the study through Year 2 or have discontinued early from the study, whichever comes later, all data are in the database, and cleaning and verification of critical variables have been completed.

1.2.1 Treatment Assignment and Blinding

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 a patient, the study site will obtain the patient number and kit assignments from the IxRS. In this extension study, the patient 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 16). Masked site staff and patients will be informed that the patient will receive faricimab 6 mg IVT injections, and that they will be masked to the faricimab treatment interval only.

During this masked period, patients will be advised that at masked study visits they will either receive faricimab or sham injection. After the Week 16 treatment procedure, the study will follow an open-label design and patients 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.

Ocular images include the following:

- CFP in both eyes (7- or 4-ETDRS fields; method used for each patient should be
- consistent with that used in the parent study and remain consistent throughout the duration of the LTE study)
- Optional ultra-wide field (UWF) CFP of both eyes (to be undertaken in patients for whom consent was obtained and images acquired in the parent study)
- FFA of both eyes (preferred method is UWF FFA if sites have capability; sites
- without UWF should capture 7- or 4-field ETDRS as per the parent study and use the same method consistently throughout their LTE study participation). FFA should be performed after blood samples obtained (if applicable).
- SD-OCT or swept-source OCT images of both eyes (to be undertaken using the
- same device as that used in the parent study)
- Optional OCT-angiography (OCT-A) of both eyes at sites with OCT-A capabilities and agreement by sites to take these images (to be undertaken using the same device as that used in the parent study)

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 patients who complete study treatment and the Week 100 visit in one of the parent studies GR40349 (YOSEMITE) or GR40398 (RHINE).

3. ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 1.

Table 1 Participant Analysis Sets

Participant Analysis Set	Description
Efficacy evaluable	All eligible patients enrolled into this study. For analyses using the parent study treatment group, patients will be grouped according to the treatment assigned at randomization in the parent study. All data starting from the LTE baseline will be used for efficacy analyses.
Safety-Evaluable	The safety-evaluable population will comprise all patients who enroll in the LTE, and receive at least one dose of faricimab during the LTE. For analyses using the parent study treatment group, patients will be grouped according to the actual treatment received in the parent study up to the Week 96 visit, as explained in the Section 4.1. All data starting from the date of first administration of faricimab will be used for safety analyses.
Pharmacokinetic-Evaluable	Safety-evaluable patients who have at least one plasma sample, and if sufficient dosing information (dose and dosing time) is available. For analyses based on the parent study treatment groups, patients will be grouped according to the actual treatment received in the parent study (see Section 4.1).

Table 1 Participant Analysis Sets (cont.)

Participant Analysis Set	Description
Immunogenicity-evaluable	All patients with at least one plasma sample for ADA assessment. The immunogenicity prevalence set will consist of all patients who received faricimab with at least one determinant anti-drug antibody (ADA against faricimab) assessment. The immunogenicity incidence set will consist of all patients who received faricimab with at least one determinant ADA assessment after the initiation of faricimab treatment. For analyses based on the parent study treatment groups, patients will be grouped according to the actual treatment received in the parent study (see Section 4.1). All data starting from the LTE baseline will be used for immunogenicity analyses.

ADA = anti-drug antibody; LTE = long-term extension.

4. STATISTICAL ANALYSES

Unless otherwise specified, the analyses described in this section are based on patients enrolled in this LTE study.

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

4.1 GENERAL CONSIDERATIONS

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

Safety summary tables will include all events collected in this LTE study from the first dose of faricimab. Additional listings will be provided for events that occurred from the LTE enrollment to the first faricimab dose for all enrolled patients.

Unless otherwise noted, the exploratory efficacy analyses will be based on the efficacy-evaluable population and will be presented overall and by parent study treatment group for the whole LTE study cohort for both binary and continuous endpoints. The exploratory efficacy analyses will be based on all available observations collected during the LTE study. Baseline will be defined as Day 1 of this study for patients randomized to faricimab Q8W or faricimab PTI in the parent study and as the first day of faricimab treatment in the LTE for patients randomized to aflibercept in the parent study. Patients with missing baseline assessments will not be imputed.

Continuous outcomes will be analyzed descriptively and additionally BCVA and CST outcomes will be analyzed using an Analysis of Covariance (ANCOVA) model. Binary endpoints will be analyzed descriptively and using stratified estimation for binomial proportions. The estimates and confidence intervals (CIs) will be provided for the mean

(for continuous variables) or proportion (for binary variables). Separate listings will be provided to present efficacy data collected from LTE Day 1 to the first faricimab dose in patients randomized to aflibercept in the parent study by parent study treatment group.

For safety analyses based on the parent study treatment groups, patients will be grouped according to the actual treatment received in the parent study up to the Week 96 visit as follows (similar algorithm used in the parent studies):

- If the only active treatment received in the parent study by a patient in the study eye was aflibercept, the patient's parent study treatment group will be aflibercept Q8W.
- If the only active treatment received in the parent study by a patient in the study eye was faricimab, the patient's parent study treatment group will be as randomized if the patient was randomized to one of the faricimab arms.
- If a patient received in the parent study a combination of different active treatments (faricimab and aflibercept) in the study eye, the patient's parent study treatment group will be as randomized.

For the purpose of visit scheduling, Year 1 is defined as the scheduled PTI visit that is earliest (between Week 48 and Week 64). Year 2 is defined as the scheduled PTI visit that is earliest (between Week 96 and Week 104) from Day 1 of the LTE study. If the earliest scheduled visit is missed, then the next visit within the period should be considered the annual visit.

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. 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 patients 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-evaluable population on the basis of the incidence and severity of ocular and non-ocular adverse events (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 summarized. A treatment emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of faricimab. 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 adverse events and evaluated as part of the adverse event assessments.

Missing data for safety analyses will not be imputed.

4.2.2 Main Analytical Approach

AEs will be tabulated by System Organ Class and Preferred Term and presented overall, and by parent study treatment group.

For ocular AEs, events in the study eye and fellow eye will be summarized separately.

Frequency tables, including patient incidence rates by parent study treatment arm, will be provided for the events listed below. In addition, graphical presentations will be included, as applicable:

- Ocular AEs and serious adverse events (SAEs)
- Non-ocular AEs and SAEs
- 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 adverse events of arterial thromboembolic event (ATE) and cerebrovascular haemorrhagic adverse events
- Externally adjudicated APTC events
- Intraocular inflammation (IOI)

- Retinal vascular occlusive disease
- Deaths

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

Ocular AEs and non-ocular AEs which occurred from the LTE enrollment to the first faricimab dose will be listed separately for all enrolled patients.

4.2.3 Sensitivity Analysis

Not Applicable

4.2.4 Supplementary Analysis

Not Applicable

4.2.4.1 Subgroup Analyses for Primary Endpoint(s)

Not Applicable

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 overall and by parent study treatment group for the whole LTE study cohort for both binary and continuous endpoints. The analyses will be based on all available observations. No formal statistical hypothesis will be tested. Missing data will not be imputed.

For patients randomized to aflibercept in the parent study, baseline is defined as the last value collected before the first faricimab injection in the LTE study. For patients randomized to faricimab Q8W or faricimab PTI in the parent study, baseline is defined as the value collected at parent study Week 100/study Day 1 prior to any LTE study assessments. If LTE study Day 1 is >2 business days but ≤ 28 days from parent study Week 100 (delayed Day 1 visit), the following exploratory efficacy assessments must be repeated and the Day 1 value is considered the baseline value:

- BCVA
- Optical Coherence Tomography (OCT) measures

In case of a delayed Day 1 visit, non- Case Report Form (CRF) Day 1 imaging data will be transferred to the Sponsor. Otherwise, if Day 1 $\leq$2 business days from parent study Week 100, values will be pulled from the parent study Week 100 for the analysis.

Descriptive summaries for the continuous endpoints will include the number of observations, arithmetic mean, SD, median, Q1, Q3, minimum, and maximum.

Separate listings will be provided to present efficacy data collected from LTE Day 1 to the first faricimab dose in patients randomized to aflibercept in the parent study.

Additional details of the analysis of each exploratory endpoint are given in the sections below.

4.4.1 Continuous Exploratory Endpoints

Change from baseline in BCVA and CST

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 score (64 letters or better vs. 63 letters or worse), prior IVT anti-VEGF therapy (yes vs. no), region (U.S. and Canada, Asia, and the rest of the world), parent study treatment arm (faricimab 6mg Q8W, faricimab 6mg PTI and aflibercept 2mg Q8W) 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), 18 months and Year 2 (Y2) timepoints. The 18 month 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 corresponding to Y1, 18 months and Y2 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 48 to Week 64
- Analysis value at 18 months 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 18 month visit window i.e., Week 72 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 96 to Week 104.

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 factors of baseline BCVA score (64 letters or better vs. 63 letters or worse), prior IVT anti-VEGF therapy (yes vs. no), region (U.S. and Canada, Asia, and the rest of the world), parent study treatment arm (faricimab 6mg Q8W, faricimab 6mg PTI and aflibercept 2mg Q8W) and baseline value (continuous). For this analysis, the first data point in the analysis window corresponding to the Year 1, 18 month 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 48 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 18 month visit window – Week 72 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 96 to Week 104

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 eCRF will be excluded from all the analyses. Invalid BCVA will be excluded from the analyses.

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 at Year 1 and Year 2 timepoints respectively.

4.4.2 Binary Exploratory Endpoints

Binary endpoints will be summarized using frequency and/or percentage. The proportion of patients in each treatment group will be estimated using the weighted average of the observed proportions over the strata defined by the parent study stratification factors of baseline BCVA score (64 letters or better vs. 63 letters or worse), prior IVT anti-VEGF therapy (yes vs. no), region (U.S. and Canada, Asia, and the rest of the world) and parent study treatment arm (faricimab 6mg Q8W, faricimab 6mg PTI and aflibercept 2 mg Q8W) using the Cochran Mantel-Haenszel (CMH) weights (Cochran 1954; Mantel and Haenszel 1959). Confidence intervals of the proportion of patients in each treatment group will be calculated using the normal approximation to the weighted proportions (Mehrotra and Railkar 2000). 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.

The following binary exploratory endpoints will be summarized descriptively.

- Proportion of patients with absence of intraretinal fluid at Year 1 and Year 2.
- Proportion of patients with absence of both intraretinal fluid and subretinal fluid at Year 1 and Year 2
- Proportion of patients with absence of DME at Year 1, 18 months and Year 2
  - Absence of DME is defined as achieving a CST of <325 microns
- Proportion of patients on a Q4W, Q8W, Q12W, or Q16W treatment at Year 1 and Year 2:
  - 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
  - For durability analyses, Year 2 analysis window is defined as Week 92 to Week 104 to include patients on Q16W treated at Week 92.
  - The last observed PTI in the visit window for Year 1 and Year 2 will be used as the patient's PTI at that time point 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.
- Proportion of patients with:
  - $\geq$2-step DRS improvement from baseline on the ETDRS DRSS at Week 16, Year 1 and Year 2
  - $\geq$3-step DRS improvement from baseline on the ETDRS DRSS at Week 16, Year 1 and Year 2
- Proportion of patients with:
  - $\geq$2-step DRS worsening from baseline on the ETDRS DRSS at Week 16, Year 1 and Year 2
  - $\geq$3-step DRS worsening from baseline on the ETDRS DRSS at Week 16, Year 1 and Year 2
- Proportion of patients who develop new PDR at Week 16, Year 1 and Year 2

4.5 OTHER SAFETY ANALYSES

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

Patients will be grouped according to the actual treatment received in the parent study up to Week 96.

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. All data starting from the date of first faricimab injection in the LTE will be included in the analyses. Baseline will be the date of first administration of faricimab in the LTE study.

Duration of treatment is the time from the first faricimab administration in the LTE study to the earlier of

- the date of treatment discontinuation or
- date of study treatment completion during the entire study.

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 patients enrolled in the LTE study.

Changes between pre-dose and post-dose IOP measurements will also be summarized over time, overall and by parent study treatment group. The presence of IOI and vitreous hemorrhage, as determined on slit lamp examination and/or indirect ophthalmoscopy, 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 indirect ophthalmoscopy will be tabulated.

4.5.3.2 Laboratory Data

There is no laboratory data collection scheduled at study visits other than PK and ADA samples. No general summary is planned.

4.5.3.3 Vital Signs

Vital signs will be collected as part of the parent Phase III Week 100 visit and will not be obtained again for LTE Day 1 if the LTE Day 1 visit is completed on the same day or within 2 business days of the parent Week 100 visit.

Vital signs will include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure. No general summary is 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 patients who enroll (including from which parent study) will be summarized by country and site. Patient disposition (the number of patients enrolled, treated, and completing the study) will be summarized overall and by parent study treatment group. Premature study drug discontinuation and study discontinuation, as well as reasons for discontinuations, will be 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. Patient 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 the LTE study baseline.

For the summaries of demographics and baseline characteristics, for patients randomized to aflibercept in the parent study, LTE baseline is defined as the last value collected before the first faricimab injection in the study.

For patients randomized to faricimab Q8W or faricimab PTI in the parent study, LTE baseline is defined as the value collected at parent study Week 100/study Day 1 prior to

any study assessments. If study Day 1 is >2 business days but ≤ 28 days from parent study Week 100, BCVA and ocular assessments (slit lamp examination, pre-dose IOP and indirect ophthalmoscopy) must be repeated at Day 1 and the Day 1 value is considered the baseline value.

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

PK analyses will be based on the pharmacokinetic-evaluable population.

For PK analyses, plasma concentration data from the date of first faricimab administration in the LTE study will be used for analysis.

The analyses will be summarized overall and by parent study treatment group using descriptive statistics.

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. 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. Details of the population PK analyses will be described in a Modeling and Simulation Analysis Plan.

4.6.4 Immunogenicity Analyses

Immunogenicity analyses will be based on the immunogenicity – evaluable population.

Immunogenicity data will be reported by the treatment arm of the parent study and for All patients.

The following properties of each sample will be listed by patient: ADA status (from the confirmatory assay): ADA positive (yes) or ADA negative (no) and titer value for the ADA positive sample.

ADA summaries will be based on data from Day 1 of parent studies to the FEOS visit of the LTE study. Baseline will be defined as the last available assessment obtained prior to the first administration of faricimab in the parent study for patients randomized to faricimab Q8W or faricimab PTI in the parent study, and as the last assessment before the first administration of faricimab treatment in the LTE for patients randomized to aflibercept in the parent study.

The following results will be summarized overall and by parent study treatment group, for patients enrolled in the LTE study:

- The number and proportion of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence).
- The number and proportion of ADA-positive patients and ADA-negative patients after LTE enrollment (post-baseline incidence).
- Treatment-boosted ADA-positive: number and percent of patients with at least one treatment-boosted ADA-positive sample. The numerator is the number of patients with an ADA-positive sample at baseline and with post-baseline samples with a titer that is equal or greater than 4-fold baseline titer. The denominator is the total number of patients in the immunogenicity incidence set.
- Treatment-induced ADA-positive: number and percent of patients with at least one treatment-induced ADA-positive sample. The numerator is the number of patients with an ADA-negative or missing sample at baseline and any post-baseline positive sample. The denominator is the total number of patients in the immunogenicity incidence set. Among the treatment –induced ADA positive, the number of patients with transient (ADA positive result detected (a) at only one post-baseline sampling time point [excluding last time point] OR (b) at 2 or more timepoints 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) and persistent (ADA positive result detected (a) at the last post-baseline sampling time point, OR (b) at 2 or more time points during treatment where the first and last ADA positive samples are separated by a period of $\geq$16 weeks, irrespective of any negative samples in between) will be listed.
- Treatment-unaffected ADA-positive patient: number and percent of patients with an ADA-positive baseline sample (level of pre-existing ADAs) that does not change following drug administration. The numerator is the number of patients with ADA positive sample and with all post-baseline titers lower than 4-fold the ADA-positive baseline titer. The denominator is the total number of patients in the immunogenicity incidence set.
- ADA-negative: number and percent of patients without positive ADA during the study period or if they are ADA positive at baseline but without positive ADA post baseline (numerator). The denominator is the total number of patients in the immunogenicity incidence set.
- ADA incidence (i.e., ADA-positive in %): number and percent of patients with at least one treatment-induced or treatment-boosted ADA-positive sample. The numerator is the number of patients positive for boosted or induced ADA. The denominator is the total number of patients in the immunogenicity incidence set.

The following summaries, both overall and by time point (including baseline) will be provided using the Immunogenicity prevalence set, according to treatment received. For

summaries by time point, the numerator is the number of patients at that time point with determinant samples.

ADA prevalence: number and percent of patients with at least one ADA-positive sample at any time point (including baseline). The numerator is the number of ADA positive patients at selected time points and overall timepoints. The denominator is the total number of evaluable patients in the study at corresponding timepoints.

The safety, efficacy and PK, will be summarized by ADA status group.

4.6.5 Biomarkers Analyses

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

Analyses may be performed to identify biomarkers that are predictive of response to faricimab, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of faricimab activity, or can increase the knowledge and understanding of disease biology.

All data from LTE baseline will be included in the analysis. Details of the biomarker analyses will be described in a separate analysis plan.

The results from these analyses will be reported in a document separate from the Clinical Study Report (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
- Discontinuations from treatment and/or study due to COVID-19

4.6.8 Safety Analyses for COVID-19

Following the MedDRA 25.1 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 2).

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 and listing 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 $\leq$7 days before and $\leq$30 days after any reported AE suggesting a confirmed COVID-19 infection (PTs listed in Table 2). AEs suspected of being caused by COVID-19 as per electronic Case Report Form (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 caused 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 $\leq$7 days before and $\leq$30 days after start date of all the confirmed COVID-19 events in Table 2.
- Summary table and listing of AEs suspected of being caused by COVID-19 as per eCRF

In addition, the following outputs will be produced:

- Listing of Adverse Events associated with COVID-19 Leading to Study Treatment Discontinuation
- Listing of Adverse Events associated with COVID-19 Leading to Study Discontinuation
- Listing of Adverse Events associated with COVID-19 Resulting in Death

Table 2 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

Interim analyses may be conducted. Details of the analyses will be described in Module 2 of the Data Analysis Plan.

5. SUPPORTING DOCUMENTATION

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

6. REFERENCES

Not Applicable.

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Approval Task	[redacted] Company Signatory 26-Jan-2024 15:47:08 GMT+0000