COVER PAGE

Official Title:	An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation
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STATISTICAL ANALYSIS PLAN

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Study Title: An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation

Name of Study Treatment: tofersen (BIIB067)

Protocol No.: 233AS102

Study Phase: 3

APPROVAL

This document has been reviewed and approved by:		
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VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
1.0	08June2021	N/A
2.0	12August2021	Changed category of secondary endpoint; updated interim data cutoff date; updated AE of note table; added listing of site transfer; Updated covariates for ANCOVA model of SVC; Remove time to permanent ventilation or death analysis.
3.0	02Feb2022	Demographic and baseline tables were removed; Added analyses of clinical/biomarker endpoints for ITT population; Subjects with at least one post-baseline CSF WBC values >5 was removed; NfL in CSF will be analyzed.
4.0	06Aug2024	Updated for final analysis of CSR reporting. Added demographic and baseline tables; Removed analyses of clinical/biomarker endpoints; Removed enriched/other subgroup; Removed type of visit summary by endpoint.

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LIST OF ABBREVIATIONS

AE	adverse event
ALS	amyotrophic lateral sclerosis
ALSFRS-R	ALS Functional Rating Scale (revised)
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BLQ	below limit quantitation
BMI	body mass index
Bpm	beats per minute
BUN	blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CO2	bicarbonate
COVID-19	Coronavirus Disease 2019
CRF	case report form
CSF	Cerebral-spinal fluid
C-SSRS	Columbia suicide severity rating scale
CTCAE	common terminology criteria for adverse events
EAIR	exposure adjusted incidence rates
ECG	electrocardiogram
EOS	end of study (visit)
[redacted]	[redacted]
ET	early termination (visit)
[redacted]	[redacted]
GGT	gamma-glutamyl transferase
HHD	hand-held dynamometry
INR	international normalized ratio
IRT	interactive randomization system
ITT	intent-to-treat
LLOQ	lower limit of quantitation
LP	lumbar puncture
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
mmHg	millimeters of mercury
MMSE	mini-mental state exam
[redacted]	[redacted]
N	number of subjects or observations
[redacted]	[redacted]
NfL	neurofilament light chain
ng/mL	nanogram/milliliter

PD	pharmacodynamics
pg/mL	picogram/milliliter
PK	pharmacokinetic(s)
[redacted]	[redacted]
PT	prothrombin time
QTc	interval between the start of the QRS complex and the end of the T wave, corrected for heart rate
QTcF	QTc interval using Fridericia's formula
RBC	red blood cell (count)
RNA	ribonucleic acid
RR	inter-beat
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SDTM	standard data tabulation model
SE	standard error
[redacted]	[redacted]
SOC	system organ class
SOD	superoxide dismutase 1
SVC	slow vital capacity
ULN	upper limit of normal
WBC	white blood cell (count)
WHO	World Health Organization
[redacted]	[redacted]
[redacted]	[redacted]

1. Introduction

Study 233AS102 is an extension study of 233AS101 to assess the long-term safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of BIIB067 administered to previously treated adults with ALS caused by SOD1 mutation, who have completed Parts A, B, or C of Study 233AS101.

Study 233AS101 is a randomized, double-blind, placebo-controlled, 3-part study to examine the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of BIIB067, administered by intrathecal bolus injection in subjects with ALS and a confirmed SOD1 mutation.

This statistical analysis plan (SAP) is prepared to describe the final analysis for the closeout clinical study report for 233AS102; separate SAPs exist for 233AS101 Parts A and B, 233AS101 Part C, and integrated analyses across the studies. Prior versions of the SAP for 233AS102 (Versions 1.0 to 3.0) were generated for the purpose of interim analyses based on interim data cuts for the study.

BIIB067 will be referred to as tofersen throughout the rest of the statistical analysis plan.

There are limitations for subjects who enrolled from 233AS101 Parts A and B which impact the interpretability of these subjects in 233AS102:

- Subjects who completed Parts A or B of 233AS101 had a significant washout period ranging from 16 weeks to over 2 years from their last dose of study treatment in 233AS101 to their first dose in 233AS102.
- Dosing paradigms varied substantially across subjects as dose levels in 233AS102 were increased over time as additional doses were deemed to have an acceptable safety profile in 233AS101.
- Many subjects had meaningful disease progression during the washout and exposure to lower doses resulting in a large proportion of discontinuations across studies

There are also some limitations on statistical analysis for subjects who enrolled into 233AS102 from 233AS101 Part C. Some subjects will be tofersen naïve and others will have received approximately 6 months of tofersen treatment prior to entry in 233AS102.

Analyses of efficacy and biomarker endpoints conducted for interim data (July 2021 and January 2022) highlighted the limitations of conducting standalone 233AS102 analyses in these endpoints as outlined below. Based on these learnings, it only makes sense to analyze the longitudinal data from 233AS102 for efficacy and biomarker endpoints as part of an integrated analysis of 233AS101 and 233AS102:

- In contrast to the prespecified integrated analyses of 233AS101 Part C and 233AS102, the standalone analyses of 233AS102 are based on data selected using post-randomization factors and therefore break the original randomization. On the other hand, the overall ITT analysis with the original 233AS101 Part C baseline provides an objective comparison of the two treatment regimens.

- Rate of progression is variable over time. Comparison of the treatment groups from 233AS102 fails to reflect the overall treatment effect due to early tofersen initiation that is evident in 233AS101 Part C. For example, if rate of progression is faster for the delayed start group in period 1 and then becomes comparable to the early start group, the comparison using only period 2 data would be misleading.
- There are imbalances at baseline of 233AS102, as expected due to the effect of tofersen in 233AS101 Part C, thus confounding interpretation of 233AS102 analyses.
- As described above, incorporation of baseline NfL as a covariate is the most objective mechanism to control for disease heterogeneity at baseline. However, baseline neurofilament in 233AS102 cannot be incorporated as a covariate due to the confounding effect of tofersen administration during 233AS102.

Therefore, the data for 233AS102 will have a limited interpretation on its own and the key interpretation for 233AS101 Part C subjects will be from the integrated analyses which will be covered in separate SAPs. The prespecified analysis of treatment effect in the full ITT population from baseline in the randomized portion of the study is the most valid approach to analysis. The final standalone analyses for 233AS102 will focus on safety and exposure data. The final 233AS102 data for efficacy, [redacted] and biomarker endpoints will not be included under the 233AS102 final CSR but will be included under the integrated analyses of 233AS101 and 233AS102.

2. Study Overview

2.1. Study Objectives and Endpoints

Study Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of tofersen in subjects with ALS and confirmed SOD1 mutation.

Study Primary Endpoint

The associated primary endpoint is the incidence of adverse events and serious adverse events.

Secondary Objectives

The secondary objectives are to evaluate the PK, PD, biomarker, and efficacy of tofersen administered to subjects with ALS and confirmed SOD1 mutation.

Secondary Endpoints

- PK endpoints: Plasma and cerebrospinal fluid (CSF) levels of tofersen.
- PD endpoints: Changes (i.e. ratio) from baseline in total SOD1 protein in CSF.
- Biomarker endpoint: Changes (i.e. ratio) from baseline in neurofilament light chain (NfL) concentration in plasma
- Efficacy endpoints:

  - Changes over time in the following:
    - ALSFRS-R total score
    - SVC
    - HHD megascore and individual muscle strength

- Time to death or permanent assisted ventilation, defined as the time to the earliest occurrence of one of the following events:
  - Death.
  - Permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days).
- Time to death

[redacted]

[redacted]

2.2. Study Design

This is a multicenter, open-label, long-term extension study to assess the long-term safety, tolerability, PK, PD, and efficacy of tofersen administered by IT injection to previously treated subjects with SOD1-ALS who have completed Parts A, B, or C of Study 233AS101. The study will be conducted at approximately 42 sites in approximately 15 countries globally.

Subjects who have completed Parts A or B of Study 233AS101 will have a washout period of at least 4 times the t½ (~16 weeks) from the time of their last dose of study treatment in Study 233AS101 to their first dose in Study 233AS102. These subjects will receive 3 loading doses of tofersen 100 mg, approximately 2 weeks apart, during the first 4 weeks.

Subjects who have completed Part C of Study 233AS101 will not have a washout period. To preserve the blinding used in Study 233AS101 until database lock, subjects who enroll in Study 233AS102 after completing Part C of Study 233AS101 will have a blinded Loading Dose Period. Subjects who received placebo while in Study 233AS101 will receive 3 doses of tofersen 100 mg, approximately once every 2 weeks (Days 1, 15, and 29), while subjects who received tofersen in Study 233AS101 will receive 2 doses of tofersen 100 mg, on Days 1 and 29, and placebo on Day 15.

After the Loading Dose Period, all subjects will receive up to 90 maintenance doses of tofersen 100 mg, approximately once every 4 weeks until the last subject enrolled has had the opportunity to have their Week 152 Maintenance Dose Visit. Subjects who were not receiving tofersen 100 mg (i.e., subjects in Parts A and B) will be dosed at tofersen 100 mg at their next scheduled Maintenance Dose Visit.

As a general note, Day 197 in 233AS101 Part C should serve as the same visit as Baseline in 233AS102 (and Day 169 as Screening visit) for the majority of subjects who were rolled over from Part C. The data should be entered under the 233AS101 Part C database but there may be a few exceptions where the incorrect lab kit was used from the 233AS102 and so the data are entered under Baseline in the 233AS102. In that situation where Day 197 for 233AS101 Part C and Baseline for 233AS102 are the same visit, the data will be taken from the 233AS102 database and incorporated into the datasets at the CDISC SDTM level. For the purpose of 233AS102 SDTM the data for Screening and Baseline will be taken from 233AS101 database where appropriate.

Ventilation data were only collected part of the way through the study for subjects who had enrolled from 233AS101 Parts A and B because ventilation data use was introduced for 233AS101 Part C and the assessment was added in 233AS102 protocol amendment when Part C subjects enrollment started.

Central genetic testing was not originally part of the 233AS101 Part A/B or 233AS102 protocol. The protocol was amended to restrict the population to subjects with a SOD1 mutation. By the time this was introduced some subjects had already completed 233AS101 A/B and enrolled into 233AS102. Therefore, central testing was incorporated into the 233AS102 protocol for these few subjects, to confirm they had a SOD1 mutation and their central genetic test results are collected as part of the study. For those subjects who had the central genetic test performed in 233AS101 Part A/B, the test results were not entered or collected as part of the clinical database. Sites had previously entered the variant in the eCRF based on local genetic testing; there was no requirement for them to enter the data from the central test as the only requirement was the subject needed to be confirmed as SOD1 based on central testing. There was also no requirement for reconciliation of the variants and classification between the data entered by sites in the eCRF and the central test results. After database lock for 233AS101 Parts A and B, the central genetic test results have since been obtained from the central lab. The variants specified in Part A/B CSR may therefore vary from what is used for these subjects in 233AS102, as the central test results will be used for reporting 233AS102.

Table 1: Schedule of Activities: 233AS102 (Protocol V6.0)

Assessments	Screening Visit[1]	Baseline/1st Loading Dose Visit			2nd Loading Dose Visit			3rd Loading Dose Visit			Maintenance Dose Visit			Final or Early Termination Visit
	Week -4 to Day -1	Day 1			Day 15 (±3 days) (Week 2)			Day 29 (±3 days) (Week 4)			Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 360 (±3 days)			4 weeks after last dose
		Pre dose	LP	Post dose	Pre dose	LP	Post dose	Pre dose	LP	Post dose	Pre dose	LP	Post dose	
ICF (main) and Genetic/Future Scientific Research Consent (optional)[2]	X													
Medical History	X	X												
Confirmation of Eligibility Criteria[3]	X													
Ventilation Use[4]	X	X			X			X			X			X
ALSFRS-R		X[5]			X[5]			X[5]			X[5, 6]			X[5]
SVC[7]		X[5]			X[5]			X[5]			X[5, 8]			X[5]
HHD		X[5]			X[5]			X[5]			X[5, 8]			X[5]
[redacted]														
C-SSRS[12]		X						X			X[6]			X

Assessments	Screening Visit[1]	Baseline/1st Loading Dose Visit			2nd Loading Dose Visit			3rd Loading Dose Visit			Maintenance Dose Visit			Final or Early Termination Visit
	Week -4 to Day -1	Day 1			Day 15 (±3 days) (Week 2)			Day 29 (±3 days) (Week 4)			Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 360 (±3 days)			4 weeks after last dose
		Pre dose	LP	Post dose	Pre dose	LP	Post dose	Pre dose	LP	Post dose	Pre dose	LP	Post dose	
Weight	X	X												X
Vital Signs (temperature, blood pressure, pulse rate, respiratory rate)	X	X		X	X		X	X		X	X		X	X
12-lead ECG[13]	X	X												X
Physical Examination[14]	X	X												X
Limited Neurological Examination[14]	X	X												X
Pregnancy Test[15]	X	X			X			X			X			X
CSF Samples[16]		X[17]			X[17]			X[17]			X[17]			
Clinical Laboratory Samples for Hematology, Coagulation, Chemistry, and Urinalysis[3]	X	X			X			X			X			X
[redacted]														
Blood Samples for Plasma anti-BIIB067 Antibody		X			X			X			X[18]			X
Blood Samples for PK		X			X			X			X[18]			X
Blood Samples for PD and Biomarkers		X			X			X			X			X
Blood Samples for DNA[19]											X			
Blood Samples for RNA Analysis (optional)[20]		X			X			X			X			X
Study Treatment Administration			X			X			X			X		

Assessments	Screening Visit[1]	Baseline/1st Loading Dose Visit			2nd Loading Dose Visit			3rd Loading Dose Visit			Maintenance Dose Visit			Final or Early Termination Visit
	Week -4 to Day -1	Day 1			Day 15 (±3 days) (Week 2)			Day 29 (±3 days) (Week 4)			Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 360 (±3 days)			4 weeks after last dose
		Pre dose	LP	Post dose	Pre dose	LP	Post dose	Pre dose	LP	Post dose	Pre dose	LP	Post dose	
AE/Concomitant Therapy and Procedures Recording		----------X (ongoing)----------												
SAE Recording	----------X (ongoing)----------													

[1] Screening assessments can be performed over ~2 days (need not be consecutive) to minimize participant burden.
[2] The main ICF will include a genetic consent for collection of DNA samples to confirm presence of SOD1 mutation and to be used for analyses of specific genes related to ALS or the response to BIIB067. DNA and RNA collection for possible future research will be optional in all regions where not prohibited by regulatory authorities or ethics committees. Consent for possible future research (optional) will be collected in a separate document.
[3] The results of the most recent centrally read coagulation tests and platelet count (i.e., those obtained at the previous visit) must be reviewed before LP is performed. Should these results suggest, in the opinion of the Investigator, that LP may be safely performed, then no further review of coagulation tests and platelet counts would be required before performing the LP. However, should repeat coagulation and platelet tests be clinically indicated in the opinion of the Investigator, then these tests may be done locally, to facilitate timely review.
[4] Participants will use a diary/eDiary to record ventilation use. The diary/eDiary should be completed only for days when the participant uses mechanical ventilation. This diary will be reviewed with study site staff at each visit. Refer to the Study Reference Guide for details.

[5] May be performed at any time on the day prior to study treatment administration, predose on the day of study treatment administration, or at the Final or Early Termination Visit.
[6] To be performed at Week 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 272, 276, 280, 284, 288, 292, 296, 300, 304, 308, 312, 316, 320, 324, 328, 332, 336, 340, 344, 348, 352, 356, and 360 Visits (i.e., every 4 weeks).
[7] If a facemask is used in Study 233AS101 or at screening and/or baseline of this study, it should be used for all SVC assessments for the duration of the study. If a facemask is not used during Study 233AS101 or at screening and/or baseline of this study, it should not be used for the duration of the study, if possible. If the participant begins the 233AS102 study not using a facemask but develops the need to use a facemask to complete the SVC during the study, then the facemask should be used for all subsequent SVC assessments for the duration of the study. Upright SVC will be determined by performing 3 to 5 measures. The results will be overread by a central reader to confirm that these criteria (at least 3 acceptable tests with the 2 highest acceptable [largest and next largest] efforts within 150 mL of vital capacity) have been achieved.
[8] To be performed at Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, 312, 324, 336, 348, and 360 (i.e., every 12 weeks) Visits only.

[redacted]

[12]"Since Last Visit" version of C-SSRS will be used after the Baseline/First Loading Dosing Visit.
[13]ECGs to be done at Screening, Day 1, Final/Early Termination Visit, and as clinically necessary per the discretion of the Investigator throughout the study. ECGs will be obtained after participants have rested in a supine position for at least 10 minutes.
[14]A physical examination and limited neurological examination will be performed at the specified timepoints (Screening, Day 1, Final/Early Termination Visit). At all other visits, the physical and/or limited neurological examination may be performed at the Investigator's discretion. The components of the limited neurological examination are coordination/cerebellar function, reflexes, and motor system.
[15]To be performed only in women of childbearing potential; results must be negative to continue participation in study. On dosing days, samples must be analyzed before study treatment administration. To be performed via urine or serum testing.
[16]CSF samples will be collected during the LP for PK, PD, safety, and biomarker analysis and will be analyzed to evaluate for blood contamination. CSF samples for safety will be tested at local laboratories.
[17]Participants will remain under observation in the clinic for ~1 hour after the LP procedure for safety monitoring and can be discharged at the discretion of the Investigator and in compliance with the institutional requirements, once the participants have adequately recovered from the procedure. Participants will receive a safety follow-up telephone contact ~24 hours after the procedure.
[18]Blood samples will be collected on every alternate visit at Week 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148, 156, 164, 172,180, 188, 196, 204, 212, 220, 228, 236, 244, 252, 260, 268, 276, 284, 292, 300, 308, 316, 324, 332, 340, 348, and 356 (i.e., every 8 weeks) Visits only. Blood samples for anti-BIIB067 antibody and PK assessments will be collected at the same time.
[19]For participants who did not have the presence or absence of a SOD1 mutation confirmed centrally in Study 233AS101, a one-time blood sample will be collected. For participants who did not have a blood sample collected for testing of other genes related to ALS and/or the response to BIIB067 in Study 233AS101, an additional blood sample will be collected. Participants undergoing this sample collection will be asked to sign an optional consent for use of DNA for possible future research in all regions where not prohibited by regulatory authorities or ethics committee.
[20]Participants who agree to provide samples will need to sign separate consent form(s). RNA sample collection for possible future research will be optional in all regions where not prohibited by regulatory authorities or ethics committees.

2.3. Protocol Amendments

During the course of study conduct, protocol amendments were developed for Study 233AS102. Due to the changes of the assessments (e.g. adding assessments to align with Study 233AS101 amendment, removing assessments to minimize burdens on the subjects, changes of assessment frequency, etc.), the collected assessments and frequency may vary among subjects enrolled from Part A/B and Part C. Part C subjects started enrolling in Study 233AS102 at protocol amendment V4.0, thus the assessments changes in protocol amendment V4.0 or prior will have no impact on Part C subjects. The new assessments introduced in protocol amendment 4.0 or later (i.e. ventilation use, [redacted]) will only be collected part of the way through the study for Parts A and B subjects. Table 2 below summarized the changes for the impacted endpoints.

MMSE was removed from the protocol amendment V6.0; however, we will include summaries for all the data collected.

Table 2: Summary of changes in protocol amendments

Endpoint	V3.0	V4.0	V5.0	V6.0
Neurological examination (excluding MMSE)	Changed to limited neurological examination (cranial nerves, coordination/cerebellar function, reflexes, motor)	Added post-dose timepoints	Removed cranial nerves examination	Removed from all dosing visits (except for pre-dose baseline)
MMSE		Added post-dose timepoints	Reduced from every 4 weeks to every 12 weeks prior to week 48, and to every 24 weeks up to week 216.	Removed
ECG				Removed from all dosing visits (except for pre-dose baseline)
Vital sign		Added post-dose timepoints		
Immunogenicity, PK		Decreased from 4 weeks to 8 weeks		
ALSFRS-R		Added Day 15		

SVC				Reduced from every 4 weeks to every 12 weeks
HHD		Added Day 15		Reduced from every 4 weeks to every 12 weeks
Ventilation use, [redacted]		Added		
[redacted]				

2.4. General Trial Conduct Mitigation Strategy under COVID-19 Pandemic

In the event of a public health emergency that results in site closure, travel restrictions, and/or the study being deprioritized at the site such that clinic visit(s) cannot occur, a protocol deviation would be incurred for any deviation from the protocol-specified visits and assessments, with additional notation that this protocol deviation is due to the public health emergency. To mitigate risk of missing dosing or assessments during the time of the COVID-19 pandemic, the following mitigating options should be pursued, in order of preference (in which the highest preference option that is feasible should be done): 1) transfer to another active study site that is open, 2) home visit, 3) telemedicine visit (e.g., by telephone or web conference), and 4) local laboratory visit.

- If a site is not closed due to COVID-19 and the site enables the subject to attend the visit in-clinic, then delayed visits within a reasonable timeframe are allowed. In the analysis,

for the loading dose period, a 7-day window will be used and a 14-day window will be used for the maintenance visits.

- Site transfers are encouraged where possible, so that subjects can be transferred to another site for assessment. Instructions are in place to enable sites to do this including transfer of the database and source documents for the patient from the transferring site to the receiving site. This will be the optimal option in order to perform dosing and all assessments for the subject, since dosing can only be performed in the clinic setting due to intrathecal administration. In particular, if screening cannot be performed in the clinic, subjects will be screened at a screening site and subsequently transferred to another site. Site transfer instructions and travel plans were already in place prior to COVID-19 pandemic to allow for subjects to travel to sites if a site was not open in their country of residence.
- If site transfers cannot be performed, subjects will be allowed to have home visits if agreed to by the participating site for the following assessments: neurological/physical examination, vital signs (including height and weight), health outcome measures ([redacted], C-SSRS, [redacted] SVC), biological sample collection, pregnancy test (if applicable), HHD, ventilation diary record.. Instructions are in place on how this will work. If a home visit is performed, ALSFRS-R will still be performed by the blinded rater at the site via telephone. Due to the nature of the ALSFRS-R, as a status assessment, the informed consent allows for telephone visits to collect safety data. It has been shown that there is a strong correlation (r^2=0.941, P < 0.05) between ALSFRS-R administered to patients in the clinic and by telephone (Mannino, 2006). Ventilation diaries recorded on paper will be collected by the staff performing home visits and provided directly to the sites.
- Currently if home visits are not possible or not yet set up for the participating site, a phone visit can be used to collect safety data (AEs, SAEs, [redacted], concomitant medications/procedures), ALSFRS-R, and assessing changes in signs and symptoms.
- Patient reported outcomes were not allowed to be collected by telemedicine based on the original informed consent. An addendum to the global informed consent will allow these assessments to be collected over the telephone after the date it is effective.
- Due to regulations at sites, some sites may allow a clinic visit but not allow SVC to be performed in which case it is preferable to perform this assessment as a home visit or transfer the patient to another site.
- Transferring sites are encouraged to enter and clean all data before transferring the subject to the receiving site. The database for a subject will remain with the transferring site until data are entered and cleaned as much as possible, but the transferring site must have access to the subject in IRT and copies of all source documents. Blinding of staff will be maintained as appropriate. Any queries raised later on for data belonging to visits at the transferring site will be cleaned by the receiving site through the source documents, and interaction between monitors at the receiving and transferring sites. The transferring site will no longer have access to the database for a subject they have transferred but the

monitors will. The Subject ID will remain the same when a subject is transferred to another site, but the transfer can be tracked via the Site ID.

These mitigating options only apply in the setting of a public health emergency in which a protocol-specified clinic visit cannot occur and should not be pursued solely because of a subject's preference. If the subject does not participate in one of these options, a Safety Telephone call must be conducted within 14 days of the last dosing visit.

In order to handle data appropriately for analysis, the method of collection for assessments is also being collected in the database.

2.5. Sample Size Considerations

The sample size for this study is based on the number of the SOD1-ALS subjects in Study 233AS101 who consent to participate in 233AS102. Up to 183 subjects will be dosed in Study 233AS101.

3. Definitions

3.1. Dates and Points of Reference

- Study Day 1: the date of the first dose of study treatment in 233AS102
- Study Day
  - For a date on or after Study Day 1

    Study Day = (Date of Interest) – (Study Day 1) + 1
  - For a date before Study Day 1

    Study Day = (Date of Interest) – (Study Day 1)
- Unless stated otherwise, baseline data are defined as the data collected prior to the time and/or on the date of first dose, which is usually the same day as the Day1/Baseline visit in 233AS102. If there is more than one value on/before the date of the first dose, the non-missing value closest to and prior to the first dose will be used as the baseline value
- *Visit window for analysis*

  If, due to the COVID-19 pandemic, subjects could not attend clinic visits during protocol defined visit windows, they were given some allowance to have a delayed visit. There may also have been subjects who attended visits outside of the protocol defined windows for other reasons. Regardless of whether the delayed visit was due to the COVID-19 pandemic or not, these are recorded under scheduled visits and are also considered to be protocol deviations. Visit windows will not be applied to scheduled visits for analysis purposes. If a subject had a phone visit followed by a delayed clinic visit, the clinic visit is still recorded as the scheduled visit. The scheduled visit will always take precedence over unscheduled visits.

  For subjects who are early terminated (ET), EOS visit is defined as the scheduled follow-up visit 4 weeks after last dose. Data from early withdrawal visits and post

baseline unscheduled assessments will be assigned to an appropriate scheduled post baseline visit using a windowing scheme for assessments that are tabulated or summarized by visit. Scheduled visits will not be windowed.
The visit windowing for endpoints is given in the table below:

Table 3 Visit Windows for Safety Endpoints and CSF PK Endpoints

	Safety Endpoints and CSF PK Concentration*		
Visit	Lower Bound (Day)	Upper Bound (Day)	Target Day
Week 2 (Day 15)	8	21	15
Week 4 (Day 29)	22	42	29
Week 8	43	70	57
Week 12	71	98	85
Week 16	99	126	113
Week 20	127	154	141
Week 24	155	182	169
Week 28	183	210	197
…	…	…	…
Week 352	2451	2478	2465
Week 356	2479	2506	2493
Week 360	2507	2534	2521
Week 364	2535	2562	2549

* This windowing covers the following endpoints: PK CSF concentration and safety endpoints: vital signs (temperature, blood pressure, pulse rate, respiratory rate), clinical laboratory tests (Hematology, Coagulation, Chemistry, and Urinalysis), pregnancy test, neurological examinations, C-SSRS, [redacted], ECG.

Note: ECG will not be collected at Week 2.

Table 4 Visit Windows for MMSE

	MMSE *		
Visit	Lower Bound (Day)	Upper Bound (Day)	Target Day

Week 12	71	98	85
Week 24	155	182	169
Week 36	239	266	253
Week 48	323	350	337
Week 72	491	518	505
Week 96	659	686	673
… (every 24 weeks)	…	…	…
Week 340	2367	2394	2381
Week 364	2535	2562	2549

* This windowing covers the safety endpoint: MMSE. To be performed at Week 12, 24, 36, and 48 Visits (i.e., every 12 weeks); Week 72, 96, 120, 144, 168, 192, and 216 Visits (i.e., every 24 weeks); and Week 228 Visit under Protocol V5. MMSE assessment is removed in Protocol V6.

For MMSE, there are some subjects who also have assessments during Screening, Day 1, Week 2, Week 4, Week 8, etc. (i.e. every 4 weeks) under Protocol V3 and Protocol V4. For part C subjects, follow **Table 3 for windowing up to and including Week 24. For part A/B subjects, follow **Table 3** for windowing up to and including Week 120. All visits up to Week 12 will be summarized for all subjects.

Table 5 Visit Windows for PK Concentration in Blood/Immunogenicity Endpoints

	PK/Immunogenicity Endpoints *		
Visit	Lower Bound (Day)	Upper Bound (Day)	Target Day
Week 12	71	98	85
Week 20	127	154	141
Week 28	183	210	197
…(every 8 weeks)	…	…	…
Week 356	2479	2506	2493
Week 364	2535	2562	2549

* This windowing covers the following safety endpoints: blood samples for PK, and blood samples for plasma anti-tofersen Ab,.

Considering the high frequency of postbaseline visits and the relatively small gap between adjacent visits, the lower bound and the upper bound for the visit windows are based on the midpoints of the scheduled visits. The date of first dose will be the reference point (Day 1).

- If more than one observation is within the same window, data from the protocol-specified scheduled visit will be used for that visit.
- If neither of the observations are from a protocol-specified scheduled visit the observation closest to the planned target date will be used. However, if both the observations are equidistant from the target date, the latest one will be used; if repeated measurements are on the same day, then the last measurement will be used.
- If there is more than one observation in a window for a dosing visit (Day 15 to Week 360 visits), the observation on the day of dosing will be chosen over the observation where dosing did not occur on the same day.
- Some of the safety assessments are collected postdose in addition to the predose assessments (e.g. vital signs at Day 15 to Week 360 visits). When windowing any predose assessments these should be the last available assessment prior to the dose. When windowing any postdose assessments they should correspond to the same dose as the predose assessment used for that visit. These summaries will present predose and postdose separately on by-visit summaries. If one of these assessments is collected at an unscheduled visit where there is no dosing, the assessment will be assigned as a predose assessment. Additionally, the protocol for 233AS102 initially collected some assessments (e.g. vital signs) only pre-dose, therefore these assessments will be summarized under pre-dose. For Part C subjects, the pre-dose assessment may need to be taken from Day 197 visit of 233AS101.

3.2. Study Group

Study participants will be assigned to one of the following study groups based on which part they enrolled from in 233AS101. All outputs will be presented using these groups unless otherwise specified:

Table 6 Study Groups of 233AS102

233AS101 Part C subjects by prior treatment		**233AS101 Part A+ Part B subjects**	**233AS101 Part A, B and C subjects**
placebo	tofersen 100 mg	All doses	Total
This includes data from 233AS102 for subjects who received placebo in 233AS101 Part C during the randomized part of the study	This includes data from 233AS102 for subjects who received tofersen in 233AS101 Part C during the randomized part of the study	Subjects enrolled from 233AS101 Part A or 233AS101 Part B regardless of dose	All subjects in 233AS102 i.e. addition of all 3 columns

3.3. Study Periods

3.3.1 Screening

Subjects Who Have Completed Parts A and B of Study 233AS101

Subjects who have completed Part A or Part B of Study 233AS101 will be eligible for screening. Subject eligibility for the study will be determined from Week -4 through Day -1.

The Screening Visit assessments may be performed over approximately 2 days, which do not need to be consecutive, to minimize subject burden. All assessments must be completed on or before the Baseline/Loading Dose Visit on Day 1.

Subjects Who Have Completed Part C of Study 233AS101

Subjects who have completed the last dosing visit in Part C of Study 233AS101 will be able to screen to determine eligibility to participate in Study 233AS102. A subject's last dosing visit in Part C of Study 233AS101 will be the start of the Screening Visit (Week -4 to Day -1) for this extension Study 233AS102. Results from assessments completed by subjects at the last dosing visit of Study 233AS101 can be used for the purpose of screening and do not need to be repeated as long as they are conducted within 4 weeks of the Baseline/Loading Dose Visit on Day 1.

3.3.2 Dosing

Eligible subjects will report to the study site on Day 1 to complete baseline assessments and reaffirm eligibility. Day 1 should occur no earlier than 28 days after the subject's last dose (i.e., Day 169 [Week 24 Visit]) in Study 233AS101 Part C.

Assessments collected at the Day 197 visit (4 weeks after last dose) of Part C of Study 233AS101 will be used as the Day 1 predose assessments for Study 233AS102 if they are collected within 48 hours of the first dose in Study 233AS102.

On dosing days, subjects will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the Investigator and in compliance with the institutional requirements, once the subjects have adequately recovered from the dosing procedure. Subjects will receive a safety follow-up telephone contact approximately 24 hours after the procedure.

3.3.2.1 Loading Dose Period

The Loading Dose Period of the study will occur from Day 1 to Day 29.

- Subjects who have completed Parts A or B of Study 233AS101:
  - Subjects will receive 3 loading doses of tofersen approximately 2 weeks apart (Day 1, Day 15, and Day 29).

- Subjects who have completed Part C of Study 233AS101:
  - Subjects randomized to receive placebo during Study 233AS101 will receive 3 loading doses of tofersen, approximately 2 weeks apart (Day 1, Day 15, and Day 29). The Investigators, study staff (except for an unblinded designated pharmacist/technician), and study subjects will be blinded to the study treatment during the Loading Dose Period.
  - Subjects randomized to receive tofersen during Study 233AS101 will receive 2 loading doses of tofersen, on Days 1 and 29, and 1 dose of placebo on Day 15. The Investigators, study staff (except for an unblinded designated pharmacist/technician), and study subjects will be blinded to the study treatment during the Loading Dose Period.

3.3.2.2 Maintenance Dose Period

During the maintenance portion of the study, subjects will receive up to 90 doses of tofersen, approximately every 4 weeks, during visits at Weeks 8, 12, 16, and every 4 weeks thereafter until the last subject enrolled has had the opportunity to have their Week 152 Maintenance Dose Visit.

3.3.3 Follow-up

Subjects will return for their Final Visit which will be 4 weeks after their last dose. Subjects who withdraw from the study early will return for an Early Termination Visit, which will be 4 weeks after their last dose.

3.4. Stratification Factors and Subgroup Variables

3.4.1. Stratification Factors

This is an open-label study and no stratification factor was applied.

3.4.2. Subgroup Variables

No subgroups will be applied for 233AS102 standalone analyses. In line with the ITT principle for efficacy and biomarker data that will be conducted in the ISE, no "enriched"/"other" analyses will be conducted.

3.5. Analysis Sets

ITT Population

The ITT population is defined as all subjects who enrolled and received at least one dose of study treatment in 233AS102.

Safety Population

The safety population is defined as all subjects who enrolled and received at least one dose of study treatment in 233AS102 (i.e. the overall ITT population of subjects).

Pharmacokinetic (PK) Population

The PK population is defined as all subjects who received at least one dose of study treatment and have at least one post-dosing PK concentration measurement in 233AS102.

Immunogenicity Population

The analysis population for immunogenicity is defined as all subjects who received at least one dose of study treatment and have at least 1 post-dosing sample evaluated for immunogenicity in 233AS102.

Populations used for analysis

Efficacy endpoints and PD/biomarker endpoints will not be summarized in 233AS102 standalone analysis and final CSR, but these data will be combined with data from 233AS101 and analyzed based on the ISE SAP.

The analysis of plasma and CSF PK concentration of tofersen will be analyzed using the PK population. All safety evaluations will be summarized using the safety population.

4. Statistical Methods for Planned Analyses

4.1. General Principles

- Descriptive summary statistics will be presented for all analyzed endpoints. Unless otherwise specified, for continuous endpoints, the summary statistics will generally include number of subjects with data, mean, standard deviation, median, 25th percentile, 75th percentile, minimum and maximum. For categorical endpoints, the summary statistics will generally include number of subjects with data, and the percentage of those with data in each category.
- All summaries and listings will be presented by study group and additionally by prior treatment group for Part C subjects unless otherwise specified. Visits in listings will be displayed as per CRF data collection rather than analysis visits.
- Listings will indicate treatment sequence, considering that subjects from Part A and B may have received different doses within 233AS102. Treatment sequence will also include prior treatment during 233AS101. Dose will also be shown where relevant e.g. dose at onset of AE in AE listings.
- The statistical software, SAS®(Version 9.4) will be used for all summaries and statistical analyses.

4.2. Participant Accountability

The number (and percentage) of subjects dosed; discontinued treatment and the reasons for discontinuation; and withdrew from study early and the reasons for withdrawal will be summarized in a table. These summaries will be presented by study group as in **Table 6**.

If there are any subjects who discontinued from treatment or withdrew from study due to COVID-19 pandemic related reasons, a separate summary will be presented to summarize reasons for discontinuation and withdrawal from study for COVID-19 related reasons. Adverse events, deaths and other reasons may fall into COVID-19 related categories. The Other category will be broken down into the following categories:

Other – COVID-19 (Movement Restrictions Related to COVID-19 Pandemic)

Other – COVID-19 (Subject Fear Related to COVID-19 Pandemic)

Other – COVID-19 (Site Closed Due to COVID-19 Pandemic)

Other – COVID-19

A listing of subjects who discontinued treatment/withdrew from study and the associated reasons for discontinuation/withdrawal will be presented.

The number (and percentage) of subjects enrolled by country and site, and number (and percentage) of subjects by analysis population will be summarized by prior treatment group for Part C subjects, and for all subjects by study group as in **Table 6**.

Listings will be provided to show subjects excluded from each population.

4.3. Demographic and Baseline Characteristics

All demographics data and ALS disease history from 233AS101 will be summarized for the overall safety population by study group as in **Table 6**.

Demographic data at baseline (Day 1) to 233AS102, including age (years), age category (18-<35,35-<50, 50-<65, ≥65), gender, ethnicity, race, height, weight and body mass index (BMI) will be presented. The derivation for age and BMI are detailed in Appendix A.

ALS disease history will also be summarized descriptively and will include summaries of:

- confirmed SOD1 mutation (per analysis report of genetic sample) i.e. Yes/No
- mutation type
- time since ALS symptom onset at baseline visit of 233AS102 (months);
- time since ALS diagnosis at baseline visit of 233AS102 (months);
- site of onset (bulbar, lower limbs, upper limbs, respiratory, thoracic; subjects may be summarized under more than one site if subject has multiple sites of onset);
- ALSFRS-R slope since symptom onset (i.e. progression rate at baseline visit of 233AS102);
- riluzole usage and edaravone usage prior to baseline of 233AS102 i.e. yes/no;

Descriptive statistics for 233AS102 baseline clinical function for ALSFRS-R total score, percent predicted SVC, total CSF SOD1 protein and plasma NfL at baseline will also be presented in a separate summary table. This will also include a summary of whether subject had any ventilation use prior to 233AS102 for subjects who enrolled from 233AS101 Part C. For percent predicted SVC, a summary will also be presented to show number and percentage of subjects with a baseline assessment with an invalid reading i.e. ATS criteria F per Appendix B.

Medical history will be classified using MedDRA version 27.0 or later. A summary of medical history by system organ class and preferred term will also be provided for the safety population. All medical history will also be listed.

4.4. Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a protocol deviation log. All protocol deviations will be listed and a summary of major protocol deviations by study group will also be provided for the safety population. A separate listing will present site level deviations for deviations that do not impact any subjects (e.g. temperature excursions where no subjects were administered impacted doses),

A separate summary of major protocol deviations related to the COVID-19 pandemic will be presented. A listing will also present all minor and major PDs related to the COVID-19 pandemic.

A summary will be presented by visit and overall showing the number and percentage of subjects with the following type of visit:

Clinic visit (with dosing)

Clinic visit (with no dosing)

Home visit only

Home visit and telephone visit

Telephone visit only

Missed visit

The overall summary will be based on number of expected visits. This summary will also present the number of delayed visits (i.e. outside protocol defined window) per subject across the study and the number of missed visits per subject.

A summary showing the number and percentage of subjects by visit will be presented with the breakdown of the reason for the missed visit i.e.

COVID-19 – Subject diagnosed with Covid-19 disease

COVID-19 – Subject fear related to Covid-19 pandemic

COVID-19 – Movement restrictions related to Covid-19 pandemic

COVID-19 – Site closed due to COVID-19 pandemic

Other

This summary will also show the total number of visits missed per subject for each reason.

4.5. Protocol Alternations

Protocol alternations are alternative methods of assessments due to the COVID-19 pandemic. For subjects who could not attend clinic visits due to the pandemic, protocol alternations in place for this study are home visits or telephone assessments. A listing of subjects with protocol alternations will be provided.

4.6. Study Treatment Exposure

Summaries for extent of exposure to study treatment will be summarized for the overall safety population by study group.

A frequency distribution for number of doses received per subject will be summarized by study group, and descriptive statistics will be presented for total cumulative dose during 233AS102 in mg. Total cumulative dose will be based on actual dose administered (calculated as volume administered multiplied by dose, and divided by 15mL). For Part A/B subjects the frequency distribution for number of doses received per subject will also be broken down by <100 mg and 100 mg.

A delayed visit or dose will be anything that falls outside of the following protocol-defined windows of +/-3 days

The following summaries will be presented by study group:

- Total number of expected doses across subjects based on actual subject duration of dosing; total number of missed doses and total number of delayed doses (percentages calculated out of total number of expected doses;
- A frequency distribution for number of consecutive missed doses per subject. If a subject has more than one period where doses were missed consecutively, the period with the maximum consecutive missed doses will be used;
- A frequency distribution for overall number of missed doses per subject (i.e. regardless of whether they were consecutive). The mean (SD) will be presented for the mean number of missed doses per subject. Subjects with no missed doses will be included as having 0 missed doses.
- The mean (SD) number of delayed doses per subject will also be summarized. Subjects with no delayed doses will be included as having 0 delayed doses. A delayed dose is based on regular scheduled visits, as dosing cannot be recorded under unscheduled visits.

The summaries described above for missed and delayed doses will be repeated based on doses that are missed or delayed due to COVID-19 impact.

A listing will also be presented to show dosing history for all subjects who missed at least one dose, indicating whether any of the missed doses are related to COVID-19. If any of the doses are due to COVID-19, then the number of impacted doses will be presented.

Study drug compliance percentage up to the last dose of study drug received will be defined as the number of doses actually received divided by the number of doses that the subject is expected to receive during the study period and will be summarized by descriptive statistics. For subjects who withdrew from study early, the number of expected doses is the planned number of doses before the time of withdrawal.

Study drug administration data will be listed which will include lot numbers, dose received, cumulative number of doses and cumulative dose. A listing of dosing errors will also be provided

i.e. where either the incorrect dose was administered as specified in protocol deviation log and kit description from IRT system. Actual dose will be calculated as volume administered multiplied by dose and divided by 15mL. The nominal dose will also be presented.

Time on study will be summarized descriptively by study group. Overall time on study will be calculated as last date on study at time of cutoff – first dose date + 1 in days. Last date on study is defined as the date of the latest visit or evaluation or telephone contact, or time of death from all available data for a given subject. The durations will also be categorized and summarized using 12-week intervals the following categories: ≤12 weeks, >12 weeks to 24 weeks, >24 weeks to 36 weeks, >36 weeks to 48 weeks, >48 weeks to 60 weeks, >60 weeks to 72 weeks, >72 weeks to 84 weeks, and so on.

A summary of time to treatment discontinuation will be provided for those subjects who discontinued study drug, calculated as last dose date – first dose date +1.

4.7. Concomitant Medications and Non-Drug Treatments/Procedures

Concomitant medications will be coded using the World Health Organization (WHO) dictionary WHODRUG (March 2024) and concomitant non-drug treatments/procedures using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 or later.

Medications and non-drug treatments are considered concomitant if they are taken during study 233AS102. This includes medications/treatment/procedures that were started prior to the date and time of first dose of study drug if their use continued on or after the date and time of first dosing. If the start date is available but start time is missing and the medications/treatment/procedure start date is the same as the first dose date, the medications/treatment/procedure will be considered concomitant. Similarly, if the stop date is available but stop time is missing and the medications/treatment/procedure stop date is the same as the first dose date, the medications/treatment/procedure will also be considered concomitant. Medications/treatment/procedures with missing start or stop dates and times, will also be considered as concomitant in the following situations:

- If both the start and stop dates and times of a medication/treatment/procedure are missing;
- If the start date and time of a medication/treatment/procedure is missing and the stop date and time of the medication/therapy occurred on or after the date and time of first dose of study drug;
- If the start date and time of a medication/treatment/procedure therapy occurred prior to the date and time of first dose of study drug and the stop date and time of the medication/treatment/procedure is missing and the medication/treatment/procedure is listed as ongoing;

In a rare situation where the start date and time of a medication/treatment/procedure occurred prior to the date and time of first dose of study drug and both the stop date and time of the

medication/treatment/procedure is missing and the medications/treatment/procedure is not listed as ongoing, then the medication/treatment/procedure will also be considered as concomitant.

For medications/treatment/procedures with a partial start date, the year/month will be compared to that of the first dosing date to determine whether the medications/treatment/procedure is concomitant.

The number and percentage of subjects taking any concomitant medications will be summarized by study group for the safety population. The number and percentage of subjects taking any concomitant non-drug treatments will also be summarized by study group for the safety population. All medications/treatment/procedures will also be listed.

A listing of any changes to rilzuole or edaravone use during the study will be presented.

If there are a sufficient number of tests or treatments reported with indication of COVID-19, a separate summary of these will be provided. This will include a summary of the number and percentage of subjects with COVID-19 diagnostic tests with the following recorded verbatim terms (these will be coded using MedDRA dictionary):

“COVID-19 Diagnostic Test Result Positive”

“COVID-19 Diagnostic Test Result Negative”

“COVID-19 Diagnostic Test Result Pending”

“COVID-19 Diagnostic Test Result Inconclusive”

and the number and percentage of subjects with COVID-19 antibody tests with the following recorded verbatim terms (these will be coded using MedDRA dictionary):

“COVID-19 Antibody Test Result Positive”

“COVID-19 Antibody Test Result Negative”

“COVID-19 Antibody Test Result Pending”

“COVID-19 Antibody Test Result Inconclusive”

If there are very few COVID-19 tests or treatments the summary will not be presented but a listing of these will be provided.

Concomitant medications will also be reviewed by a medical reviewer prior to the final database lock to determine disallowed medications according to the protocol. These will be summarized separately.

4.8. Efficacy Endpoints

4.8.1. General Analysis Methods for Efficacy Endpoints

ALSFRS-R, SVC, HHD, [redacted], and time to death or permanent ventilation will not be summarized or analyzed based on baseline of 233AS102, but these data will be combined with data from 233AS101 and summarized and analyzed based on the ISE SAP.

4.9. Safety Endpoints

The safety population will be used for the analyses of the safety data Safety data will be summarized using frequency counts and percentages and descriptive statistics by study group.

A summary of missing safety data by visit and overall (i.e. C-SSRS, laboratory data broken down by panel, vital signs) will be presented. The summary will also be broken down by whether the visit was missed due to COVID-19 or other reason. Missing summary will not be performed for MMSE, ECG and neurological examination due to only limited data collected based on protocol amendment V6.0; MMSE was removed and all dosing visits were removed for ECG and neurological.

4.9.1. Adverse Events

All AEs will be classified using MedDRA version 27.0 or later. All AEs will be listed but only treatment emergent AEs will be summarized, where treatment emergence will be relative to the first dose of study drug. A treatment emergent AE/SAE is defined as any AE/SAE with an onset date and time that is on or after the first dose of study drug or any pre-existing condition that has worsened in severity after the first dose of study drug. In case of missing dates,

- Any AE/SAE with both a missing onset date and resolution date, or any AE/SAE with a missing onset date and a resolution date which is after the first dose of study drug, will be considered treatment emergent.
- If the onset date is available but onset time is missing and the AE onset date is the same as the first dose date the AE will be considered treatment emergent.
- For AEs with a partial start date, the year/month of the event date will be compared to that of the first dose date to determine whether the event is treatment emergent.

The incidence of treatment emergent AEs will be summarized by study group as follows:

- by primary system organ class (SOC) and MedDRA preferred term sorted by decreasing frequency
- by SOC and MedDRA preferred term sorted by alphabetical order
- by MedDRA preferred term
- by SOC

- The most common treatment emergent AEs i.e. occurring in ≥5%subjects in any study group will be presented by MedDRA preferred term.
- For Part C subjects only, the most common treatment emergent AEs i.e. occurring in 2 or more subjects in subjects previously on tofersen in 233AS101 compared to subjects who were on placebo will be presented by MedDRA preferred term.
- By maximum CTCAE grade, primary SOC and MedDRA preferred term
- By maximum CTCAE grade and MedDRA preferred term
- AEs with a CTCAE grade>=3 by primary SOC and MedDRA preferred term
- Related AEs by primary SOC and MedDRA preferred term
- SAEs by primary SOC and MedDRA preferred term
- SAEs by MedDRA preferred term
- Related SAEs by primary SOC and MedDRA preferred term
- AEs related to lumbar puncture (as assessed by the investigator) by primary SOC and MedDRA preferred term
- AEs that occurred within 24 hours of dosing by primary SOC and MedDRA preferred term (in case of partial AE start date, if the month and year are available and day is missing, the AE will be included for any dose that occurs in the same month and year as the AE)
- AEs which led to discontinuation of study drug by primary SOC and MedDRA preferred term
- AEs which led to withdrawal from study by primary SOC and MedDRA preferred term
- AEs which led to drug interrupted by primary SOC and MedDRA preferred term
- AEs which led to hospitalization by primary SOC and MedDRA preferred term (showing number and percentage of subjects with at least one occurrence in that SOC or preferred term, as well as total number of events). Further summaries of hospitalization data are also included later in this section.
- AEs that led to death
- AEs of note (serious neurologic events, falls, CSF laboratory abnormalities) for which preferred terms will be based on a medical review before final analysis and unblinding. This summary will include number and percentage of subjects with at least one event and total number of events. The follow-up adjusted incidence rates based on number of subjects as well as number of events will also be presented in the same table. If any of these are defined based on more than one preferred term, the preferred terms will also be broken down under the overall category.

The sorting order for AE incidence tables, unless otherwise specified, will be by decreasing frequency order of "Total tofersen all doses" column. For the AE summary by primary system organ class and preferred term, subjects will be counted only once within each primary SOC/MedDRA preferred term. For the summary of AEs by maximum CTCAE grade, primary system organ class and preferred term, subjects will be counted only once within each primary SOC/MedDRA preferred term and will only be counted under the maximum CTCAE grade. For the summary of related AEs, if the relationship is missing then this will be summarized as unknown.

For AEs that occurred within 24 hours of dosing, if time of AE is missing and the event occurs on the same day as the day for dosing or the day following dosing, the AE will be counted as occurring within 24 hours of dosing.

An overall summary of AEs will also be presented. A separate table will also be presented to show an overall summary of COVID-19 pandemic related AEs.

Listings of the following events will be produced.

- AEs which led to discontinuation of study drug
- AEs which led to withdrawal from study
- AEs which led to drug interrupted
- AEs related to lumbar puncture
- AEs which led to hospitalization
- SAEs
- AEs

A listing of deaths will be provided if applicable.

An additional table for hospitalizations will present the number and percentage of subjects in each treatment group with at least one hospitalization, the number of hospitalizations per subject, total number of hospitalization and a descriptive summary for the total cumulative duration of hospitalizations per subject.

Pre-treatment SAEs i.e. those that occurred between screening and first dose are not considered treatment emergent and so will be summarized separately if there is a sufficient number. Pre-treatment AEs should not be collected unless classed as serious. All SAEs will be listed, with an indicator for pre-treatment SAEs. Only treatment emergent AEs will be summarized, unless otherwise specified.

A separate summary will be presented for each confirmed COVID-19 AE and suspected COVID-19 AE. These will be identified as AEs that are recorded with an entry of '(Confirmed)' and '(Suspected)'. As per the guidance, confirmed cases are those confirmed via a diagnostic test and suspected cases are those diagnosed based on typical symptoms, travel/contact history. A listing will also be provided.

Incidence rate tables

Incidence and incidence rate will be provided in incidence rate tables and will be summarized by primary SOC and MedDRA preferred term by study group. Two different kinds of incidence rate tables will be provided. Definitions are provided below:

1) Follow-up adjusted incidence rate – defined as the number of subjects who experienced an event divided by the total of entire follow-up time among the subjects in the analysis population. The entire follow-up time for subject is defined as the time from the first dose until the last day (the earliest date of last study day and interim cutoff date) on study. Each subject will be counted only once within each category. A similar table will also be based on total number of events divided by the total of entire follow-up time among the subjects in the

analysis population. This may count a subject more than once within each category of they experienced an event more than once.

2) Exposure-adjusted incidence rate (EAIR) – defined as the number of subjects who experience an event divided by the total exposure adjusted follow-up time among the subjects in the analysis population. The exposure adjusted follow-up time is defined as the time from the first dose until the initial occurrence of the event for those who experienced an event, or from the first dose until the end of follow-up (the last day (the earliest date of last study day and interim cutoff date) on study) for those who did not. Each subject will be counted only once within each category. If the initial occurrence of the event has a partial start date, the following rules will be applied. If only month and year of the AE are available, and the month and year are same as that of the first dose then it will be assumed that the event started on date of first dose. Otherwise it will be assumed that the event started on the first of the month. If only year is available, and the year is same as that of the first dose then it will be assumed that the event started on the date of first dose. Otherwise it will be assumed that it started on the 1st January.

4.9.2. Laboratory Data

Laboratory data will be evaluated to determine the incidence of abnormalities that emerge during the course of the study. Changes in laboratory evaluations will be presented relative to baseline, which is defined as the closest visit prior to the subject starting treatment.

The following clinical laboratory parameters are assessed in the protocol:

- Hematology panel: complete blood count with differential and platelet count (hematocrit, hemoglobin, platelets, red blood cell count [RBC], white blood cell count [WBC], basophils, eosinophils, lymphocytes, monocytes, neutrophils)
- Blood chemistry panel: albumin, total bilirubin, direct bilirubin, alkaline phosphatase, alanine aminotransferase (ALT) (SGPT), aspartate aminotransferase (AST) (SGOT), gamma-glutamyl transferase (GGT), sodium, potassium, calcium, chloride, phosphate, blood urea nitrogen (BUN), creatinine, uric acid, bicarbonate (CO2), glucose, total protein.
- Urinalysis: blood, glucose, protein, and microscopic examination if abnormal
- CSF analysis: RBC, WBC, protein, glucose.
- Coagulation: PT (prothrombin time), aPTT (activated partial thromboplastin time), and INR (international normalized ratio).

If multiple samples are collected at the same visit, the samples collected at the earliest date/time will be analyzed after applying visit window rules. For CSF laboratory parameters, tube 2 results will be analyzed if available.

Baseline value is defined as data collected which are prior to and/or on the date of the first dose, usually also the same day as the Day 1 visit. If there is more than one value on or before Day 1, then the last non-missing value prior to (including on) the date of first dose will be used as the baseline value.

Each hematology, blood chemistry, coagulation and CSF laboratory parameter will be flagged as "low" or "high" relative to the parameter's normal range or as "unknown" if no result is available. For each urinalysis laboratory parameter, the number and percentage of subjects experiencing post-dosing shifts to abnormal will be summarized. For each hematology, blood chemistry, coagulation and CSF parameter, the number and percentage of subjects experiencing post-dosing shifts to 'low' or 'high' will be summarized. In each summary, the denominator for the percentage is the number of subjects at risk for the shift. The number at risk for the shift to low is the number of subjects whose baseline value was not low and who had at least one post-baseline value. The number at risk for the shift to high is the number of subjects whose baseline value was not high and who had at least one-post baseline value. Subjects will be counted only once for each parameter and each shift regardless of how many post-dosing assessments had that type of shift. Subjects with shift will be listed by laboratory parameter and shift type. All postbaseline data will be used in the shift tables, regardless of whether a scheduled or unscheduled visit. For CSF laboratory parameters, both tubes will be used in this assessment for the shift tables.

Summary statistics for actual values and change from baseline in laboratory values will be summarized by dose group and visit. Line plots for chemistry, hematology and CSF showing mean value for each dose group at each visit will also be presented.

To evaluate potential serious hepatotoxicity subjects with a post-baseline AST and/or ALT value ≥3 times the upper limit of normal (ULN) and a post-baseline bilirubin value >2 times ULN at any time, not necessarily concurrent, will be listed with their values. In addition, a plot will be presented with each subject's maximum post-baseline AST or ALT value relative to the ULN against the subject's maximum post-baseline bilirubin value relative to the ULN; values do not have to be concurrent. All postbaseline data will be used in the shift tables, regardless of whether a scheduled or unscheduled visit.

Listings of all chemistry, hematology, coagulation, CSF, urinalysis values and pregnancy test (serum and urine) will be provided. Abnormal values and potentially clinically significant values will be flagged.

Subjects with at least one post-baseline CSF WBC values >10 will have their CSF WBC plotted over time in a spaghetti plot. Corresponding listing will also be presented with AEs that occurred at any time on or after the subject had a post-baseline CSF WBC value >10. A summary table will also present number and percentage of subjects with at least one post-baseline CSF leukocyte >5 and number and percentage with at least one post-baseline CSF leukocyte >10. The summary will also present total number and percentage of individual values >5 and total number and percentage of individual values >10. All postbaseline data will be used in the shift tables, regardless of whether a scheduled or unscheduled visit.

A summary table and listing of lumbar puncture and CSF sample collection data other than CSF laboratory results (i.e. lumbar puncture position, number of attempts, interspaces, additional guidance used, CSF volume collected, needle and gauge information) will also be provided.

4.9.3. Vital Signs

Summary statistics for actual values and change from baseline will be presented for each vital sign parameter (temperature, pulse, respiration, systolic and diastolic blood pressure) by dose group and visit. Weight will be summarized at baseline and the last visit by dose group. A listing of vital sign data will also be provided.

Vital signs (temperature, pulse, systolic and diastolic blood pressure) will also be examined to determine the incidence of potentially clinically relevant abnormalities. The number of subjects evaluated and the number of subjects with potentially clinically relevant abnormalities will be presented. All postbaseline data will be used to identify abnormalities, regardless of whether a scheduled or unscheduled visit. The criteria for potentially clinically relevant post-dosing abnormalities are shown in **Table 7** below:

Table 7: Criteria to determine potentially clinically relevant abnormalities in vital signs

Vital Sign	Criteria for Abnormalities
Temperature	<36°C >38°C
Pulse	>100 beats per minute (bpm) <60 bpm
Systolic Blood Pressure	<90 mmHg >140 mmHg >160 mmHg
Diastolic Blood Pressure	<50 mmHg >90 mmHg >100 mmHg
Weight	7% or more increase from baseline 7% or more decrease from baseline
Respiratory Rate	<12 >20

4.9.4. ECG

The ECG test includes heart rate, PR interval, QRS interval, QT interval, QTc interval using Bazett's formula, QTc interval using Fridericia's formula, and RR interval. Summary statistics for actual values and change from baseline in each ECG parameter will be presented by study group and visit.

The number and percentage of subjects with shifts from normal to each of the categorical values denoting an abnormal scan (abnormal not AE, abnormal AE) will be summarized by study group. A listing of subjects with abnormal status in ECG will be presented.

QTc (interval using Fridericia's formula) will also be examined to determine the incidence of clinically relevant abnormalities. The number of subjects evaluated and the number of subjects with clinically relevant abnormalities will be presented. The criteria for clinically relevant post-dosing abnormalities are:

- Maximum increase from baseline QTcF > 30 to 60 ms
- Maximum increase from baseline QTcF > 60 ms
- Maximum post-baseline QTcF > 480 to 500 ms
- Maximum post-baseline QTcF > 500 ms

4.9.5. Mini-Mental State Exam (MMSE)

MMSE was collected based on earlier versions of 233AS102 Protocols and then removed from Protocol Amendment V6.0. All collected data will be still summarized for final analysis. Summary statistics for actual values and change from baseline of the total score of MMSE will be presented for each visit by study group. When there are multiple assessments during a single visit, the minimal value will be taken as the value for that visit. A listing of MMSE data for individual patients will also be provided.

4.9.6. Limited neurological examinations

The number and percentages of the status in each assessment of coordination/cerebellar function and each assessment of reflexes will be summarized by study group and visit. The reflexes neurological examination of upper and lower extremities will be analyzed as continuous variables (0 = absent, 1 = trace, 2 = normal, 3 = brisk, 4 = clonus). The descriptive statistics will be summarized by study group and visit.

The motor neurological examination will be analyzed as continuous variable (0 = no contraction or can't position limb; 1 = flicker or trace contraction, no movement; 2 = movement only with gravity eliminated; 3 = movement against gravity; 4 = movement against gravity and resistance; 5 = normal strength). Summary statistics will be presented by study group and visit.

The Ashworth spasticity scale will also be analyzed as continuous variable (1 = normal; 2 = slight increase in tone; 3 = more marked increase in tone; 4 = considerable increase in tone; 5 = affected part rigid, immobile). Summary statistics will be presented by study group and visit.

The number and percentages of the status in each assessment of general neurological examination will be summarized by study group and visit. El Escorial data will be listed.

Baseline values will be taken from Day 1 pre-dose unless an entire section of the neurological exam (i.e. coordination/cerebellar function, reflexes, motor) is missing or not done, in which case for that specific section baseline will be taken from the Screening visit for all items within that section of the exam.

Listings will also be provided with complete details for the neurological examinations.

4.9.7. Columbia Suicide Severity Rating Scale (C-SSRS)

The details of derivation and imputation for C-SSRS is described in Appendix B. The following analyses on C-SSRS measurements will be conducted:

- Descriptive summary of subjects who answered "Yes" to any question 1-12 as well as subjects who had suicidal ideation or suicidal behavior at baseline and at any post-baseline visit. The denominator for baseline summary is the number of subjects who were dosed and had baseline assessment; the denominator for post-baseline summary is the number of subjects who were dosed and had at least one post-baseline assessment for each question.
- Descriptive summary of subjects who had treatment-emergent suicidal ideation, subjects who had new suicidal ideation as well as subjects who had worsening suicidal ideation. The denominator is the number of dosed subjects with both baseline and at least one post-baseline suicidal ideation assessment.
- Descriptive summary of subjects who had treatment-emergent suicidal behavior. The denominator is the number of subjects who answered "No" to all suicidal behavior questions at baseline and had at least one post-baseline suicidal behavior assessment.

Listing of subjects having treatment-emergent suicidal ideation will be provided. Subjects who had new suicidal ideation and subjects who had worsening suicidal ideation will be flagged. The listing will display both baseline and post-baseline Suicidal Ideation Scores for each subject. Listing of subjects having treatment-emergent suicidal behavior will also be provided.

4.10. Pharmacokinetic Endpoints

The PK population will be used for the primary analyses of the PK data. PK summaries/analyses will be displayed for 233AS101 Part C subjects only. For subjects from Part A and B different dosing regimens and different durations make it difficult to pool these subjects.

Values below limit of quantitation (BLQ) are set to half of the lower limit of quantitation (LLOQ, 1 ng/mL) at day 1 pre-dose rather than zero so that geometric means can be calculated. Values that are BLQ at all other visits will also be set to half of LLOQ (1 ng/mL) in calculations.

Both plasma and CSF tofersen concentrations will be listed and summary statistics will be presented for each visit. Listings will present the concentrations with the scheduled (nominal) and actual sampling times (i.e. time from dosing) for each subject at each visit. Differences between scheduled and actual sampling times will also be listed for all subjects. Percentage differences between actual administered dose and nominal dose will also be listed.

Summary statistics will also include both the arithmetic and geometric means with corresponding standard errors, as well as the coefficient of variation. Plots of arithmetic and mean concentrations of tofersen versus time will be provided, including standard error bars on both the linear and semi-log scales. The summaries and plots will be based on scheduled visits/timepoints. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling days or times, or large deviations between actual dose and nominal dose.

A summary of missing plasma and CSF tofersen concentrations will also be provided for PK population for 233AS101 Part C subjects only.

4.11. Pharmacodynamic Endpoints and Biomarker Endpoints

PD/biomarker endpoints will not be summarized or analyzed for Study 102 alone; these data will be combined with data from 233AS101 and summarized and analyzed based on the ISE SAP.

4.12. Immunogenicity Data

The immunogenicity population will be used for all analyses of immunogenicity data.

- For immunogenicity, the baseline value is defined as the latest immunogenicity data collected at any time prior to the first dose in 233AS102. If no immunogenicity data are collected immediately prior to the first dose in 233AS102, the baseline value is missing and will be imputed as anti-drug antibody negative for immunogenicity analyses.
- Subjects with at least one confirmed post-treatment positive result will be considered treatment-emergent positive for anti-drug antibodies if their baseline result is negative.
- Subjects where none of the post-treatment samples were positive for anti-drug antibodies will be considered negative regardless of their baseline result.
- For subjects who are confirmed positive at baseline and have at least one post-treatment sample with a ≥ 2-fold increase in titer will be considered positive for anti-drug antibodies. Subjects that are positive at baseline, with subsequent post-treatment samples titers that are within 2-fold will be considered negative for anti-drug antibodies. If there

are any samples which the lab was able to confirm the screen was ADA positive but could not determine the magnitude of the positive response in time for interim datacut off date these will be considered as being ≥2-fold for the purpose of this analysis.

Number and percentage of subjects who has positive result and negative result at baseline, subjects with any post-baseline positive result and negative result, subjects with any positive ADA will be summarized by prior treatment groups.

In addition, for subjects that are considered anti-drug antibody positive with immunogenicity data, the following may be evaluated:

- Persistent anti-drug antibody response:
  - More than one positive time point that are ≥112 days apart

  or

  - One or more positive time point, but < 112 days of evaluable data post first positive time point.
- Transient anti-drug antibody response:
  - A single positive time point, followed by ≥112 days results which are all negative.

  Or

  - Two or more positive data points with <112 days apart, with later negative samples that are ≥112 days apart from the first positive result.
- Caveat: Since the data are only being considered from baseline of 233AS102, a subject who became persistent in 101 will not be accounted for as persistent based on their prior data in 233AS101. Therefore, the subject could be summarized as being transient if there is no change in their titer in 233AS102.
- If a subject has just one positive postbaseline ADA in 233AS102 at last available assessment at the time of Interim cutoff date and is still ongoing, then this subject will be summarized as transient.

Number and percentage of subjects who have persistent ADA result and transient ADA result will also be summarized by prior treatment groups.

The incidence of AEs selected by anaphylactic reaction SMQ, angioedema SMQ, and hypersensitivity SMQ will also be presented for subjects with at least 1 positive ADA result at post-baseline by prior treatment groups. Percentages will be calculated out of the immunogenicity population.

The incidence of AEs selected by anaphylactic reaction SMQ, angioedema SMQ, and hypersensitivity SMQ will also be presented for subjects with negative ADA result at post-

baseline by prior treatment groups. Percentages will be calculated out of the immunogenicity population.

5. Changes to Planned Analyses

- Analysis of efficacy, [redacted] and biomarker endpoints are specified in the Protocol; however, they will not be included in 233AS102 final CSR but will be included under the integrated analyses of 233AS101 and 233AS102. Analyses of efficacy and biomarker endpoints conducted for interim data (July 2021 and January 2022) highlighted the limitations of conducting standalone 233AS102 analyses in these endpoints as outlined in section 1. Based on these learnings, it only makes sense to analyze the longitudinal data from 233AS102 for efficacy and biomarker endpoints as part of an integrated analysis of 233AS101 and 233AS102. The analyses from 233AS102 baseline specified in the protocol will therefore not be appropriate and will not be conducted; analyses from other baseline definitions will be discussed in the ISE SAP.
- Safety evaluations are specified to be presented by disease progression subgroup (i.e. 'enriched' vs 'other'); however, no mITT ("enriched")/non mITT ("other") analyses will be conducted in 233AS102 final CSR. Previously the subgroups 'enriched'/'other' were provided in support of the mITT/non mITT populations defined as part of the enrichment strategy in 233AS101 Part C. However, based on the learnings, this was not the optimal way to enrich and to account for disease heterogeneity. The most valid analysis is in the ITT population with adjustment for baseline NfL for efficacy [redacted] endpoints. For safety, the most appropriate population is the overall safety population. This approach will also be consistent with ITT principle for efficacy and biomarker data which will be conducted based on the ISE.

6. Summary of Changes from the Previous Version of the SAP

The SAP Version 1.0 to 3.0 were based on interim data cuts (July 2021 and January 2022). This version is the final SAP for final CSR reporting. The details of the changes in previous versions can be found in SAP Version 2.0 and 3.0.

6.1. Changes in Version 4.0

- Updated schedule of activities and the corresponding text changes to align with protocol amendment V6.0; added a summary of protocol amendments
- Added demographics and baseline disease characteristics tables for final CSR.
- Removed ALSFRS-R, SVC, HHD analyses which will be analyzed in ISE SAP.
- Removed PD/biomarker endpoint analyses which will be analyzed in ISE SAP.
- Removed the subgroup of 'enriched' and 'other'.
- Removed type of visit summary by endpoint.

7. References

Balendra R, Jones A, Jivraj N, et al. J Neurol Neurosurg Psychiatry 2014; 0:1-5

Chio A, Hammond E, Mora G, et al. Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2015; 86:38-44

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Appendix A: Derivation of Demographic and Baseline Characteristics

BMI will be calculated as weight (kg) / height^2 (m^2).

Time since ALS symptom onset will be calculated in months as (Baseline of ALSFRS-R in 233AS102 – date of ALS symptom onset)/30.4375. Time since ALS diagnosis will be calculated in months as (Baseline of ALSFRS-R in 233AS102 – date of ALS diagnosis)/30.4375. For the purpose of these calculations partial dates for ALS symptom onset or ALS diagnosis will be imputed as follows: missing day will be imputed with 15th and missing month/day will be imputed with January 15th.

The ALSFRS-R slope at 233AS102 baseline will be calculated using the ALSFRS-R score at baseline (Day 1) in 233AS102 i.e. Baseline ALSFRS-R score – maximum possible score of 48/ Time since ALS symptom onset. Partial dates for symptom onset will be handled as defined above.

Age at onset of 233AS102 will be determined based on age collected at screening of 233AS102.

Riluzole usage and edaravone usage prior to baseline of 233AS102 will be calculated based on any data from ventilation diaries or ventilation log in combination with concomitant medications from 233AS101.

Appendix B: Derivation of C-SSRS

The Columbia Suicide Severity Rating Scale (C-SSRS) is an assessment that evaluates suicidal ideation and behavior. C-SSRS measurements are collected with respect to "Lifetime: time he/she felt most suicidal" at baseline, and with respect to "Since last visit" at last visit (Day 57 for Part A and Day 169 for Part B) and ET visit.

There are 11 common "Yes/No" questions at baseline and postbaseline visits. Five questions on *suicidal ideation* and five questions on *suicidal behavior* are re-ordered and follow increasing severity order respectively as shown in **Table 8**. In particular, only patients who answered "Yes" to question 2 will proceed to question 3, 4 and 5. Thus, for any subjects who answered "No" to question 2, an answer "No" will also be assumed to question 3, 4, and 5. An additional "Yes/No" question is used to record if subject had committed suicide in postbaseline visits.

Table 8: C-SSRS re-ordered questions

Suicidal Ideation	
Question 1	Wish to be dead
Question 2	Non-specific active suicidal thoughts
Question 3	Active suicidal ideation with any methods (not plan) without intent to act
Question 4	Active suicidal ideation with some intent to act, without specific plan
Question 5	Active suicidal ideation with specific plan and intent
Suicidal Behavior	
Question 6	Preparatory acts or behavior
Question 7	Aborted attempt
Question 8	Interrupted attempt
Question 9	Actual attempt
Question 10	Suicidal behavior
Question 11 (postbaseline visit only)	Suicide
Self-Injurious Behaviour without Suicidal Intent	
Question 12	Self-injurious behavior without suicidal intent

A subject is considered to have *suicidal ideation* at the period of interest if a "Yes" is answered to any of the five suicidal ideation questions (Question 1-5). A subject is considered to have *suicidal behavior* at the period of interest if a "Yes" is answered to any of the five suicidal behavior questions (Question 6-10) at baseline or a "Yes" is answered to any of the six suicidal behavior questions (Question 6-11) at postbaseline visit.

A subject's *Suicidal Ideation Score* is defined as the maximal suicidal ideation question number (maximal of 1-5) with an answer "Yes" per visit. The score is defined as 0 if the subject answered "No" to all 5 Suicidal Ideation questions at that visit. A subject is considered to have treatment-emergent suicidal ideation if the subject had either new or worsening suicidal ideation. A subject is considered to have new suicidal ideation if the subject's Suicidal Ideation Score increased at postbaseline visit compared to a score 0 at baseline. A subject is considered to have worsening suicidal ideation if the subject's Suicidal Ideation Score increased at postbaseline visit compared to a positive score at baseline.

A subject is considered to have treatment-emergent suicidal behavior if the subject answered "Yes" to any suicidal behavior questions at any postbaseline visit while answered "No" to all suicidal behavior questions at baseline.

Signature Page

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