A PHASE 1/2, TWO-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED MULTI-PERIOD CROSSOVER (N-OF-1) STUDY TO EVALUATE THE FEASIBILITY, SAFETY, AND EFFICACY OF TJ-68 IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS) AND MUSCLE CRAMPS

NCT04998305

June 27, 2024

1. Background

This is the statistical analysis plan for is a phase 1/2 trial of TJ-68 in participants with amyotrophic lateral sclerosis (ALS) and muscle cramps. This trial aims to evaluate the efficacy of TJ-68 for improving muscle cramps in the participants using a double-blind, randomized, crossover design. This trial also aims to evaluate safety of TJ-68.

2. Study Design

2.1. Design Overview

This is a multi-period crossover study where each participant will receive four 2-week treatment periods of TJ-68/placebo. We plan to randomize a total of 26 participants, with 13 randomized to Treatment Sequence A: TJ-68-Placebo-Placebo-TJ-68, and another 13 to Treatment Sequence B: Placebo-TJ-68-TJ-68-Placebo, with a 1-week washout period between treatment periods. That is, each participant will receive TJ-68 and Placebo each in two separate treatment periods. Assuming 15% attrition, we expect to have 22 evaluable participants. Balanced randomization of the two alternating treatment sequences will eliminate linear trend in the primary analysis.

2.2. Randomization Procedures

The 22 evaluable participants will be randomized 1:1 to the two treatment sequences based on the study schedule, using blocked randomization stratified by site. To ensure power with anticipated dropout (15%), we anticipate randomizing up to 2 additional participants to each treatment sequence.

2.3. Analysis Populations and Missing Data

All efficacy analyses will be performed using the modified intent-to-treat (mITT) population. The mITT population consists of all randomized participants with outcomes evaluated in at least two (out of four) post-randomization periods with at least one period in TJ-68 and one in Placebo.

As sensitivity analyses, we will also perform efficacy analyses in the completers only, that is, participants with outcome evaluated in all 4 treatment periods.

Safety analyses will be performed as treated.

Missing data patterns will be compared by treatment sequence as well as by the treatment periods. While the primary analyses will be performed in the mITT population defined above, we will perform sensitivity analyses using imputed data sets under different imputation approaches:

(A) Mean imputations: Missing data within a treatment period will be imputed using averages from other data points within the same treatment period. If data in the entire treatment period is missing, the observations from the previous period will be carried forward.
(B) Worst-outcome imputations: All missing data will be imputed using the worst values observed in a treatment group.

3. Primary Efficacy Analysis

3.1. Primary Outcome

The primary outcome of the study will be calculated using the Columbia Muscle Cramp Scale (MCS). We will use MCS item #5, visual analog scale (VAS) (0-10) for Muscle Cramps Affecting Overall Daily Activity of Columbia MCS as the primary outcome. The MCS will be assessed on the phone twice a week; thus, there will be a total of four MCS assessments per treatment period. However, for the primary analysis, only data in the second week of each treatment period will be used to minimize carryover effects.

3.2. Statistical Analysis for the Primary Outcome

The primary analysis will be performed using linear mixed effect (LME) model to estimate the effect of TJ-68 compared to placebo on MCS VAS. The LME model will use all available MCS VAS measured in the second week of all treatment periods per mITT. The model will include TJ-68 as a main effect with a random participant effect to account for within-individual correlation. While balanced randomization of Treatment Sequences A and B will eliminate linear time trend, we will also explore linear and non-linear time effects in the LME model to explore the impact on the primary comparison between TJ-68 and Placebo.

3.3. Sample Size Consideration

We aim to enroll 22 evaluable participants equally to the two alternating TJ-68/Placebo sequences over the four treatment periods, i.e., each participant will have 4 observations. Under the LME model, assuming a within-participant standard deviation of 1.4 based on our pilot data, this sample size will yield about 85% power to detect a 1-point shift on MCS VAS Assuming 15% attrition, we will plan to enroll a total of 22 participants.

4. Safety Analysis

Adverse events (AE), including the presence of hypokalemia, will be summarized by treatment per participant. The AE will be attributed to the period in which it is observed. AE rate by treatment will be summarized using proportion and 95% confidence intervals and will be compared using McNemar test. Longitudinal AE data will be modeled using generalized linear mixed effect model with a logit link.

5. Secondary Outcome Analyses

5.1. Additional Analyses of MCS

Secondary outcomes based on the MCS include (i) total MCS score, (ii) cramp frequency, severity, or both measured via the Cramp Diary (CD), (iii) MCS Additional Questions, and (iv) VAS of Cramp Pain. These secondary outcomes will be analyzed using LME in the same manner as in the analysis of the primary outcome.

5.2. Other Secondary outcomes

Other secondary outcomes of the study include ALSFRS-R within each treatment period, clinical global impression of changes (CGIC) within each treatment period, qualify of life measured via ALSAQ-5 within each treatment period, and goal assessment scale (GAS) within each treatment period. As these outcomes are measured longitudinally, they will be analyzed using LME models.

5.3. Heterogeneity of treatment effects and plasma metabolomics

We will perform exploratory analysis to understand treatment mechanism via heterogeneity of treatment effects. Specifically, plasma metabolomics will be measured longitudinally, and will be included as a longitudinal covariate in the LME models. Its interaction with treatment effects will also be explored.