ALS Study

Statistical Analysis Plan

A Phase II pilot safety and tolerability study of ILB in patients with Motor Neurone Disease (MND) / Amyotrophic Lateral Sclerosis (ALS)

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UNIVERSITY OF BIRMINGHAM

KEY PERSONNEL INVOLVED IN THE PREPARATION OF THE STATISTICAL ANALYSIS PLAN:

NAME	TRIAL ROLE
Dr Venkataramanan Srinivasan	Chief Investigator
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DOCUMENT CONTROL SHEET

STATISTICAL ANALYSIS PLAN VERSION:	REASON FOR UPDATE:	TO MATCH PROTOCOL
0.1	Initial creation	V0.11, 27-Mar-2018
1.0, 14-Jun-2018	First release	V2.0 31-May-2018

1. INTRODUCTION

1.1 PURPOSE OF THE STATISTICAL ANALYSIS PLAN

This statistical analysis plan (SAP) provides guidelines for the analysis and presentation of results for the TikoMed ALS trial. This plan, along with all other documents relating to the analysis of this trial, will be stored in the 'Statistical Documentation' section of the Trial Master File. The statistical analysis will be carried out by the Trial Statistician.

2. TIMING AND REPORTING OF INTERIM AND FINAL ANALYSES

INTERIM ANALYSES

Interim analyses of safety outcomes and available efficacy outcomes will be presented to the relevant independent oversight committee after the sentinel patients and periodically thereafter.

Furthermore, we propose to conduct and submit for publication an analysis of available primary and secondary outcomes for the first five patients after the fifth patient has been evaluated to the fullest extent over the initial 10 week dosing period.

FINAL ANALYSIS

We will seek to conduct and distribute for publication the final analysis within 6 months of the final protocol assessment of the final patient.

3. ANALYSIS

3.1 DEFINITION AND CALCULATION OF OUTCOME MEASURES

Outcome measures are identified in the trial protocol.

3.2 DESCRIPTIVE ANALYSES

Numerical outcomes will be summarised and presented as means and standard deviations where the outcome is approximately normal; or median and inter-quartile ranges where non-normal.

SAFETY

The number of SAEs and AEs will be calculated and summarised. Furthermore, the number of patients experiencing each will be calculated. Each of these analyses will be broken down by grade, relatedness, event type (admitting event for SAEs); expectedness (SAEs only) and sequelae (SAEs only).

TOLERABILITY

Line listings for all intolerable adverse events will be given. The number of intolerable events will be calculated for each patient and summarised.

QUANTITY OF STUDY DRUG ADMINISTERED

Total drug administered, number of administrations, number and length of interruptions, and number of discontinuations will be calculated for each patient and summarised.

ALSFRS-R & ALSAQ-40

ALSFRS-R and ALSAQ-40 are very granular ordinal variables. They have 49 and 101 levels respectively so a categorical analysis is not feasible. There are many instances in the literature of these outcomes being analysed as numbers[1-5]. As such, we will analyse these outcomes as numbers using the method described below for repeated measures.

The PRO-ACT database (https://nctu.partners.org/ProACT) has collated the outcomes, including ALSFRS-R, of thousands of ALS patients. We will construct priors based on this data for use in a Bayesian analysis.

Refer to the following for how to cite the PRO-ACT database:

https://nctu.partners.org/ProACT/Document/DisplayLatest/6

3.2.1 METHODS

REPEATED MEASURES

Repeated measures numerical outcomes will be analysed by hierarchical models, with patient-level effects to account for baseline value and progression with respect to time. Transformations of the time variable and smoothed terms (e.g. splines) will be considered if the outcomes are found to be non-linear in time.

3.2.2 SAMPLE SIZE DETERMINATIONS

No sample size calculations have been undertaken. The sample size has been selected based on what is feasible to be recruited at a single centre in a reasonable timeframe for this phase of clinical trial.

3.3 SUBGROUP ANALYSIS

There are no sub-group analyses planned.

4. STATISTICAL SOFTWARE

Analysis will be conducted using R and associated packages.

5. STORAGE AND ARCHIVING

Snapshots of data for analyses related to DMC meetings will be stored in:

T:\Trials Work\D3B\TikoMed\ALS\DMC\YYYYMMDD\Analysis\Snapshots\<Date of snapshot YYYYMMDD>\

Snapshots of data for analyses related to publications (including abstracts and presentations) will be stored in:

T:\Trials Work\D3B\TikoMed\ALS\Publications\<publication id\YYYYMMDD\Analysis\Snapshots\<Date of snapshot YYYYMMDD>\

Snapshots of data for analyses related to the end of trial report will be stored in:

T:\Trials Work\D3B\TikoMed\ALS\End of trial\YYYYMMDD>\Analysis\Snapshots\<Date of snapshot YYYYMMDD>\

Analysis programs will be stored in:

T:\Code\R\CRCTU\Trials\D3B\TikoMed\ALS\

6. REFERENCES

1. Jenkinson, C., Levvy, G., Fitzpatrick, R., & Garratt, A. (2000). The amyotrophic lateral sclerosis assessment questionnaire (ALSAQ-40): Tests of data quality, score reliability and response rate in a survey of patients. *Journal of the Neurological Sciences*, *180*(1–2), 94–100. http://doi.org/10.1016/S0022-510X(00)00420-2

2. Jenkinson, C., Peto, V., Jones, G., & Fitzpatrick, R. (2003). Interpreting change scores on the Amyotrophic Lateral Sclerosis Assessment Questionnaire. *Amyotrophic Lateral Sclerosis*, 380–385.

3. Epton, J., Harris, R., & Jenkinson, C. (2009). Quality of life in amyotrophic lateral sclerosis/motor neuron disease: A structured review. *Amyotrophic Lateral Sclerosis*, *10*(1), 15–26. http://doi.org/10.1080/17482960802163721

4. Atassi, N., Berry, J., Shui, A., Zach, N., Sherman, A., Sinani, E., Leitner, M. (2014). The PRO-ACT database: Design, initial analyses, and predictive features. *Neurology*, *83*(19), 1719–1725. http://doi.org/10.1212/WNL.0000000000000951

5. Cudkowicz, M. E., van den Berg, L. H., Shefner, J. M., Mitsumoto, H., Mora, J. S., Ludolph, A., Kerr, D. A. (2013). Dexpramipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): A randomised, double-blind, phase 3 trial. *The Lancet Neurology*, *12*(11), 1059–1067. http://doi.org/10.1016/S1474-4422(13)70221-7