Evaluating Efficacy and Safety of Tofersen in Adults with SOD1-ALS: Results from the Phase 3 VALOR Trial and Open-Label Extension

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Disclosures

• TMM: advisory board and clinical research support for Biogen; licensing agreement with, and consulting for, Ionis Pharmaceuticals, Inc.; consultant for Cytokinetics; licensing agreements with C2N; advisory board for Disarm Therapeutics; and advisory board for UCB Pharma

• MEC: compensation from an advisory board for Biogen; compensation from QurAlis, RRD, Sunovian, Cytokinetics, Takeda, Regeneron, Transposon, and Locust Walk; member of Praxis Board of Directors

• AG: ad hoc consultant for genetic testing for Biogen; consultant on ALS trial design for Alexion, AL-S Pharma, Calico, Cytokinetics, and Sanofi; and CMO at QurAlis

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Tofersen is an investigational antisense oligonucleotide (ASO) designed to reduce synthesis of SOD1 protein through degradation of SOD1 mRNA\textsuperscript{1,2}

mRNA = messenger ribonucleic acid, SOD1 = superoxide dismutase 1
VALOR and its Open-Label Extension

**VALOR**
- 28 weeks
- Tofersen 100 mg vs. placebo

**OLE**
- ~3–7 years
- Tofersen 100 mg

Data were integrated to evaluate early- vs. delayed-start tofersen initiation

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**Data presented October 2021**
- Data cut date: July 2021
  - VALOR completion + first interim of the OLE
  - All participants had the opportunity for at least 6 months of follow-up
- Prespecified subgroups based on:
  - Mutation/ALSFRS-R slope OR
  - Baseline neurofilament

**Data in this presentation**
- Data cut date: January 2022
  - New interim cut of the OLE
  - All participants had the opportunity for at least 12 months of follow-up
  - Prior to database lock, baseline plasma NfL was incorporated as a covariate, thus controlling for heterogeneity of disease progression in the overall (ITT) population

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ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale-Revised; ITT = intention-to-treat; OLE = open-label extension; NfL = neurofilament light chain
Participant Disposition

Study 101 Part C (VALOR)
(N = 108 randomised and dosed, ITT population)

Placebo
n = 36
- Discontinued study, n = 3 (8%)
  - Consent withdrawn, n = 1 (3%)
  - Disease progression, n = 2 (6%)

Completed VALOR
n = 33 (92%)
- Did not enroll in OLE, n = 1 (3%)

Tofersen
n = 72
- Discontinued study, n = 8 (11%)
  - Adverse event, n = 2 (3%)
  - Consent withdrawn, n = 2 (3%)
  - Death, n = 1 (1%)
  - Disease progression, n = 3 (4%)

Completed VALOR
n = 64 (89%)
- Did not enroll in OLE, n = 1 (1%)

Study 102 (OLE)
(N = 95 [88%] enrolled and dosed)

Discontinued study, n = 14 (39%)
- Consent withdrawn, n = 3 (8%)
- Death, n = 8 (17%)
- Disease progression, n = 5 (14%)

Ongoing in OLE
n = 18 (50%)

Discontinued study, n = 14 (19%)
- Consent withdrawn, n = 2 (3%)
- Death, n = 7 (10%)
- Disease progression, n = 5 (7%)

Ongoing in OLE
n = 49 (68%)

ITT = intention-to-treat; OLE = open-label extension
Target Engagement
Adjusted geometric mean ratio (95% CI) to baseline of total CSF SOD1 protein

Week 52 percent reduction (GMR) from baseline:
21% (95% CI, 4–35%)
33% (95% CI, 21–42%)

CSF = cerebrospinal fluid; OLE = open-label extension; SOD1 = superoxide dismutase 1
Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data; based on natural log transformed data. The model includes covariates for the corresponding baseline value i.e. log value, and use of rituzole or edaravone.
Effect on Neurofilament

Adjusted geometric mean ratio (95% CI) to baseline of plasma NfL

Week 52 percent reduction (GMR) from baseline:

- 41% (95% CI, 26–54%)
- 51% (95% CI, 42–60%)
Effect on Clinical Function
Adjusted mean (±SE) change from baseline in ALSFRS-R total score

**VALOR** (placebo-controlled)

**OLE** (open-label tofersen)

ALSFRS-R total score
Adjusted mean difference at Week 52:
3.5 (95% CI, 0.4–6.7)
p = 0.0272

ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale–Revised; OLE = open-label extension
Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NfL, and use of rituximab or edaravone.
Effect on Respiratory Function
Adjusted mean (±SE) change from baseline in percent-predicted SVC

![Graph showing the effect on respiratory function.](image)

- **VALOR (placebo-controlled)**
- **OLE (open-label tofersen)**

Percent-predicted SVC
Adjusted mean difference at Week 52:
- 9.2 (95% CI, 1.7–16.6)
- \( p = 0.0159 \)

**Percentages:**
- Placebo → Delayed-start tofersen, \( n = \) 36, 34, 25, 20, 20
- Early-start tofersen, \( n = \) 72, 59, 52, 39, 38

**Notes:**
- OLE = open-label extension; SVC = slow vital capacity
- Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NtL, and use of rituximab or edaravone.
Effect on Muscle Strength
Adjusted mean (±SE) change from baseline in HHD megascoring

HHD megascoring
Adjusted mean difference at Week 52:
0.28 (95% CI, 0.05–0.52)
p = 0.0186

HHD = handheld dynamometry; OLE = open-label extension
Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NTL, and use of rituximab or edaravone.
Time-to-Event Analyses
Kaplan-Meier plot of time to death or PV

<table>
<thead>
<tr>
<th>Events</th>
<th>Early-start tofersen</th>
<th>Placebo → delayed-start tofersen</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or Permanent Ventilation</td>
<td>12/72 (16.7%)</td>
<td>8/36 (22.2%)</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI, 0.137–0.941)</td>
</tr>
<tr>
<td>Death</td>
<td>8/72 (11.1%)</td>
<td>6/36 (16.7%)</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI, 0.084–0.890)</td>
</tr>
<tr>
<td>Death with additional post-withdrawal vital status data</td>
<td>12/72 (16.7%)</td>
<td>11/36 (30.6%)</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI: 0.096, 0.602)</td>
</tr>
<tr>
<td>Death, PV, or withdrawal due to disease progression</td>
<td>18/72 (25.0%)</td>
<td>13/36 (36.1%)</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI: 0.180, 0.821)</td>
</tr>
</tbody>
</table>

Median time to death and time to death or PV were non-estimable due to the number of events.

OLE = open-label extension; PV = permanent ventilation
Time to death or permanent ventilation is defined as the time from first dose to death or PV (≥22 hours of mechanical ventilation per day for ≥21 consecutive days), whichever comes first. Participants who do not meet the endpoint definition are censored a participant’s last known alive date. Events are based on adjudicated events by an independent committee. Plots are Kaplan-Meier curves. Hazard ratios and confidence intervals are based on a Cox regression model adjusted for baseline plasma NTx and rituximab or edaravone use.
Effect on ALS PROs

Adjusted mean (±SE) change from baseline

**ALSAQ-5 (0 to 100 points)**

**VALOR** (placebo-controlled) vs **OLE** (open-label tofersen)

- **Weeks:** 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52
- **Values:**
  - VALOR: 36, 36, 31, 28, 26
  - OLE: 72, 66, 61, 50, 49

- **Adjusted mean difference, Week 52:**
  - −10.3
  - (95% CI: −17.3 to −3.2), p=0.0044

**EQ-5D-5L utility score (−0.594 to 1.0°)**

**VALOR** (placebo-controlled) vs **OLE** (open-label tofersen)

- **Weeks:** 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52
- **Values:**
  - VALOR: 36, 35, 31, 28, 26
  - OLE: 72, 65, 61, 49, 47

- **Adjusted mean difference, Week 52:**
  - 0.2
  - (95% CI: 0.13 to 0.32), p<0.0001

**FSS (9 to 63 score)**

**VALOR** (placebo-controlled) vs **OLE** (open-label tofersen)

- **Weeks:** 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52
- **Values:**
  - VALOR: 36, 35, 31, 28, 26
  - OLE: 72, 66, 61, 50, 49

- **Adjusted mean difference, Week 52:**
  - −3.8
  - (95% CI: −9.0 to 1.38), p=0.1493

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ALS = amyotrophic lateral sclerosis; ALSAQ-5 = 5 Item ALS Assessment Questionnaire; EQ-5D = EuroQOL 5 Dimension 5-Level Questionnaire; FSS = Fatigue Severity Scale; OLE = open-label extension; PRO = patient-reported outcome

Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NTL, and use of riuzole or edaravone.

*Using UK valuation weights.*
## Summary of Adverse Events

<table>
<thead>
<tr>
<th>Event Description</th>
<th>VALOR Placebo (N = 36)</th>
<th>Tofersen 100 mg (N = 72)</th>
<th>VALOR and OLE Integrated (N = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants with treatment-emergent eventa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>34 (94.4)</td>
<td>69 (95.8)</td>
<td>102 (96.1)</td>
</tr>
<tr>
<td>Related eventb</td>
<td>2 (5.6)</td>
<td>28 (38.9)</td>
<td>63 (60.6)</td>
</tr>
<tr>
<td>Events related to lumbar punctureb</td>
<td>29 (80.6)</td>
<td>58 (80.6)</td>
<td>84 (80.8)</td>
</tr>
<tr>
<td>Events with fatal outcome</td>
<td>0</td>
<td>1 (1.4)</td>
<td>14 (13.5)</td>
</tr>
<tr>
<td>Events leading to drug discontinuation</td>
<td>0</td>
<td>4 (5.6)</td>
<td>18 (17.3)</td>
</tr>
<tr>
<td>Serious event</td>
<td>5 (13.9)</td>
<td>13 (18.1)</td>
<td>38 (36.5)</td>
</tr>
<tr>
<td>No. of participants with SAEs of note c</td>
<td>0</td>
<td>4 (5.6)</td>
<td>7 (6.7)</td>
</tr>
<tr>
<td>Intracranial pressure increased</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Myelitis/myelitis transverse</td>
<td>0</td>
<td>2 (2.8)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Lumbar radiculopathy</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Meningitis aseptic/chemical</td>
<td>0</td>
<td>1 (1.4)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Papilloedema</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

OLE = open-label extension; SAE = serious adverse event.

*a A Participant can appear in more than one category; 
b Related as assessed by the investigator; 
c A participant is counted only once in each preferred term (MedDRA version 24.0); 
d An event in a placebo participant during VALOR is only counted once; an event in a tofersen participant during VALOR is counted in both the “VALOR/tofersen 100 mg” column, and again in the “VALOR and OLE Integrated” column.
Evidence of Biologic Effect Precedes Evidence of Clinical Benefit

Weeks

8
- Tofersen reduces total CSF SOD1 (target engagement)

12
- Tofersen reduces plasma NfL (reduced axonal injury and neurodegeneration)

28
- Trends suggest slowing of clinical decline in tofersen-treated participants with faster-progressing disease

OE
- Earlier initiation of tofersen reduced decline in clinical function, respiratory function, strength, and quality of life

52+
- Earlier initiation of tofersen reduced hazard of death or permanent ventilation and death

CSF = cerebrospinal fluid; OLE = open-label extension; NfL = neurofilament light chain; SOD1 = superoxide dismutase.
Many thanks!

Thank you to the **study participants** and their **caregivers and families**, the VALOR and OLE Steering Committee, investigators and site staff, and the entire community, without whom these important studies could not have been conducted.

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