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Protocol Title: A PHASE 3, MULTICENTER, OPEN-LABEL 52-WEEK EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN JAPANESE PARTICIPANTS WITH CHRONIC OR EPISODIC MIGRAINE

Protocol Number: 3101-306-002

Compound Number: AGN-241689

Sponsor Name: Allergan Pharmaceuticals International Limited (a subsidiary of AbbVie)

Legal Registered Address: **Marlow International**
The Parkway, Marlow SL7 1YL
United Kingdom

Japan Agent: **Allergan Japan K.K. (AJKK)**
Yebisu Garden Place Tower 35F
4-20-3 Ebisu
Shibuya-ku, Tokyo, Japan 150-6035

SAP Final: 10 Sep 2020

SAP Amendment 1: 02 Feb 2023

SAP Amendment 2: 26 Jun 2024

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SAP Version History

This Statistical Analysis Plan (SAP) for Study 3101-306-002 is based on the Protocol Amendment 3 dated 08Jul2022.

Summary of Changes from the Final SAP to SAP Amendment 1:

Date	Section: Description	Reason
03/18/21	Added EQ-5D-5L text in Sections 5.3.4.5 and 6.4.3	Consistent with 3101-301-002 and -302 HO SAP text
03/18/21	Section 5.1: replaced 'extension' to 'lead-in' in baseline definition.	to align with other extension Atogepant studies
03/18/21	Section 6.3.1: replaced 'White' by 'Asian'	study is Japanese
03/18/21	Section 6.3.2: removed 'migraine severity'	specified neither in the study protocol, nor in prior Atogepant studies.
03/18/21	Table 6-1: removed 'Insulin'	Because it is not collected.
03/24/21	Added 'evaluable baseline' to Section 4.	
5/20/21	Updated analysis visit windows	
5/20/21	Added 95% CI for primary and key secondary endpoints from 3101-303-002 study	Consistent with current Atogepant LTS extension studies (except for study 311 due to small sample size).
7/6/2021	In Section 1.1, added six endpoints, Change from baseline in monthly severe headache days at each monthly period, Change from baseline in monthly cumulative headache hours at each monthly period, At least a 5-point improvement (decrease) from baseline in total HIT-6 score at each monthly period, Change from baseline in the EQ-5D-5L VAS score at each monthly period, Change from baseline in MIDAS absenteeism score (Questions 1, 3, and 5) at Weeks 12, 24, 36, 48, and 52, and Change from baseline in MIDAS presenteeism score (Questions 2 and 4) at Weeks 12, 24, 36, 48, and 52	To align with the protocol.
7/6/2021	In Section 5.3.1, updated analysis methods	Consistent with current Atogepant LTS extension studies (except for study 311 due to small sample size).
7/6/2021	In Section 6.3.4, updated the derivation for AIM-D total score, MIDAS absenteeism score, and MIDAS presenteeism score.	New endpoints added.
12/7/2022	In Section 1, updated the wording in introduction	To align with the protocol.

Date	Section: Description	Reason
12/7/2022	In Section 1.1, added three endpoints, Change from baseline in monthly AIM-D total score at each monthly period, Change from baseline in monthly activity level at each monthly period and Change from baseline in monthly activity limitation at each monthly period	To align with the protocol.
12/7/2022	In Section 1.2, updated study design, study schema, and schedule of activities	To reflect addition of De Novo EM Participants in Protocol Amendment 3.
12/7/2022	In Section 3, updated sample size	To reflect addition of De Novo EM Participants in Protocol Amendment 3.
12/7/2022	In Section 4, updated the definition of Screened population and mITT population	To account for De Novo EM Participants and for clarification.
12/7/2022	In Section 5.1, updated the definition of baseline for monthly endpoints and efficacy endpoints and updated MedDRA version to 25.1	To account for De Novo EM Participants and for clarification.
12/7/2022	In Section 5.2, updated enrollment category	To account for De Novo EM Participants.
12/7/2022	In Section 5.3.1, updated endpoints, same to Section 1.1; updated the definition of a headache day	To align with the protocol. For clarification.
12/7/2022	In Section 5.3.4, added text for activity level and activity limitation	To align with the protocol.
12/7/2022	In Section 5.4.3, updated MedDRA version to 25.1; added summary for treatment-related TESAEs	To be consistent with TFLs.
12/7/2022	Added new Section 5.5.1 Subgroup Analyses	To account for De Novo EM Participants and for alignment with protocol.
12/7/2022	In Section 6.2, updated Changes to Protocol-Planned Analyses	To align with protocol
12/7/2022	In Section 6.3, updated supporting study information	To account for De Novo EM Participants and for clarification.
12/7/2022	In Section 6.4.1, updated analysis windows	To account for De Novo EM Participants and for clarification.
12/7/2022	In Section 6.4.2, removed "monthly headache day pain intensity,"	To align with protocol.
12/7/2022	In Section 6.4.3, added Monthly Total Score of the AIM-D	New endpoints added.
12/7/2022	In Section 7, updated Covid-19 related analysis	To align with other Atogepant studies.
12/7/2022	Updated Appendix 1 List of Abbreviations	For clarification.

Summary of Changes from the SAP Amendment 1 to SAP Amendment 2:

Date	Section: Description	Reason
11/7/2023	In Section 6.4.2.1, added text for diary time handling.	For clarification.
12/12/2023	In Section 5.4.3, updated MedDRA version to 27.0; added treatment-related TESAEs in overall summary of AEs; updated the description for the incidence of comment TEAEs.	To be consistent with TFLs. For clarification.
12/12/2023	In Section 5.4.4.2, added BMI in vital signs for descriptive statistics.	To be consistent with TFLs.
12/12/2023	In Section 5.4.4.4, added a listing of all AEs occurring in participants who have suicidal ideation or suicidal behavior	To be consistent with TFLs.
12/26/2023	In Section 1.1, added one endpoint ≥ 30% improvement (decrease) in monthly migraine days at each monthly period.	To align with the endpoints in the lead-in Study 3101-303-002.
12/26/2023	In Section 5.4.4.3 and Section 6.3.7.5, removed QTc calculated using the Bazett correction (QTcB).	To algin with protocol.
12/26/2023	In Section 5.5.1, updated efficacy subgroup analyses.	For better interpretation in analysis result.
12/26/2023	In Section 6.2, added the new endpoint as changes to protocol-planned analyses.	
12/26/2023	In Section 6.3.1, updated the age group.	To align with the other Japan atogepant study.
12/26/2023	In Section 6.4.6, updated "intensity" to "severity."	To align with data collection.
3/28/2024	In Section 5.4.3, added one table for treatment-related TEAEs by SOC, PT, and AE onset time interval.	Per Japan team's request.
5/10/2024	In Section 6.3.3, updated protocol deviation information.	To clarify the categories for significant deviations.
5/10/2024	Updated Appendix 1 List of Abbreviations	For clarification.
5/30/2024	In Section 5.3.4, added clarification sentences for AIM-D.	For clarification.
5/30/2024	In Section 6.4.3, removed unused sentence for EQ-5D-5L derivation	For clarification.

1. Introduction

This SAP provides a more technical and detailed elaboration of the statistical analyses of the clinical Phase 3 data as outlined and specified in the **protocol amendment 3 of Study 3101-306-002** dated 08Jul2022. 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
Primary • To evaluate the safety and tolerability of treatment with atogepant 60 mg once daily when administered over 52 weeks for the prevention of migraine in Japanese participants with chronic migraine (CM) or episodic migraine (EM).	**Safety Assessments** Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS).
Other • To evaluate the efficacy of treatment with atogepant 60 mg once daily when administered over 52 weeks for the prevention of migraine in Japanese participants with CM or EM.	**Endpoints** • Change from baseline in monthly migraine days at each monthly period • 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%, ≥ 30%, ≥ 50%, ≥ 75%, and 100% improvement (decrease) in monthly migraine days 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 • Change from baseline in monthly cumulative headache hours at each monthly period • At least a 5-point improvement (decrease) from baseline in total HIT-6 score at each monthly period

Objectives	Endpoints
	• Change from baseline in the HIT-6 total score at each monthly period • Rating of "much better" or "very much better" at Weeks 12, 24, 36, 48, and 52 assessed by the PGIC • Change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at each monthly period as assessed by the WPAI:MIGRAINE • Change from baseline in EQ-5D-5L descriptive system index score at each monthly period • Change from baseline in the EQ-5D-5L VAS score at each monthly period • Participants "satisfied" or "extremely satisfied" with study medication for migraine prevention at each monthly period • Change from baseline in monthly Performance of Daily Activities domain score of the AIM-D at each monthly period • Change from baseline in monthly Physical Impairment domain score of the AIM-D at each monthly period • Change from baseline in monthly AIM-D total score at each monthly period • Change from baseline in monthly activity level at each monthly period • Change from baseline in monthly activity limitation at each monthly period • Change from baseline in the MIDAS total score at Weeks 12, 24, 36, 48, and 52 • Change from baseline in MIDAS absenteeism score (Questions 1, 3, and 5) at Weeks 12, 24, 36, 48, and 52 • Change from baseline in MIDAS presenteeism score (Questions 2 and 4) at Weeks 12, 24, 36, 48, and 52 • Change from baseline in PGI-S at each monthly period

Objectives	Endpoints
	• Change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Weeks 12, 24, 36, 48, 52, and 56 • Change from baseline in the MSQ v2.1 Role Function-Preventive domain score at Weeks 12, 24, 36, 48, 52, and 56 • Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 12, 24, 36, 48, 52, and 56

1.2. Study Design

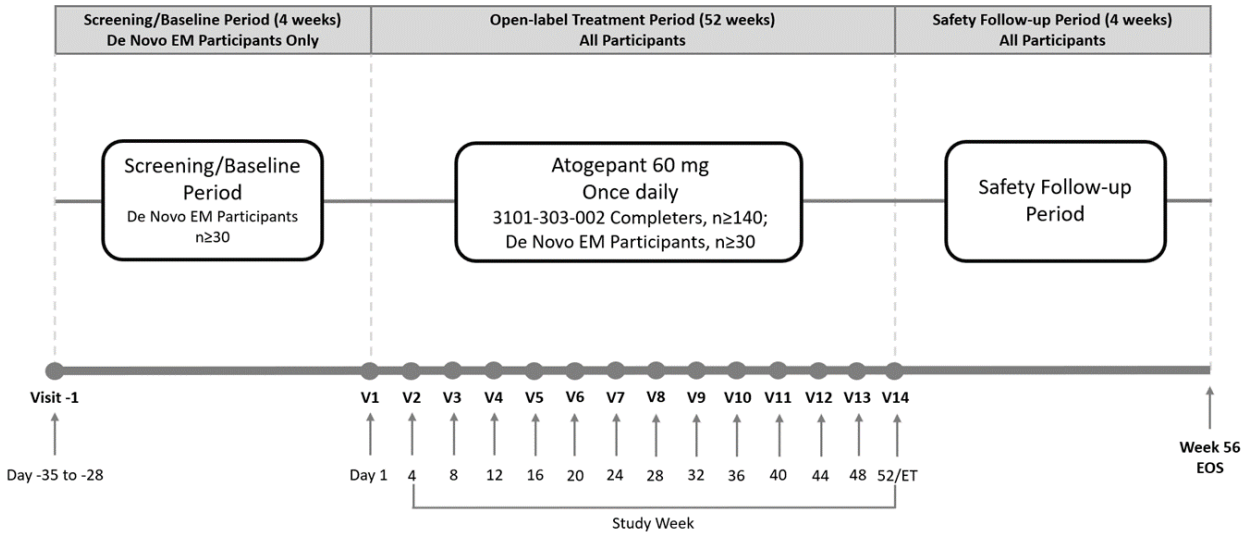
The study design can be described as below with schema and schedule activities to follow in the subsections.

- It is a Phase 3 safety extension study enrolling participants with chronic migraine (3101-303-002 study completers) or De Novo participants with episodic migraine.
- It is a multicenter, open-label study to evaluate the long-term safety and tolerability of oral atogepant for the prevention of migraine.
- At least 170 participants will be enrolled to meet a target of a minimum of 100 participants with EM or CM exposed to atogepant for 1 year. A minimum of 30 De Novo participants (enrolled at selected sites only) must have EM and meet all eligibility criteria.
- Participants will be treated with atogepant 60 mg once daily.
- The study will consist of a 4-5 weeks screening/baseline period (for De Novo EM participant only), a 52-week treatment period and a 4-week safety follow-up period; total study duration is 56-61 weeks.
- No interim analyses are planned for this study.

1.2.1. Schema

Presented below is the study schema.

Figure 1-1 Study Schema



EOS end of study; ET early termination; V visit.

1.2.2. Schedule of Activities

Study procedures are to be done in sequence as listed in the schedule below.

Table 1-1 Schedule of Activities (as per the Original Protocol)

Study Period	**Screening/ Baseline Period (4 weeks)[a]**	**Open-label Treatment Period (52 weeks)**														**Safety Follow-up Period (4 weeks)**
Visit #	**Visit -1**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week 4***	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	**Day -35 to -28**	**N/A**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**+ 3 days**	**± 3 days**
Obtain Informed consent and participant privacy[c]	X	X[d]														
Access IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect demographic information	X															
Assess inclusion/ exclusion criteria	X	X[e]														
Collect medical history[f]	X	X[d]														

Study Period	Screening/ Baseline Period (4 weeks)[a]	Open-label Treatment Period (52 weeks)														Safety Follow-up Period (4 weeks)
Visit #	**Visit -1**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week 4***	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	**Day -35 to -28**	**N/A**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**+ 3 days**	**± 3 days**
Collect migraine/ headache history and confirm diagnosis	X															
Collect start date (first day) of last menstrual cycle for women having menstrual cycles	X															
Review and record prior medications taken in the past 6 months and all prior headache medications and concomitant medications	X															

Study Period	**Screening/ Baseline Period (4 weeks)[a]**	**Open-label Treatment Period (52 weeks)**														**Safety Follow-up Period (4 weeks)**
Visit #	**Visit -1**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week 4***	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	**Day -35 to -28**	**N/A**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**+ 3 days**	**± 3 days**
Perform physical examination	X	X													X	X
Collect vital sign measurements[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Perform ECG	X	X[d]			X			X			X				X	
Perform urine pregnancy test[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory determinations[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide eDiary device with instructions and training[j]	X	X[d]														
Participant eDiary data collection[j,k]		X														

Study Period	Screening/ Baseline Period (4 weeks)[a]	Open-label Treatment Period (52 weeks)														Safety Follow-up Period (4 weeks)
Visit #	**Visit -1**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week 4***	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	**Day -35 to -28**	**N/A**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**+ 3 days**	**± 3 days**
Review eDiary data (headache duration, frequency, characteristics and symptoms, acute medication use, AIM D activity level and activity limitation) and compliance[l]		X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	
C SSRS (eTablet)[m,n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect ASC 12 (eTablet)[o,p]	X															
HIT 6 (eTablet)[o,p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGIC (eTablet)[o,p]					X			X			X			X	X	

Study Period	**Screening/ Baseline Period (4 weeks)[a]**	**Open-label Treatment Period (52 weeks)**														**Safety Follow-up Period (4 weeks)**
Visit #	**Visit -1**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week 4***	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	**Day -35 to -28**	**N/A**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**+ 3 days**	**± 3 days**
PGI S (eTablet)[o,p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
WPAI MIGRAINE (eTablet)[o,p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Satisfaction with Study Medication (eTablet)[o,p]			X	X	X	X	X	X	X	X	X	X	X	X	X	
EQ 5D 5L (eTablet)[o,p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MIDAS (eTablet)[o,p]		X			X			X			X			X	X	
MSQ v2.1 (eTablet)[o,p]		X			X			X			X			X	X	X
Collect eDiary		X[q]													X	
Dispense study intervention (i.e., atogepant)		X	X	X	X	X	X	X	X	X	X	X	X	X		

Study Period	**Screening/ Baseline Period (4 weeks)[a]**	**Open-label Treatment Period (52 weeks)**														**Safety Follow-up Period (4 weeks)**
Visit #	**Visit -1**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week 4***	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	**Day -35 to -28**	**N/A**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**+ 3 days**	**± 3 days**
Review of study intervention (i.e., atogepant) compliance and accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X															
Concomitant medications/ concurrent procedures	X															

a. De Novo EM Participants only.

b. After providing informed consent for this study, Visit 7 of the lead in study (Study 3101 303 002 [Phase 3 CM study]) will function as Visit 1 for this study (see Section 3 for further information).

c. Obtained from the participant.

d. 3101 303 002 Completers only.

e. Review of inclusion/exclusion criteria includes the review of eDiary data and compliance during Screening/Baseline for De Novo EM Participants.

f. Medical history will be collected for 3101 303 002 Completers who have a gap between the last visit of the lead in study and Visit 1 of this extension study and also for De Novo EM Participants.

g. Vital sign measurements: height, weight, sitting and standing pulse rate, respiratory rate, sitting and standing blood pressure, and body temperature. Height will be measured only at Visit 1.

h. For WOCBP only, a urine pregnancy test will be performed at all visits. At the first study visit, discuss the method of contraception with WOCBP and document this method. Counsel participants on the importance of maintaining their agreed upon method of contraception throughout the study.

i. 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 for 3101 303 002 Completers and only at Visit 1 for De Novo EM Participants.

j. Participants should begin using the eDiary as soon as it is dispensed and for the duration of the screening/baseline (for De Novo EM Participants) and treatment period (for all participants). Training for the eDiary will be provided for qualified participants during the first study visit (Visit 1 for De Novo EM Participants and Visit 1 for Study 3101 303 002 Completers).

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

l. Participants must bring their eDiary to all visits (except Visit 15).

m. At all visits except Visit 1, the "Since Last Visit" C SSRS will be completed for all participants. For Visit 1, the 'Screening/Baseline' assessment of the C SSRS will be completed for the participant's lifetime history and for the 6 months prior to screening.

n. Clinicians will complete on eTablet.

o. Participants will complete on eTablet.

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

q. eDiary will be collected on Visit 1 for screen failures (De Novo EM Participants only).

Table 1-2 Schedule of Procedures for Remote Visits

Study Period	Open-label Treatment Period (52 weeks)													Safety Follow-up Period (4 weeks)
	Potential for Remote Visit[a]													
Visit #	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**+ 3 days**	**± 3 days**
Dispense study intervention (i.e., atogepant)[b]	X	X	X	X	X	X	X	X	X	X	X	X		
Review of study intervention (i.e., atogepant) compliance and accountability	X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant daily eDiary data collection[c]	X													
Review eDiary data and compliance[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect eDiary[d]													X	X
Perform urine pregnancy test[b,e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C SSRS (eTablet or web portal)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIT 6[g] (web portal)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGIC[g] (web portal)			X			X			X			X	X	
PGI S[g] (web portal)	X	X	X	X	X	X	X	X	X	X	X	X	X	
WPAI:MIGRAINE[g] (web portal)	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period	Open-label Treatment Period (52 weeks)													Safety Follow-up Period (4 weeks)
	Potential for Remote Visit[a]													
Visit #	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**+ 3 days**	**± 3 days**
Patient Satisfaction with Study Medication[g] (web portal)	X	X	X	X	X	X	X	X	X	X	X	X		
EQ 5D 5L[g] (web portal)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MIDAS[g] (web portal)			X			X			X			X	X	
MSQ v2.1[g] (web portal)			X			X			X			X	X	X
Adverse events	X													
Concomitant medications/ concurrent procedures	X													

a. Visit -1 and Visit 1 must be performed onsite.
b. Study medication to cover 1 remote study visit and urine pregnancy tests may be dispensed at an office visit (if the next visit is anticipated to be remote), for curbside pick-up or shipped to participants via an overnight courier.
c. Daily eDiary data collection includes: headache frequency, duration, characteristics, and symptoms; acute medication use, AIM-D, Activity Level, and Activity Limitation.
d. Device may be dropped off or returned at Visit 15/EOS.
e. WOCBP only are to take an at-home pregnancy test (provided by sites) and report the results during virtual visits.
f. The "Since the Last Visit C-SSRS" will be completed. Clinicians will complete the C-SSRS on eTablet or web-based backup portal.
g. If available, participants will complete on a web-based portal.

2. Statistical Hypotheses

Since the primary objective of this study is to assess the safety and tolerability over 52 weeks of atogepant 60 mg once daily treatment, there is no statistical hypothesis specified for the study.

3. Sample Size Determination

The study sample size was driven by regulatory safety requirements for the duration and number of participants exposed rather than statistical considerations. At least 170 participants will be enrolled into this long-term, open label, safety extension study including at least 140 participants from the lead-in study (Study 3101-303-002) and approximately 30 De Novo EM Participants (from selected sites only) to meet a target of a minimum of 100 participants exposed to atogepant at 1 year.

4. Populations for Analysis

The analysis populations will consist of participants as defined below.

The Screened population will consist of all rollover participants with chronic migraine from lead-in 3101-303-002 study and De Novo EM participants, who signed informed consent for this extension study.

The Safety population will consist of all participants who receive at least 1 dose of 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 study, an evaluable baseline (in this study for De Novo EM Participants or in the lead-in study for the rollover participants), 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.

5. Statistical Analyses

5.1. General Considerations

- Efficacy endpoints will be analyzed descriptively based on the mITT population.
- Safety endpoints will be performed using the Safety population.
- Continuous variables will be summarized by number of participants with observed values (n), mean, standard deviation (SD), median, 1st and 3rd quartiles (Q1, Q3), minimum (min), and maximum (max).
- Categorical variables will be summarized by number of participants with observed values, events (n), frequency count (n1), and percentage of participants with observed values.
- 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.
- For monthly endpoints, baseline is defined as assessments during the last 28 days of baseline period in the lead-in study for 3101-303-002 rollover participants, and the last 28 days of the screening/baseline period for De Novo EM Participants. For efficacy endpoints that are assessed at clinical visits, baseline is defined as the last non-missing efficacy assessment before the first dose of study intervention in the lead-in study (3101-303-002) for 3101-303-002 Completers, and the last non-missing efficacy assessment before the first dose of study for De Novo EM Participants. For each of the clinical, laboratory, vital sign, and ECG parameters, the baseline is defined as the baseline value in the lead-in study (3101-303-002) for 3101-303-002 Completers, and the last nonmissing safety assessment before the first dose of study drug for De Novo EM Participants.
- The change from baseline values will be computed as the post-baseline value minus the baseline value.
- Study intervention is treatment administered (atogepant 60 mg QD).
- All statistical analysis will be performed using SAS version 9.4 or higher.
- Medical Dictionary for Regulatory Activities (MedDRA), Version 27.0 or higher, will be used to code adverse events and medical history.
- WHO Drug Global B3 (v.202403 or higher) will be used to code medications.

5.2. Participant Dispositions

The number of participants in the Safety and mITT populations will be summarized; the number of participants screened will be summarized overall.

Screen-failure participants (i.e., participants who consent to participate in the study but are not subsequently treated) and the associated reasons for failure to enter into the open-label treatment period will be tabulated for all screened participants. The number and percentage of participants who enter the open-label treatment period, complete the open-label treatment period and of participants who prematurely discontinue during the open-label period will be tabulated by 3101-303-002 rollover CM participants, De Novo EM Participants, and overall for Safety population. The reasons for premature discontinuation from the open-label treatment period as recorded on the disposition page of the electronic case report forms (eCRFs) will be summarized (number and percentage). The percentage is relevant to the total number of participants in the Safety population. Similar disposition information will be presented for the safety follow-up period. All participants in the all screened population who prematurely discontinue during the open-label treatment period or the safety follow-up period will be listed by discontinuation reason.

The number of participants in the Safety population will be summarized by lead-in study treatments (placebo, Atogepant 60 mg QD, Atogepant 30 mg BID), enrollment category (3101-303-002 completer (3101-303-002 Visit 7 completer, Visit 8 completer, Completer with Gap prior to start) and De Novo EM participants), and overall.

5.3. Efficacy Endpoint Analyses and Health Outcome Measures

5.3.1. Definition of Endpoints

Since the primary objective of this open-label extension study is to assess the safety and tolerability over 52 weeks of atogepant treatment, efficacy endpoints are not classified as primary, secondary, or additional.

Efficacy endpoints are listed below, and will be analyzed descriptively.

- Change from baseline in monthly migraine days at each monthly period (i.e., each consecutive 4-week period)
- 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%, ≥ 30%, ≥ 50%, ≥ 75%, and 100% improvement (decrease) in monthly migraine days 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

- Change from baseline in monthly cumulative headache hours at each monthly period
- At least a 5-point improvement (decrease) from baseline in total HIT-6 score at each monthly period
- Change from baseline in the HIT-6 total score at each monthly period
- Rating of "much better" or "very much better" at Weeks 12, 24, 36, 48, and 52 assessed by the PGIC
- Change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at each monthly period as assessed by the WPAI:MIGRAINE
- Change from baseline in EQ-5D-5L descriptive system index score at each monthly period
- Change from baseline in the EQ-5D-5L VAS score at each monthly period
- Participants reporting "satisfied" or "extremely satisfied" with study medication for migraine prevention at each monthly period
- Change from baseline in monthly Performance of Daily Activities domain score of the AIM-D at each monthly period
- Change from baseline in monthly Physical Impairment domain score of the AIM-D at each monthly period
- Change from baseline in monthly AIM-D total score at each monthly period
- Change from baseline in monthly activity level at each monthly period
- Change from baseline in monthly activity limitation at each monthly period
- Change from baseline in MIDAS absenteeism score (Questions 1, 3, and 5) at Weeks 12, 24, 36, 48, and 52
- Change from baseline in MIDAS presenteeism score (Questions 2 and 4) at Weeks 12, 24, 36, 48, and 52
- Change from baseline in the MIDAS total score at Weeks 12, 24, 36, 48, and 52
- Change from baseline in PGI-S at each monthly period
- Change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Weeks 12, 24, 36, 48, 52, and 56
- Change from baseline in the MSQ v2.1 Role Function-Preventive domain score at Weeks 12, 24, 36, 48, 52, and 56
- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 12, 24, 36, 48, 52, and 56

All efficacy endpoints listed above will be summarized descriptively. In addition, for the primary endpoint of the lead-in 3101-303-002 study (Change from baseline in monthly migraine days at

each monthly period) and for the key secondary endpoints of the lead-in 3101-303-002 study (Change from baseline in monthly headache days at each monthly period, Change from baseline in monthly acute medication use days at each monthly period, ≥ 50% improvement (decrease) in monthly migraine days at each monthly period, change from baseline in MSQ v2.1 Role Function Restrictive Domain at each monthly period, change from baseline in monthly Performance of Daily Activities domain score of the AIM-D at each monthly period, change from baseline in the Physical Impairment domain score of the AIM-D at each monthly period, change from baseline in the HIT-6 total score at each monthly period), point estimates and 95% CIs will be provided. The 95% CI for the continuous endpoints will be based on a mixed-effects model for repeated measures (MMRM). The model will include visit (derived as month) as a categorical fixed effect, and the baseline score, baseline-by-visit interaction as covariates. Restricted maximum likelihood method will be used. An unstructured covariance matrix will be used to model the covariance of within-participant repeated measurements. If the model does not converge, then simplified covariance structures will be used to fit the model in the following order: (1) Toeplitz and (2) compound symmetry. The Kenward Roger approximation (Kenward 1997) will be used to estimate the denominator degrees of freedom. Each treatment effect will be estimated by the least square mean along with the corresponding standard error and 95% confidence interval. The analysis will be performed based on all post-baseline values using only the observed cases without imputation of missing values. The 95% CI for percent improvement (decrease) in monthly migraine days at each monthly period will be based on the normal approximation to the binomial.

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.

For analysis purpose, change from baseline will be calculated for consecutive 28-day periods beginning with study Day 1 (i.e., Weeks 1-4, 5-8 and 9-12, corresponding to Days 1-28, 29-56 and 57-84, etc.), where Day 1 is the first dose date of the open-label study treatment.

5.3.2. Main Analytical Approach

Descriptive statistics will be provided by visit for all efficacy endpoints based on the mITT population using the observed case (OC) approach. No inferential statistical analyses will be performed for the efficacy endpoints except where noted above.

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 (e.g., walking or climbing stairs)
B. At least one of the following:
   i. Nausea and/or vomiting
   ii. Photophobia and phonophobia
   iii. Typical aura (i.e., 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 (i.e., 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 (e.g., walking or climbing stairs)
   2) Symptoms:
      i. Nausea and/or vomiting
      ii. Photophobia and phonophobia
      iii. Typical aura (i.e., visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins
E. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (i.e., 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 (e.g., 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

5.3.4.1. HIT-6

The HIT-6 is a 6-question assessment used to measure the impact headaches have on a participant's ability to function on the job, at school, at home, and in social situations. It assesses the effect that headaches have on normal daily life and the participant's ability to function. Responses are based on frequency using a 5-point scale ranging from "never" to "always." The HIT-6 total score, which ranges from 36 to 78, is the sum of the responses each of which is assigned a score ranging from 6 points (never) to 13 points (always).

5.3.4.2. Migraine Disability Assessment (MIDAS)

The MIDAS is a 7-item questionnaire designed to quantify headache-related disability over a 3-month period. The MIDAS score is the sum of missed work or school days, missed household work days, days at work or school plus days of household work where productivity was reduced by half or more, and missed non-work activity days due to headaches in the last 3 months.

5.3.4.3. Patient Global Impression of Change (PGIC)

The PGIC is a single item questionnaire used to measure the participant's impression of overall change in migraine since the first dose of study medication. The measure uses a 7-point rating scale with responses ranging from "very much better" to "very much worse."

5.3.4.4. Work Productivity and Activity Impairment Questionnaire: Migraine V2.0 (WPAI:MIGRAINE)

The WPAI:MIGRAINE will be used to assess work productivity specific to migraine. The measure uses a one-week recall and contains six questions related to work productivity. The WPAI measures both presenteeism and absenteeism. The measure yields four scores expressed as impairment percentages ranging from 0 to 100%: Percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment due to migraine.

5.3.4.5. European Quality of Life - 5 Dimensional (EQ-5D-5L)

EQ-5D-5L is a generic instrument for use as a measure of health status. As of 2009, the European Quality of Life - 5 Dimension - 5-Level (EQ-5D-5L) has also been available for use; this version was developed to improve the sensitivity of the instrument and to reduce ceiling effects (The EuroQol Group, 2020). The EQ-5D-5L consists of 2 components - the EQ-5D descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The mobility dimension queries the participant's walking ability. The self-care dimension queries the participant's ability to wash or dress by himself. The usual activities dimension assesses the participant's performance in "work, study, housework, family or leisure activities." The pain/discomfort dimension measures how much pain or discomfort a participant has. The anxiety/depression dimension assesses how anxious or depressed a participant is. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The scoring range of the EQ-5D descriptive system is typically from 0 (dead) to 1 (full health). The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled "Best imaginable health state" and "Worst imaginable health state." The scoring range of the EQ VAS is from 0 (worst imaginable health) to 100 (best imaginable health).

5.3.4.6. Patient Global Impression – Severity (PGI-S)

The PGI-S is a single item questionnaire used to measure the participant's impression of severity in relation to migraine symptoms overall at the time of administration of the measure. The measure uses a 5-point rating scale with responses ranging from "none" to "very severe."

5.3.4.7. Patient Satisfaction with Study Medication

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).

5.3.4.8. Activity Impairment in Migraine – Diary (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 (i.e., 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 (i.e., 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 version. 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).

5.3.4.9. Activity Level and Activity Limitation

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."

5.3.4.10. Migraine Specific Quality of Life Questionnaire, Version 2.1 (MSQ v2.1)

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. Safety Analyses

The safety analysis will be performed using descriptive statistics as described in Section 5.1 based upon the Safety population.

5.4.1. Extent of Exposure

The study will consist of a 52-week treatment period and a 4-week safety follow up period; total study duration is 56 weeks.

Exposure to extension study treatment for the Safety population during the open-label treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of extension study treatment to the date of the last dose taken, inclusive.

The number and percentage of participants with each treatment duration of ≥ 1 day, ≥ 28 days, ≥ 56 days, ≥ 84 days, ≥ 90 days, ≥ 112 days, ≥ 140 days, ≥ 168 days, ≥ 180 days, ≥ 196 days, ≥ 224 days, ≥ 252 days, ≥ 270 days, ≥ 280 days, and ≥ 360 will be summarized.

Participant-years, defined as exposure to the study treatment in years, will be summarized for the Safety population.

5.4.2. Treatment Compliance

Dosing compliance for the open-label treatment period is defined as the total number of open-label study treatments actually taken by a participant during that period divided by the number of open-label study treatments that were expected to be taken by a participant during the same period multiplied by 100. The total number of tablets actually taken during a specific period will be calculated from the study treatment record. Descriptive statistics for treatment compliance together with the compliance categories (< 80%, 80% - 120%, > 120%) will be summarized for

open-label study treatment period between 2 consecutive visits, as well as for the whole open-label treatment period of the study based on the Safety population.

5.4.3. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 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 open-label study treatment. An AE that occurs more than 30 days after the last dose of open-label study treatment or the safety follow-up visit (Visit 15) 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 3101-306-002 with recorded onset date on or after the date of the first dose of open-label study treatment and within 30 days after the last dose of open-label study treatment or Visit 15 whichever comes later.

An AE is a TESAE if it is a TEAE that additionally meets any SAE criterion below (as specified in the protocol Section 9.1.2):

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent disability/incapacity
- Is a congenital anomaly/birth defect
- Other situations that the medical or scientific judgment considers to be serious.

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

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

Overall summary of AEs will be provided on a per-participant basis for categories of TEAEs, treatment-related TEAEs, TESAEs, treatment-related TESAEs, TEAEs leading to study intervention discontinuation, and deaths.

The number and percentage of participants reporting TEAEs will be tabulated by system organ class (SOC) and preferred term (PT), and further categorized by severity. If more than 1 AE is coded to the same preferred term for the same participants, the participant will be counted only once for that preferred term using the greatest severity for the summarization by severity.

The number and percentage of participants reporting treatment-related TEAEs will be tabulated by SOC and PT.

The number and percentage of participants reporting treatment-related TEAEs will be tabulated by SOC, PT, and the following AE onset time intervals: < 3 months, ≥ 3 and < 6 months, ≥ 6 and < 9 months, ≥ 9 and < 12 months, ≥ 12 months, where a month is defined as 30 days for analysis purposes.

The number and percentage of participants reporting NEAEs will be tabulated by SOC and PT.

The number and percentage of participants who have TEAEs leading to study intervention discontinuation will be summarized by SOC and PT.

The incidence of common (≥ 2% of participants [after rounding] in either CM completer cohort or De Novo EM cohort) TEAEs will be summarized by PT and sorted by decreasing frequency in total.

The incidence of common (≥ 5% of participants [after rounding] in either CM completer cohort or De Novo EM cohort) TEAEs will be summarized by PT and sorted by decreasing frequency in total.

The number and percentage of participants who have TESAE will be tabulated by SOC and PT.

The number and percentage of participants reporting treatment-related TESAEs will be tabulated by SOC and PT.

In addition, separate tabular displays will be presented for participants who died, participants with SAEs, and participants with TEAEs leading to study intervention discontinuation.

5.4.4. Additional Safety Assessments

5.4.4.1. Clinical Laboratory Parameters

Descriptive statistics for values and changes from the baseline in standard (SI) units at each assessment time point will be presented 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

In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment time point will be presented for selected clinical laboratory parameters listed in Table 6-1. A description of reporting the laboratory values in conventional units in participant narratives (along with the standard reporting in SI units) is presented at the end of Table 6-2.

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. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment for the open-label treatment period. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value during the study. A supportive tabular display of participants with PCS values will be provided.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline clinical laboratory values will be provided.

The number and percentage of participants with an adjudicated case (i.e., ALT $\geq 3 \times$ ULN and/or AST $\geq 3 \times$ ULN) will be summarized by relationship of ALT or AST elevation to study treatment. The percentages will be calculated relative to the number of participants with at least 1 adjudicated case. The numerator will be the number of participants with at least 1 adjudicated case in the specific category of relationship. If a participant has more than 1 adjudicated case, he or she will be counted in the most relevant category of relationship.

Participants with an adjudicated case (i.e., ALT $\geq 3 \times$ ULN or AST $\geq 3 \times$ ULN) will be listed with their ALT and AST assessments, adjudication dates, relationship of ALT or AST elevation to study treatment, and confounding factor(s). Additional listings will be provided for

participants who meet ALT ≥ 3 × ULN or AST ≥ 3 × 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 is defined by a postbaseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × ULN, along with total bilirubin (TBL) ≥ 2 × ULN and a non-elevated alkaline phosphatase (ALP) < 2 × ULN, all based on blood draws collected within a 24-hour period. Participants who meet the potential Hy's Law criteria from the first dose of study treatment to the end of study will be summarized. Supportive tabular displays will also be provided.

The number and percentage of participants meeting each of the postbaseline hepatic laboratory abnormalities criteria listed in Table 6-4 will be summarized. The percentages will be calculated relative to the number of participants with at least 1 available postbaseline assessment. The numerator will be the total number of participants having at least 1 postbaseline value that meets the specific category during the study. A supportive listing will also be provided.

5.4.4.2. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures [sitting and standing], pulse rate [sitting and standing], respiratory rate, temperature, weight, body mass index (BMI), orthostatic systolic blood pressure, orthostatic diastolic blood pressure, and orthostatic pulse rate) and their changes from baseline at each assessment timepoint will be presented. 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. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated. For criteria related with systolic blood pressure, diastolic blood pressure, pulse rate and weight, the denominator will be the number of participants who have available baseline and at least 1 postbaseline assessment. For criteria related with orthostatic measures, the denominator will be the number of participants who have available non-PCS baseline and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value during the study. A supportive listing of PCS values will be provided.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline vital sign values will be provided.

5.4.4.3. Electrocardiogram

Descriptive statistics for ECG parameters (i.e., heart rate, PR interval, QRS interval, RR interval, QT interval, and QTc interval) and changes from baseline values at each assessment timepoint will be presented. The QTc will be calculated using the Fridericia 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. The number and percentage of participants with PCS postbaseline values will be tabulated. The percentages will be calculated relative to the number of participants with an available non-PCS baseline value and at least 1 postbaseline assessment. The numerator will be the total number of participants with an available non-PCS baseline value and at least 1 PCS postbaseline ECG value during the study. A supportive listing of participants with PCS postbaseline values will be provided. A listing of all AEs for participants with PCS ECG values will also be provided.

To evaluate ECG postbaseline values of clinical interest, the number and percentage of participants with post-treatment QTcF > 450 msec, > 480 msec, and > 500 msec will be tabulated. A supportive listing of participants with postbaseline clinical interest will be provided. A listing of all AEs for participants with postbaseline clinical interest will also be provided.

The number and percentage of participants with an increase > 30 msec but ≤ 60 msec, and with an increase > 60 msec in QTcF will be tabulated. Participants will be counted only once for the most severe category. A supportive listing of participants with postbaseline QTcF increases > 30 msec will be provided, including the PID number and all QTc values (including changes from baseline). A listing of all AEs for participants with postbaseline QTcF increases > 30 msec will also be provided.

A shift table from baseline to the end of open-label treatment period in the investigator's overall interpretation of the ECG will be presented for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A tabular display of participants with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

5.4.4.4. Columbia-Suicide Severity Rating Scale

For C-SSRS, the number and percentage of participants with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized for the Safety population. The

distribution of responses for most severe suicidal ideation and most severe suicidal behavior in the participant's lifetime history, in the past 6 months, in the open-label treatment period, and in the safety follow-up period will also be presented. Supportive listings will be provided and will include the PID number, lifetime history, and postbaseline values. Intensity of suicidal ideation and suicidal behavior type will also be included in these listings. A listing of all AEs occurring in participants who have suicidal ideation or suicidal behavior will also be provided.

5.5. Other Analyses

5.5.1. Subgroup Analyses

Efficacy Subgroup Analyses

For all efficacy and health outcome endpoints, subgroup analyses will be performed by 3101-303-002 Completers or De Novo EM Participants and overall.

For the following efficacy endpoints, separate figures will be presented by 3101-303-002 Completers or De Novo EM Participants. The figures for over time change during the 12-Week Double-Blind treatment period and the 52-Week Open-label treatment period for 3101-303-002 CM Completers in mITT population will also be presented, for the following efficacy endpoints.

- Change from baseline in monthly migraine days at each monthly period
- Change from baseline in monthly headache days at each monthly period
- Change from baseline in monthly acute medication use days at each monthly period

Safety Subgroup Analyses

For all safety endpoints, subgroup analyses will be performed by 3101-303-002 Completers or De Novo EM Participants and overall.

5.6. Interim Analyses

No interim analysis is planned for this study.

6. Supporting Documentation

Additional specifications on study population's demographics and baseline characteristics, as well as pre-defined safety criteria can be found in Appendix 3.

6.1. Appendix 1: List of Abbreviations

Abbreviation/Term	Definition
AE	adverse event
AIM-D	activity impairment in migraine – diary
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CM	chronic migraine
C-SSRS	Columbia–Suicide Severity Rating Scale
eCRF	electronic case report form
eDiary	electronic diary
ECG	electrocardiogram, electrocardiographic
EM	episodic migraine
EOS	end of study
EQ 5D 5L	European Quality of Life - 5 Dimensional
ET	early termination
HIT-6	Headache Impact Test
INR	international normalized ratio
IWRS	interactive web response system
LLN	lower limit of normal value
MedDRA	Medication Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
mITT	modified intent-to-treat
MSQ v2.1	Migraine Specific Quality of Life Questionnaire, Version 2.1
PCS	potentially clinically significant
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression - Severity
PID	participant identification
PRO	patient reported outcome
PT	preferred term
Q1	first quartile (25th percentile of the data)
Q3	third quartile (75th percentile of the data)
QD	once daily
QTc	QT interval corrected for heart rate

Abbreviation/Term	Definition
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SI	Le Système International d'Unités (International System of Units)
SOC	standard of care
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal value
WHO	World Health Organization
WOCBP	women of childbearing potential
WPAI:MIGRAINE	Work Productivity and Activity Impairment Questionnaire: Migraine V2.0

6.2. Appendix 2: Changes to Protocol-Planned Analyses

Add the following efficacy endpoint:

Change from baseline in monthly acute medication use days at each monthly period ≥ 30% improvement (decrease) in monthly migraine days at each monthly period.

6.3. Appendix 3: Supporting Study Information

6.3.1. Demographic

Demographic parameters (age; age group [< 20, 20-29, 30-39, 40-49, 50-59, 60-69, and ≥ 70]; < 40 years, ≥ 40 - < 65 years, ≥ 65 years; < 75 years, ≥ 75 years; race group [Asian, all other races]; ethnicity; sex) will be summarized descriptively by 3101-303-002 Completers from the lead-in study, De Novo EM Participants, and overall for the Safety and mITT populations.

6.3.2. Baseline and Disease Characteristics

Baseline characteristics (weight; height; and BMI, calculated as weight [kg]/(height [m])^2, and BMI category [underweight [< 18.5], normal [> 18.5 - < 25], overweight [> 25 - < 30], and obese [> 30]) will be summarized descriptively for the Safety and mITT populations.

Baseline efficacy parameters (e.g., monthly migraine days, monthly headache days, and monthly acute medication use days) will be summarized by 3101-303-002 Completers from the lead-in study, De Novo EM Participants, and overall for mITT population.

For monthly endpoints, baseline is the baseline value in the lead-in study (3101-303-002) for 3103-303-002 Completers or the last 28 days of the screening/baseline period for De Novo EM Participants. For efficacy endpoints that are assessed at clinical visits, baseline is the last nonmissing efficacy assessment before the first dose of study intervention in the lead-in study (3101-303-002) for 3103-303-002 Completers or the last nonmissing efficacy assessment before the first dose of study drug for De Novo EM Participants.

6.3.3. Protocol Deviations

For each of the following significant protocol deviation categories and across all categories, the number and percentage of randomized subjects with at least one protocol deviation will be summarized overall and by 3101-303-002 Completers from the lead-in study, De Novo EM Participants, and overall for Safety population. A listing of subjects with significant protocol deviations will be provided.

- Participant entered into the study even though did not met inclusion criteria;
- Participant entered into the study even though met exclusion criteria;
- Participant developed withdrawal criteria during the study but was not withdrawn;
- Participant received wrong treatment or incorrect dose;
- Participant received excluded concomitant treatment.

6.3.4. Medical History

Abnormalities in participants' medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities, version 27.0 or newer. The number and percentage of 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 summarized 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 alterations will be reported by 3101-303-002 Completers from the lead-in study and De Novo EM Participants for the Safety population.

6.3.5. Prior/Concomitant/Follow-up medications

Prior medication is defined as any medication taken before the date of the first dose of lead-in study treatment for participants who rolled over from the lead-in study and collected in this study, or before the first dose of study treatment in this study for De Novo EM participants.

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.

The number and percentage of participants will be tabulated by 3101-303-002 Completers from the lead-in study and De Novo EM Participants and 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 summarized by period, for the open-label treatment period and the safety follow-up period, respectively.

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 2024 or higher.

6.3.6. Adverse Events of Special Interest

Per the 3101-306-002 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, (i.e., 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 summaries of above are described in the corresponding SAP Section 5.4.4.1 and Section 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	µIU/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 descriptive statistics for the selected laboratory parameters (Table 6-1) will be reported in conventional units using the similar layout for the summary table in SI unit.

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 'µmol/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 (µmol/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		—	At least 1+
	Protein		—	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[a]	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[a]	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)

a. 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
QTcF interval	msec	> 500
QTcF interval	msec	Increase from baseline > 60

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 treatment. There is no Day 0 or Week 0. Treatment day is relative to the date of the first dose of open-label study dose.

6.4.1. Analysis Window

The analysis visit windows for monthly efficacy endpoints based on daily eDiary data are defined as follows:

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

Analysis Phase	Analysis Visit (Derived)	eDiary Window
Pretreatment	Baseline	Baseline from lead-in study for 3101-303-002 Completer Last 28 days prior to treatment start date for De Novo EM Participant
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]
	Weeks 13 - 16	Treatment Day [85,112]
	Weeks 17 - 20	Treatment Day [113,140]
	Weeks 21 - 24	Treatment Day [141,168]
	Weeks 25 - 28	Treatment Day [169,196]
	Weeks 29 - 32	Treatment Day [197,224]
	Weeks 33 - 36	Treatment Day [225,252]
	Weeks 37 - 40	Treatment Day [253,280]
	Weeks 41 - 44	Treatment Day [281,308]
	Weeks 45 - 48	Treatment Day [309,336]
	Weeks 49 - 52	Treatment Day [337, minimum (the end of open-label treatment period, 364)]

The analysis visit windows for MSQ v2.1, PGIC, and MIDAS are defined as follows:

Table 6-8 Efficacy Analysis Visit Definitions for MSQ v2.1, PGIC, and MIDAS

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Pretreatment*	Baseline	Visit 1 for De Novo EM Participant only	Baseline from lead-in study for 3101-303-002 Completer Treatment Day ≤ 1 for De Novo EM Participant
Open-label Treatment Period	Week 12	Visit 4	Treatment Day [1, 126] for 3101-303-002 Completer Treatment Day [2, 126] for De Novo EM Participant
	Week 24	Visit 7	Treatment Day [127, 210]
	Week 36	Visit 10	Treatment Day [211, 294]
	Week 48	Visit 13	Treatment Day [295, 350]
	Week 52	Visit 14/ET	Treatment Day >= 351 and within open-label treatment period
Safety Follow-up Period**	Week 56 (Follow-up)	Visit 15	Treatment Day [the end of open-label treatment period +1, the last study visit]

ET early termination

* Only for MSQ v2.1 and MIDAS.

** Only for MSQ v2.1.

The analysis visit windows for HIT-6, EQ-5D-5L, PGI-S, Patient Satisfaction with Study Medication, and WPAI:MIGRAINE are defined as follows:

Table 6-9 Efficacy Analysis Visit Definitions for HIT-6, EQ-5D-5L, PGI-S, Patient Satisfaction with Study Medication, and WPAI:MIGRAINE

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Pretreatment*	Baseline	Visit 1 for De Novo EM Participant only	Baseline from lead-in study for 3101-303-002 Completer Treatment Day ≤ 1 for De Novo EM Participant
Open-label Treatment Period	Week 4	Visit 2	Treatment Day [1, 42] for 3101-303-002 Completer Treatment Day [2, 42] for De Novo EM Participant
	Week 8	Visit 3	Treatment Day [43, 70]
	Week 12	Visit 4	Treatment Day [71, 98]
	Week 16	Visit 5	Treatment Day [99, 126]
	Week 20	Visit 6	Treatment Day [127, 154]
	Week 24	Visit 7	Treatment Day [155, 182]
	Week 28	Visit 8	Treatment Day [183, 210]
	Week 32	Visit 9	Treatment Day [211, 238]
	Week 36	Visit 10	Treatment Day [239, 266]
	Week 40	Visit 11	Treatment Day [267, 294]
	Week 44	Visit 12	Treatment Day [295, 322]
	Week 48	Visit 13	Treatment Day [323, 350]
	Week 52	Visit 14/ET	Treatment Day >= 351 and within open-label treatment period
Safety Follow-up Period**	Week 56 (Follow-up)	Visit 15	Treatment Day [the end of open-label treatment period +1, the last study visit]

ET early termination

* Only for HIT 6, EQ 5D 5L and PGI S.

** Only for HIT 6 and EQ 5D 5L.

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

Table 6-10 Safety Analysis Visit Definitions

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Pretreatment	Baseline	Visit 1 for De Novo EM Participant only	Baseline from lead-in study for 3101-303-002 Completer Treatment Day ≤ 1 for De Novo EM Participant
Open-label Treatment Period	Week 4	Visit 2	Treatment Day [1, 42] for 3101-303-002 Completer Treatment Day [2, 42] for De Novo EM Participant
	Week 8	Visit 3	Treatment Day [43,70]
	Week 12	Visit 4	Treatment Day [71,98]
	Week 16	Visit 5	Treatment Day [99,126]
	Week 20	Visit 6	Treatment Day [127,154]
	Week 24	Visit 7	Treatment Day [155,182]
	Week 28	Visit 8	Treatment Day [183,210]
	Week 32	Visit 9	Treatment Day [211,238]
	Week 36	Visit 10	Treatment Day [239,266]
	Week 40	Visit 11	Treatment Day [267,294]
	Week 44	Visit 12	Treatment Day [295,322]
	Week 48	Visit 13	Treatment Day [323,350]
	Week 52	Visit 14/ET	Treatment Day >= 351 and within open-label treatment period
	End of treatment		Last available assessment during open-label treatment period
Safety Follow-up Period	Week 56 (Safety follow-up)	Visit 15	Treatment Day [the end of 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 392) or ET

ET early termination

Safety follow up visit will be presented in analysis tables for clinical laboratory values and vital signs.

End of Open label Treatment is defined as the last available assessment during open label treatment period. End of Open label Treatment results will be presented in analysis tables for clinical laboratory values, electrocardiograms 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 analysis tables for safety parameters, including but not limited to clinical laboratory values, and vital signs.

For endpoints collected by visit, the last visit with a non-missing value will be used for analysis, if a participant has 2 or more visits within the same window.

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 "todays 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"

The date (COLLDAT) and time of the daily headache diary will be used for merging "today's diary" and "yesterday's diary" for 3101-303-002 rollover CM participants to align with the eDiary data derivation in 3101-303-002 study. The collection date (COLLDAT) is the date the daily headache diary is for, and collection time (COLLTIM) is triggered by the opening of the daily headache diary. Due to the eCOA vendor no longer collecting collection time in the EM cohort, the start date (STDAT) and time (STTIM) of the daily headache diary, which is the date and time when the daily headache diary is opened, will be used for merging "today's diary" and "yesterday's diary" for De Novo EM participants.

If a participant confirmed no headache for the Question 1 in eDiary, then the participant will not answer subsequent questions related to headache symptoms, duration, and acute headache mediation use by design. Thus, the acute medication use for that diary ('today' or 'yesterday') will be treated as 'No' when deriving acute medication use day.

If a participant reported multiple records on the same day for one specific category ('Today' or 'Yesterday') and records are inconsistent, then the records for that eDiary category on the date with discrepancy will be excluded from endpoint derivation and thus excluded from the analyses. The corresponding records will be flagged in the analysis datasets.

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. **For baseline, a minimum of 20 days' eDiary data during the 4-week baseline period is required for the migraine days to be evaluable**. 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, 13-16, 17-20, 21-24, 25-28, 29-32, 33-36, 37-40, 41-44, 45-48, 49-52). 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 moderate/severe headache days, and monthly severe headache days.

If a participant confirmed that acute medications were taken and entered medications in the eDiary, then the acute medication use day will be set to 'Yes.' If a participant 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 and vice versa.

6.4.3. Derivation of Health Outcome Endpoints

AIM-D Related Endpoints Derivation

As described in SAP Section 5.3.4.8 (copied from protocol Section 6.3.1), 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 Total Score of the AIM-D

Step 1: Calculate AIM-D daily domain 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 domain, 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 6-11.

Table 6-11 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 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 2.1 domain are listed below:

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

HIT-6 Total Score Derivation

For HIT-6 total score, pre-coded item values and final item values for each item response are shown in Table 6-12. Total score is calculated by summing 6 sub-item responses, resulting in the total score ranging from 36 to 78 with higher scores indicating greater impact. If any sub-item is missing, then total score will be missing.

Table 6-12 Item Values for HIT-6 Item Response

Response Categories	Precoded Item Value	Final Item Value
Never	0	6
Rarely	1	8
Sometimes	2	10
Very Often	3	11
Always	4	13

The HIT-6 instrument has a recall period of 4 weeks for 3 of the 6 items.

MIDAS Related Endpoints Derivation

MIDAS total score is derived as the sum of first 5 of questions (i.e., the sum of days missing work or school, Productivity at work or school reduced, Not do household work, Productivity in household work reduced, Miss family social or leisure activities). If any sub item is missing, the MIDAS total score will be missing.

The MIDAS absenteeism score is derived as the sum of Questions 1, 3 and 5. If any sub item is missing, then the MIDAS absenteeism score will be missing. The MIDAS presenteeism score is derived as the sum of Questions 2 and 4. If any sub item is missing, then the MIDAS presenteeism score will be missing.

WPAI:MIGRAINE Related Endpoints Derivation

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

Questions:

- Q1 currently employed (working for pay).
- Q2 missed work hours because of problems associated with your migraine
- Q3 missed work hours due to other reason.
- Q4 hours actually worked.
- Q5 migraine affected productivity while working.
- Q6 migraine affected regular daily activity.

Scores:

Multiply scores by 100 to express in percentages.

- Percent work time missed due to migraine (absenteeism): Q2/(Q2 + Q4)
- Percent impairment while working due to migraine (presenteeism): Q5/10
- Percent overall work impairment due to migraine (overall work productivity loss): Q2/(Q2 + Q4) + [(1- (Q2/(Q2 + Q4)))×(Q5/10)]
- Percent activity impairment due to migraine (regular activity impairment): Q6/10

If the response to Q1 ("Currently employed?") is *No* or missing, absenteeism, presenteeism, and overall work productivity loss will all be set to missing.

EQ-5D-5L

With the EQ-5D-5L, rating levels can be coded as numbers 1, 2, 3, 4 or 5 which correspond to having no problems, having slight problems, having moderate problems, having severe problems, and being unable to do/having extreme problem. As a result, a participants health state can be defined by a 5-digit number by combining the numeric levels from the 5 dimensions, ranging from 11111 (having no problems in all 5 dimensions) to 55555 (having extreme problem in all 5 dimensions). The US-based value set for the EQ-5D-5L will be derived using an international standardized protocol (Pickard et al., 2019).

The EQ-5D-5L will be completed by the participants at Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and 56.

6.4.4. Repeated or Unscheduled Assessments of Safety Parameters

Baseline is defined as the last assessment made before the first dose of study treatment. If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing 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 Treatment

When the date of the last dose of the open-label study treatment 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 treatment 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, a severity 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, a severity 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 (i.e., 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 (i.e., 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.

7. Covid-19 Related Analyses

7.1. Efficacy Evaluation

For the endpoints are collected via eDiary, minimal disruption is expected for these endpoints because participants are expected to complete eDiary at home and submit the responses every day.

The health outcome measures will be collected using eTablet as electronic patient reported outcomes (ePRO) at site. To evaluate the missing rate for these efficacy endpoints, the number of participants who missed at least one visit due to COVID-19 will be summarized at each visit in the efficacy analysis population.

7.2. Safety and Other Evaluations

This section specifies 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 infection and supplemental signs and symptoms
- COVID-19 status (COVID-19 testing results or contact with a COVID-19 positive person)
- COVID-19 vaccination

The Safety Population will be used for the planned COVID-19 related analyses, except where noted below.

The number of participants impacted by COVID-19 during the study will be summarized. In addition, the number of participants impacted by COVID-19 and their corresponding disposition status in the open-label treatment period and the follow-up period will be summarized respectively.

The number of participants who missed at least one entire visit due to COVID-19 will be summarized. Furthermore, the number of participants who missed at least one assessment due to COVID-19 will be summarized by assessment category (laboratory, C-SSRS, urine pregnancy test, vital signs, ECG, and ePRO) and overall. Similar summaries will be provided by visit.

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.

The number and percentage of participants who received a COVID-19 vaccine will be tabulated by Anatomical Therapeutic Chemical (ATC) 4 class and preferred term (PT) in participants received COVID-19 vaccine in Safety Population during this study. The number and percentage of participants with TEAEs and serious TEAEs related to COVID-19 vaccine will be summarized in Safety Population and participants received COVID-19 vaccine in Safety Population during this study. Supporting listings for the described analyses above will be provided.

8. References

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