A piece of paper with writing on it

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 40% from their baseline level
  + **Placebo group:** Increased by 19% from their baseline level
  + **Difference:** 59% 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

**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.

The study considers changes log plasma NfL concentration as the surrogate endpoint. 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)

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 = -.36/0.81 = 1.7.

Assuming Alpha = .1, and two sides alternative, and with the sample of size 12 in treated and 4 in placebo, the study would provide 94% power and for sample of size 12 and 4, the study would have 88% power to detect the 30% reduction in the change from baseline in treated group compared to the placebo.

pwr.t2n.test(n1 = 12, n2 = 4, d = -.36/0.21, sig.level = .10, alternative = "two.sided")

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