# Safety, PK, PD, and Exploratory Efficacy in Single and Multiple Dose Study of a SOD1 Antisense Oligonucleotide (BIIB067) Administered to Participants With ALS

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## Conclusions

- Administration of multiple doses of tofersen was generally safe and well tolerated at doses up to and including 100 mg in participants with SOD1-ALS.
- PK data show tofersen concentrations are dose proportional in plasma; less than dose proportional in CSF.
- PD data show a dose- and time-dependent reduction of SOD1 in CSF.
- These preliminary and exploratory analyses of clinical outcomes show a lessening of decline in functional, respiratory, and strength measures.
- This first report of tofersen in participants with SOD1-ALS supports continued development of tofersen. Participants are currently being recruited for the Phase 3 study, VALOR.

## Introduction

- Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder characterized by progressive muscular paralysis from degeneration of motor neurons in the primary motor cortex, corticospinal tracts, brainstem, and spinal cord.[1]
- Although most cases of ALS are sporadic,[2] ~10% are familial, of which ~20% are caused by a variety of gain-of-toxic function mutations in superoxide dismutase 1 (SOD1).[2-4]
- Although SOD1-ALS disease progression is heterogeneous, the underlying pathophysiology, attributable to mutant SOD1 toxicity, is thought to be consistent across SOD1 mutation types.
  - As such, effective reduction of SOD1 protein, irrespective of mutation, has the potential to alter the disease course of people with SOD1-ALS.
- Tofersen (BIIB067, IONIS-SOD1$_{Rx}$) is an antisense oligonucleotide RNase H1-mediated inhibitor of SOD1 messenger RNA under development for the treatment of SOD1-ALS.

## Objective

- To evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and exploratory efficacy of tofersen in people with SOD1-ALS.

## Methods

- This was a double-blind, randomized, placebo-controlled, Phase 1/2 single and multiple ascending dose (SAD/MAD) study conducted at 17 sites in the United States, Canada, and Western Europe.
- Part A was a SAD study of tofersen (10, 20, 40, or 60 mg) versus placebo in adults with ALS (data not shown).
- Part B (MAD, Figure 1).
  - MAD data are from an interim analysis of safety data through at least Day 106 (clinical and biomarker data through at least Day 85).
  - Adult participants with a SOD1 mutation were randomized 3:1 (tofersen:placebo) in 4 cohorts to receive tofersen (20, 40, 60, or 100 mg) or placebo.
    - Tofersen was administered by intrathecal bolus over 1–3 minutes. Participants received a loading regimen of 3 doses on Days 1, 15, and 29, followed by maintenance dosing on Days 57 and 85 for each cohort (Figure 1).
  - This study lasted ~31 weeks including a screening period of up to 7-weeks, a 12-week dosing period, and a 12-week follow-up period.
  - Tofersen concentrations in the plasma and cerebrospinal fluid (CSF) and SOD1 protein concentrations in the CSF were determined using validated assays.
  - The MAD population was characterized post hoc for the purposes of analyses (fast progressing vs. other) based on mutation and prerandomization Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) slope.

## Results

### Multiple Ascending Dose

*Demographics and Baseline Characteristics*

- A total of 50 participants were randomized 3:1 tofersen to placebo in 4 ascending dose cohorts.
  - Two of the 50 participants received an initial dose in the SAD portion of the study and enrolled in MAD after a washout period of ~20 weeks.
- All participants received ≥ 1 dose of study treatment with 48 of the 50 participants completing study treatment (5 doses).
  - Three deaths occurred during the study: 1 (20-mg group) owing to pulmonary embolism and 2 (60-mg group and placebo) owing to respiratory failure. All were considered by the Investigators secondary to ALS or comorbidities and not drug related.
- Demographics and baseline characteristics were similar among treatment groups (Table 1).
- Baseline measures of clinical function (ALSFRS-R, slow vital capacity [SVC]) were similar between the fast-progressing and other mutation groups with notable differences in time since symptom onset, prerandomization slope of ALSFRS-R decline, and baseline CSF phosphorylated axonal neurofilament heavy chain (data not shown) consistent with published natural history of fast progressing mutations.[5]

### Primary Interim Safety Endpoints

- Most adverse events (AEs) were mild or moderate in severity.
- The most common AEs occurring in ≥ 3 participants who received tofersen were headache (n = 16), procedural pain (n = 14), and postlumbar puncture syndrome (n = 13; Table 2).
- Five tofersen- and 2 placebo-treated participants experienced serious AEs (SAEs), with no SAEs reported in the highest dose group (data not shown).

### Primary Interim PK Endpoints

- Plasma concentration of tofersen was dose proportional (data not shown), while tofersen exposure in the CSF showed a less than dose-proportional response (Figure 2).

### Secondary Interim Endpoint

- A reduction from baseline in CSF SOD1 concentrations was observed in the tofersen 40, 60, and 100 mg cohorts with the maximal reduction observed in the 100 mg–treated group (37% vs. no reduction in the placebo group; p < 0.002) at Day 85 (Figure 3).

### Exploratory Endpoints

- Treatment with tofersen 100 mg demonstrated a slowing of functional decline (ASLFRS-R; tofersen mean change from baseline to Day 85 –1.1 vs. –5.3 for placebo group), a slowing of decline in respiratory function (as measured by SVC; tofersen mean change from baseline to Day 85 –6.4 vs. –14.8 for placebo), and a slowing in decline of muscle strength (as measured by handheld dynamometry [HHD] megascore; tofersen mean change from baseline to Day 92 –0.03 vs. –0.30 for placebo; Figure 4A, B, C).
  - Across clinical measures, separation from placebo was most apparent in participants with fast progressing disease compared to those with other mutations.
- Lowering of CSF phosphorylated neurofilament heavy was observed in the tofersen 100 mg cohort compared with placebo and a greater difference between the tofersen 100 mg and placebo groups was observed in participants with fast-progressing SOD1 mutations (data not shown).

**Table 1.** Part B (MAD): Demography and Baseline Characteristics in the ITT population

| | Placebo[a] n = 12 | Tofersen 20 mg n = 10 | Tofersen 40 mg n = 9 | Tofersen 60 mg n = 9 | Tofersen 100 mg n = 10 |
|---|---|---|---|---|---|
| Mean (SD) age, y | 49.2 (11.0) | 41.5 (10.7) | 58.0 (11.1) | 45.6 (10.7) | 48.9 (10.8) |
| Male, n (%) | 7 (58.3) | 7 (70.0) | 4 (44.4) | 6 (66.7) | 4 (40.0) |
| Riluzole use, n (%) | 5 (41.7) | 8 (80.0) | 5 (55.6) | 8 (88.9) | 7 (70.0) |
| Mean (SD) time since symptom onset, mo | 49.3 (49.1) | 61.4 (44.0) | 64.0 (58.2) | 72.1 (83.6) | 41.3 (41.6) |
| Mean (SD) baseline ALSFRS-R score | 36.0 (4.8) | 34.4 (7.4) | 36.7 (6.9) | 38.3 (6.5) | 38.2 (2.4) |
| Mean (SD) prerandomization ALSFRS-R slope (score change/month) | −0.64 (0.59) | −0.41 (0.37) | −0.26 (0.19) | −0.35 (0.43) | −0.63 (0.62) |
| Mean (SD) baseline % predicted SVC | 77.3 (21.9) | 79.9 (17.9) | 88.3 (15.6)[b] | 72.8 (17.3) | 85.6 (10.3) |
| Mean (SD) baseline HHD megascore | 0.02 (1.06) | −0.11 (0.36) | 0.09 (1.16) | 0.08 (0.67) | −0.05 (0.67) |
| Geometric mean (±SD) baseline CSF SOD1, ng/mL | 84.6 (56.7, 126.3) | 79.9 (56.1, 114.0) | 140.9 (87.6, 226.7) | 102.5 (72.2, 145.4) | 139.7 (92.6, 211.0) |

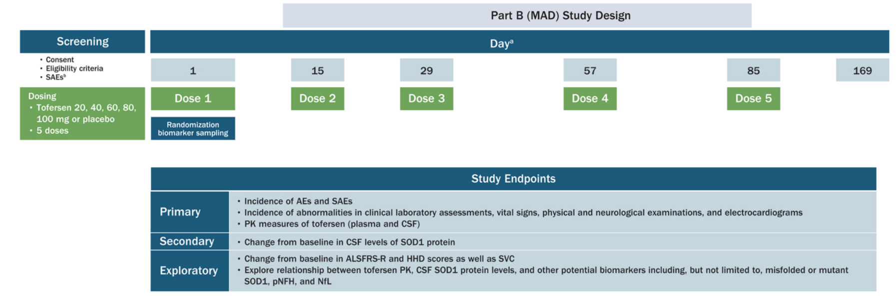
ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; CSF = cerebrospinal fluid; HHD = handheld dynamometry; ITT = intent-to-treat; MAD = multiple ascending dose; NA = not available; SOD1 = superoxide dismutase 1; SVC = slow vital capacity
[a]Combined placebo from all 4 cohorts.
[b]n = 8 due to unavailable sample.

**Table 2.** Part B (MAD): Summary of AEs in ≥ 3 Participants in the Safety Population

| AE, n (%) | Placebo[a] n = 12 | Tofersen Total n = 38 | Tofersen 20 mg n = 10 | Tofersen 40 mg n = 9 | Tofersen 60 mg n = 9 | Tofersen 100 mg n = 10 |
|---|---|---|---|---|---|---|
| No. of participants with any AE | 12 (100.0) | 38 (100.0) | 10 (100.0) | 9 (100.0) | 9 (100.0) | 10 (100.0) |
| Headache | 7 (58.3) | 16 (42.1) | 4 (40.0) | 2 (22.2) | 4 (44.4) | 6 (60.0) |
| Procedural pain | 5 (41.7) | 14 (36.8) | 4 (40.0) | 1 (11.1) | 4 (44.4) | 5 (50.0) |
| Postlumbar puncture syndrome | 3 (25.0) | 13 (34.2) | 4 (40.0) | 3 (33.3) | 3 (33.3) | 3 (30.0) |
| Fall | 3 (25.0) | 12 (31.6) | 3 (30.0) | 3 (33.3) | 2 (22.2) | 4 (40.0) |
| Back pain | 0 | 8 (21.1) | 1 (10.0) | 1 (11.1) | 1 (11.1) | 5 (50.0) |
| Fatigue | 2 (16.7) | 6 (15.8) | 1 (10.0) | 1 (11.1) | 2 (22.2) | 2 (20.0) |
| Nasopharyngitis | 1 (8.3) | 6 (15.8) | 1 (10.0) | 1 (11.1) | 3 (33.3) | 1 (10.0) |
| Nausea | 0 | 6 (15.8) | 1 (10.0) | 2 (22.2) | 1 (11.1) | 2 (20.0) |
| Upper respiratory tract infection | 0 | 6 (15.8) | 4 (40.0) | 0 | 2 (22.2) | 0 |
| CSF protein increased | 1 ( 8.3) | 5 (13.2) | 0 | 0 | 4 (44.4) | 1 (10.0) |
| Contusion | 1 (8.3) | 5 (13.2) | 2 (20.0) | 1 (11.1) | 0 | 2 (20.0) |
| Arthralgia | 1 (8.3) | 4 (10.5) | 1 (10.0) | 1 (11.1) | 1 (11.1) | 1 (10.0) |
| CSF white blood cell count increased | 0 | 4 (10.5) | 0 | 1 (11.1) | 3 (33.3) | 0 |
| Arthropod bite | 0 | 3 (7.9) | 1 (10.0) | 1 (11.1) | 1 (11.1) | 0 |
| Dyspnoea | 1 (8.3) | 3 (7.9) | 1 (10.0) | 1 (11.1) | 1 (11.1) | 0 |
| Oropharyngeal pain | 0 | 3 (7.9) | 2 (20.0) | 0 | 1 (11.1) | 0 |
| Pain in extremity | 2 (16.7) | 3 (7.9) | 0 | 1 (11.1) | 0 | 2 (20.0) |
| Pleocytosis | 0 | 3 (7.9) | 2 (20.0) | 1 (11.1) | 0 | 0 |
| Postprocedural contusion | 0 | 3 (7.9) | 2 (20.0) | 1 (11.1) | 0 | 0 |
| Salivary hypersecretion | 0 | 3 (7.9) | 1 (10.0) | 0 | 1 (11.1) | 1 (10.0) |

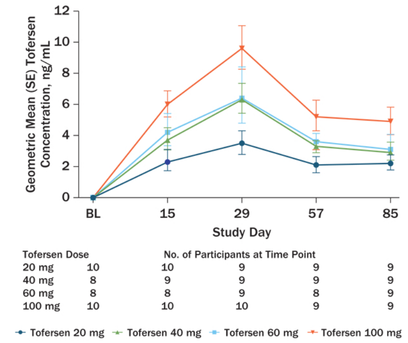
AE = adverse event; CSF = cerebrospinal fluid; MAD = multiple ascending dose
[a]Combined placebo from all 4 cohorts.

**Figure 1.** Study Design



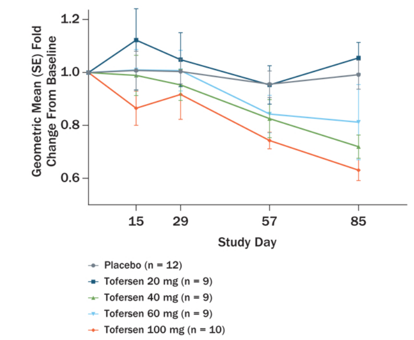

AE = adverse event; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; CSF = cerebrospinal fluid; HHD = handheld dynamometry; NfL = neurofilament light chain; PK = pharmacokinetics; pNFH= phosphorylated axonal neurofilament heavy chain; SAE = serious adverse event; SOD1 = superoxide dismutase 1; SVC = slow vital capacity
[a]Except Days 1 and 2, ±3 days.
[b]SAE monitoring began at Screening Visit. AE and concomitant medication monitoring began on Day 1.

**Figure 2.** MAD Interim: Geometric Mean (SE) Trough CSF Tofersen Concentrations by Study Day



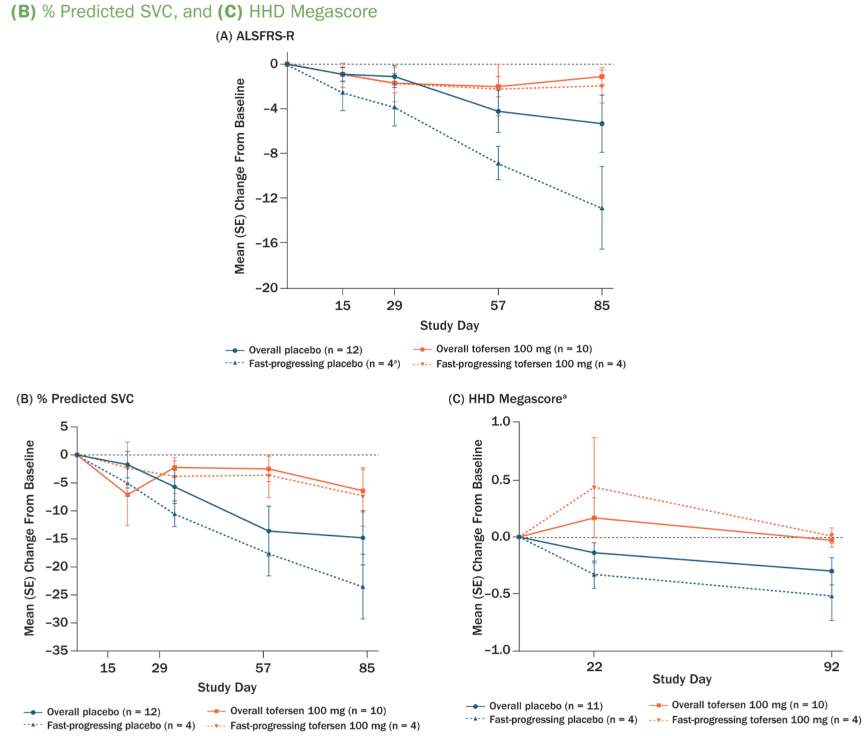

CSF = cerebrospinal fluid; MAD = multiple ascending dose
Values below limit of quantitation are set to zero at day 1 predose and sent to half of lower limit of quantitation (1 ng/mL) at other time points in calculations.

**Figure 3.** MAD Interim: CSF SOD1 Protein Concentrations in Tofersen Dosing Cohorts




CSF = cerebrospinal fluid; SOD1 = superoxide dismutase 1

**Figure 4.** MAD Interim Change From Baseline (Tofersen 100 mg Versus Placebo) in: **(A)** ALSFRS-R, **(B)** % Predicted SVC, and **(C)** HHD Megascore




ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; HHD = handheld dynamometry; SVC = slow vital capacity
[a]Missing values due to deaths were imputed using last observation carried forward.

**References** 1. Wijesekera LC, Leigh PN. *Orphanet J Rare Dis*. 2009;4:3. 2. Brown RH, Al-Chalabi A. *N Eng J Med*. 2017;377(2):162-172. 3. Byrne S, et al. *J Neurol Neurosurg Psychiatry*. 2011;82(6):623-627. 4.Gros-Louis F, et al. *Biochimica et Biophysica Acta*. 2006;1762(11):956-972. 5. Bali T, et al. *J Neurol Neurosurg Psychiatry*. 2017;88(2):99-105. **Disclosures** TM: advisory board and clinical research support for Biogen; consultant for Cytokinetics; licensing agreements with C2N; licensing agreement with and reagents for Ionis Pharmaceuticals, Inc.; Principal Investigator for Amylyx and Orion; MC: compensation from Aclipse, AvXis, Biohaven, Lilly, and Takeda; compensation from and advisory board for Biogen; PJS: advisory board for Biogen; speaker and symposium organization for Cytokinetics; research support from Pfizer for investigation of molecular mechanisms of neuronal injury in C9orf72 ALS; DG, SF, HH, IN, LF, IC, and TAF: employees of and hold stock/stock options in Biogen; CFB and RL: employees of and hold stock/stock options in Ionis Pharmaceuticals, Inc. **Acknowledgments** The authors thank the participants sites and investigators. Tofersen was discovered by Ionis Pharmaceuticals, Inc. This study was sponsored by Biogen (Cambridge, MA, USA). Writing and editorial support for the preparation of this poster was provided by Excel Scientific Solutions (Southport, CT, USA): funding was provided by Biogen.