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:

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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
1.1, 11-Sept-2020	Update in line with version 7.0 of the protocol. Includes updates to interim analyses and treatment extensions, and the inclusion of the summarising of DILIs.	V7.0, 28-Jan-2020
2.0, 11-Sept-2020	Sign off of the above	V7.0, 28-Jan-2020

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, proposed analysis for publications will occur at the following end points:

- We propose to conduct and submit for publication an analysis of available primary and secondary outcomes for all fifteen patients after the fifteenth patient has been evaluated to the fullest extent over the initial 10 week dosing period.
- Further analysis of outcomes will be submitted for publication after all patients who continue treatment complete 24 weeks of treatment.

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

PRIMARY OUTCOME MEASURE

Our primary outcome measures will inform whether the therapy is feasible in this patient group.

- Safety
    - Measured by the incidence of serious adverse events (SAEs) and adverse events (AEs) using CTCAE v4.0. Events will be summarised by grade, relatedness, admitting event (for SAEs); expectedness and sequelae.
- Tolerability
    - Measured by the incidence of *intolerable adverse events*. An intolerable adverse event will satisfy all of the following criteria:
      1. Associated with a serious adverse event or a drug discontinuation of greater than three weeks;
      2. Grade 3, 4 or 5 in severity according to CTCAE version 4;
      3. In the opinion of the Investigator is i) definitely related or ii) probably related or iii) possibly related to the study drug treatment.
    - Adverse events which are considered unrelated or probably not related will not be classed as intolerable events.
- Quantity of study drug administered

- Total drug administered, number of administrations, number and length of interruptions, and number of discontinuations will be reported.

SECONDARY OUTCOME MEASURES

Our secondary outcome measures will provide data on patient function and disease progression

- Revised ALS Functional Rating Scale (ALSFRS-R)
  - This is a functional rating scale, including assessments of communication, mobility, feeding, dressing and respiration.
- ALS Assessment Questionnaire (ALS AQ-40)
  - This patient-reported outcome measures the subjective well-being of patients. It is broader than ALSFRS-R and adds assessment of emotional reactions.
- Urinary p75ECD
  - This is a biological fluid-based biomarker of ALS disease progression
- NfL in plasma
  - This is a blood-based biomarker for neurodegeneration

EXPLORATORY OUTCOME MEASURES

- HPLC analyses of purine-pyrimidine metabolites (serum)
- HPLC analysis of fat-soluble vitamins and antioxidants (serum) HPLC analyses of amino acids (AA) and amino-group containing compounds (ACCG) (serum)
- Spectrophotometric analysis of lactate
- PBMC samples will be collected for analysis of change in phenotypic balance

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).

Further summaries of safety data (not related to the primary outcome) will include any incidents of elevated LFTs which satisfy the criteria for a drug induced liver injury (DILI), as defined in appendix 5 of the protocol.

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.

The number of patients who go on to each of the treatment extensions (as defined in the protocol) will also be 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

3.3 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.

3.3.1 SAMPLE SIZE DETERMINATIONS

This study seeks to recruit 15 patients.

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.

3.4 SUBGROUP ANALYSIS

There are no sub-group analyses planned.

4. ANALYSIS POPULATIONS

Statistical analyses will be carried out on a modified intention-to-treat (mITT) basis in which only patients who have received at least one infusion of ILB, and thus are considered evaluable, will be analysed.

The per-protocol population is defined as those patients who complete the initial treatment period (the first 10 treatment weeks) without missing a week of therapy. Where appropriate, in summary tables and graphs, these patients will be highlighted.

5. STATISTICAL SOFTWARE

Analysis will be conducted using R and associated packages.

6. STORAGE AND ARCHIVING

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

T:\Trials Work\D3B\TikoMed\ALS\ALSAnalysis\DMC\YYYY-MM-DD\Snapshot\<Date of snapshot YYYY-MM-DD>\

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

T:\Trials Work\D3B\TikoMed\ALS\ALSAnalysis\Publications\<publication id\Snapshot\<Date of snapshot YYYY-MM-DD>\

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\YYYY-MM-DD\LockedDataset\<Date of snapshot YYYY-MM-DD>\

7. REFERENCES

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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