1.0 TITLE PAGE

STATISTICAL ANALYSIS PLAN

A Phase 3, Multicenter, Open-label 40-week Extension Study to Evaluate the Long-Term Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants with Episodic Migraine

Final SAP Date: 25 JULY 2019
Amendment 1: 30 APR 2021

Protocol Number:	3101-309-002
Development Phase:	3
Product Name:	AGN-241689
Sponsor Name and Legal Registered Address**:**	Allergan Pharmaceuticals International Limited Marlow International The Parkway, Marlow SL7 1YL United Kingdom

2.0 TABLE OF CONTENTS

2.1 LIST OF TABLES

2.2 LIST OF FIGURES

3.0 LIST OF ABBREVIATIONS

Term/Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CM	chronic migraine
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
EM	episodic migraine
EOS	end of study
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd edition
LLN	low limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
OL	open-label
PCS	potentially clinically significant
PID	participant identification
PK	pharmacokinetic
PT	preferred term
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SD	standard deviation
SI	*Le Système International d'Unités* (International System of Units)
SOC	system organ class
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
ULN	upper limit of normal
V	Visit
WHO	World Health Organization
WK	Week

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the safety data as outlined and/or specified in the final protocol of Study 3101-309-002 (dated 22 Feb 2019) and protocol amendment 1 (dated 15 Sept 2020). Specifications of tables, figures, and data listings are contained in a separate document.

Study 3101-309-002 is a Phase 3, multicenter, open-label, 40-week, long-term safety extension study conducted in the United States and will enroll approximately 750 participants from the United States. Participants will be treated with atogepant 60 mg once daily.

The study will consist of a 40-week open-label treatment period, and a safety follow-up period of 4 weeks.

Participants will directly rollover from Study 3101-301-002 (Phase 3 EM). As such, participants will have Visit 7 from Study 3101-301-002 function as the Visit 1 for this study after the participant signs the informed consent. After Visit 1, study visits will occur every 4 weeks for the duration of the study. An EOS Visit will occur 4 weeks after the last dose of atogepant.

Note, there may be participants who complete Visit 7 in the lead-in Study 3101-301-002 before extension Study 3101-309-002 has been initiated. Those participants should complete Visit 7/ET and Visit 8/EOS Visit (including discontinuation of study intervention) per the Study 3101-301-002 Schedule of Visits and Procedures.

Depending on the timing of the initiation of this extension study, in relation to each participant's planned Visit 8 schedule, Visit 1 Study 3101-309-002 can be conducted on the same day as Visit 8/EOS Visit for Study 3101-301-002 or soon thereafter.

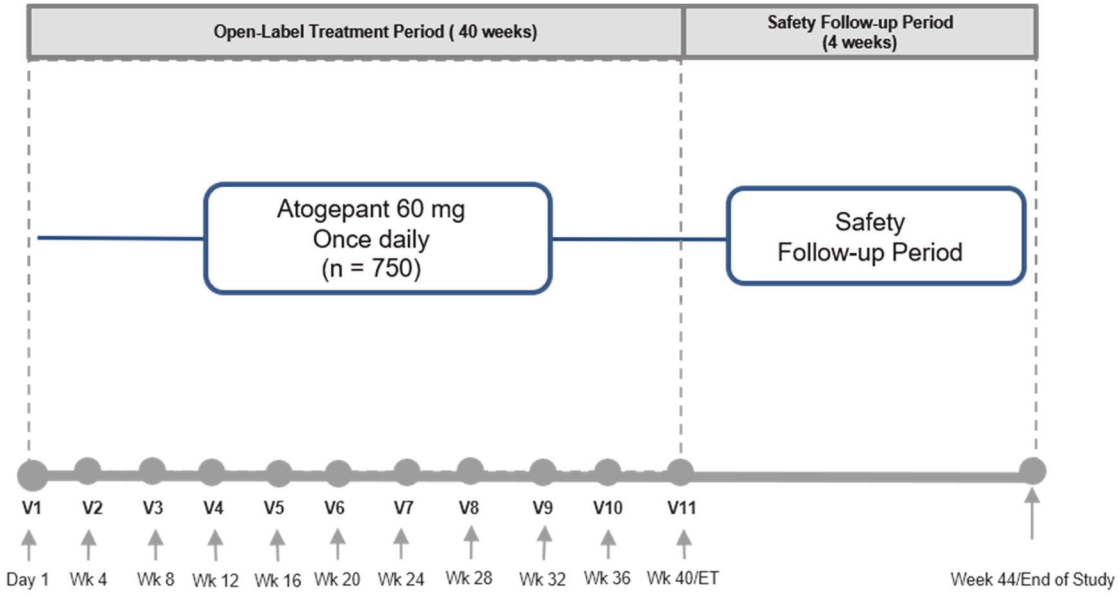
- If this extension study is initiated prior to the participant's planned Visit 8 in the lead-in study, then Visit 8/EOS Visit for Study 3101-301-002 should be conducted on the same day as Visit 1 for Study 3101-309-002.

- If this extension study is not initiated prior to the participant's planned Visit 8 in the lead-in study (ie, there is a gap between Visit 8 and Visit 1), then Visit 8/EOS Visit should be conducted as planned per the Study 3101-301-002 Schedule of Visits and Procedures. When this extension study is initiated, the participant should return to the clinic as soon as possible, and Visit 1 should be conducted per the Study 3101-309-002 Schedule of Visits and Procedures.

After Visit 1, study visits will occur every 4 weeks for the duration of the 40-week treatment period. Participants will return to the clinic for safety assessments at 4, 8, 12, 16, 20, 24, 28, 32, 36 and 40 weeks relative to Visit 1 (Day 1). An EOS Visit will occur 4 weeks after the last dose of atogepant 60 mg once daily. For details, Please see Table 4-1 Study Design Diagram, and Figure 4-1 Schedule of Visits and Procedures.

To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity, the protocol has been updated to allow investigators/appropriately designated study staff to perform study visits remotely in protocol amendment 1. For the schedule of visits and procedures conducted remotely, see Table 4-2.

Figure 4–1 Study Design Diagram



ET = early termination; V = visit; Wk = week.

Table 4-1 Schedule of Visits and Procedures for In-person Visits Conducted Prior to or During the COVID-19 Pandemic

Study Period	**Open-label Treatment Period (40 weeks)**											**Safety Follow-up Period (4 weeks)**
Visit #	**Visit 1[a]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11/ET**	**Visit 12/ EOS[e]**
Day/Week	***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)***
Visit Windows		± 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 participan privacy	X											
Access IWRS	X	X	X	X	X	X	X	X	X	X	X	X
Assess inclusion/exclusion criteria	X											
Perform physical examination	X										X	X
Collect vital sign measurements[b]	X	X	X	X	X	X	X	X	X	X	X	X
Perform ECG	X			X			X				X	
Perform urine pregnancy test[c]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory determinations[d]	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study intervention (ie, atogepant)	X	X	X	X	X	X	X	X	X	X		
Review of study intervention (ie, atogepant) compliance and accountability		X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	X

C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; INR = international normalized ratio; IWRS = interactive web response system.

[a] After providing informed consent for the current study, Visit 1 will be conducted on the same day as Study 3101-301-002 Visit 7; procedures collected as part of Study 3101-301-002 Visit 7 should not be repeated. Visit 1 must be conducted as an in-person visit.

[b] Vital sign measurements: Weight, sitting and standing pulse rate, respiratory rate, sitting and standing blood pressure, and body temperature.

[c] For women of child-bearing potential only, a urine pregnancy test will be performed at all visits.

[d] 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 screening (Visit 1).

[e] During the COVID-19 pandemic, Visit 12 (Follow-up/End of Study) should be conducted remotely for all participants.

Table 4-2 Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID-19 Pandemic

Study Period	**Open-label Treatment Period (40 weeks)[a]**										**Safety Follow-up Period (4 weeks)**
Visit #	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11/ET**	**Visit 12/ EOS[c]**
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)***
Visit Windows	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Access IWRS	X	X	X	X	X	X	X	X	X	X	X
Provide urine pregnancy test and instructions[b]	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X
Dispense study intervention (ie, atogepant	X	X	X	X	X	X	X	X	X		
Review of study intervention (ie, atogepant) compliance and accountability	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/concurrent procedures	X	X	X	X	X	X	X	X	X	X	X

C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; IWRS = interactive web response system.

[a] For participants who have a study visit replaced by a remote study visit, all missed in-person safety assessments (clinical laboratory determinations, vital signs, and ECGs) will be collected at the next in-person visit. To ensure participant safety, remote study visits can be performed for up to 8 weeks at the discretion of the investigator, after which, participants who cannot attend in-person for a study visit must be discontinued from the study.

[b] For women of childbearing potential only, a urine pregnancy test must be performed within 48 hours prior to the remote visits. Investigators/site staff will provide participants with study-supplied urine pregnancy tests and corresponding written instructions to be used at home by participants for remote study visits. Sites are required to verbally review testing instructions with all participants.

[c] During the COVID-19 pandemic, Visit 12 (Follow-up/End of Study) should be conducted remotely for all participants.

5.0 OBJECTIVES

The study objective is to evaluate the safety and tolerability of treatment with atogepant 60 mg once daily for the prevention of migraine over a 40-week duration.

6.0 ANALYSIS POPULATIONS

6.1 SCREENED POPULATION

The Screened Population consists of all participants who signed an informed consent form to enroll in this study.

6.2 SAFETY POPULATION

The Safety Population consists of all participants who received at least 1 dose of atogepant in this extension study.

7.0 PARTICIPANT DISPOSITION

Screen-failures and the associated reasons for failure will be tabulated for all screened participants.

The number of participants in the 2 study populations (Screened, Safety) will be summarized overall.

The number of participants in the safety population will be summarized by lead-in study treatments (placebo, Atogepant 10 mg, Atogepant 30 mg, Atogepant 60 mg) and enrollment category (3101-301-002 Visit 7 Completer, 3101-301-002 Visit 8 Completer, 3101-301-002 Study Completer) and overall.

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 same period will be presented for the Safety Population. The reasons for premature discontinuation from the open-label treatment period will be summarized (number and percentage). Similar disposition information to the treatment period will be presented for the safety follow-up period. All participants who prematurely discontinue during the open-label treatment period or the safety follow-up period will be listed by discontinuation reason.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; age group[<20, 20-29, 30-39, 40-49, 50-59, 60-69, and >=70]; race; race group [white, non-white]; ethnicity; sex), baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2 will be summarized descriptively for the Safety Population. For all participants in 3101-309-002, demographics and other baseline characteristics from the lead-in study (Study 3101-301-002) will be used. Continuous variables will be summarized by number of participants and mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Abnormalities in participants' medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities, version 22.0 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 and preferred term 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 from the lead-in study will be reported for the Safety Population.

Prior medication is defined as any medication taken before the date of the first dose of lead-in study treatment. *Concomitant medication* 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 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 for the open-label treatment period and 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 World Health Organization (WHO) Drug Dictionary Enhanced, March 2019 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Protocol deviations will be defined in Protocol Deviation Requirement Specification, including significant deviation classification. The number and percentage of participants with significant protocol deviations will be summarized for the Safety Population.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Exposure to study treatment for the Safety Population during the treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of open-label study treatment taken 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 will be summarized. Descriptive statistics (number of participants, mean, SD, median, Q1, Q3, minimum, and maximum) will also be summarized.

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

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for a specified period is defined as the total number of study medications actually taken by a participant during that period divided by the number of open-label study medications that were expected to be taken during the same period multiplied by 100. The total number of tablets actually taken during the treatment period will be calculated from the study medication record. Descriptive statistics for open-label study medication dosing 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 period from the first dose of the open-label study interventions actually taken to the last dose of open-label study intervention actually taken for the Safety Population.

10.0 EFFICACY ANALYSES

No efficacy analysis is planned.

11.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs), clinical laboratory, vital sign, electrocardiographic (ECG), and C-SSRS. For each of the clinical laboratory, vital sign, and ECG parameters, the last non-missing safety assessment before the first dose of treatment from lead-in study (Study 3101-301-002) will be used as the baseline. Continuous variables will be summarized by number of participants and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

11.1 ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities* (MedDRA), version 22.0 or newer.

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 double-blinded dose of the lead-in study treatment. An AE that occurs more than 30 days after the last dose of study treatment in this study or safety follow-up visit (Visit 12) 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 with recorded onset date on or after the date of the first dose of lead-in study treatment and within 30 days after the last dose of open-label study treatment or Visit 12 whichever comes later. An AE will be considered as a treatment-emergent SAE (TESAE) if it is a TEAE that also meets SAE criteria. TEAEs that started after the date of last dose of open-label study treatment will be considered as newly emergent. Only TEAEs that started on or after the date of first dose of open-label study treatment will be summarized for this study.

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

The number and percentage of participants reporting TEAEs will be tabulated by system organ class and preferred term, and further categorized by severity and causal relationship to the study treatment. 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 and strictest causality for the summarization by severity and causal relationship.

The number and percentage of participants reporting newly emergent TEAEs will be tabulated by system organ class and preferred term.

The number and percentage of participants who have TEAEs leading to premature discontinuation of the study intervention will be summarized by system organ class, preferred term.

The incidence of common (≥ 2% [after rounding] of participants) TEAEs will be summarized by preferred term.

The number and percentage of participants who have TESAE will be tabulated by system organ class and preferred term.

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

All AE reports in this study will be summarized or listed.

11.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented for the following laboratory parameters.

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 Appendix I. A description of reporting the lab values in conventional units in patient narratives (along with the standard reporting in SI units) is presented at the end of Appendix I.

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
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, estimated glomerular filtration rate
Urinalysis:	Specific gravity, pH

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11-1 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. 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 postbaseline values will be provided, including the participant identification (PID) number, baseline and all postbaseline (including non-PCS) values.

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

Potential Hy's Law criteria within a 24-hour window is defined by a postbaseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq$ 3 x ULN, along with total bilirubin (TBL) $\geq$ 2 x ULN and a non-elevated alkaline phosphatase (ALP) < 2 x 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.

Table 11-1 Criteria for Potentially Clinically Significant Laboratory Values

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 mL/min/1.73 m^2	—
	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).

The number and percentage of participants meeting each of the following criteria for postbaseline hepatic laboratory abnormalities listed in Table 11-2 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.

Table 11-2 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

Laboratory Parameter	Categories
Concurrent Elevations[1]	ALT or AST >= 3 × ULN and Bilirubin Total ≥ 1.5 × ULN
	ALT or AST >= 3 × ULN and Bilirubin Total ≥ 2 × ULN
Potential Hy's Law within 24-hour window[1]	Postbaseline assessment of the following laboratory parameters based on blood draws collected within a 24-hour period: • ALT or AST ≥ 3 × ULN • TBL ≥ 2 × ULN • ALP < 2 × ULN
e-DISH	Postbaseline assessment of the following laboratory parameters at any time: • Maximum ALT or AST ≥ 3 ×ULN • Maximum TBL ≥ 2 × ULN
ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ALP = alkaline phosphatase; ULN = upper limit of normal (value provided by the laboratory). [1] Elevations are from the same day	

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

11.3 VITAL SIGNS

Descriptive statistics for vital signs (systolic and diastolic blood pressures [sitting and standing], pulse rate [sitting and standing], respiratory rate, temperature, weight, orthostatic systolic blood pressure, orthostatic diastolic blood pressure, and orthostatic pulse rate) values at baseline, postbaseline, and changes from baseline values at each postbaseline 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 Table 11-3.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 participants with PCS postbaseline 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.

Table 11-3 Criteria for Potentially Clinically Significant 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.

11.4 ELECTROCARDIOGRAM

Descriptive statistics for ECG parameters (ie, heart rate, PR interval, QRS interval, QT interval, and QTc interval) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented.

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in Table 11-4.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 ms, >480 ms, or >500 ms will be tabulated by treatment group. 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, study center, 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.

Table 11-4 Criteria for Potentially Clinically Significant Electrocardiograms

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

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

11.5 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 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, study center number, lifetime history, and postbaseline values. Intensity of suicidal ideation and suicidal behavior type will also be included in these listings.

12.0 COVID-19 RELATED ANALYSES

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 and supplemental signs and symptoms
- COVID-19 status (COVID-19 testing results or contact with a COVID-19 positive person)

Safety population will be used for the planned analyses described above. The number of participants impacted by COVID-19 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 tabulated, respectively.

The number of participants with study visits impacted by COVID-19 will be summarized by the classification of study visits (missed, clinical visits in person, remote [auto/video]).

Furthermore, the number of participants who missed at least one entire visit due to COVID-19 will be summarized; the number of participants who missed at least one assessment due to COVID-19 will be summarized by assessment procedures (laboratory, C-SSRS, urine pregnancy test, vital signs and ECG) and visit. The number of participants with remote assessments of C-SSRS and pregnancy test will be summarized 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.

Supporting listings for the described analyses above will be provided.

13.0 HEALTH OUTCOMES ANALYSES

Not Applicable.

14.0 SUBGROUP ANALYSES

No subgroup analysis is planned.

15.0 INTERIM ANALYSIS

Interim data-cuts are planned to provide ongoing safety data to support global regulatory submissions.

16.0 DETERMINATION OF SAMPLE SIZE

As this is a safety extension study from the lead-in Study 3101-301-002, all participants from the lead-in study who are eligible for this extension study will be enrolled. No separate sample size calculation was performed. Based on expected completion rate from the lead-in Study 3101-301-002, approximately 750 participants will be enrolled into this long-term, open-label, safety extension study.

17.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.4 or newer of SAS.

18.0 DATA HANDLING CONVENTIONS

18.1 VISIT TIME WINDOWS

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

Table 18.1–1. Safety Analysis Visit Definitions

Analysis Visit (Derived)	***Scheduled Visit Day[a]***	***Window***
Baseline	Baseline from lead-in study	
Week 4	Day 28 (Visit 2)	Treatment Day [1, 42]
Week 8	Day 56 (Visit 3)	Treatment Day [43, 70]
Week 12	Day 84 (Visit 4)	Treatment Day [71, 98]
Week 16	Day 112 (Visit 5)	Treatment Day [99, 126]
Week 20	Day 140 (Visit 6)	Treatment Day [127, 154]
Week 24	Day 168 (Visit 7)	Treatment Day [155, 182]
Week 28	Day 196 (Visit 8)	Treatment Day [183, 210]
Week 32	Day 224 (Visit 9)	Treatment Day [211, 238]
Week 36	Day 252 (Visit 10)	Treatment Day [239, 266]
Week 40	Day 280 (Visit 11)	Treatment Day [267, the last open-label visit]
End of open-label treatment period		Last available assessment during open-label treatment period
Safety Follow-up/EOS	Day 308 (Visit 12)	Treatment Day [the last open-label visit +1, the last study visit]
End of Study		Last available assessment Day after treatment start date, i.e. occurs at final visit (expected Day 280) or ET

[a] Relative to the date of the first dose of study treatment. Day 1 = the date of the first dose of study treatment. There is no Day 0 or Week 0.

End of Treatment is defined as the last available assessment during open-label treatment period, i.e. on or before the treatment end date. End of Treatment results will be presented in analysis tables for clinical laboratory values, electrocardiogram and vital signs.

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

ET = early termination. EOS=end of study.

18.2 DERIVED VARIABLES

Not applicable.

18.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

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

18.4 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT

When the date of the last dose of 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 medication date will be used in the calculation of treatment duration.

18.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

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

18.6 MISSING CAUSAL RELATIONSHIP TO STUYD DRUG 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 study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

18.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

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

Missing month and day

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

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

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

Missing month only

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

Missing day only

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

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

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

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

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

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

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

18.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

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

18.8.1 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

18.8.2 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 open-label study treatment is missing, impute it as descripted in Section 18.4. 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 open-label study treatment, the month and day of the last dose of open-label 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 open-label 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 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 stop date are the same as the month and year of the last dose of open-label study treatment, the day of the last dose of open-label 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 open-label 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 open-label 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 open-label 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 open-label study treatment, the first day of the month will be assigned to the missing day

18.9 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

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

Table 18.9–1 shows examples of how some possible laboratory results should be coded for the analysis.

Table 18.9–1 Examples of Coding Special Character Values for Clinical Laboratory Parameters

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

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

19.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

None

20.0 APPENDICES

APPENDIX I. REPORTING SELECTED LABORATORY PARAMETERS IN CONVENTIONAL UNIT

All clinical laboratory parameters will be reported in the International System (SI) units as standard practice. In addition, descriptive statistics for values and changes from baseline in conventional units at all assessed visits will be reported for selected laboratory parameters as listed in Table19.I–1 below.

Table19.I–1 List of Selected Parameters to be Reported in Conventional Units

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

Patient narratives will also include the values in conventional units for the selected lab parameters (Table19.I–1). That will be accomplished by presenting the values in conventional units within the parentheses next to the values in SI units. As shown in Table19.I–2 below for 'Bilirubin, Total' parameter, for which 'umol/L' is the SI unit and 'mg/dL' is the conventional unit.

Table19.I–2 Presenting Laboratory Data Using SI and Conventional Units in Narratives

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

Summary of Changes from Original to Amendment 1

Date	Section	Description
August 6, 2019	11.2	Added eGFR in Chemistry to be consistent with the protocol.
August 6, 2019	17.1	Updated visit window definitions to ease ISS preparation.
October 2, 2019	11.3	Deleted Vital Signs of Clinical Interest since it would be summarized in ISS.
October 2, 2019	11.1	Clarified the definition of newly emergent adverse event.
October 15, 2019	9.1	Added more categories for ISS purpose.
October 17, 2019	11.1	Added another sentence to accommodate AE captured at the shared visits for both lead-in study and extension study.
October 22, 2019	11.4	Added ECG of clinical interest to align with all other Atogepant studies.
December 4, 2019	11.1	Updated to include only "study intervention discontinuation"
December 4, 2019	7.0	Clarified the "Screened Population" for disposition
January 3, 2020	11.2	Updated PCS High for Urinalysis in Table 11-1
February 13, 2020	11.2	Deleted the shift table for lab parameters
February 25, 2020	11.2	Updated eGFR's PCS lower limit in Table 11-1 since central lab did not provide the lower level of normal
February 25, 2020	Appendix I	Updated the unit for Albumin and Hemoglobin

Date	Section	Description
		for CDISC compliance purpose
April 22, 2020	11.3	Clarified the denominator of PCS table for vital signs
May 6, 2020	7.0	Deleted "by study center" since it is not necessary
April 26, 2021	Title Page	Added Amendment 1 Date, and removed statistician name
April 26, 2021	4.0	Added protocol amendment 1 information; indicated Schedule of assessments is updated and remote assessment schedule is provided.
April 26, 2021	Table 4.1 and Table 4.2	Updated Table 4.1 to align with protocol amendment 1; Added Table 4.2 of "Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID 19 Pandemic" to describe remote study visits.
April 26, 2021	9.2	The overall period for compliance calculation is clarified
April 26, 2021	11.2	Deleted the criteria for potential Hy's law without window. Clarified the criteria for e-DISH in Table 11-2
April 26, 2021	Section 12	Added the section to describe COVID-19 related analyses.