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Description automatically generated**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\* |  |  |  |  |  |  | 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 |  |  |  |  |  |  | Log | 33 | T | B |
| Tofersen P1/2\*| |  |  |  |  |  |  | Log | 12 | 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

**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)]
* **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

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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 99% 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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GNG

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

*Notes: 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 is 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. ANCOVA model will be used to compare the group. Baselineplasma NfL will be added as a covariate in the ANCOVA model*

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)

ALS is a rare disease. In the US, the prevalence of ALS is estimated to be 9.1 per 100,000, equating to approximately 29,824 cases (Mehta et al. 2023). In Europe, estimated prevalence has been published as 6.22 per 100,000 and 3.01 per 100,000 for Asia (excluding Japan) and 7.96 per 100,000 for Japan (Wolfson 2023).

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/)