COVER PAGE

Official Title:	A Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BIIB067 Administered to Adult Subjects With Amyotrophic Lateral Sclerosis and Confirmed Superoxide Dismutase 1 Mutation
NCT number:	NCT02623699
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Name of Sponsor/Company:	Biogen MA Inc.
Name of Finish Product:	Tofersen
Name of Active Ingredient:	Tofersen (BIIB067)
Study Indication:	Amyotrophic Lateral Sclerosis (ALS)

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2. STUDY SYNOPSIS

Name of Sponsor/Company: Biogen MA Inc./Biogen Idec Research Limited	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: Tofersen (BIIB067)	**Name of Active Ingredient:** Tofersen (BIIB067)	**Study Indication:** Amyotrophic lateral sclerosis (ALS)

Title of Study:

A Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BIIB067 Administered to Adult Subjects with Amyotrophic Lateral Sclerosis and Confirmed Superoxide Dismutase 1 Mutation

Principal Investigator/Coordinating Investigator:

Dr. [redacted], MD, PhD
[redacted]
USA

Study Period:	**Phase of Development: 1 (Parts A and B only)**
Date of first treatment: 20 January 2016 End of Study Date: 16 January 2019	

Study Objectives:

Primary Objectives:

To evaluate the safety, tolerability, and pharmacokinetics (PK) of BIIB067 in adult participants with ALS and confirmed superoxide dismutase 1 (SOD1) mutation.

Secondary Objectives:

- To evaluate the effects of BIIB067 on levels of SOD1 protein in the CSF.

Exploratory Objectives:

- To evaluate the effect of BIIB067 on [redacted] handheld dynamometry (HHD)
- To evaluate the effect of BIIB067 on measures of clinical function.
- To explore possible relationships [redacted] phosphorylated neurofilament heavy chain (pNfH), and neurofilament light chain (NfL).

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Study Design:

This was a randomized, double-blind, placebo-controlled, dose escalation study to examine the efficacy, safety, tolerability, PK, and pharmacodynamics (PD) of BIIB067 administered by intrathecal bolus injection to adult participants with ALS. The study was conducted in 3 parts; however, only Part A, a single ascending dose (SAD) evaluation, and Part B, a multiple ascending dose (MAD) evaluation, are detailed in this clinical study report (CSR).

In Part A, participants with ALS were randomized to receive a single dose of BIIB067 or placebo in a 3:1 (active:placebo) ratio. Four dose levels of BIIB067 (10 mg, 20, mg, 40 mg, and 60 mg), were evaluated. The first 3 dose levels were assessed in cohorts of at least 4 participants each (3 active:1 placebo) while the 4th dose level was assessed in a cohort of at least 8 participants (6 active:2 placebo).

In Part B, participants with SOD1 ALS were randomized to receive up to 5 administrations of BIIB067 or placebo in a 3:1 (active:placebo) ratio. Four dose levels of BIIB067 (20 mg, 40 mg, 60 mg, and 100 mg) were evaluated. Each dose level was assessed in cohorts of approximately 12 participants each (9 active:3 placebo).

Number of Participants (Planned and Analyzed):

Part A: SAD

Planned: minimum of 20 and maximum of 36 (adjustable base on the incidence of dose-limiting toxicity [DLT])

Analyzed: 20 participants (no DLTs were encountered)

Part B: MAD

Planned: Approximately 48 participants

Analyzed: 50 participants

Approximately 17 sites globally were originally planned for Parts A and B of the study. Subjects were ultimately randomized at 15 sites globally.

Study Population:

Main Inclusion Criteria:

- Aged ≥18 years at the time of informed consent.
- Weakness attributable to ALS. This inclusion criteria was amended during Part A (Protocol V2) of the study to require all participants to have documentation of a SOD1 mutation.
- If taking riluzole, participant must have been on a stable dose for ≥30 days prior to Day 1 and was expected to remain at that dose until the final study visit.

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Main Exclusion Criteria:

- Treatment with another investigational drug (including investigational drugs for ALS through compassionate use programs), biological agent, or device within 1 month or 5 half-lives of study agent, whichever was longer. Specifically, no prior treatment with small interfering ribonucleic acid (RNA), stem cell therapy, or gene therapy was allowed.
- Current or recent use (within 30 hours prior to screening), or anticipated need of edaravone (Radicava™).
- Presence of risk for increased or uncontrolled bleeding and/or risk of bleeding that was not managed optimally and could place a participant at an increased risk for intraoperative or postoperative bleeding. These could have included, but were not limited to, anatomical factors at or near the LP site (e.g., vascular abnormalities, neoplasms, or other abnormalities) and underlying disorders of the coagulation cascade, platelet function, or platelet count (e.g., hemophilia, Von Willebrand's disease, liver disease).

Study Treatment, Dose, Mode of Administration:

Tofersen (BIIB067) was supplied as liquid drug product containing 20 mg/mL of BIIB067. Artificial CSF, supplied by the Sponsor, was used as placebo. A total of 15 lots of BIIB067 were used.

In Part A (SAD), a single dose of study treatment was administered by intrathecal bolus injection at the following dose levels:

- Cohort 1: 10 mg BIIB067 or placebo
- Cohort 2: 20 mg BIIB067 or placebo
- Cohort 3: 40 mg BIIB067 or placebo
- Cohort 4: 60 mg BIIB067 or placebo

In Part B (MAD), 5 doses of study treatment were administered by intrathecal bolus injection at the following dose levels. Participants received 3 doses on Days 1, 15, and 29, followed by maintenance dosing on Days 57 and 85:

- Cohort 5: 20 mg BIIB067 or placebo
- Cohort 6: 40 mg BIIB067 or placebo
- Cohort 7: 60 mg BIIB067 or placebo
- Cohort 8: 100 mg BIIB067 or placebo

Duration of Treatment and Follow-Up:

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Part A: SAD

The planned duration of study participation for a single participant was up to 15 weeks, including:

- 7-week screening period
- 8-week follow-up period

Part B: MAD

The planned duration of study participation for a single participant was up to 31 weeks, including:

- 7-week screening period
- 12-week treatment period and
- 12-week follow-up period*

*The follow-up period for some United Kingdom participants was extended up to 29 weeks due to regulatory requirements.

Criteria for Evaluation:

Following is a description of all safety, clinical function, PK, PD assessments that were planned for this study.

Safety:

The following clinical assessments were performed to evaluate the safety profile of BIIB067:

- Medical history
- Physical examinations
- Limited neurological examinations (to be assessed by a trained specialist)
  - cranial nerves, coordination/cerebellar function, reflexes, motor, and Mini-Mental State Examination (MMSE) [a 30-point questionnaire that is used to measure cognitive impairment] (in Part B)
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate (after the participant has rested in a sitting position for at least 5 minutes)
- Weight measurements
- 12-lead ECGs in triplicate (paper, as applicable)
- Columbia Suicide Severity Rating Scale (C-SSRS)

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- Concomitant therapy and procedure recording
- AE and SAE recording

The following laboratory assessments were performed to evaluate the safety profile of BIIB067:

- Hematology: complete blood count with differential and platelet count, absolute neutrophil count
- Coagulation: INR, PT, and APTT
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal)
- Urine pregnancy tests
- CSF analysis: red blood cell count, white blood cell count, protein, and glucose

Additionally, anti-BIIB067 antibody assessments were performed to evaluate the immunogenicity of BIIB067.

Pharmacokinetics:

The following PK parameters were assessed in plasma, when feasible:

- Maximum observed concentration (C_{max})
- Time to reach the maximum observed concentration (T_{max})
- Area under the concentration-time curve from time 0 to infinity (AUC_{inf})
- AUC from time 0 to time of the last measurable concentration
- Apparent terminal $t_{½}$ (assessed in CSF, when feasible)

[redacted]

- [redacted]

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- [redacted]
- [redacted]
  - [redacted]
  - pNfH
  - NfL

[redacted]

- Functional status as measured by ALS Functional Rating Scale-Revised (ALSFRS-R). [redacted]
- Pulmonary function as measured by slow vital capacity (SVC).
- Motor function as measured by handheld dynamometry (HHD). [redacted]

Statistical Methods:

Planned Analyses:

Analysis populations were defined as follows for Parts A and B:

- The intent-to-treat (ITT) population is defined as all randomized participants who received at least 1 dose or a part of 1 dose of study treatment (BIIB067 or placebo).
- The Safety population is defined as the ITT population of participants. This is the primary population for the analysis of safety endpoints.
- The PK population is defined as the subset of the ITT population of participants with at least 1 postdose PK measurement.
- The PD population is defined as the subset of the ITT population of participants with at least 1 postdose PD measurement.
- The Clinical Function set is defined as the subset of the ITT population of participants who have at least 1 postdose clinical function measurement.
- The Immunogenicity population is defined as all participants in the Safety population who have at least 1 postdose sample evaluated for immunogenicity.

Demographics and Baseline Disease Characteristics:

Demographic data, including age (years), age category (18 to <35, 35 to <50, 50 to <65, ≥65), sex, ethnicity, race, height, weight, and body mass index (BMI), were summarized by dose group and for all participants. BMI is calculated as weight (kg)/height^2 (m^2).

ALS disease history was also summarized by dose group and for all participants using descriptive statistics.

Medical history was classified using MedDRA version 22.0. A summary of medical history by system organ class and preferred term is also provided.

Part B only:

For disease progression subtype analysis, participants were classified as "fast progressors" if they had one of the SAP-defined fast-progressing SOD1 mutations and a prerandomization ALSFRS-R slope decline of at least 0.2 points per month; all other participants were characterized as "other." The list of fast-progressing SOD1 mutations was determined in a blinded fashion following the interim analysis of Cohorts 1 to 7 but prior to the unblinding and interim analysis of Cohort 8. The mutations recorded for all participants in Part B were reviewed to assess which were classified as fast-progressing SOD1 mutations through genetic and literature review. The following 3 SOD1 mutations from Part B Cohorts 5 to 8 were identified as fast progressing: p.Ala5Val (A4V), p.Arg116Gly (R115G), and p.Leu107Val (L106V).

Safety:

All AEs and medical history were classified using MedDRA version 22.0.

The incidence of treatment-emergent AEs (TEAEs) and SAEs were summarized by system organ class and preferred term for each dose level. TEAEs were also summarized by severity (toxicity grade), by relationship to study treatment, and by relationship to lumbar puncture. AEs leading to withdrawal, AEs leading to discontinuation of study treatment, and AEs leading to drug interruption were also summarized. Deaths were listed.

Descriptive summaries and summaries of abnormalities and clinically significant changes were also presented for other safety parameters, including laboratory data, vital signs, ECG, MMSE, C-SSRS, and neurological examination. Numbers and percentages of participants who developed antibodies were summarized by dose level and visit.

Pharmacokinetics:

Both plasma and CSF BIIB067 concentrations were listed, and summary statistics, including both the arithmetic and geometric means with corresponding standard errors, were presented for each visit. Noncompartmental methods were used to calculate AUC_{0-24}, C_{max}, and T_{max} at Day 1 (Parts A and B) and Day 85 (for Part B only).

Pharmacodynamics and Clinical Function:

The change from baseline in PD and clinical function were summarized by visit and dose level using descriptive statistics and plotted graphically.

For Part A, there was no imputation for missing data and no statistical testing of endpoints.

For Part B, mixed model for repeated measures (MMRM) was applied as the primary method of imputation to account for missing data for PD endpoints (CSF and plasma SOD1 ratio to baseline), exploratory biomarkers (CSF and plasma pNfH and NfL levels), and the majority of clinical function endpoints including [redacted] ALSFRS-R total score and functional domain scores, percent predicted SVC, [redacted]. LOCF was applied as a supportive method of imputation to account for missing data with the exception of HHD megascore, where only LOCF was applied to account for missing data. The Wilcoxon rank sum test was used as the primary method of inference based on imputed data to test endpoints at Day 85 (or Day 92, depending on whether the endpoint was assessed at Day 85). Statistical testing was based on the imputed datasets after MMRM or LOCF had been applied. The MMRM model for change from baseline in PD and relevant clinical function endpoints was also used for statistical inference as supportive analysis and not only to account for missing data.

Descriptive statistics using observed data were also presented for completers (i.e., participants who completed all assessments for an endpoint per the protocol version under which the participant was consented) through Day 169, and also observed data for all patients through to Day 169 if available, for PD and clinical function endpoints.

Subgroup analysis was performed by disease progression type ("fast progressing," "other").

Sample Size Calculations:

For Part A (SAD), the maximum sample size of 36 participants was based on clinical rather than statistical considerations. Participants were randomized to receive BIIB067 or placebo in a 3:1 ratio in each cohort. Each cohort in Part A had a minimum of 4 participants (3 active and 1 placebo) and a maximum of 12 participants (9 active and 3 placebo). The final number for each cohort was based on the dose-limiting toxicity (DLT) profile. If no DLT occurred in any dose level, then a total of 20 participants (15 active and 5 placebo) would be randomized. This design both allowed for adequate evaluation of the safety of BIIB067 if DLT was encountered and minimized participant exposure at subtherapeutic single doses.

For Part B (MAD), up to 48 participants were enrolled in up to 4 cohorts, with up to 9 participants randomized to receive BIIB067 and 3 participants randomized to receive placebo for each cohort. This design provided approximately 80% power to detect a difference in SOD1 reduction between 25% from the BIIB067 group and 12% from the placebo group at a 10% significance level. The sample size calculation assumed the same 10.5% standard deviation in the 2 treatment groups.

Results:

Data are summarized by treatment group. All participants receiving placebo were combined to form placebo control group.

Participant Accountability:

Part A: SAD

Twenty participants were enrolled and dosed in Part A. Five participants were assigned to placebo and 3, 3, 3, and 6 to BIIB067 10, 20, 40, and 60 mg, respectively. A total of 19 participants (95%) completed all of Part A, with 1 prematurely discontinuing treatment after dosing due to withdrawal of consent. Two of the participants who completed Part A of the study enrolled into Part B.

Part B: MAD

Fifty participants were enrolled and dosed in Part B, with12 participants assigned to placebo and 10, 9, 9, and 10 assigned to BIIB067 20, 40, 60, and 100 mg, respectively. A total of 48 participants (96%) completed all study treatments (5 doses), while 45 participants (90%) completed all of Part B.

Demographics and Baseline Disease Characteristics:

Part A: SAD

- The majority of participants (80%) were White, with a significant proportion (16%) who did not report their race due to confidentiality regulations. The gender balance was split equally between males and females. The average participant BMI was 26.9 kg/m^2. Participant ages ranged from 21 to 66 years old, with the placebo group having a slightly higher mean participant age (58.4) than the BIIB067 treatment groups (45.0 to 55.3).
- The majority of participants carried a SOD1 gene mutation; however, Cohort 1 consisted entirely of ALS participants without a confirmed SOD1 mutation, since they were enrolled prior to an amendment that added this inclusion criterion.
- The most common site of disease onset was in the limbs (19 participants; 95%). Measures of baseline disease progression were generally similar across BIIB067-treated groups, whereas placebo-treated participants had a slightly longer time between ALS symptom onset and diagnosis and a slower rate of decline.

Part B: MAD

- The majority of participants (56%) were White, with a significant proportion (38%) who did not report their race due to confidentiality regulations. There were slightly more males (56.0%) than females (44%), with the highest male-to-female ratio occurring in the 20 mg group. The average participant BMI was 26.8 kg/m^2. Participant ages ranged from 26 to 75 years old with the 40 mg treatment group having a slightly higher mean participant age (58.0 years) than the other groups (41.5 to 49.2 years).
- All participants had limb onset of paresis and carried a SOD1 gene mutation.
- Baseline characteristics related to disease progression were most balanced in the BIIB067 100 mg and placebo groups, consistent with the proportion of fast progressors in each group. These groups had a higher mean prerandomization ALSFRS-R slope, a shorter time since ALS symptom onset and diagnosis, and higher baseline CSF neurofilament levels as compared to the 20, 40, and 60 mg treatment groups.

Safety:

- Overall, IT administration of up to BIIB067 100 mg was well tolerated by participants with ALS.

Part A: SAD

- There were no deaths or SAEs reported during the SAD evaluation.

- The majority of participants experienced AEs, all of which were mild or moderate in severity. The most commonly reported were procedural pain, headache, and back pain. Slightly fewer AEs were reported in the placebo and BIIB067 10 mg treatment groups. Two AEs were assessed as related to study treatment.
- About half of all participants experienced AEs considered by the Investigator to be related to the LP procedure across both the placebo and BIIB067 treatment groups. These were most frequently categorized as procedural pain, with other musculoskeletal/connective tissue and nervous system disorders also reported.
- Overall, no remarkable findings were observed for clinical laboratories, vital signs, physical/neurological examinations, ECG, or C-SSRS. Only 1 neurological finding, hyporeflexia, was reported as an AE.
- [redacted]

Part B: MAD

- Three deaths occurred during the MAD portion of the study (1 each in the placebo, 20 mg, and 60 mg treatment groups); however, none were considered by the Investigator to be related to study treatment.
- Five BIIB067-treated participants and 2 placebo-treated participants reported SAEs. None occurred in the highest dose group and incidence of these SAEs did not suggest a relationship to dose. Two SAEs (CSF protein increased and CSF white blood cell [WBC] count increased), both occurring in a single participant in the BIIB067 60 mg treatment group, were assessed by the Investigator to be related to study treatment. The only SAE occurring in more than 1 participant was respiratory failure, with all occurrences considered to be unrelated to study treatment.
- All participants experienced AEs, with the greatest overall numbers of AEs reported in the highest dose group (100 mg). The most frequently reported AEs were procedural pain, headache, post lumbar puncture syndrome, and fall. With the exception of the non-treatment-related deaths, no AEs resulted in withdrawal from the study.
- The majority of AEs were mild or moderate in severity, with events of all toxicity grades occurring at a similar rate across placebo and BIIB067 treatment groups. About a quarter of reported AEs were considered by the Investigator as related to study treatment, with slightly more related AEs occurring in the highest dose groups (BIIB067 60 and 100 mg).
- CSF protein and CSF WBC count abnormalities were the most common treatment-related AEs. Additional participants had abnormalities in these CSF parameters that were not reported as AEs. These participants did not have symptoms consistent with meningitis or meningeal inflammation and none of these abnormalities lead to treatment discontinuation.
- The majority of participants across all groups experienced AEs considered by the Investigator to be related to the LP procedure. These were most frequently categorized as procedural pain, post lumbar

puncture syndrome, and headache, with musculoskeletal/connective tissue and nervous system disorders also reported.

- Overall, no remarkable findings were observed for clinical laboratory tests, vital signs, and physical/neurological examinations. Changes to neurological findings were consistent with ALS disease progression. Two participants, 1 in the placebo group and 1 in the BIIB067 20 mg dose group, had adverse ECG abnormalities identified as sinus tachycardia and atrial flutter, respectively.

[redacted]

Pharmacokinetics:

Part A: SAD

- In CSF, at and above the 20 mg dose level, BIIB067 concentrations increased with dose in a less-than-dose-proportional fashion. In plasma, significant PK variability was observed; however, median C_{max} and AUC_{0-24} seemed roughly dose proportional.

Part B: MAD

- BIIB067 concentrations in CSF increased with dose in a less-than-dose-proportional manner, with steady-state concentrations achieved immediately after the loading period (3 doses administered every 2 weeks). BIIB067 AUC and C_{max} in plasma were dose related; however, dose proportionality could not be evaluated. Minimal or no accumulation in CSF or plasma was observed.

Pharmacodynamics:

Part A: SAD

No meaningful changes in PD markers (CSF SOD1 protein) and exploratory biomarkers (CSF and plasma neurofilament proteins) were observed following a single dose of BIIB067 at any dose level.

Part B: MAD

Consistent with CSF and plasma exposures, the greatest reduction in total CSF SOD1 was achieved with BIIB067 100 mg. From baseline to Day 85, a statistically significant reduction in total CSF SOD1 protein was observed in the 100 mg treatment group (36%) as compared to placebo (3%).

CSF and plasma pNfH and NfL showed concordant trends, suggesting a slowing of decline and underlying disease activity with BIIB067 100 mg as compared to placebo. These trends are primarily driven by the fast-progressor subgroup.

[redacted]

Efficacy

Part A: SAD

- No meaningful change in efficacy assessments (ALSFRS-R scores, SVC, [redacted] and HHD) were observed following a single dose of BIIB067 at any dose level.

Part B: MAD

- Several exploratory efficacy endpoints (i.e., ALSFRS-R, SVC, HHD, [redacted]) showed concordant trends, suggesting a slowing of decline and underlying disease activity with BIIB067 100 mg as compared to placebo. These trends were primarily driven by the fast-progressor subgroup.
- [redacted]

Conclusions:

The well-tolerated safety profile, evidence of target engagement, and apparent slowing of disease progression across multiple measures of clinical function and underlying disease activity with BIIB067 100 mg support the continued development of BIIB067 for the treatment of SOD1-ALS.

Date of Report: 24 September 2021

Version: 2

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Title of Study:

A Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BIIB067 Administered to Adult Subjects with Amyotrophic Lateral Sclerosis and Confirmed Superoxide Dismutase 1 Mutation

Coordinating Investigator:

Dr. [redacted], MD, PhD, [redacted] USA

Study Period: Date of first treatment: 27 March 2019 End of Study Date: 16 July 2021	**Phase of Development:** 3

Study Objectives:

Primary Objective:

To evaluate the clinical efficacy of tofersen administered to adult participants with ALS and a confirmed SOD1 mutation.

Secondary Objective:

To evaluate the safety, tolerability, pharmacodynamics (PD), and biomarker effects of tofersen administered to adult participants with ALS and a confirmed SOD1 mutation.

Exploratory Objective:

[redacted]

Study Design:

This was a randomized, double-blind, placebo-controlled study to examine the efficacy, safety, tolerability, PK, and PD of tofersen administered by intrathecal bolus injection to adult participants with ALS. The study was conducted in 3 parts; however, only Part C, a Phase 3 pivotal study, is detailed in this clinical study report (CSR). Participants were randomized to receive tofersen 100 mg or placebo in a 2:1 (active:placebo) ratio for 28 weeks (197 days) at 32 sites globally. Participants who completed the study had the opportunity to be screened for Study 233AS102, an open-label long-term extension study.

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Number of Participants (Planned and Analyzed):

Planned:

Approximately 99 participants were planned to be randomized, with approximately 66 participants administered tofersen 100 mg and approximately 33 participants administered placebo.

Analyzed:

A total of 108 participants were randomized and dosed, with 72 participants receiving tofersen and 36 participants receiving placebo. A total of 97 participants completed the study.

Study Population:

Main Inclusion Criteria:

- Aged ≥18 years at the time of informed consent.
- Weakness attributable to ALS and a confirmed SOD1 mutation.
  a. SOD1 mutation had to be confirmed by the central reader based on the sample obtained during the Screening Visit; participants with an SOD1 mutation interpreted by the central reader to be pathogenic or likely pathogenic were eligible.
  b. Additionally:
- Prognostic enrichment criteria for rapid disease progression (participants may have been eligible based on 1 of the following 2 criteria):
  a. One of the following SOD1 mutations and a prerandomization Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) slope decline of ≥ 0.2 per month (calculated as [48-baseline score]/time since symptom onset):

     p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly
     OR
  b. SOD1 mutation other than those listed in item "a." with prerandomization ALSFRS-R slope decline of ≥ 0.9 per month (calculated as [48-baseline score]/time since symptom onset)
- Criteria for all other eligible participants: SOD1 mutation other than those listed in item "a." (no ALSFRS-R slope decline requirement).
- For participants who met prognostic enrichment criteria for rapid disease progression, slow vital capacity (SVC) ≥ 65% of predicted value as adjusted for sex, age, and height (from the sitting position). For all other eligible participants, SVC ≥ 50% of predicted value as adjusted for sex, age, and height (from the sitting position).
  Note: For SVC testing, at least 3 acceptable tests with the 2 highest acceptable (largest and next largest)

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efforts within 150 mL of vital capacity should have been achieved.

- Participants taking riluzole at study entry must have been on a stable dose for at least 30 days prior to Day 1 and dose was expected to remain stable for the duration of the study.
- Participants taking concomitant edaravone at study entry must have initiated edaravone ≥ 60 days (2 treatment cycles) prior to Day 1 and have continued with the same dose regimen throughout the study. Edaravone may not have been administered on dosing days of this study.

Main Exclusion Criteria:

- Treatment with another investigational drug (including investigational drugs for ALS through compassionate use programs), biological agent, or device within 1 month or 5 half-lives of study agent, whichever was longer. Specifically, no prior treatment with small interfering ribonucleic acid (RNA), stem cell therapy, or gene therapy was allowed.
- Presence of risk for increased or uncontrolled bleeding and/or risk of bleeding that was not managed optimally could have placed a participant at an increased risk for intraoperative or postoperative bleeding. These could have included, but were not limited to, anatomical factors at or near the lumbar puncture (LP) site (e.g., vascular abnormalities, neoplasms, or other abnormalities) and underlying disorders of the coagulation cascade, platelet function, or platelet count (e.g., hemophilia, Von Willebrand's disease, liver disease).

Study Treatment, Dose, Mode of Administration:

Tofersen (BIIB067) was supplied as a liquid in vials containing 6.7 mg/mL of BIIB067. Artificial cerebrospinal fluid (CSF) was used as placebo. A total of 8 lots of tofersen and placebo were used.

A total of 100 mg of tofersen or placebo was administered 8 times (3 loading doses once every 2 weeks and 5 maintenance doses once every 4 weeks) by intrathecal administration. A total volume of 15 mL tofersen or placebo was administered over a 1- to 3-minute bolus injection.

Duration of Treatment and Follow-Up:

Study duration was approximately 32 to 36 weeks:

- 4-week screening period
- 24-week treatment period
- 4- to 8-week follow-up period as follows:
  - Participants who enrolled (uninterrupted) in the long-term extension (LTE) study (233AS102),

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the Week 28 Visit served as the end of study (EOS) Visit.

- Participants with delayed enrollment in the LTE study, the Week 32 Visit served as the EOS Visit (either in person or by telephone contact).
  - If enrollment in the LTE occurred ≤ 28 days from the planned Week 28 Visit, the Week 32 Visit (EOS) assessments were conducted at the time of enrollment in the LTE.
  - If enrollment in the LTE occurred > 28 days from the planned Week 28 Visit, the Week 32 Visit (EOS) assessments were conducted as planned (4 weeks from the planned Week 28 Visit).
- Participants who did not enroll in the LTE study, the Week 32 Visit served as the EOS Visit (either in person or by telephone contact).

Criteria for Evaluation:

Following is a description of all efficacy, PD, PK, biomarkers, and safety assessments that were originally planned for this study.

Efficacy:

- ALSFRS-R
- SVC
- Handheld dynamometry (HHD)
- Participant diary/eDiary to record ventilation use
- Time to death
- [redacted]
- [redacted]

Pharmacodynamics:

- total SOD1 protein in CSF

[redacted]

- [redacted]

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[redacted]

Safety:

Clinical Safety Assessments

The following clinical assessments were performed to evaluate the safety profile of tofersen:

- Medical history
- Physical examinations
- Limited neurological examinations
- Vital sign measurements
- Weight measurements
- 12-lead electrocardiograms (ECGs)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Mini-Mental State Examinations (MMSE)
- Concomitant therapy and procedures
- Incidence of adverse events (AEs) and serious AEs (SAEs)

Laboratory Safety Assessments

The following laboratory assessments were performed to evaluate the safety profile of tofersen by determining clinical laboratory abnormalities:

- Hematology: complete blood count with differential and platelet count
- Coagulation: international normalized ratio, prothrombin time, and activated partial thromboplastin

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time

- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium
- Urinalysis: dipstick for blood, protein, and glucose
- Urine and/or serum pregnancy tests
- CSF analysis: red blood cell count, white blood cell count, protein, and glucose

Statistical Methods:

Planned Analyses:

Analysis populations were defined as follows:

- Intent-to-treat (ITT) population: all participants who were randomized and received at least 1 dose of study treatment
- Modified intent-to-treat (mITT) ["enriched"] population: subset of the population who met prognostic enrichment criteria for rapid disease progression, who were randomized, and received at least 1 dose of study treatment
- non-mITT ("other") population: all other eligible participants who were randomized and received at least 1 dose of study treatment
- PK population: all participants who received at least 1 dose of study treatment and have at least 1 post-randomization PK concentration measurement
- Safety population: all participants who were randomized and received at least 1 dose of study treatment (i.e., the overall ITT population)
- Immunogenicity population: all participants who received at least 1 dose of study treatment and had at least 1 post-dose sample evaluated for immunogenicity

Demographics and Baseline Disease Characteristics:

Demographic data, including age (years), age category (18-<35,35-<50, 50-<65, ≥65), gender, ethnicity, race, height, weight and body mass index (BMI) were summarized. ALS disease history was also summarized descriptively. Descriptive statistics for baseline clinical function and biomarkers were be presented. Medical history was classified using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. A summary of medical history by system organ class (SOC) and preferred term (PT) was provided for the safety population.

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Efficacy, Pharmacodynamics, Biomarkers, Pharmacokinetics

For each of the primary efficacy and secondary efficacy endpoints, the key analysis, which was in the mITT population and was used for formal testing, was classified as the "primary analysis" for that efficacy endpoint. The analyses in the non-mITT population and overall ITT population were classified as secondary analyses of each of the primary and secondary endpoints, with the exception of total SOD1 protein in CSF, which was the primary endpoint for the non-mITT population

- *Primary Analyses*

  Primary Endpoint

  The primary analysis of the change from baseline in ALSFRS-R was analyzed using the joint-rank test (JRT) methodology to account for mortality for the primary inference. Multiple imputation (MI) was used to handle withdrawals. The estimates were obtained from an analysis of covariance (ANCOVA) for change from baseline in ALSFRS-R at Week 28 (Day 197), with missing data imputed using MI. The corresponding nominal p-value from the ANCOVA was presented as a sensitivity analysis.

  The estimand of the primary analysis was defined as follows:

  - Population: all participants in the mITT population.
  - Variable: change from baseline to Day 197 in the ALSFRS-R total score.
  - Intercurrent events: relevant intercurrent events (death and withdrawals) were handled using a composite strategy in which participants who had these intercurrent events were ranked against each other and against participants without any intercurrent event using the JRT methodology based on MI datasets. Participants were ranked using their Day 197 value (or imputed Day 197 value for withdrawals).
  - Summary statistics: difference between treatment groups in least square (LS) means of Day 197 change from baseline with corresponding standard errors (SEs) and 95% confidence intervals (CIs) taken from the ANCOVA for change from baseline to Day 197, based on the MI dataset. The ANCOVA model included treatment group as a fixed effect and covariates for ALSFRS-R total score, baseline disease duration since symptom onset, and use of riluzole or edaravone. In addition, median changes from baseline to Day 197 with corresponding 95% CIs were provided by treating death as worse than the median.

  The ranked scores were analyzed for each of the 100 MI complete datasets using an ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline disease duration since symptom onset, baseline ALSFRS-R total score, and use of riluzole or edaravone. The difference between treatment groups in median changes from baseline to each visit was presented with 95% CIs based on the MI datasets, as well as the p-value from the JRT for Day 197.

  Secondary Endpoints

  Change from baseline to Week 28 (Day 197) in percent predicted SVC for the mITT population was analyzed as for the primary efficacy endpoint.

  Changes from baseline to Week 28 (Day 197) in each of total CSF SOD1 protein, plasma NfL and HHD megascore were analyzed for the mITT population using ANCOVA with MI. Total CSF SOD1 protein

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was also analyzed similarly in the non-mITT population.

Data for PD/biomarker endpoints were log-transformed for the ANCOVA analysis with MI. MI was used to impute data for withdrawals and missing intermittent data. In the ANCOVA analysis for change from baseline to Day 197, assessments following death were also imputed using MI; in the JRT analysis, deaths were ranked lowest based on the time to death. LS means, i.e., adjusted means of each treatment group were presented with LS mean treatment group differences and their corresponding 95% CIs and p-values.

Kaplan-Meier estimates of the cumulative probability of the time to death or permanent ventilation over time and for time to death were determined for the mITT population. Treatment comparisons were based on a stratified log rank test. A Cox proportional hazards model was used to obtain the hazard ratio and 95% CIs.

- *Sensitivity analyses* were performed for primary and secondary endpoints to check the robustness of the assumptions for the primary analysis, i.e., confirm that the estimate derived was reliable for interpretation.
- *Secondary analyses*

  For ANCOVA analysis on change from baseline endpoints, LS means with SEs were presented, as were the LS mean treatment differences and their corresponding 95% CI and nominal p-values. For time to event analysis, a Kaplan-Meier analysis and Cox proportional hazards model were performed in the non-mITT and ITT populations. No p-values were initially presented for the overall ITT population, these were added post-hoc.

  As a secondary analysis on ALSFRS-R total score, the following secondary analyses were performed on the JRT:

  - Permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days) was incorporated into the joint-rank analysis for ALSFRS-R total score to obtain the p-value; analysis of ranked scores was performed using ANCOVA with MI.
  - Both withdrawal from study due to disease progression and permanent ventilation were incorporated into the joint-rank analysis for ALSFRS-R total score to obtain the p-value; analysis of ranked scores was performed using ANCOVA with MI.

  The ANCOVA analysis based on MI datasets was also performed at all visits over time other than Day 197 for the primary and secondary endpoints. LS means and LS mean changes over time were also presented in line plots. For the non-mITT population, baseline plasma NfL was also included as an additional secondary analysis of the ANCOVA analysis of change from baseline to Day 197 for ALSFRS-R total score.

  Descriptive statistics were presented for actual values and changes from baseline in ALSFRS-R total score, percent predicted SVC, HHD megascore, [redacted], and PD and biomarker endpoints based on observed data over time for each of the mITT, non-mITT, and overall ITT populations.

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- All other analyses were classed as *supplementary or additional analyses*, i.e., any analyses to investigate and understand the data more fully. A forest plot presented the estimate of the treatment difference and corresponding 95% CI for change from baseline in ALSFRS-R to Day 197 based on all primary, secondary, supportive, and sensitivity analyses.
- *Subgroup analyses* were performed for the primary efficacy endpoint and for the following secondary endpoints: change from baseline in percent predicted SVC, change from baseline in HHD megascore, and ratio to baseline for each of total CSF SOD1 protein and plasma NfL for each of the mITT, non-mITT, and ITT populations. Each subgroup category was analyzed separately using the ANCOVA based on MI imputed datasets. Descriptive statistics for observed data were also presented by treatment group. Subgroups analyzed were gender, baseline disease duration since symptom onset, baseline plasma NfL, site of onset, geographic region, and riluzole/edaravone use. Due to the concern with the predictive value of prerandomization slope, other forms of enrichment criteria were specified as part of the subgroup analysis. This included baseline plasma NfL, as mentioned above, given the potential utility of neurofilament as a biomarker of ALS disease activity, as well as the following enrichment criteria: an analysis was also performed for the mITT population on the subgroup of subjects with a prerandomization ALSFRS-R slope decline of at least 0.9 per month. This analysis was performed for each of the 5 endpoints mentioned above. An analysis was also performed for each of the mITT and ITT population on the subgroup of subjects with a Screening to Day 15 ALSFRS-R "run-in" slope decline of at least 0.9. This analysis was performed for each of the 5 endpoints mentioned above.
- *Additional analyses* were performed for exploratory endpoints of [redacted], exploratory biomarkers and exploratory analyses for ALSFRS-R.
- *Post-hoc analyses* were conducted for clinical function and quality of life endpoints in the ITT population with adjustment for baseline plasma NfL instead of baseline disease duration since symptom onset due to the challenges with defining the optimal enrichment criteria and the better predictive value of baseline NfL for disease progression.

[redacted]

Safety:

Safety and tolerability were part of the secondary endpoints. Summaries of AEs and SAEs were presented overall

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and by disease progression subgroup ("enriched" or "other"). AEs were also presented by maximum Common Terminology Criteria for Adverse Events (CTCAE) grade, relationship to lumbar puncture, and relationship to study treatment. Incidence and incidence rates were provided and summarized by primary SOC and MedDRA v24.0 PT by treatment group.

Summary statistics of actual values and changes from baseline over time were presented for laboratory data, vital signs, ECG, and MMSE by treatment group. Shift tables of postbaseline abnormalities were presented for laboratory data, ECG, and vital signs. Descriptive statistics for neurological examinations and C-SSRS were also presented.

A summary of the number and percentage of participants who were anti-drug antibodies (ADA) positive was presented by treatment group, with separate summaries for those with a negative result at baseline and those who were positive at baseline. For those participants considered ADA positive, a summary was provided showing those participants with a persistent ADA response and those participants with a transient ADA response. The incidence of AEs was also presented for participants with at least 1 positive ADA result at post-baseline using Standardized MedDRA Queries (SMQ) for hypersensitivity, anaphylactic reaction, and angioedema.

Sample Size Calculations:

The sample size for Part C was selected primarily based on the JRT combining the Week 28 change from baseline in ALSFRS-R and mortality in the mITT population (N = 60). With a 2-sided significance level of 0.05, the JRT gave 84% power.

Results:

Participant Accountability:

A total of 108 participants were enrolled. All participants received at least 1 dose of study treatment and were included in the ITT population. Of these, 60 participants (55.6%) were included in the "enriched" subgroup (mITT population) and 48 participants (44.4%) were included in the "other" subgroup (non-mITT population).

A total of 97 participants completed the study. Treatment discontinuations and study withdrawals were similar in the tofersen group compared to the placebo group; treatment discontinuations and study withdrawals were more common in the "enriched" subgroup. The most common reason for discontinuation of study treatment was disease progression (n = 5, 4.6%), all of which occurred in the "enriched" subgroup, followed by AEs (n = 3, 2.8%). One participant (in the "enriched" subgroup) died 114 days after being randomized to tofersen 100 mg. The cause of death was reported as congestive cardiac failure and the Investigator assessed the event to be unrelated to tofersen.

Demographics and Baseline Disease Characteristics:

Most participants were White (63.9%), followed by Asian (8.3%). A large proportion of participants did not report their race and ethnicity (25.9%) due to confidentiality regulations. The percentage of males and females was similar across treatment groups and populations, with more males enrolled overall (males, 57.4% and females, 42.6%). Participant ages ranged from 23 to 78 years with a higher mean participant age in the placebo group in the "enriched" subgroup (54.0 years) compared with the tofersen group (47.3 years). Other demographic characteristics were generally balanced between treatment groups and populations.

Baseline and disease characteristics were balanced across treatment arms for use of riluzole and/or edaravone and

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characteristics related to the stage of disease, including time from onset, total ALSFRS-R score, and SVC. However, baseline plasma NfL levels were approximately 15% to 25% higher in the tofersen group compared to the placebo group, suggestive that these participants were progressing more quickly at Baseline. Consistently, the rate of decline on ALSFRS-R from screening to Day 15 (approximate 42-day period) was greater in the tofersen group compared to the placebo group. Subgrouping the population by baseline plasma NfL levels (rather than mutation type and pre-randomization ALSFRS-R slope decline) appeared to correct these imbalances between the tofersen and placebo groups. The population enrolled in this study was representative of the broad SOD1-ALS population. Forty-two unique SOD1 mutations centrally confirmed as pathogenic or likely pathogenic were enrolled. The most commonly identified SOD1 mutation types (> 10% of participants) were p.Ile114Thr (n= 20/108; 18.5%) and p.Ala5Val (n = 17/108; 15.7%).

Efficacy, Pharmacodynamics, Biomarkers:

- *Primary endpoint: Change from baseline to Day 197 (Week 28) in the ALSFRS-R total score*

Functional decline as measured by ALSFRS-R at 28 weeks was reduced but not statistically significantly different in the tofersen group compared to the placebo group (1.2-point treatment difference [95% CI: -3.2, 5.5], p = 0.9689, in the mITT population). The results from the ANCOVA + MI (sensitivity analysis) support the results from the JRT + MI (p = 0.5998). In the non-mITT population (secondary analysis), there was a 1.4-point treatment difference favoring tofersen (95%CI: -1.1, 3.9), nominal ANCOVA + MI p = 0.2726. A larger effect was observed in the ITT population in the more homogenized faster-progressing subgroup according to baseline plasma NfL ≥ median (3.9-point treatment difference [95% CI: -1.00, 8.86], post-hoc p = 0.1184), as well as in the in the faster-progressing subgroup with a run-in slope decline ≥ 0.9 (3.0-point treatment difference [95% CI: -2.23, 8.19], p = 0.3815).

Consistently, in a post-hoc analysis including baseline plasma NfL levels in the imputation model for the ITT population and replacing disease duration since symptom onset with baseline plasma NfL in the ANCOVA model, the treatment difference increased to 2.1 (95% CI: -0.33, 4.54; nominal JRT + MI p = 0.5015; ANCOVA nominal p = 0.0904). Due to various reasons, such as drug interruptions and inability to attend clinic, some participants missed doses of study treatment; 2 or more consecutive missed doses may have a potential impact on efficacy. [redacted]. By excluding this participant prior to the imputation model for the ITT population and by including baseline plasma NfL, a 2.4-point treatment difference favoring tofersen was observed in ALSFRS-R total score change from baseline at Week 28 (95% CI: 0.15, 4.66). This treatment difference showed nominal statistical significance on the ANCOVA + MI analysis (nominal p = 0.0369) but not on the JRT + MI analysis (nominal p = 0.4359). This post-hoc analysis demonstrates the influence of outliers in a small study.

- *Secondary endpoints in order of hierarchical testing*
  - *Change (i.e., ratio) from baseline in total SOD1 protein concentration in CSF*

Consistent with the intended mechanism of action of tofersen, total CSF SOD1 protein levels were reduced at Week 28 in the tofersen group compared to the placebo group, with a 38% reduction (nominal p<0.0001) in the mITT population and a 26% reduction (nominal p = 0.0007) in the non-mITT population. Similar reductions were

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observed in the ITT population in the faster-progressing subgroups according to baseline plasma NfL levels and run-in slope decline ≥ 0.9.

– *Change (i.e., ratio) from baseline in NfL concentration in plasma*

Despite lower levels at Baseline in the non-mITT population, reductions in plasma NfL levels from baseline to Week 28 were observed in both the mITT and non-mITT populations, with a 67% reduction (nominal p<0.0001) in the mITT population and a 48% reduction (nominal p < 0.0001) in the non-mITT population. Similar reductions were observed in the ITT population in the faster-progressing subgroups according to baseline plasma NfL levels and run-in slope decline ≥ 0.9. These reductions in plasma NfL suggest tofersen is reducing axonal injury and motor neuron loss.

– *Change from baseline to Day 197(Week 28) in SVC*

Change from baseline to Week 28 in percent predicted SVC showed a lesser decline in the tofersen group compared to the placebo group (7.9% predicted treatment difference [95% CI: -3.5, 19.3], nominal p = 0.3233 [JRT] in the mITT population). A larger effect favoring tofersen was observed in the ITT population in the faster-progressing subgroup according to baseline plasma NfL ≥ median (9.9% predicted treatment difference [95% CI: -2.3, 22.1], post-hoc nominal p = 0.1108), as well as in the in the faster-progressing subgroup with a run-in slope decline ≥ 0.9 (12.3%-point treatment difference [95% CI: -2.0, 26.5], nominal p = 0.1629).

– *Change from baseline to Day 197 in HHD megascore*

A modest trend suggesting slowing of decline in muscle strength in the tofersen group compared to the placebo group (0.02-point treatment difference, 95% CI: -0.21, 0.26, ANCOVA + MI nominal p = 0.8390 in the mITT population). A similar trend was observed in the non-mITT population, with a 0.09-point treatment difference (95% CI: -0.08, 0.26); nominal p = 0.28320 (ANCOVA + MI). A larger effect favoring tofersen was observed in the ITT population in the faster-progressing subgroup according to baseline plasma NfL ≥ median (0.13-point treatment difference [95% CI: -0.10, 0.37], post-hoc nominal p = 0.2690), as well as in the faster-progressing subgroup with a run-in slope decline ≥ 0.9 (0.12-point treatment difference [95% CI: -0.14, 0.37], nominal p = 0.3673).

– *Time to death or permanent ventilation, and time to death*

There was no difference in time to death or permanent ventilation, or time to death, as compared to placebo due to the small number of events observed (there was only 1 death).

- *Exploratory PD and biomarkers*

[redacted]

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Safety:

- Overall, administration of tofersen was generally well tolerated in participants with ALS and a confirmed SOD1 mutation.
- AEs were experienced by the majority of participants (95.8% in the tofersen group and 94.4% in the placebo group); the most common AEs (reported in ≥ 20%) were procedural pain, headache, pain in extremity, fall, back pain, and post LP syndrome.
- Most AEs were mild or moderate in severity. There was a higher incidence of AEs that were CTCAE Grade ≥3 in the tofersen group (16.7%) compared to the placebo group (11.1%).
- One participant who received tofersen died during the study. This participant was in the "enriched" subgroup (1/39 participants [2.6%]) and experienced a fatal, CTCAE Grade 5 SAE of congestive cardiac failure that was not considered treatment related.
- Overall, in the safety population, the incidence of SAEs was higher in the tofersen group (18.1%) compared with the placebo group (5.6%). The most frequently reported SAEs (≥ 2%) were dyspnea, pulmonary embolism, pneumonia aspiration, dehydration, and atelectasis.
- Four SAEs, lumbar radiculopathy, myelitis transverse, myelitis, and chemical meningitis (1.4% each), were considered tofersen-treatment–related by the Investigator. Myelitis was reported in the "other"

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subgroup, and the other SAEs were reported in the "enriched" subgroup. These 4 events were serious neurological events.

- AEs that led to discontinuation of study treatment were only reported in the tofersen group (5.6%) and included the following AEs: congestive cardiac failure, myelitis, chemical meningitis, and pulmonary embolism.
- AEs related to the LP were experienced by the majority of participants in both the tofersen group (80.6%) and placebo group (80.6%).
- Overall, 2/72 participants (2.8%) in the tofersen group and 3/36 participants (8.3%) in the placebo group experienced coronavirus disease 2019-related AEs. None of these AEs led to discontinuation of study treatment or study withdrawal.
- There were no clinically meaningful treatment-related changes in hematology, blood chemistry, urinalysis parameters, liver function, ECGs, vital signs, C-SSRS, or MMSE.
- CSF laboratory abnormalities, including CSF white blood cell count increased, CSF protein increased, pleocytosis, CSF cell count increased, and CSF test abnormal were observed more commonly in the tofersen group than in the placebo group.
- Overall, 19/72 participants (26.4%) in the tofersen group and 2/36 participants (5.6%) in the placebo group were persistently positive for anti-tofersen antibodies during the study.

Conclusions:

Tofersen administration did not result in a statistically significant difference from placebo on the primary endpoint, the change from baseline to Week 28 in ALSFRS-R total score. However, consistently favorable trends across secondary and exploratory measures suggest a biological and clinical effect of tofersen in SOD1-ALS.
The safety of tofersen has been well-characterized in this randomized, placebo-controlled study.
Tofersen, and its administration via lumbar puncture, has been shown to be generally safe and well tolerated for the treatment of SOD1-ALS.

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