**Note for the ALS ePOC evaluation**

Information originated from the folder C:\Users\bvi5314\OneDrive - Takeda\Documents\Study\UNC 13A

Table 1 Summary statistics for NfL from Tofersen studies in different scale

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| NfL/Study | Min | Max | Mean | SD | GM | Median | Scale | n | Sample | Time |
| Tofersen P2/3\* | 9 | 370 | 127.3 | 94.4 | 92.7 | **92.7** | Pg/ml | 21 | P | B |
| Tofersen P2/3\* | **2.19** | **5.9** | **4.6** | **0.66** |  |  | Log | 21 | P | B |
| Tofersen P2/3 | 8 | 99 | 37.0 | 29.5 | 28.4 | **28.4** | Pg/ml | 15 | P | B |
| Tofersen P2/3 | **2.1** | **4.6** | **3.4** | **0.70** |  |  | Log | 15 | P | B |
| Tofersen P1/2\*| | 2 | 4.5 | 4.3 |  |  |  | Log | 12 | P | B |
| Tofersen P2/3\* | 12 | 329 | 146.2 | 82.6 | 121.8 | **121.8** | Pg/ml | 39 | T | B |
| Tofersen P2/3\* |  |  | **5.0** | **0.06** |  |  | Log | 39 | T | B |
| Tofersen P2/3 | 5 | 211 | 47.6 | 41.8 | 33.2 | **33.2** | Pg/ml | 33 | T | B |
| Tofersen P2/3 |  |  | **3.9** | **0.14** |  |  | Log | 33 | T | B |
| BIIB078 | 46 | 383.1 | 107.7 | 77.3 | 92.4 |  | Pg/ml | 27 | P | B |
|  |  |  | 5.94 | 0.28 |  |  |  | 27 | P | B |
| BIIB078\*\* | 28.9 | 326.3 | 116.5 | 66.5 | 101.9 |  | Pg/ml | 18 | T | B |
|  |  |  | **5.8** | **0.21** |  |  |  | 18 | T | B |

\*Fast progressing, Bold faces are calculated assuming the outcome is log-normal; B = Baseline, T = Treatment, P = Placebo. Blang cell indicates data not available

\*\* Treated group with the highest baseline mean plasma NfL

**Change from baseline**

In the VALOR trial, the percent change from baseline in the concentration of neurofilament light chains (NfL) in plasma for the treated group (tofersen group) compared to the placebo group in log scale was as follows:

* **Faster-progression subgroup:**
  + **Treated group:** Reduced by 60% from their baseline level
  + **Placebo group:** Increased by 20% from their baseline level
  + **Difference:** Comparing the change from baseline between groups, an 80% reduction in the treated group compared to the placebo group was observed [1.2 – (1-0.6)]
  + **Adjusted geometric mean ratio to placebo:** (1-.8/1.2) = 0.33 (95% CI: 0.25, 0.45)
* **Slower-progression subgroup:**
  + **Treated group:** Reduced by 50% from their baseline level
  + **Placebo group:** Reduced by 5% from their baseline level
  + **Difference:** 45% reduction in change from baseline in the treated group compared to the placebo group
  + **Adjusted geometric mean ratio to placebo:** (1-.0.59/1.19) = 0.52 (95% CI: 0.43, 0.63)

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The geometric mean ratio of .33 and .52 need to be clarified further. Ideally this should be .8 and .59. The SD for gm ration .33 is 0.051

**UNC13 A Sample Size Justification**

Table 2. Proposed sample size with 3:1 Allocation Ratio for Multiple Ascending Dose (MAD) study

|  |  |  |  |
| --- | --- | --- | --- |
|  | Treatment | Placebo | Total |
| Cohort A | 6 | 2 | 8 |
| Cohort B | 6 | 2 | 8 |
| Cohort C | 9 | 3 | 12 |
| Cohort D | 12 | 4 | 16 |
| Total | 33 | 11 | 44 |

**Justification of Sample Size and Power Analysis**

The total estimated sample size is 44 across 4 dose level cohorts.  Each cohort will have an overall ratio of 3 active to 1 placebo.  The initial 2 dose level cohorts will have N=8 patients each and N=12 and N=16 in the two higher subsequent cohorts. The sample size power was evaluated based on the higher dose cohorts.

In Tofersen Phase 2/3 trial consider changes in log plasma NfL concentration as the surrogate endpoint. Difference in changes in log plasma Nfl between Treated and Placebo group is equivalent to the log(GM ratio of treatment group to Placebo). The study observed the NfL changes as follows in the **Slower-progression subgroup:**

* + **Treated group:** Reduced by 50% from their baseline level
  + **Placebo group:** Decreased by 5% from their baseline level

This attributes to the 52% reduction in the geometric mean ratio of treatment to placebo (-0.65 in log scale with SD = 0.051). Again, Tofersen Phase1/2 study assumed pooled SD = .11 for sample size calculation.

From Tofersen Phase 2/3, the slow progressing placebo group has SD of 0.7 at baseline. Assuming the same SD for 16-week follow-up, the SD for the change would be 0.81 (using the design matrix)

Also, based on the observed SD, with the proposed sample size 16 (12 treatment, 4 placebo) and the baseline SD = 0.7, the study would expect estimate of SD for the log(GM ratio) = 0.15 (need to run the simulation)

We have performed the power analysis considering the SD = 0.11

The study aims to observe at least 30% reduction in change from baseline (expressed as a ratio) in treated group compared to the placebo group in log scale. A 30% reduction we expect to observe 70% of the placebo in treated group. So we will require to observe a difference of log(Change from baseline in Treatment [in ratio scale]) – log(Change from baseline in placebo)= Log(.7) = -.36 unit in log scale. Results the effect size (Cohen’s d) d = -.36/0.11 = -3.2. Assuming Alpha = .1, one sided alternative, and with the sample of size 12 in treated and 4 in placebo, the study would provide 99% power and for sample of size 12 and 4, the study would have 96% power to detect the 30% reduction in GM treated compared to GM placebo. The power with this sample size of 16 would still be more than 80% until the SD is less than 0.28. (include the sphere of SD estimate from the simulation which is quite large SD).

pwr.t2n.test(n1 = 12, n2 = 4, d = -.36/0.11, sig.level = .10, alternative = "less")

Since we are dealing with GM ratio, the change in scale should not affect the power analysis.

change from baseline (expressed as a ratio) to Week 28 in plasma NfL (copied from phase 3 appendix)

**log(ratio of 24 week to baseline in treated)/log(ratio of 24 week to baseline in placebo) = .3**

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Slow progressing .52 has SD = 0.051

**GNG**

Go if the posterior control adjusted treatment effect is 30% with probability 70%

Plasma NfL geometric mean ratio to baseline. In log scale that ratio for a subject is log(endline nfl) – log(baseline NfL) which could be greater or less than zero. Negative implies improvement. This could be translated as the log(percent change from baseline in ratio).

Taking geometric mean and geometric SD across subjects provides the estimate of desired group level estimates for treatment and placebo. Ideally an ANCOVA model will be used to compare the group in the percentage change from baseline. The Baseline plasma NfL will be added as a covariate in the ANCOVA model

The expert group make decisions, based on the Tofersen study that, A 30% reduction in treated group compared to the placebo in the log percent change from baseline would be clinically significant. So if the study observe a this level of reduction, the Quantitative Decision Framework should retain the recommendation of Go with high probability.

We look for a threshold for ratio of the log percentage change for the GnG criteria so that the posterior probability of ‘go’ is > 80% given the study observed a 30% reduction.

In evaluating different thresholds, the team decided to adopt the following criteria using the posterior probability of improvement:

1. **Decision Thresholds:**
   * **Go Criteria:** P(Δμ<−0.16)>0.7
   * **No-Go Criteria:** P(Δμ<−0.16) <0.1
2. **Definition of Δμ:**
   * Δμ is defined as the median (treatment ratio of NfL level at follow-up to baseline) divided by the median (placebo ratio of NfL level at follow-up to baseline) in log scale.
3. **Translation to Original Scale:**
   * Δμ<−0.16implies μ<0.78 (a 15% reduction) with a posterior probability >70% for a ‘go’ decision.
   * A ‘No-Go’ decision is made if the posterior probability of observing the threshold is <10%.
4. **Impact of Threshold:**
   * If the study observes a 30% reduction, the posterior probability of a ‘go’ decision is 100%, the study will observe SD of changes from baseline in both are <= 0.11
5. **Operating Characteristics:**
   * Detailed operating characteristics for Go/No-Go decisions across various reduction levels are included in Table 3. With sample of size 12 in treatment and 11 in placebo and SD = 0.1, If the study observes a reduction of >20% reduction with, the QDM will recommend go, if observes a reduction 13%, the QDM would recommend No-go. Between the range of 13-20% reduction, the decision would be neutral and need expert team involvement to make the decision of go or No-go by evaluating the other criteria.

Table 3. Go/No-Go probabilities for different levels of reduction. Negative reduction implies increase



|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| SD | N\_t | Reduction  % | Pr(Go)  % | Pr(No-Go)  % | Pr(Consider)  % |
| 0.11 | 12 | 10 | 4.32 | 46.35 | 49.33 |
| 0.11 | 12 | 20 | 80.26 | 0.39 | 19.35 |
| 0.11 | 12 | 30 | 100 | 0 | 0 |
| 0.11 | 9 | 10 | 5.16 | 43 | 51.84 |
| 0.11 | 9 | 20 | 77.42 | 0.53 | 22.05 |
| 0.11 | 9 | 30 | 99.97 | 0 | 0.03 |
| 0.11 | 6 | 10 | 6.64 | 38.10 | 55.26 |
| 0.11 | 6 | 20 | 72.80 | 0.79 | 26.41 |
| 0.11 | 6 | 30 | 99.86 | 0 | 0.14 |
| 0.7 | 12 | 10 | 23.84 | 13.69 | 62.47 |
| 0.7 | 12 | 20 | 37.89 | 6.71 | 55.40 |
| 0.7 | 12 | 30 | 55.91 | 2.53 | 41.56 |
| 0.7 | 9 | 10 | 24.26 | 13.40 | 62.35 |
| 0.7 | 9 | 20 | 37.31 | 6.91 | 55.78 |
| 0.7 | 9 | 30 | 54.01 | 2.83 | 43.16 |
| 0.7 | 6 | 10 | 24.88 | 12.97 | 62.15 |
| 0.7 | 6 | 20 | 36.44 | 7.22 | 56.33 |
| 0.7 | 6 | 30 | 51.16 | 3.32 | 45.51 |

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Figure 1. Quantitative Decision Metric. Operating characteristics of the proposed QDM for two different standard deviation 0.11 and 0.7. The sample size and the other considerations was the same. X axis indicates the difference in change from baseline between treatment and placebo arms in log scale.  The left one is for SD = 0.11 and the right one is for SD = 0.7

A summary of the operating characteristics of this quantitative decision-making framework is presented on Figure 1. Higher SD would lead to a wider gray zone and require higher difference to observe to have go decision with the QDM.

**Figure 8: Operating characteristics of the quantitative decision making**

Noted that, for lognormal distribution the median and GM are the same theoretically.

**Sample size estimation in AMBRoSIA study data**

Determined sample size using clinical trial simulations based on AMBRoSIA study data. These simulations aimed to estimate the power to detect significant differences between groups using plasma neurofilament light chain (NFL) or the ALS Functional Rating Scale (ALSFRS-R) as outcomes. They varied participant numbers and treatment effects, with 1000 replicated trials per scenario. To achieve 80% power for a treatment effect with a proportional reduction in progression rate (PR) of 0.4, the estimated sample size was about 75 participants per group using ALSFRS-R and about 40 participants per group using plasma NFL. Did not provide the detail data generation algorithm

**ALS patients**: Mean age at sampling is 62.3 years with a standard deviation (SD) of 11.8 years.

* **Healthy controls**: Mean age at sampling is 55.2 years with a standard deviation (SD) of 13.2 years.
* **Plasma NfL levels for ALS patients**: Mean 216.70 pg/ml
* **Plasma NfL levels for healthy controls**: Mean 50.2 pg/ml
* **ALSFRS-R score for ALS patients**: Median 85 [IQR: 76.2-90]
* **CSF NfL levels for ALS patients**: Mean 13,994.7 pg/ml
* **CSF NfL levels for healthy controls**: Mean 1,729.2 pg/ml

Helpful information link: <https://stats.stackexchange.com/questions/427770/can-someone-explain-to-me-the-parameters-of-a-lognormal-distribution>

Existing therapies

Riluzone (Sanofi) in UK

Tofersen.

Edaravone (Mitshubishi Tanabe)

Dosing frequency Ph 1/2 study would be on days 1, 29, 57, and 85

Specifically, the projected benefit was in the range of a 2-8 percentage point increase in UNC13A protein relative to normal.

FDA and EMA guidance summary

The use of the ALSFRS-R is a recommended primary endpoint for measuring functional change. However, the ALSFRS-R alone does not incorporate survival which can be problematic in ALS since the incidence of death in ALS may be high, leading to functional data that is missing not at random. Thus, a combined analysis of function and survival, such as the joint rank analysis, should be utilized if there are more than a few deaths. Outcomes that measure other disease attributes such as survival, respiratory function, or muscle strength, are recommended as key secondary efficacy assessments. Disease modifying treatment benefit can be established in trials of 12-18 months duration. Trials should include prespecified plans for a long-term, open-label extension that should allow for additional prespecified effectiveness assessments. The accelerated approval pathway with NfL as a surrogate endpoint has also been used in the US for the approval of Qalsody.

CDP

The first study is a Ph1/2 first-in-human, multiple dose-escalation, ePOC study. If met the pre-defined criteria, go or Phase 2/3 (9-12 month RCT). Both studies will have open label extension

MAD, 4 Dose level, 3-month dosing and three month follow-up for each dose level.

Clinical Outcomes

NfL as surrogate

ALS Functional Rating Scale (ALSFRS-R)

**Enrollment Rate**

* **Participation Rate:** Approximately 10% of the ALS patient population participates in clinical trials.  
  [Source: Journal of Medical Internet Research](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8693186/)
* **Recruitment Numbers:** Over 2000 ALS patients were recruited between 2013 and 2019 across 46 institutions.  
  [Source: Journal of Medical Internet Research](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8693186/)
* **Enrollment Time:** The median time to enroll the first participant is about 252 days after the protocol is submitted.  
  [Source: Neurology](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3806927/)

**Tofersen ALSFRS-R score**

The endpoint associated with ALSFRS-R in the trial was an exploratory outcome. The ALSFRS-R (Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised) score was used to assess clinical function over time. The ALSFRS-R measures 12 items in four domains of function, each scored on a scale from 0 to 4, with higher scores indicating better function. Changes in the ALSFRS-R score were evaluated at various time points to determine the effect of tofersen on clinical function in participants with ALS due to SOD1 mutations.

**Tofersen Phase 2/3 Valor study ALSFRS-R score**

In the VALOR trial, the change in the ALSFRS-R total score from baseline to week 28 among participants predicted to have faster-progressing disease was -6.98 points in the tofersen group and -8.14 points in the placebo group. The difference between the two groups was 1.2 points with a 95% confidence interval of -3.2 to 5.5, and the P value was 0.97. This indicates that there was no significant difference between the tofersen and placebo groups in terms of the ALSFRS-R score.

**Phase 1/2 study**

The ALSFRS-R (Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised) score results from the paper are summarized below. These results indicate the changes in ALSFRS-R scores from baseline, with higher scores indicating better function.

* **At Day 15:**
  + Placebo: -1.11 (95% CI, -2.17 to -0.05)
  + Tofersen 20 mg: -0.34 (95% CI, -1.59 to 0.91)
  + Tofersen 40 mg: -0.46 (95% CI, -1.75 to 0.83)
  + Tofersen 60 mg: -0.40 (95% CI, -1.66 to 0.86)
  + Tofersen 100 mg: -1.13 (95% CI, -2.29 to 0.02)
* **At Day 29:**
  + Placebo: -1.29 (95% CI, -2.88 to 0.30)
  + Tofersen 20 mg: -0.88 (95% CI, -2.73 to 0.96)
  + Tofersen 40 mg: -0.69 (95% CI, -2.56 to 1.19)
  + Tofersen 60 mg: -0.82 (95% CI, -2.68 to 1.04)
  + Tofersen 100 mg: -1.91 (95% CI, -3.65 to 0.17)
* **At Day 57:**
  + Placebo: -4.50 (95% CI, -7.21 to -1.78)
  + Tofersen 20 mg: -1.35 (95% CI, -4.44 to 1.74)
  + Tofersen 40 mg: -1.97 (95% CI, -5.06 to 1.13)
  + Tofersen 60 mg: -2.24 (95% CI, -5.16 to 0.67)
  + Tofersen 100 mg: -2.13 (95% CI, -5.82 to 1.56)
* **At Day 85:**
  + Placebo: -5.63 (95% CI, -8.90 to -2.36)
  + Tofersen 20 mg: -0.76 (95% CI, -4.49 to 2.97)
  + Tofersen 40 mg: -0.82 (95% CI, -4.50 to 2.85)
  + Tofersen 60 mg: -1.19 (95% CI, -4.67 to 2.29)
  + Tofersen 100 mg: -1.19 (95% CI, -4.67 to 2.29)

In the fast-progression subgroup at day 85:

* Tofersen 100 mg: 0.84 points (95% CI, -5.58 to 7.26)
* Placebo: -16.73 points (95% CI, -23.28 to -10.18)

Data from Tofersen Phase 1 study

**Results on Neurofilament (NfL) in Plasma and CSF**

**Key Findings:**

1. **Baseline Neurofilament Concentrations**:
   * The baseline neurofilament concentrations were at least 3.5 times higher in the fast-progression subgroup compared to the other subgroup.
2. **Changes in Neurofilament Concentrations**:
   * Among the 12 participants in the placebo group, the concentrations of phosphorylated neurofilament heavy chains and neurofilament light chains in plasma and CSF were largely unchanged during the intervention period.
   * Among the 10 participants who received 100 mg of tofersen, the concentrations of both phosphorylated neurofilament heavy chains and neurofilament light chains decreased from baseline to day 85.

These findings suggest that tofersen may have a beneficial effect on reducing neurofilament concentrations, which are biomarkers of neuronal damage and disease progression in ALS. The reductions in neurofilament concentrations observed in the tofersen groups, particularly at the 100-mg dose, indicate a potential slowing of neuronal degeneration in participants with SOD1 ALS.

**Phase 2/3**

In the faster-progression subgroup, the concentration of neurofilament light chains (NfL) in plasma was reduced by 60% in participants who received tofersen (geometric mean ratio to baseline, 0.40; 95% CI, 0.33 to 0.48), compared with an increase of 20% in those who received placebo (geometric mean ratio to baseline, 1.20; 95% CI, 0.98 to 1.47). The between-group difference in the geometric mean ratio was 0.33 (95% CI, 0.25 to 0.45).

In the slower-progression subgroup, the concentration of NfL in plasma was reduced by 45% in the tofersen-treated group, compared with a reduction of 16% in the placebo group. The between-group difference in the geometric mean ratio was 0.54 (95% CI, 0.43 to 0.68).