Title Page

Protocol Title: A PHASE 3, MULTICENTER, OPEN-LABEL, 12-WEEK STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN CHINESE PARTICIPANTS WITH CHRONIC MIGRAINE

Protocol Number:	**3101-311-002**
Compound Number:	**AGN-241689**
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SAP Version History

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
1	18 Mar 2020	Not Applicable	Original version
2	31 Mar 2022	See table below	Updates to protocol and expected number of subjects in study

Summary of Changes from the Final SAP (dated 18-Mar-2020):

	Section: Description	Reason
1.	Added Health Outcome endpoints from the Protocol.	There will be no separate HO SAP.
2.	From the title of the Final SAP removed "or Episodic"	Per the updated title of the Protocol Amendment 1.
3.	Removed 3101-305-002 study throughout the SAP, and subgroup analysis by lead-in study, and updated the Sample size (with 120 participants).	Per the Protocol Amendment 1.
4.	Section 1.1.: Removed "Primary" from 'Objectives'	Per the protocol synopsis.
5.	Section 6.3.4: Clarified the collection of medical history.	
6.	Added COVID-19 related data summary	(The study CRF is planned to be updated with COVID-19 later, ~by January)
7.	Updated sample size (to approximately 3).	Decreased due to stopping enrollment of Chinese patients in the lead-in 3101-303-002 study.
8.	Remove the summary tables and present in listings.	Due to small number of subjects expected in the study

1. Introduction

This Statistical Analysis Plan (SAP) amendment 1 provides a technical and detailed elaboration of the statistical analyses of the safety and/or efficacy data as outlined and specified in the protocol amendment 1 of 3101-311-002 dated 06-Jul-2020. The major changes to the SAP are to eliminate or modify specified efficacy, safety and demographic endpoints, remove lead-in study 3101-305-002, and adding the COVID-19 data summaries. Specifications of tables, figures and data listings are contained in a separate document.

1.1. Objectives and Endpoints

Each study objective is presented with corresponding endpoint below:

Objectives	Endpoints
• To evaluate the safety and tolerability of treatment with atogepant 60 mg once daily (QD) over a 12-week duration for the prevention of migraine in Chinese participants who completed Study 3101-303-002 (Chronic migraine (CM)).	**Safety Assessments** Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS).
• To evaluate the efficacy of treatment with atogepant 60 mg QD when administered over 12 weeks for the prevention of migraine in Chinese participants with CM.	**Endpoints** • Change from baseline in monthly migraine days at each monthly period (i.e. each consecutive 4-week period).

1.2. Study Design

This is a multicenter, open-label, 12-week, safety extension study conducted in China. Participants will be treated with atogepant 60 mg once daily, to be taken on an outpatient basis at approximately 2 centers.

The study will consist of a 12-week treatment period and a 4-week safety follow up period. All participants who complete Study 3101-303-002, and meet all eligibility requirements may participate in this study.

After signing the informed consent, Chinese participants will directly rollover from Study 3101303-002 (Phase 3 CM); hereafter referred to as the lead-in study. As such, participants will have Visit 7 from the lead-in study function as Visit 1 for this extension study (3101-311-002). After Visit 1, study visits will occur every 4 weeks during the 12-week open-label treatment period. A safety follow-up visit will occur 4 weeks after the last dose of atogepant 60 mg in the open-label treatment period.

Note, there may be participants who complete Visit 7 in the lead-in study before this extension study (3101-311-002) has been initiated. Those participants should complete Visit 7/ET and Visit 8/end of study (EOS) Visit (including discontinuation of study intervention) per the lead-in study Schedule of Visits and Procedures.

Depending on the timing of the initiation of this extension study (3101-311-002), in relation to each participant's planned Visit 8 schedule in the lead-in study, Visit 1 for this extension study can be conducted on the same day as Visit 8/EOS Visit for the lead-in study, or soon thereafter.

- If this extension study is initiated prior to the participant's planned Visit 8 in the lead-in study, then Visit 8/EOS Visit in the lead-in study should be conducted on the same day as Visit 1 for this extension study (3101-311-002).

- If this extension study is not initiated prior to the participant's planned Visit 8 in the lead-in study (ie, there is a gap between Visit 8 of the lead-in study and Visit 1 of this extension study), then Visit 8/EOS should be conducted as planned per the lead-in study Schedule of Visits and Procedures. When this extension study is initiated, the participant should return to the clinic as soon as possible, and Visit 1 for this extension study should be conducted per Table 1-1 Schedule of Visits and Procedures.

Participants will return to the clinic for safety assessments at 4, 8, and 12 weeks relative to Visit 1. A safety follow-up visit will occur 4 weeks after the last dose of atogepant 60 mg once daily. For details, please see Table 1-1 Schedule of Visits and Procedures.

The primary objective of the study is to assess the safety and tolerability of treatment with atogepant 60 mg once daily over a 12-week duration for the prevention of migraine in Chinese participants who completed Study 3101-303-002 (CM). The planned safety assessments include collection of AEs, clinical laboratory determinations, ECGs, vital sign measurements, physical examinations, and the C-SSRS.

Table 1-1 Schedule of Visits and Procedures

Study Period	Open-label Treatment Period (12 weeks)				Safety Follow-up Period (4 weeks)
Visit #	Visit 1[a]	Visit 2	Visit 3	Visit 4	Visit 5/EOS
Week (Day)	*Day 1*	*Week 4 (Day 28)*	*Week 8 (Day 56)*	*Week 12 (Day 84)*	*Week 16 (Day 112)*
Visit Windows	N/A	± 3 days	± 3 days	± 3 days	± 3 days
Obtain Informed Consent and participant privacy	X				
Access IWRS	X	X	X	X	X
Assess inclusion/exclusion criteria	X				
Collect medical history[b]	X				
Perform physical examination	X			X	X
Collect vital sign measurements[c]	X	X	X	X	X
Perform ECG	X		X	X	
Perform urine pregnancy test[d]	X	X	X	X	X
Clinical laboratory determinations[e]	X	X	X	X	X
eDiary instructions and training[f]	X				
Participant eDiary data collection[f,g]	X				
eDiary data (headache duration, frequency, characteristics and symptoms, acute medication use, AIM-D, activity level and activity limitation) and compliance review[h]		X	X	X	
MSQ v2.1 (eTablet)[i,j]	X	X	X	X	X
C-SSRS (eTablet)[k]	X	X	X	X	X
Collect eDiary				X	
Dispense atogepant	X	X	X		
Review atogepant compliance and accountability		X	X	X	
Adverse events	X				
Concomitant medications/concurrent procedures	X				

CM = chronic migraine; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; eTablet = electronic tablet; INR = international normalized ratio; IWRS = interactive web response system; WOCBP = women of childbearing potential.

a After providing informed consent for this study, Visit 1 will be conducted on the same day as Visit 7/Visit 8 of the lead-in study (Study 3101-303-002 [Phase 3 CM]); procedures conducted as part of Visit 7 of the lead-in study should not be repeated. Visit 1 must be conducted in office. All other visits, should be conducted in office unless it is necessary to conduct a remote visits for the safety of participants (eg, COVID-19 or other pandemic): for details please refer to the Remote Visit Schedule of Assessments in the protocol).

b Medical history will be collected for participants who have a gap between the last visit of the lead-in study and Visit 1 of this extension study and only new medical history during the gap need to be collected.

c Vital sign measurements: weight, sitting and standing pulse rate, respiratory rate, sitting and standing blood pressure, and body temperature.

d For WOCBP only, a urine pregnancy test will be performed at all visits.

e Clinical laboratory determinations include chemistry, hematology, coagulation parameters (INR), and urinalysis to be collected for all visits. Samples for serology and the urine drug screen will be collected only at Visit 1.

f Participants should begin using the eDiary at Visit 1 and for the duration of the treatment period.

g Daily eDiary data collection includes: headache frequency, duration, characteristics, symptoms, acute medication use, AIM-D, Activity Level, and Activity Limitation.

h Participants must bring their eDiary to all visits (except Visit 5).

i Participant will complete on eTablet.

j PRO measures should be administered prior to any tests and/or evaluations unless indicated otherwise in the protocol.

k At all visits, the "Since Last Visit" C-SSRS will be completed for all participants. Clinicians will complete on eTablet.

2. Statistical Hypotheses

Since the primary objective of this study is to assess the safety and tolerability of 12 weeks of atogepant treatment, there is no statistical hypothesis specified for the study.

3. Sample Size Determination

Chinese participants who complete Study 3101-303-002, and meet all eligibility requirements, may participate in this extension study. Approximately 3 Chinese participants are expected to participate in this extension study. The sample size is different from the sample size planned in the protocol.

4. Populations for Analysis

The analysis populations will consist of participants as defined below.

- The Safety population will consist of all participants who receive at least one dose of the study intervention (atogepant) in this extension study.
- The mITT population will consist of all participants who received at least 1 dose of study intervention (atogepant) in this extension study and had at least 1 evaluable post-baseline 4-week period of eDiary data in this extension study.
- The listing of serious adverse events and participants who died will be provided for the Screened population. The Screened population will consist of all rollover participants from lead-in 3101-303-002, who signed informed consent for the study.

5. Statistical Analyses

5.1. General Considerations

- Efficacy endpoints will be listed using the mITT population.
- Safety endpoints will be listed using the Safety population.
- Partial dates will be treated as missing in computation or in variable derivation unless specified otherwise, but will be listed in the data listings as they appear on the eCRF.
- The baseline value as defined for the lead-in study will be used as the baseline in this extension study. For monthly endpoints, baseline is defined as assessments during the last 28 days of baseline period in the lead-in study. For efficacy and safety endpoints that are assessed at clinical visits, baseline is defined as the last non-missing efficacy or safety assessment, respectively, before the first dose of study intervention in the lead-in study.
- Study intervention is treatment administered (atogepant 60 mg QD).
- In general, statistical analyses will be performed using SAS version 9.4 or higher
- MedDRA version 24.0 or higher will be used to code adverse events, and medical history
- WHODrug Global B3 (v.202103 or higher) will be used to code medications.

5.2. Participant Disposition

The disposition will be listed for participants.

5.3. Efficacy Endpoint Analysis and Health Outcome Measures

5.3.1. Definition of Endpoint

Since the primary objective of this open-label extension study is to assess the safety and tolerability of 12 weeks of atogepant treatment, efficacy endpoints are not classified as primary, secondary, or additional.

- The following endpoint will be listed:Change from baseline in monthly migraine days at each monthly period (ie, each consecutive 4-week period)

Other efficacy measures collected, including health outcome endpoints, will be presented in listings.

On a daily basis during the open-label treatment period, participants are to record into an eDiary information on the daily total duration of headache, headache specific characteristics and symptoms, the worst pain severity, and use of any acute headache pain medication. Participants will be able to report headache data, including absence of headache, for the day of the eDiary report and for the day immediately prior to the day of the eDiary report, as long as information reported is for a time subsequent to the participant's most recent report. This is defined as a one-day "missing-recall" window.

Following Visit 1, there are 3 visits at 4-week intervals encompassing a 12-week open-label treatment period of the study and a 4-week safety follow-up period. In practice, there may or may not be exact 4-week durations between two consecutive visits and the visits might not align with each 28-day period recorded in the eDiary (ie, Weeks 1 to 4, 5 to 8 and 9 to 12,

corresponding to Days 1 to 28, 29 to 56, and 57 to 84). Therefore, for monthly data analysis purposes, the number of migraine days will be calculated for consecutive 28-day periods beginning with Day 1, the first dose date of the open-label study intervention.

For more details refer to the Protocol Amendment 1 Sections 6.2 and 6.3.

5.3.2. Main Analytical Approach

Migraine days will be listed based on the mITT population.

5.3.3. Key Efficacy Measures

A migraine day is defined as any calendar day on which a headache occurs which meets criteria A, B, and C OR meets criteria D and E, as listed below, as per participant eDiary. Calendar days begin at midnight and last until 11:59 PM (23:59).

A. Headache has at least two of the following four characteristics:
   i. Unilateral location
   ii. Pulsating quality
   iii. Moderate or severe pain intensity
   iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
B. At least one of the following:
   i. Nausea and/or vomiting
   ii. Photophobia and phonophobia
   iii. Typical aura (ie, visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins
C. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (ie, triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified.

OR

D. Any headache which fulfills one criterion from (1) and at least one criterion from (2) OR fulfills at least two criteria from (1) and no criteria from (2).
   1) Headache characteristics:
      i. Unilateral location
      ii. Pulsating quality
      iii. Moderate or severe pain intensity
      iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
   2) Symptoms:
      i. Nausea and/or vomiting
      ii. Photophobia and phonophobia
      iii. Typical aura (ie, visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins

B. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (ie, triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified.

A headache day is defined as any calendar day on which headache pain lasting 2 hours or longer occurs unless an acute headache medication (eg, ibuprofen, triptan) was used after the start of the headache, in which case no minimum duration will be specified. Note that antiemetics will not be counted as an acute headache medication for headache day identification. Calendar days begin at midnight and last until 11:59 PM (23:59).

An acute medication use day is defined as any day on which a participant reports, per eDiary, the intake of allowed medication(s) to treat an acute migraine. The allowed medications include the following categories of drugs: triptans, ergots, opioids, analgesics (including acetaminophen), NSAIDs (including aspirin), and antiemetics.

A triptan use day is defined as any day on which a participant reports intake of a triptan to treat a migraine per eDiary.

Headache day pain intensity is defined as the worst pain intensity on any headache day where headache pain intensity will be subjectively rated by the patient on a scale from mild to severe:

- Mild pain (=1)
- Moderate pain (=2)
- Severe pain (=3)

If participants experience no headache in a day, then the corresponding pain intensity of that day will be set as missing.

5.3.4. Health Outcome Measures

The AIM-D, Activity Level, and Activity Limitation will also be collected daily via an eDiary.

The MSQ v2.1 will be administered in an eTablet at specified visits.

AIM-D and MSQ v2.1 will be listed on mITT population.

5.3.4.1. AIM-D

The AIM-D is an 11-item daily diary measure that assesses the impact of migraine and is comprised of two domains that evaluate performance of daily activities (7 items) and physical impairment (4 items). Participants are asked to rate the level of difficulty experienced in the past 24 hours with performance of daily activities (ie, difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly) and physical impairment (ie, difficulty walking, moving body, bending forward, and moving head) using a 6-point rating scale ranging from "Not difficult at all," "A little difficult," "Somewhat difficult," "Very difficult," "Extremely difficult," and "I could not do it at all." Three items include a response of "I did not…," for example, "I did not have errands planned." The AIM-D was developed as an electronic daily diary with the same set of questions administered in headache and non-headache versions. The Headache version is administered on days when a participant reports a headache and the Non-Headache version is administered on days when a participant does not report having a headache. The AIM-D instructs

participants to answer each question based on the level of difficulty experienced in the past 24 hours for both versions, with "during your headache" indicated for the AIM-D Headache. In addition to the two domain scores, a total score using all 11 items can also be calculated. Each raw daily domain score, as well as the raw daily total score, are transformed to a 0-100 scale, with higher scores indicating greater impact of migraine (i.e., higher disease burden).

Two items based on a 24-hour recall will be administered daily using Headache and Non headache versions as additional health outcome measures and for evaluation of the AIM-D. The first item will be used to assess activity level within the past 24 hours with a 5 level response scale ranging from "No activity – Spent all day lying down" to "Exercised – Brisk walk, running, jogging, biking or other activity for 30 or more minutes." The second item will be used to evaluate activity limitation with a 5-level response scale ranging from "Not at all limited – I could do everything" to "Extremely limited".

Overall satisfaction with the study medication for prevention of migraine will be assessed using a single item and a 7-point rating scale ranging from extremely satisfied (0) to extremely dissatisfied (6).

5.3.4.2. MSQ

The MSQ v2.1 is a 14-item questionnaire designed to measure health-related quality-of-life impairments attributed to migraine in the past 4 weeks. It is divided into three domains: Role Function-Restrictive assesses how migraines limit one's daily social and work-related activities; Role Function-Preventive assesses how migraines prevent these activities; and the Emotional Function domain assesses the emotions associated with migraines. Participants respond to items using a 6-point scale ranging from "none of the time" to "all of the time." Raw dimension scores are computed as a sum of item responses and rescaled to a 0 to 100 scale, where higher scores indicate better quality of life.

The detailed algorithms for derivation of the above health outcome measures are presented in Section 6.4.3

5.4. Other Safety Analyses

5.4.1. Extent of Exposure

Treatment daily dose will be listed on Safety Population.

5.4.2. Treatment Compliance

Dosing compliance for a specified period is defined as the total number of open-label study interventions actually taken by a participant during that period divided by the number of open-label study interventions that were expected to be taken during the same period multiplied by 100. The total number of tablets actually taken during a specific period will be calculated from the study intervention record. Treatment compliance and duration will be listed for the Safety population.

5.4.3. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher.

An AE will be considered as a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of double-blind study treatment in the lead-in study. An AE that occurs more than 30 days after the last dose of open-label study treatment or the safety follow-up visit (Visit 5) in this extension study whichever comes later will not be counted as a TEAE. Per case report form instructions, a new AE record will be created for any AE that worsens; therefore, TEAEs can be identified as those AEs captured in Study 3101-311-002 with recorded onset date on or after the date of the first dose of lead-in double-blind study treatment and within 30 days after the last dose of open-label study treatment or Visit 5 whichever comes later.

An AE will be considered as a treatment-emergent SAE (TESAE) if it is a TEAE that also meets SAE criteria.

TEAEs that started after the date of last dose of open-label study treatment will be considered as newly emergent TEAEs (NEAE).

Only TEAEs that started on or after the date of first dose of open-label study treatment will be summarized.

AEs will be listed on the Safety Population.

5.4.4. Additional Safety Assessments

5.4.4.1. Clinical Laboratory Parameters

Laboratory parameters in standard units at each assessment time point will be listed by study intervention group for the following laboratory parameters:

Category	Parameter
Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol, the estimated glomerular filtration rate
Hematology	Hemoglobin, hematocrit, red blood cell count, red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), white blood cell count, including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count
Urinalysis	Specific gravity, pH

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Section 6.3.7.2. PCS laboratory values will be listed.

Participants with an adjudicated case (i.e. ALT ≥ 3 x ULN or AST ≥ 3 x ULN) will be listed with their ALT and AST assessments, adjudication dates, relationship of ALT or AST elevation to study intervention, and confounding factor(s). Additional listings will be provided for participants who meet ALT ≥ 3 x ULN or AST ≥ 3 x ULN and/or potential Hy's law and have one of the following categories: at least 1 abnormal liver biochemistry risk factor, at least 1 liver disease sign and symptom, at least 1 liver diagnostic test performed, consultation with a specialist for liver evaluation, liver lab tests performed, and drug screen performed, respectively.

Potential Hy's Law criteria within a 24-hour window is defined by a post baseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 x ULN, along with total bilirubin (TBL) ≥ 2 x ULN and a non-elevated alkaline phosphatase (ALP) < 2 x ULN, all based on blood draws collected within a 24-hour period.

5.4.4.2. Vital Signs

Listings for vital signs (systolic and diastolic blood pressures [sitting and standing], pulse rate [sitting and standing], respiratory rate, temperature, weight, orthostatic systolic blood pressure, orthostatic diastolic blood pressure, and orthostatic pulse rate) at each assessment timepoint will be listed. Orthostatic vital sign values (orthostatic systolic and diastolic blood pressures, and orthostatic pulse rate) are defined as the corresponding standing measurement minus sitting measurement of systolic and diastolic blood pressures and pulse rate respectively.

Vital sign values will be considered PCS if they meet both the observed value criterion and the change from baseline value criterion, if both criteria are available, or meet either the observed value criterion or the change from baseline value criterion that will be detailed in Section 6.3.7.4. Participants who have PCS postbaseline vital sign values will be listed.

5.4.4.3. Electrocardiogram

Listings for ECG parameters (ie, heart rate, PR interval, QRS interval, RR interval, QT interval, and QTc interval) at each assessment timepoint will be presented. The QTc will be calculated using both the Fridericia correction and the Bazett correction.

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in Table 6-5. Participants with PCS postbaseline values will be listed.

5.4.4.4. Columbia-Suicide Severity Rating Scale

For C-SSRS, participants with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be listed for the Safety population.

5.5. Interim Analyses

No interim analysis is planned.

6. Supporting Documentation

6.1. Appendix 1 List of Abbreviations

Term/ Abbreviation	Definition
AE	adverse event
AIM-D	Activity Impairment in Migraine – Diary
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CM	chronic migraine
CNS	central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
ET	early termination
eTablet	electronic tablet
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MSQ v2.1	Migraine Specific Quality of Life Questionnaire, version 2.1
NEAE	newly emergent TEAE (NEAE)
PT	preferred term
QD	once daily
QTcF	QT interval corrected for heart rate using the Fridericia formula
QTcB	QT interval corrected for heart rate using the Bazett formula
SAE	serious adverse event
SBP	systolic blood pressure
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

6.2. Appendix 2: Changes to Protocol-Planned Analyses

The following changes to the Protocol amendment 1 were made in this SAP:

1. Section 7.2.2 of the protocol amendment 1 stated that "The related health outcome analyses will be documented in the health economics and outcomes research statistical analysis plan." Instead, these health outcome analyses are added to this SAP document.
2. Removed following efficacy variables:
   - Change from baseline in monthly headache days at each monthly period.
   - Change from baseline in monthly acute medication use days at each monthly period.
   - ≥ 25%, ≥ 50%, ≥ 75%, and 100% improvement (decrease) in monthly migraine days at each monthly period.
   - Change from baseline in monthly cumulative headache hours at each monthly period
   - Change from baseline in monthly triptan use days at each monthly period
   - Change from baseline in monthly moderate/severe headache days at each monthly period
   - Change from baseline in monthly severe headache days at each monthly period.
   - Other Health Outcome endpoints (see Section 5.3.1)
3. Efficacy variables will be listed, and will not be summarized.
4. Removed following demographic table summaries. Where noted in the body of the SAP, data will be presented in listings:
   - Analysis populations
   - Summary of enrollment category
   - Concomitant medication during the follow-up period
5. Removed following safety summaries. Where noted in the body of the SAP, data will be presented in listings:
   - TEAEs by SOC, PT and severity
   - NEAEs
   - Common (≥2%) TEAEs by PT
   - Summary of baseline, post-baseline, and change from baseline in laboratory parameters
   - Summary of baseline, post-baseline, and change from baseline in vital signs
   - Summary of baseline, post-baseline, and change from baseline in ECG

6.3. Appendix 3: Supporting Study Information

6.3.1. Demographic

Demographic parameters will be listed for the Safety populations.

6.3.2. Baseline and Disease Characteristics

Baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2 will be listed for the Safety.

6.3.3. Protocol Deviations

Protocol deviations will be defined in Protocol Deviation Requirement Specification, including importance classification. Participants with important protocol deviations will be listed for Safety population.

6.3.4. Medical History

Medical history in this study will be collected for participants who have a gap between the last visit of the lead-in study and Visit 1 of this extension study and only new medical history collected during the gap will be listed.

Abnormalities in participants' medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities, version 23.0 or newer. Participants with abnormalities in medical and surgical histories from the lead-in study in each system organ class (SOC) and preferred term (PT) will be listed for the Safety population.

Migraine history, including diagnosis, duration of disorder, use of migraine prevention medication in the past, average number of migraine or headache days per month in the last 3 months, acute medications taken to treat migraine headaches, and advice on lifestyle alternations from the lead-in study will be listed for the Safety population.

6.3.5. Prior/Concomitant medications

Prior medication is defined as any medication taken before the date of the first dose of lead-in study treatment.

Concomitant medication for this study is defined as any medication taken on or after the date of the first dose of open-label study treatment.

Participants will be listed by Anatomical Therapeutic Chemical (ATC) 4 class and preferred term (PT) for both prior medications and concomitant medications in the Safety population. Concomitant medications will be listed fort he Safety Population.

If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class. Any prior and concomitant medications will be included in listings.

The medication data will be coded using the World Health Organization (WHO) Drug Global B3 version March 2019 or higher.

6.3.6. Adverse Events of Special Interest

Per the 3101-311-002 Protocol Section 6.1.2, selected non-serious and serious adverse events are of special interest and will require immediate reporting, recording, and follow-up. The following events will be closely monitored:

- Treatment-emergent suicidal ideations with intent, with or without a plan, (ie, Type 4 or 5 on the C-SSRS) or any suicidal behaviors.
- Treatment-emergent elevated ALT or AST lab value $\geq 3 \times$ ULN.
- Potential Hy's law cases: elevated ALT or AST lab value that is $\geq 3 \times$ ULN and an elevated total bilirubin lab value that is $\geq 2 \times$ ULN and, at the same time, an alkaline phosphatase lab value that is $< 2 \times$ ULN.

The display of above are described in the corresponding SAP Sections 5.4.4.1 and 5.4.4.4.

6.3.7. Potentially Clinically Significant Criteria for Safety Endpoints

Laboratory values in conventional unit, the potentially clinically significant criteria for clinical laboratory parameters, Hepatic laboratory abnormalities, vital signs and ECG parameters are provided in the following sections.

6.3.7.1. Laboratory values in Conventional Unit

6.3.7.1.1. Background

All laboratory parameters are reported in the International System (SI) units as standard practice. In addition, selected laboratory parameters (listed in Table 6-1) will be reported in conventional units to facilitate interpretation and reporting for the CSR and future labeling.

6.3.7.1.2. List of Parameters Reported in Conventional Unit

The list of selected parameters required to be reported in conventional unit is provided in Table 6-1.

Table 6-1 List of Selected Parameters Reported in Conventional Unit

Number	*Laboratory Parameter*	*Conventional Unit*	*Decimal Places*
1	Alanine Aminotransferase (SGPT)	U/L	0
2	Albumin	g/dL	1
3	Alkaline Phosphatase	U/L	0
4	Aspartate Aminotransferase (SGOT)	U/L	0
5	Bilirubin, Direct (Conjugated)	mg/dL	1
6	Bilirubin, Indirect (Unconjugated)	mg/dL	1
7	Bilirubin, Total	mg/dL	1
8	Blood Urea Nitrogen	mg/dL	0
9	Calcium	mg/dL	1
10	Cholesterol, HDL	mg/dL	0
11	Cholesterol, LDL	mg/dL	0
12	Cholesterol, LDL direct and calculated (combined) *(This lab parameter could be the same as #11)*	mg/dL	0
13	Cholesterol, Total	mg/dL	0
14	Creatine Kinase	U/L	0
15	Creatinine	mg/dL	1
16	Glucose	mg/dL	0
17	Insulin	uIU/mL	1
19	Uric Acid	mg/dL	1
20	Hemoglobin	g/dL	1

6.3.7.1.3. Analysis and Reporting Format in Conventional Units

1) For individual clinical study reports for the central nervous system (CNS) projects, the selected laboratory parameters (Table 6-1) will be listed in conventional units
2) Participant narratives generated by the statistical programming team will also include the values in conventional units for the selected lab parameters (Table 6-1). That will be accomplished by presenting the values in conventional units within the parentheses next to the values in SI units. An example is provided in Table 6-2 for lab parameter 'Bilirubin, Total', for which 'umol/L' is the SI unit and 'mg/dL' is the conventional unit.

Table 6-2 Presenting Laboratory Data Using SI and Conventional Units in Narratives

LABORATORY DATA						
Lab Test	Test Name	Normal Range		VISIT01	VISIT05	VISIT07
		Low	High	2012-07-03	2012-08-07	2012-09-04
...						
CHEMISTRY	Bilirubin, Total (umol/L (mg/dL))	0 (0)	18.81 (1.1)	6.84 (0.4)	5.13 (0.3)	5.13 (0.3)
...						

6.3.7.2. Potentially Clinically Significant Criteria for Clinical Laboratory Parameters

Table 6-3 Potentially Clinically Significant Criteria for Clinical Laboratory Parameters

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
Chemistry	Albumin	g/L	< 0.8 × LLN	> 1.2 × ULN
	Alanine aminotransferase	U/L	—	≥ 3.0 × ULN
	Alkaline phosphatase	U/L	—	≥ 3.0 × ULN
	Aspartate aminotransferase	U/L	—	≥ 3.0 × ULN
	Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Bilirubin, total	µmol/L	—	≥ 1.5 × ULN
	Blood urea nitrogen	mmol/L	—	> 1.5 × ULN
	Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Cholesterol, total	mmol/L	—	> 1.6 × ULN
	Creatinine	µmol/L	—	> 1.5 × ULN
	Creatine kinase	U/L	—	> 2.0 × ULN
	Estimated glomerular filtration rate	mL/min/1.73m^2	< 60	—
	Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 2.0 × ULN
	Lactate dehydrogenase (LDH)	U/L	—	> 3.0 × ULN
	Phosphorus	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
	Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Uric acid	µmol/L	—	> 1.2 × ULN
Hematology	Basophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Eosinophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
	Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
	Lymphocytes, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Monocytes, absolute cell count	10^9/L	< 0.5 × LLN	> 2.0 × ULN
	Neutrophils, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Platelet count	10^9/L	< 0.5 × LLN	> 1.5 × ULN
	Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
	White blood cell count	10^9/L	< 0.9 × LLN	> 1.5 × ULN
Urinalysis	pH	pH	< 0.9 × LLN	> 1.1 × ULN
	Glucose	mmol/L	—	At least 1+
	Protein	g/L	—	At least 1+
	Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal value; ULN = upper limit of normal value; normal value provided by laboratory.
SI = Le Système International d'Unités (International System of Units).

6.3.7.3. Criteria for Hepatic Laboratory Abnormalities

Table 6-4 Criteria for Hepatic Laboratory Abnormalities

Laboratory Parameter	Categories
ALT	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
AST	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
ALT or AST	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Bilirubin Total	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Alkaline Phosphatase	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Concurrent Elevations[1]	ALT or AST >= 3 × ULN and Bilirubin Total ≥ 1.5 × ULN
	ALT or AST >= 3 × ULN and Bilirubin Total ≥ 2 × ULN
Potential Hy's Law[1]	ALT or AST ≥ 3 × ULN and Bilirubin Total ≥ 2 × ULN and ALP < 2 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ALP = alkaline phosphatase; ULN = upper limit of normal (value provided by the laboratory).
[1] Elevations are from the same day

6.3.7.4. Potentially Clinically Significant Criteria for Vital Signs

Table 6-5 Potentially Clinically Significant Criteria for Vital Signs

Parameter	Flag	Criteria	
		Observed Value	Change from Baseline
Systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%
Orthostatic SBP change, mm Hg	Low	≤ -20	—
Orthostatic DBP change, mm Hg	Low	≤ -15	—
Orthostatic Pulse rate change, bpm	High	≥ 25	—

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, bpm = beats per minute.

6.3.7.5. Potentially Clinically Significant Criteria for ECG parameters

Table 6-6 Potentially Clinically Significant Criteria for ECG parameters

Parameter	Unit	Criterion
QRS interval	msec	≥ 150
PR interval	msec	≥ 250
QTc (QTcB or QTcF) interval	msec	> 500
QTc (QTcB or QTcF) interval	msec	Increase from baseline > 60

QTc = QT interval corrected for heart rate.
QTcB = QT interval corrected for heart rate using the Bazett formula.
QTcF = QT interval corrected for heart rate using the Fridericia formula.

6.4. Data handling convention

Day 1 is defined as day for the date of the first dose of open-label study intervention. There is no Day 0 or Week 0. Treatment day is relative to the date of the first dose of open-label study intervention.

6.4.1. Analysis Window

The analysis visit windows for monthly efficacy and health outcome (except for MSQ) endpoints based on daily eDiary data are defined as follows:

Table 6-7 Efficacy and Health Outcome Analysis Visit Definitions for eDiary Data (Monthly)

Analysis Phase	Analysis Visit (Derived)	eDiary Window
Lead-in Study	Baseline	Baseline from lead-in study
Open-label Treatment Period	Weeks 1 – 4	Treatment Day [1, 28]
	Weeks 5 – 8	Treatment Day [29, 56]
	Weeks 9 – 12	Treatment Day [57, 84]

The analysis visit windows for MSQ v2.1 are defined as follows:

Table 6-8 Efficacy Analysis Visit Definitions for MSQ v2.1

Analysis Visit (Derived)	Scheduled Visit Day[a]	Window
Baseline	Visit 1 (Enrollment)	Baseline from lead-in study
Week 4	Day 28 (Visit 2)	Treatment Day [1, 42]
Week 8	Day 56 (Visit 3)	Treatment Day [43, 70]
Week 12	Day 84 (Visit 4/ET)	Treatment Day >=71 and within the open-label treatment period
Week 16 (Follow-up)	Day 112 (Visit 5)	Treatment Day [end of the open-label treatment period +1, the last study visit]

ET = early termination.
a Relative to the date of the first dose of open-label study treatment.

The analysis visit windows for safety endpoints are defined as follows:

Table 6-9 Safety Analysis Visit Definitions

Analysis Visit (Derived)	Scheduled Visit Day[a]	Window
Baseline	Baseline from lead-in study	
Week 4	Day 28 (Visit 2)	Treatment Day [1, 42]
Week 8	Day 56 (Visit 3)	Treatment Day [43, 70]
Week 12	Day 84 (Visit 4)	Treatment Day >=71 and within the open-label treatment period
End of the Open-label treatment Period		Last available assessment during the open-label treatment period
Week 16 (Follow-up)	Day 112 (Visit 5)	Treatment Day [end of the open-label treatment period +1, the last study visit]
End of study		Last available assessment after treatment start date, i.e. occurs at final visit (expected Day 112) or ET

[a] Relative to the date of the first dose of open-label study intervention.
End of Treatment is defined as the last available assessment during open-label treatment period, i.e. on or before the treatment end date. End of Treatment results will be presented in summary tables for clinical laboratory values, electrocardiogram and vital signs.
End of Study is defined as the last available assessment during the study, including open-label and safety follow-up period. End of Study results will be presented in summary tables for safety parameters, including but not limited to clinical laboratory values, and vital signs (not for electrocardiograms, as these data were not collected during follow-up period).
ET = early termination. EOS=end of study.

6.4.2. Derived Efficacy Data

6.4.2.1. Derivation of Efficacy Endpoints Based on eDiary Data

For analysis purposes, four weeks (28 days) will be considered as one month. On a daily basis during the 4-week baseline period and throughout the open-label treatment period, participants are to record eDiary information on the duration of headache, headache specific characteristics and symptoms, the pain severity, and use of any acute headache pain medication. Daily headache diary data consists of data from "today's dairy" completed on that day and "yesterday's diary" completed on the following day. Participants are to report headache data in "today's diary" in the evening at any time from 19:00 to 23:59 and to complete "yesterday's diary" on the following day to add the remaining headache data of previous evening until midnight. In case participants miss "today's diary", they can report the whole-day headache data in "yesterday's diary" on the following day. In case participants miss "yesterday's diary", headache data from "today's diary" alone will be used as daily headache diary data. If both "today's diary" and "yesterday's dairy" are missing on one day, the daily headache diary data will be treated as missing.

Daily headache diary data will be merged from "today's diary" and "yesterday's diary" as following and will be used to derive migraine day and headache day.

- Daily headache total duration: summation of headache durations from "today's diary" and "yesterday's diary"
- Daily headache pain severity: the worst pain severity from "today's diary" and "yesterday's diary"
- Daily headache characteristics and symptoms: present if present in one of "today's diary" and "yesterday's diary"
- Daily acute headache medication usage: combination of acute headache medications usage from "today's diary" and "yesterday's diary"

If there are duplicate records of daily diary data for the same participant on the same day with the same type, the set of records with the last form access datetime will be used in the analysis.

The monthly migraine days is defined the total number of recorded migraine days in the eDiary divided by the total number of days with eDiary records during each monthly period and multiplied by 28. The baseline value as defined for the lead-in study will be used as the baseline in this extension study. For each postbaseline 4-week treatment period, a minimum of 14 days' eDiary data during that period is required for the migraine days to be evaluable. If a participant does not have at least 14 days of diary data for a monthly treatment period, the migraine days for that period will be considered as missing. Migraine days will be derived for each participant at baseline and for each postbaseline monthly treatment period (Weeks 1-4, 5-8, 9-12). The same method to derive monthly migraine days will be used to derive monthly headache days, monthly acute medication use days, monthly triptan use days, monthly cumulative headache hours, monthly headache day pain intensity, monthly moderate/severe headache days, and monthly severe headache days.

If a subject reports 'Yes' to the intake of allowed medication(s) to treat an acute migraine but does not list any of them in the diary, then the acute medication use days will not be counted in this situation.

Subsequent to Day 1, the number of headache days will be counted in successive and non-overlapping 4-week (ie, 28-day) windows. Headaches that continue into a subsequent 4-week period will be counted (with recorded severity and duration) as occurring in each period.

If any postbaseline eDiary window for a participant has at least 14 but less than 28 days of reported data, the prorated approach will be used. If a participant reports less than 14 days of headache data, the participant's observed counts in that particular 28-day eDiary window will be set to missing for that window. These prorating rules will be applied to all efficacy analyses of eDiary data unless otherwise stated.

Monthly efficacy endpoints are defined in a prorated fashion. For example, monthly migraine days are defined as the total number of recorded migraine days in the eDiary divided by the total number of days with eDiary records during each monthly period and multiplied by 28.

6.4.3. Derivation of Health Outcome Endpoints

AIM-D Related Endpoints Derivation

As described in Protocol Amendment 1 Section 6.3, the AIM-D was developed as a daily eDiary with a recall period 24 hours. By design, it is collected in the today diary only. The scoring of the following endpoints is completed in 2 steps.

- Monthly Performance of Daily Activities domain score of the AIM-D
- Monthly Physical Impairment domain score of the AIM -D
- Monthly AIM -D total score

Step 1: Calculate AIM-D daily domain score and total score

Daily Performance of Daily Activities score will be calculated based on the summation of items 1-5 and 10 and 11, ranging from 0-35. A daily Performance of Daily Activities domain score will be calculated if 4 or more item scores have non-missing responses. When the response category "I did not have <errands, leisure or social, strenuous activities> planned" (items 2, 4, and 5), is selected, the response will be considered missing. The corresponding Performance of Daily Activities domain score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 7, provided that 4 or more item scores are available; otherwise it will be set to missing. The raw daily score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (35).

Daily Physical Impairment scores will be calculated based on the summation of items 6-9, ranging from 0-20. A daily Physical Impairment score will be calculated if 2 or more item scores have non-missing responses. The corresponding Physical Impairment score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 4, provided that 2 or more item scores are available; otherwise it will be set to missing. The raw daily score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (20).

A daily total score will be calculated based on the summation of items 1-11, ranging from 0-55. A Total Score will be calculated if 6 or more items scores have non-missing responses. When the response category "I did not have <errands, leisure or social, strenuous activities> planned" (items 2, 4, and 5), is selected, the response will be considered missing. The corresponding Total Score will be calculated by summing the non-missing item scores and dividing by the number of

non-missing items and then multiplying by 11, provided that 6 or more item scores are available; otherwise it will be set to missing. The raw score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (55).

Step 2: Calculate Monthly Scores and Baseline Score

Monthly scores will be calculated using the average daily scores only if there are at least 14 non-missing daily scores in the corresponding monthly (28-day) period. The corresponding monthly scores will be calculated by summing the non-missing daily domain scores and dividing by the number of non-missing daily scores, provided that 14 or more daily scores are available; otherwise it will be set to missing.

Monthly activity level score will be calculated by summing the non-missing daily scores and dividing by the number of these scores, provided that 14 or more daily scores are available in the corresponding monthly (28-day) period; otherwise it will be set to missing. Same rule will be applied to the calculation of monthly activity limitation score.

MSQ Related Endpoints Derivation

MSQ v2.1 consists of 14 items with a 4-week recall period. The scoring of the MSQ is completed in following 3 steps.

Step 1: Final item value assignment.

Precoded item values and final item values for each MSQ item response are shown in Table 6-10.

Table 6-10 Item Values for MSQ Item Responses

Response Categories	Precoded Item Value	Final Item Value
None of the time	1	6
A little bit of the time	2	5
Some of the time	3	4
A good bit of the time	4	3
Most of the time	5	2
All of the time	6	1

Step 2: Computation of raw domain(dimension) scores

Once a final item value has been assigned to each item, a raw score can be computed for each MSQ domain. Role Function-Restrictive domain includes Items 1 - 7, Role Function-Preventive domain includes Items 8 - 11, and Emotional Function domain includes Items 12 - 14. The raw score for each domain is the algebraic sum of the final item values for all items in that domain.

Missing data handling: if a respondent answered at least half of the items in a domain (or half plus one in the case of scales with an odd number of items), a missing item value can be estimated using the average of the other completed items within the same dimension.

In detail, for MSQ v2.1 Role Function-Restrictive domain, the 7 individual item responses using final item value will be summed, resulting in the raw domain score ranging from 7 to 42 with higher scores indicating better quality of life. If there are missing item responses, the raw domain score will be calculated by summing the non-missing item responses using final item value and

dividing by the number of non-missing items and then multiplying by 7 provided that 4 or more items in the domain are completed; otherwise it will be set to missing. For MSQ v2.1 Role Function-Preventive and Emotional Function domains, the raw domain scores will be calculated similarly using final item value respectively. If there are missing item responses, the corresponding raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by the number of questions in that domain provided that 2 or more domain items are completed; otherwise it will be set to missing.

Step 3: Linear transformation to a 0 to 100 scale.

The transformation formula for each MSQ v2.1 domain are listed below

- Role Function-Restrictive: $\frac{(raw\ score-7)*100}{35}$
- Role Function-Preventive: $\frac{(raw\ score-4)*100}{20}$
- Emotional Function: $\frac{(raw\ score-3)*100}{15}$

6.4.4. Repeated or Unscheduled Assessments of Safety Parameters

Baseline is defined as the last assessment made before the first dose of double-blind study treatment in the lead-in study. If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

6.4.5. Missing Date of the Last Dose of Study Intervention

When the date of the last dose of the open-label study intervention is missing, all efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts have been made, the last available study intervention date will be used in the calculation of treatment duration.

6.4.6. Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of open-label study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of open-label study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

6.4.7. Missing Causal Relationship to Study treatment for Adverse Events

If the causal relationship to the open-label study treatment is missing for an AE that started on or after the date of the first dose of open-label study treatment, a causality of yes will be assigned. The imputed values for causal relationship to open-label treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

6.4.8. Missing Date Imputation

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

Missing month and day

If the year of the incomplete start date is the same as the year of the first dose of open-label study treatment, the month and day of the first dose of open-label study treatment will be assigned to the missing fields

If the year of the incomplete start date is before the year of the first dose of open-label study treatment, December 31 will be assigned to the missing fields

If the year of the incomplete start date is after the year of the first dose of open-label study treatment, January 1 will be assigned to the missing fields

Missing month only

If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

If the month and year of the incomplete start date are the same as the month and year of the first dose of open-label study treatment, the day of the first dose of open-label study treatment will be assigned to the missing day

If either the year of the incomplete start date is before the year of the date of the first dose of open-label study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of open-label study treatment, the last day of the month will be assigned to the missing day

If either the year of the incomplete start date is after the year of the date of the first dose of open-label study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of open-label study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of open-label study treatment, the date of the first dose of open-label study treatment will be assigned to the missing start date

If the stop date is before the date of the first dose of open-label study treatment, the stop date will be assigned to the missing start date

6.4.9. Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

6.4.9.1. Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

If the year of the incomplete start date is the same as the year of the first dose of open-label study treatment, the month and day of the first dose of open-label study treatment will be assigned to the missing fields

If the year of the incomplete start date is before the year of the first dose of open-label study treatment, *December 31* will be assigned to the missing fields

If the year of the incomplete start date is after the year of the first dose of open-label study treatment, *January 1* will be assigned to the missing fields

Missing month only

If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

If the month and year of the incomplete start date are the same as the month and year of the first dose of open-label study treatment, the day of the first dose of open-label study treatment will be assigned to the missing day

If either the year of the incomplete start date is before the year of the date of the first dose of open-label study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of open-label study treatment, the last day of the month will be assigned to the missing day.

If either the year of the incomplete start date is after the year of the date of the first dose of open-label study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of open-label study treatment, the first day of the month will be assigned to the missing day

6.4.9.2. Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, replace it with the last visit date in the imputations described below. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

Missing month and day

If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields

If the year of the incomplete stop date is before the year of the last dose of study treatment, December 31 will be assigned to the missing fields

If the year of the incomplete stop date is after the year of the last dose of study treatment, January 1 will be assigned to the missing fields

Missing month only

If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day

If either the year of the incomplete stop date is before the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study treatment, the last day of the month will be assigned to the missing day

If either the year of the incomplete stop date is after the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study treatment, the first day of the month will be assigned to the missing day

6.4.10. Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

Table 6-11 shows examples of how some possible laboratory results should be coded for the analysis.

Table 6-11 Examples of Coding Special Character Values for Clinical Laboratory Parameters

Laboratory Test, SI Unit	*Possible Laboratory Results*	*Coded Value for Analysis*
CHEMISTRY		
ALT, U/L	< 5	5
AST, U/L	< 5	5
Bilirubin, total, µmol/L	< 2	2
URINALYSIS		
Glucose, mmol/L	= OR > 55, ≥ 55, > 0	Positive
	≤ 0, negative	Negative
pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5	8.5
Protein	= OR > 3.0, ≥ 3.0, > 0	Positive
	≤ 0	Negative

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = *Le Système International d'Unités* (International System of Units).

7. Covid-19 Related Analyses

This section specified analyses related to COVID-19 pandemic from the following aspects:

- Disposition
- Study visits and study procedures
- Protocol deviation
- Treatment interruption due to COVID-19
- TEAEs related with COVID-19 and supplemental signs and symptoms
- COVID-19 status (COVID-19 testing results or contact with a COVID-19 positive person)

Safety Population will be used for the planned analyses described above. The number of participants with study visits impacted by COVID-19 will be summarized by the classification of study visits. Furthermore, the number of participants who missed at least one entire visit due to COVID-19 will be summarized.

The number of participants with significant protocol deviation due to COVID-19 will be provided. The number of participants with study drug disruption due to COVID-19 will be provided as well. The number of participants with TEAEs related to COVID-19 will be tabulated by preferred terms, and related supplemental signs and symptoms will be listed. COVID-19 status, i.e., testing results or contact with a COVID-19 positive person, will be summarized.

Supporting listings for the described analyses above will be provided.

8. References

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