A RANDOMIZED, BALANCED, PHASE 1, MULTIPLE-DOSE, OPEN-LABEL, TWO-TREATMENT, TWO-PERIOD, TWO-SEQUENCE, CROSSOVER, RELATIVE BIOAVAILABILITY STUDY TO INVESTIGATE LITHIUM BRAIN/PLASMA PHARMACOKINETICS AND SAFETY OF AN AL001 ORAL CAPSULE COMPARED TO A MARKETED IMMEDIATE-RELEASE LITHIUM CARBONATE CAPSULE IN HEALTHY ADULT SUBJECTS

NCT #: NCT06921590

Statistical Analysis Plan Date: 20 January 2026

STATISTICAL ANALYSIS PLAN

VERSION: 1.0

DATE OF PLAN:

20 January 2026

STUDY DRUG:

AL001 (LITHIUM SALICYLATE/L-PROLINE COCRYSTAL)

BASED ON PROTOCOL:

AL001-ALZ03 Version 4.0: 04 November 2025

STUDY TITLE:

A RANDOMIZED, BALANCED, PHASE 1, MULTIPLE-DOSE, OPEN-LABEL, TWO-TREATMENT, TWO-PERIOD, TWO-SEQUENCE, CROSSOVER, RELATIVE BIOAVAILABILITY STUDY TO INVESTIGATE LITHIUM BRAIN/PLASMA PHARMACOKINETICS AND SAFETY OF AN AL001 ORAL CAPSULE COMPARED TO A MARKETED IMMEDIATE-RELEASE LITHIUM CARBONATE CAPSULE IN HEALTHY ADULT SUBJECTS

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Alzamend, Neuro, Inc.
3480 Peachtree Road NE
Second Floor, Suite 103
Atlanta, GA 30326

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	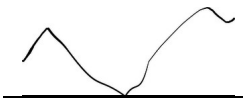 ID: CBFD6D91-9058-497E-A2... Digitally signed by <wdenney@humanpredictions.com> January 20, 2026 10:13 AM EST	01/20/2026
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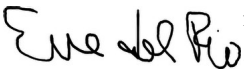
	 ID: EDE8CD78-F6C3-4EA0-9B... Digitally signed by <eve@riopharma.com> January 20, 2026 10:47 AM EST	01/20/2026
Eve del Rio, MD, PhD Clinical Study Lead Rio Pharmaceutical Services, LLC	Signature	Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALQ	Above the upper limit of quantification
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
$AUC_{tau\ ss}$	Area under the concentration versus time curve from time zero to the end of the 24-hour 3-dose interval at steady state
BLQ	Below limit of quantification
BMI	Body mass index
CI	Confidence interval
CL_{oral}	Apparent oral clearance
$C_{max\ ss}$	Maximum concentration at steady state
$C_{min\ ss}$	Minimum concentration at steady state
CPKP	Complete Pharmacokinetic Analysis Set
CS	Clinically significant
CSR	Clinical Study Report
$C_{ss\ ave\ brain}$	Average brain concentration at steady state
$C_{ss\ ave\ plasma}$	Average plasma concentration at steady state
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
$FI_{brain\ ss}$	Brain degree of fluctuation at steady state
$FI_{plasma\ ss}$	Plasma degree of fluctuation at steady state
HbA1c	Glycated hemoglobin
HDRS-17	Hamilton Depression Rating Scale
HR	Heart rate
IQR	Interquartile range
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MMRM	mixed model with repeated measures
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
n	Number of samples contributing to the measure

Abbreviation	Term
N	Number of participants
nALQ	Number of samples above the upper limit of quantification
nBLQ	Number of samples below the lower limit of quantification
NCA	Noncompartmental analysis
NCS	Not clinically significant
PD	Pharmacodynamic
PDP	Pharmacodynamics Analysis Set
PK	Pharmacokinetic
PKP	Pharmacokinetic Analysis Set
PT	Preferred term
RANDP	Randomized Analysis Set
SD	Standard deviation
SAE	Serious adverse event
SAFP	Safety Analysis Set
SAP	Statistical analysis plan
SCRP	Screened Analysis Set
SE	Standard error
SF-36	36-Item Short Form Health Survey
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TID	Three times a day
$t_{max\ ss}$	Time to reach the maximum concentration at steady state
$t_{min\ ss}$	Time to reach the minimum concentration at steady state
TSH	Thyroid-stimulating hormone
US	United States
WHODD	World Health Organization Drug Dictionary
YMRS	Young Mania Rating Scale

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods and data handling procedures to be followed during the analyses and reporting of data collected for study protocol AL001-ALZ03.

This SAP should be read in conjunction with the study protocol and electronic Case Report Form (eCRF). This version of the SAP has been developed using the protocol (Version 4 dated 04 November 2025) and eCRF (Version 3.0 dated 18 December 2025).

Where differences occur, the SAP will supersede the protocol and the differences will be documented in the clinical study report (CSR).

The SAP will be finalized before database lock. Any changes made after finalization of the SAP will be documented in the CSR.

2. STUDY DETAILS

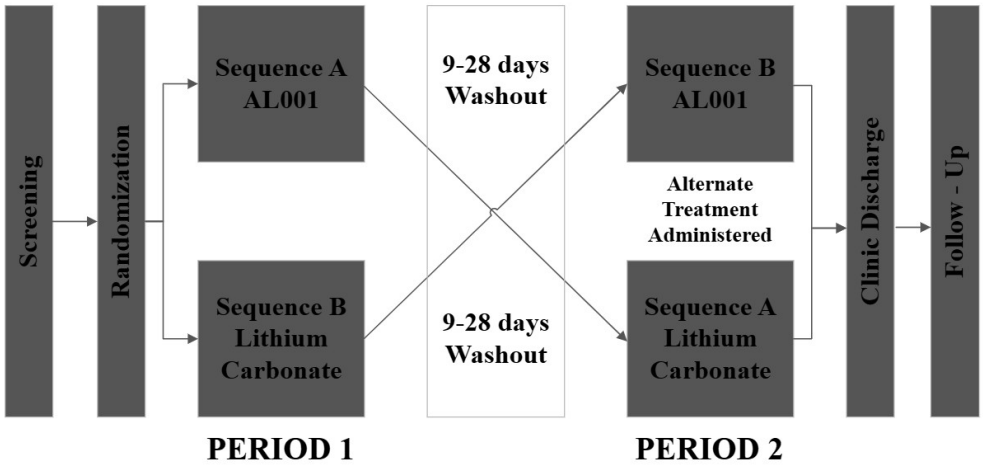
Statements in this section are incorporated from the protocol for context of the planned activities from the protocol with minimal modifications. All text should be read with the understanding that these statistical analysis plans reflect the intent of the protocol prior to clinical execution and changes may have occurred in study progress that can guide modification in statistical methods. Changes will be described either in the changes to planned analysis section of this SAP or in the CSR, as applicable.

2.1. Design

Study AL001-ALZ03 is a randomized, open-label, two-period crossover Phase 1 study to evaluate the pharmacokinetic (PK), safety, and pharmacodynamic (PD) effects of orally administered AL001 compared to a marketed immediate-release lithium carbonate capsule in healthy adult (ages ≥18 to <65 years) participants.

Following a Screening period of up to 28 days, 6 eligible healthy adults were to be randomized to one of 2 groups to receive AL001 1050 mg and lithium carbonate 150 mg each given 3 times a day (TID) during 2 sequential treatment periods separated by a washout period of 9 to 28 days. Participants randomized to sequence A received AL001 in treatment period 1 and lithium carbonate in period 2 while those randomized to sequence B received lithium carbonate in treatment period 1 and AL001 in period 2. Study drug was orally administered with water under fasted conditions. During each treatment period, study participants were confined to the clinic from 1 day prior to their first dose through 1 day after their last dose (ie, from Days -1 to 15). All participants were followed for safety for 6 weeks after their last dose of study drug (AL001 or lithium carbonate) with an in clinic visit 1 week and a telephone call 6 weeks after their last dose. A diagram of the study design is provided in Figure 1.

Figure 1: AL001-ALZ03 Study Design



For each study drug Treatment Period, 14 days of TID dosing with a 24-hour intensive PK blood sampling and 7Li-MRI-MRS neuroimaging on Day 14 (into Day15).

During each treatment period, blood samples for PK were collected prior to the morning dose on Days 1, 13, and 14, and for 24 hours after the morning dose on Day 14 (and 15). Safety data were collected at the timepoints specified in the Schedule of Activities (Table 3 in Protocol AL001-ALZ03 Version 4.0), and lithium brain distribution and mass/concentrations were characterized using ^{7}Li-magnetic resonance imaging (MRI)-magnetic resonance spectroscopy prior to and at 3, 6, 8, 12, 16, 20, 24 hours after the initial morning dose of study drug (AL001 or lithium carbonate) on Day 14.

2.2. Objective(s) and Endpoint(s)

The study's objectives and corresponding endpoints are specified in the table below.

OBJECTIVES	ENDPOINTS
Primary	
To evaluate differences in brain and/or brain structure lithium PK relative to plasma PK for AL001 capsule compared to a lithium carbonate capsule.	Brain (and brain structures)-to-plasma ratios between AL001 and lithium carbonate for steady-state PK measures/parameters. Similarities and differences between steady-state brain and brain structures lithium PK measures/parameters for AL001 and lithium carbonate. PK parameters specified in the protocol included: • Plasma and brain $AUC_{tau\ ss}$ = Area under the concentration versus time curve from time zero to the end of the 24-hour 3-dose interval at steady state • Plasma and brain $C_{max\ ss}$ = Maximum

OBJECTIVES	ENDPOINTS
	concentration at steady state • Plasma and brain $t_{max\ ss}$ = Time to reach the maximum concentration at steady state • Plasma and brain $C_{min\ ss}$ = Minimum concentration at steady state (if at end-of-24-hour dosing interval: C_{trough}) • Plasma and brain $t_{min\ ss}$ = Time to reach the minimum concentration at steady state over 24 hours • Brain/Plasma $AUC_{tau\ ss}$ ratio = Ratio of brain/plasma areas under the plasma concentration versus time curve from time zero to the end of the 24-hour 3-dose interval at steady state • Brain/Plasma $C_{max\ ss}$ ratio = Ratio of brain/plasma maximum concentrations from time zero to the end of the 24-hour 3-dose interval at steady state • Brain/Plasma $C_{min\ ss}$ ratio = Ratio of brain/plasma minimum concentrations from time zero to the end of the 24-hour 3-dose interval at steady state • Plasma apparent oral clearance (CL_{oral}) = $Dose_{24\ hours}$/Plasma $AUC_{tau\ ss}$ • Average plasma concentration at steady state ($C_{ss\ ave\ plasma}$) = Plasma 24 h $AUC_{tau\ ss}$/24 hours • Average brain concentration at steady state ($C_{ss\ ave\ brain}$) = Brain 24 h $AUC_{tau\ ss}$/24 hours • Plasma degree of fluctuation at steady state ($FI_{plasma\ ss}$) = Ratio of plasma 24 h ($C_{max\ ss}$ - $C_{min\ ss}$) to $C_{ss\ ave\ plasma}$ • Brain degree of fluctuation at steady state ($FI_{brain\ ss}$) = Ratio of brain 24 h ($C_{max\ ss}$ - $C_{min\ ss}$) to $C_{ss\ ave\ brain}$ • Plasma and brain swing 24 h = [($C_{max\ ss}$ - $C_{min\ ss}$)/$C_{min\ ss}$] • MRT oral doses $_{(0\text{-}24h\ ss)}$ = Mean Residence Time following oral doses at steady state (0 to tau, end of 24-hour dosing interval)
Primary	
To evaluate the safety and tolerability of AL001 under multiple-dose, steady-state conditions in	Vital signs (blood pressure, heart rate, and temporal artery body temperature)

OBJECTIVES	ENDPOINTS
healthy adult participants under the conditions of this study.	12-lead electrocardiogram (ECG) Physical examination Safety laboratory tests (hematology, chemistry [including thyroid-stimulating hormone (TSH), vitamin B12, and Mg], glycated hemoglobin (HbA1c), and urinalysis) Reported and observed adverse events (AEs)/ serious AEs/tolerability observations including signs and/or symptoms of lithium and/or salicylate toxicity.
Exploratory	
To characterize AL001 salicylate PK under the conditions of this study.	Analysis of exploratory endpoints for AL001 plasma salicylate PK will be the same as for the primary endpoints for AL001 and lithium carbonate plasma lithium PK.
Pharmacodynamics	Magnetic resonance spectroscopy (MRS) techniques will be also applied to explore brain metabolism, including possible metabolic similarities/differences between treatments.

2.3. Determination of Sample Size

The sample size for this study of 6 participants is not based upon any available statistical data for human brain lithium nor on any statistical power considerations.

3. ANALYSIS POPULATIONS

The following analysis populations were specified in the protocol and will be used for analyses.

Screened Analysis Set (SCRP): The SCRP will include all participants who have signed the informed consent form.

Randomized Analysis Set (RANDP): The RANDP will include all participants who are randomized within one of the sequence cohorts.

Safety Analysis Set (SAFP): The SAFP will include all participants in the RANDP who receive any dose of study drug. This analysis set will be utilized for all safety analyses.

Pharmacokinetic Analysis Set (PKP): The PKP will include all participants in the SAFP who receive AL001 capsule or lithium carbonate capsule and have at least 1 complete plasma or brain/brain structure PK profile.

Complete Pharmacokinetic Analysis Set (CPKP): The CPKP will include participants in the PKP with data from each treatment. In addition, the selection of inclusion in the CPKP will be made at the period level such that periods with complete data required for analysis are included. In the case of multiple periods with data for a participant, the period with the most complete contemporaneous data will be included so that only 1 period with each treatment is included for each participant.

Pharmacodynamics Analysis Set (PDP): The PDP will include all participants in the SAFP who receive AL001 capsule or lithium carbonate capsule and have at least 1 complete plasma or brain/brain structure PK profile.

4. STATISTICAL METHODOLOGY

4.1. General Data Analysis Considerations

The following conventions will be applied to analyses/data presentation:

All dates will be displayed in DDMMMYYYY format.

Repeat assessments, which are not intended per-protocol, will be considered as unscheduled, and the first repeat that is not intended per-protocol will be considered as scheduled. Unscheduled data will be presented in Listings, but not in Tables and Figures.

All statistical analyses will be performed using R (Version 4.5.0 or higher); the analysis of variance (ANOVA) will be performed with the mmrm (Version 0.3.15 or higher) and emmeans (Version 1.11.2-8 or higher) libraries for R, and noncompartmental analysis will be performed with the PKNCA library (Version 0.12.1 or higher). The version of R and each library will be reported in a listing. In general, all data collected during the study will be presented in the data listings.

Data will be summarized by treatment group, where appropriate.

All statistical tests will be tested at $\alpha = 0.05$ with a 2-sided significance level, unless otherwise stated.

Data will be summarized using descriptive statistics. For continuous variables, descriptive statistics will include number of participants (N), number of samples contributing to the measure (n), arithmetic mean, arithmetic standard deviation (SD), geometric mean (ie, the mean calculated on the $\log_e$ scale transformed back to the original scale), geometric coefficient of variation, minimum, median, maximum, and either interquartile range (IQR) or 95% confidence interval (CI). For categorical variables, data will be summarized using counts and percentages.

The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The arithmetic mean, geometric mean, median, and CIs will be presented to 1 more decimal place than the original data, and the SD and Standard Error (SE) will be presented to 2 more decimal places than the original data. P-values will be presented with

3 decimal places. If the p-value is closer to 0 than 0.0005, then it should be reported as "<0.001" and if it is closer to 1 than 0.9995, then it should be reported as ">0.999".

For all analyses, baseline will be defined as the most recent measurement prior to the first dose of study drug, unless otherwise specified.

Grouping for descriptive statistics will include treatment, visit, and nominal time point, unless otherwise specified.

4.1.1. Data Analysis for Censored Parameters

If a continuous variable has samples below or above the limit of quantification, additional summary statistics and modifications to parameters will be calculated:

- number of samples below the lower limit of quantification (nBLQ),
- number of samples above the upper limit of quantification (nALQ),
- the arithmetic mean will be calculated by imputing below the lower limit of quantification (BLQ) will be imputed as zero while values above the upper limit of quantification (ALQ) will be imputed at the upper limit of quantification,
- the Tobit arithmetic mean (means calculated using Tobit regression techniques to handle censored values), and
- the Tobit geometric mean (means calculated using Tobit regression techniques with the natural logarithm-transformed values then back-transformed to the linear scale to handle censored values).

4.2. Interim Analyses

No interim analyses were planned or performed.

4.3. Pooled Analyses

Not applicable for this study in healthy participants. Upon completion of this and other related studies, pooled analyses similar to the ones described in this SAP will be applied to all analogous studies conducted. This may include healthy, bipolar I disorder, major depressive disorder, post-traumatic stress disorder, and Alzheimer's disease participants.

4.4. Multicenter Studies

Not applicable as this study was performed at a single site in the United States (US).

4.5. Handling of Missing Data

Missing data will be omitted from summary statistics. Missing data will not be imputed for the ANOVA analysis.

4.6. Subgroup Analyses

Not applicable.

4.7. Handling of Covariates

Not applicable.

4.8. Multiple Comparisons and Multiplicity

No multiplicity adjustments will be performed. Collected data, except for definitive bioequivalence in plasma, are intended for hypothesis generation.

5. ANALYSIS METHODS

5.1. Study Population

5.1.1. Participant Disposition

The number of participants in each analysis set will be summarized by treatment group for each sequence cohort/neuroimaging group and overall. In addition, the number of participants in the Randomized and SAFP who complete the clinical trial and who prematurely discontinue, including the reasons for premature discontinuation, will be summarized by treatment group sequence cohort/neuroimaging group and overall.

Participant disposition will be summarized for all participants randomized. The following will be presented:

- Number of participants (N) screened
- N of participants randomized
- N and % of participants who completed the study
- N and % of participants who withdrew from the study by primary reason for withdrawal
- N and % of participants included in each analysis set

The percentages will be calculated using the number of randomized participants as the denominator.

5.1.2. Demographic and Baseline Characteristics

The demographic and baseline characteristics will include age (years), sex, ethnicity, race, height (cm), weight (kg), and body mass index (BMI; kg/m^2), and will be summarized by treatment

group for each sequence cohort and overall. Individual participant data listings for demographic and baseline characteristics will be presented.

5.1.3. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 27.1, English.

Medical/surgical history will be summarized by treatment group with the number and percentage of participants in each system organ class (SOC), preferred term (PT), and overall. Participants will be counted only once at the PT, only once at the SOC, and only once at the participant level for counting the total number of participants with a medical history term. Individual participant data listings for medical/surgical history will be presented.

5.1.4. Prior and Concomitant Medication

Prior medications are those medications that are taken before the first dose of study drug, ie, prior medications have a stop date/time before study treatment starts. Medications stopped on the same day as the start of first study drug administration will be considered as prior medication only. Concomitant medications are medications taken by participant on/after the start of first study drug administration. If a medication starts before the first dose of study drug and continues during the study it will be considered both as prior and concomitant. Prior and concomitant medications will be classified according to the World Health Organization Drug Dictionary (WHODD) Version C3, March 2025.

Prior and concomitant medications will each be summarized by Anatomical Therapeutic Chemical (ATC) classes and PT by treatment group.

For participants with both start and end dates unknown, the medication will be considered as both prior and concomitant, considering the conservative approach.

Individual participant data listings will be presented for prior medications and concomitant medications.

5.1.5. Protocol Deviations

Individual participant data listings for protocol deviations will be presented. Protocol deviations will be summarized by treatment group.

5.1.6. Study Drug Exposure and Treatment Compliance

Treatment exposure will be summarized as extent of exposure to the study drug. Measures of extent of exposure include the following and will be presented by treatment group:

- actual number of *capsules* taken,
  - Actual Number of Capsules taken at that dose level = Number of Capsules dispensed - (Number of capsules returned + Number of capsules lost) at that dose level.
- number of mg taken,
  - Sum of all doses administered
- duration of exposure, and
  - (Date of Last study drug administration – Date of first study drug administration) +1 excluding the number of days participants were not on study medication
- compliance/adherence.
  - (Actual number of capsules taken at that dose (mg) level / scheduled number of capsules at that dose (mg) level should have been taken during time on treatment) *100

Individual participant data listings for treatment exposure will be provided for study drug administration and accountability, drug modification and drug interruption.

5.2. Efficacy Analyses

Not applicable.

5.3. Clinical Pharmacology Analysis

5.3.1. PK Analyses

A non-compartmental analysis with linear trapezoidal AUC_{tau} approximations will be used for PK analyses.

The relative bioavailability and other comparisons between AL001 and lithium carbonate will use PK and statistical conventions consistent with Food and Drug Administration (FDA) guidance for bioequivalence testing:

- Statistical Approaches to Establishing Bioequivalence (2001)
- Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations (draft 2014)

- Bioavailability Studies Submitted in NDAs or INDs – General Considerations (2022)

5.3.1.1. Analysis of PK Concentrations and Derived PK Parameters

The analyses in this section will be performed using the PKP population.

Plasma concentrations of lithium and salicylate, total brain and brain structure concentrations of lithium as measured by ^{7}Li MRI-MRS, and derived PK measures are to be listed by treatment, participant identifier, nominal and actual times of sampling (where appropriate, for MRI measurements the midpoint of the MRI acquisition start and end actual times will be used), and summarized by nominal time point and by treatment. PK samples outside of the collection window will be excluded from nominal time summaries and included in noncompartmental analysis (NCA) parameter calculations, when applicable, and listings.

PK parameters related to time since dose will be considered relative to the first dose on Day 14. For example, if the maximum concentration occurred 1 hour after the third dose, it will be reported as 13 hours and not 1 hour; this example assumes that all times are exactly followed and does not change the fact that actual times will be used for all calculations.

In order to assess whether PK steady state has been approximately achieved, descriptive statistics for 3 trough measurements of lithium and salicylate will be presented for Day 13 (8AM), Day 14 (8AM), and Day 15 (8AM, the 24-hour sample for the last dosing day) of each study drug treatment; these will be presented and a linear regression method will be applied to determine statistical similarity.

The linear regression will be a mixed model with repeated measures (MMRM) of natural logarithm transformed concentrations with fixed effects for slope and intercept and random effects by participant for both slope and intercept and homoscedastic residual additive error. If the model does not converge, the random effect for intercept will be omitted. Steady state will be defined as the 90% CI of the fixed-effect slope including zero (Panebianco 2011).

Concentration data from individual participants will be used to derive the following NCA parameters for AL001 and lithium carbonate. Brain in the list below includes whole brain and all brain regions reported. Plasma includes lithium and salicylate. Brain to plasma ratios are only for lithium.

- Plasma and brain:
  - $AUC_{tau\ ss}$
  - $C_{max\ ss}$
  - $t_{max\ ss}$
  - $C_{min\ ss}$
  - $t_{min\ ss}$

- Css_{ave}
- FI_{ss}
- Swing

- Brain/Plasma ratio:
  - $AUC_{tau\ ss}$
  - $C_{max\ ss}$
  - $C_{min\ ss}$
- Brain region (each region separately)/whole brain ratio:
  - $AUC_{tau\ ss}$
  - $C_{max\ ss}$
  - $C_{min\ ss}$
- Plasma:
  - Cloral
  - MRT_{oral}

Individual brain structure (eg, hypothalamus, frontal cortex) PK measures, parameters, and ratios compared to plasma values will be determined that are analogous to the whole brain assessments above for all individual-structure lithium concentration/mass values.

Individual brain structure (eg, hypothalamus, frontal cortex) $AUC_{tau\ ss}$ to total brain $AUC_{tau\ ss\ brain}$ ratios will be calculated. Statistical analysis will be conducted as for $AUC_{brain\ ss}$ to $AUC_{plasma\ ss}$.

5.3.1.2. Analysis of PK Parameters

ANOVA will be performed on $\log_e(AUC_{tau})$ and $\log_e(C_{max})$ in the CPKP. Point estimates and 90% CIs for treatment differences on the log scale will be exponentiated to obtain estimates for geometric means and ratios of geometric means on the original scale. These CIs will be compared to the standard bioequivalence reference ranges of 80.00% to 125.00%.

Each combination of matrix/analyte will be analyzed with the ANOVA model such as plasma lithium, plasma salicylate, whole brain lithium, and lithium in each brain region.

The R code for the ANOVA model will be:

```
fit <- mmrm::mmrm(formula = lnAVAL ~ TRTA + us(TRTA|USUBJID), …)
emm <- emmeans(fit, specs = ~TRTA)
emm_comp <- contrast(emm, method = "trt.vs.ctrl1")
```

Where:

- lnAVAL is the natural logarithm of the exposure parameter (AUC_{τ} or C_{max})
- TRTA is the actual treatment received
- USUBJID is the unique participant identifier

Exposure parameters excluded from summary statistics will be excluded from the ANOVA model.

5.3.2. PD Analyses

PD parameters will be analyzed as described in the PD analysis plan (a separate document) and reported separately by Massachusetts General Hospital.

5.4. Safety Analyses

All safety analyses will be performed on the SAFP population.

5.4.1. Adverse Events

Adverse events (AE) will be coded using MedDRA Version 27.1, English, with severity (toxicity) of AEs graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Treatment-emergent AEs (TEAEs) will be summarized by treatment group *and overall* for the following categories:

- a TEAE
- a serious TEAE
- a treatment-related TEAE (related TEAEs are defined as those assessed as possibly, probably, or definitely related)
- a treatment-related serious TEAE
- a TEAE resulting in death
- a TEAE leading to treatment discontinuation
- a TEAE leading to study discontinuation

The incidence of each of the above will be summarized by SOC and PT. Summaries of TEAEs will also be presented by severity/toxicity (mild [CTCAE Grade 1], moderate [CTCAE Grade 2], severe [CTCAE Grade 3], life threatening [CTCAE Grade 4], or fatal [CTCAE Grade 5]) by SOC and PT.

AEs without an onset date will be considered to be TEAEs. A participant experiencing the same AE more than once will be counted only once for that PT, using the worst severity and worst relatedness to study drug. Separate individual participant data listings for AEs, serious AEs (SAEs), death due to AEs, TEAEs related to study drug, and TEAEs leading to treatment and study discontinuation will be presented.

5.4.2. Vital signs

Vital sign measurements will include heart rate (beats per minute), respiratory rate (breaths per minute), blood pressure (diastolic and systolic) (mmHg), and oral body temperature (°C), if collected.

Observed values and change from baseline in vital sign parameters will be summarized descriptively. Individual participant data listings for vital signs will be presented.

5.4.3. 12-Lead ECG

The 12-lead ECG will be summarized descriptively and will include the following measurements: heart rate (HR; bpm), PR interval (msec), RR interval (msec), QRS duration (msec), QT interval (msec), and QTcF (msec).

Observed values and change from baseline in ECG parameters will be summarized descriptively. The overall interpretation of ECG findings (Normal, Abnormal Not Clinically Significant [NCS] and Abnormal Clinically Significant [CS]) will be summarized categorically. Additionally, a shift table comparing overall interpretation (normal, abnormal – NCS, abnormal – CS) of the ECG parameters at post baseline visits against baseline visit will also be presented.

If required, the QTcF will be derived using QT interval and HR as follows:

- QTcF (msec) = QT (msec) / (60/HR)^(1/3)

A categorical analysis for QTcF Intervals (msec) will be performed for the following categories: ≤450, >450 to ≤480, >480 to ≤500, and >500 msec. The number and percentage of participants belonging to these categories will be categorically summarized at baseline and any time post baseline. Any time post baseline will include any scheduled, unscheduled or early termination post baseline assessments. Participants who met specified criteria more than once during post baseline assessment will be considered only once. Participants who met multiple criteria's during post baseline assessment will be considered only in the highest/worst criteria.

Individual participant data listings for ECG results will be presented.

5.4.4. Clinical Laboratory Data

The clinical laboratory test category will include assessments of hematology, clinical chemistry, urinalysis, serology, toxicology, and pregnancy testing as specified in the study protocol. Separate tables will be created for each category and continuous/categorical assessment type for any measures with post-dose assessments.

Laboratory values will be compared to normal ranges of the applicable local laboratory and values that fall outside of the normal ranges will be flagged in the listings as H (High) or L (Low).

Shift tables comparing the post baseline visit assessment value (low, normal, and high) to baseline visit assessment value will be presented. For the shift tables comparing predose to all post-dose times, all shifts will be included, which may include a single participant in multiple categories (for example, an individual with a normal baseline and both low and high shifts at varying post-dose times would be included in both the low and high shifts for that lab). A footnote will be added to the table indicating, "Participants may be included in more than 1 shift category if they are in multiple post-baseline categories. Therefore, the count of shifts may be greater than the number of participants."

Any time post baseline will include any scheduled, unscheduled, or early termination post baseline assessments. Participants who met specified criteria more than once during post baseline assessment will be considered only once.

Individual participant data listings of all laboratory results will be presented.

Where applicable, individual participant data listings for pregnancy test results will be presented.

5.4.5. Physical and Neurological Examination

Individual participant data listings for physical and neurological examination results will be presented.

5.4.6. Mental health status and health status assessments

The mental health status assessment results (Columbia-Suicide Severity Rating Scale [C-SSRS], Young Mania Rating Scale [YMRS], and the Hamilton Depression Rating Scale [HDRS-17]) will be summarized by a predose/maximum on treatment shift table. Health status (Short Form Health Survey [SF-36]) results will be summarized by dimension over time. Each of the questionnaires will be listed individually.

For C-SSRS, the shift table will summarize the following categories:

1. No suicidal ideation or behavior
2. Suicidal ideation
3. Suicidal behavior

For YMRS, the shift table will summarize the following categories:

1. No or minimal manic symptoms (score of 0 to 12)
2. Mild mania (13 to 19)
3. Moderate mania (20 to 25)
4. Severe mania (≥26)

For HDRS-17, the shift table will summarize the following categories:

1. None (≤9)
2. Mild (10 to 13)
3. Mild to moderate (14 to 17)
4. Moderate to severe (≥18)

For SF-36, each of the dimensions (Physical Functioning, Physical Role Functioning, Bodily Pain, General Health, Vitality, Social Functioning, Emotional Role Functioning, and Mental Health) will be summarized by treatment over time.

6. CHANGES TO PLANNED ANALYSES

The CPKP was added to allow for a clear definition to handle participants with repeated periods with the same treatment.

7. REFERENCES

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8. APPENDIX 1: LIST OF TABLES, LISTINGS, AND FIGURES

Entries in the tables with square brackets ("[ ]") indicate analyses of related items that will be repeated.

Table 1: Index of Tables

Number(s)	Title	Population	Topline?
14.1.1	Participant disposition	SCRP	Y
14.1.2	Analysis populations	All	Y
14.1.2.[1-3]	Demographics and baseline characteristics	[SAFP, PKP, PDP]	Y
14.1.3	Extent of exposure	SAFP	
14.2.1.1.[1-x]	Pharmacokinetic concentration summary statistics over time [plasma lithium, plasma salicylate, whole brain, each brain region]	PKP	Y
14.2.2.1.[1-x]	Pharmacokinetic parameter summary statistics [plasma lithium, plasma salicylate, each brain region]	PKP	Y
14.2.3.1.[1-2].[1-x]	Pharmacokinetic parameters inferential statistics [AUC_{τ}, C_{max}] for [plasma lithium, whole brain lithium, lithium in each brain region] comparing formulations	PKP	Y
14.2.4	Ratio of lithium AUC_{τ} in brain regions and plasma lithium	PKP	Y
14.2.5	Ratio of lithium AUC_{τ} in brain regions and the whole brain	PKP	Y
14.2.6.[1-2]	Pharmacokinetic inferential statistics for plasma [lithium, salicylate] attainment of steady-state	PKP	Y
14.3.1	Overall summary of treatment-emergent adverse events	SAFP	
14.3.2	Treatment-emergent adverse events by MedDRA system organ class and preferred term	SAFP	Y
14.3.3	Treatment-emergent adverse events by MedDRA system organ class, preferred term, and severity	SAFP	Y
14.3.4	Serious adverse events by MedDRA system organ class, preferred term, and severity	SAFP	
14.3.5.1.[1-2]	Overall summary of [plasma lithium concentrations above 1.2 mEq/L, plasma salicylate concentrations above 30 mg/dL]	PKP	
14.3.5.2.[1-2]	Summary of [plasma lithium concentrations above 1.2 mEq/L, plasma salicylate concentrations above 30 mg/dL] over time	PKP	

Table 1: Index of Tables

Number(s)	Title	Population	Topline?
14.4.1.1.[1-4]	Laboratory summary statistics, continuous measurements over time [hematology, clinical chemistry, urinalysis, pregnancy]	SAFP	
14.4.1.2.[1-4]	Laboratory shift table comparing predose to maximal post-dose, continuous measurements [hematology, clinical chemistry, urinalysis, pregnancy]	SAFP	
14.4.1.3.[1-4]	Laboratory shift table comparing predose to post-dose over time, continuous measurements [hematology, clinical chemistry, urinalysis, pregnancy]	SAFP	
14.4.1.4.[1-4]	Laboratory summary statistics, categorical measurements over time [hematology, clinical chemistry, urinalysis, pregnancy]	SAFP	
14.4.2	Vital sign summary statistics	SAFP	
14.4.3.1.1	Electrocardiogram (ECG) summary statistics, continuous measurements	SAFP	
14.4.3.1.2	QTcF summary of overall post-baseline interval categories	SAFP	
14.4.3.1.3	QTcF summary of interval categories over time	SAFP	
14.4.3.1.4	QTcF summary of changes from baseline over time	SAFP	
14.4.3.2.1	Electrocardiogram (ECG) summary statistics, categorical results	SAFP	
14.4.3.2.2	Electrocardiogram (ECG) summary statistics, categorical results shift table	SAFP	
14.5	Summary of prior and concomitant medications by Anatomical Therapeutic Chemical (ATC) classes and preferred term (PT)	SAFP	
14.6.1	Summary of Columbia-Suicide Severity Rating Scale (C-SSRS) as a shift table	SAFP	
14.6.2	Summary of Young Mania Rating Scale (YMRS) as a shift table	SAFP	
14.6.3	Summary of Hamilton Depression Rating Scale (HDRS-17) as a shift table	SAFP	
14.6.4	Summary of Short Form Health Survey (SF-36) by dimension over time	SAFP	

Table 2: Index of Figures

Number(s)	Title	Population	Topline?
14.2.1.2.1.[1-x]	Pharmacokinetic concentration arithmetic mean and +1 standard deviation over time [plasma lithium, plasma salicylate, whole brain, each brain region] (linear scale)	PKP	Y
14.2.1.2.2.[1-x]	Pharmacokinetic concentration geometric mean and +1 arithmetic standard deviation over time [plasma lithium, plasma salicylate, whole brain, each brain region] (semi-log scale)	PKP	Y
14.2.1.2.3.[1-x]	Pharmacokinetic individual concentrations over time [plasma lithium, plasma salicylate, whole brain, each brain region] (linear scale)	PKP	Y
14.2.1.2.4.[1-x]	Pharmacokinetic individual concentrations over time [plasma lithium, plasma salicylate, whole brain, each brain region] (semi-log scale)	PKP	Y
14.2.2.2.[1-2].[1-x]	Pharmacokinetic parameter ([AUC_{τ}, C_{max}]) box and whisker plot [plasma lithium, plasma salicylate, each brain region] (semi-log scale)	PKP	Y
14.2.3.2.[1-2].[1-x]	Pharmacokinetic parameters inferential statistics point estimate and confidence interval [AUC_{τ}, C_{max}] for [plasma lithium, whole brain lithium, lithium in each brain region]	CPKP	Y-plasma only

Table 3: Index of Listings

Number(s)	Title	Topline?
16.2.1	Participant informed consent and disposition	
16.2.2	Protocol deviations	
16.2.3	Inclusion/exclusion criteria	
16.2.4	Analysis populations and reasons for exclusion	
16.2.5.1	Demographics and baseline characteristics	
16.2.5.2	Medical/surgical history	
16.2.5.3	Prior and concomitant medications	
16.2.5.4	Urine drug screening and alcohol test	
16.2.5.5	Physical examinations	
16.2.5.6.1	Adverse events	
16.2.5.6.2	Serious adverse events	Y

Table 3: Index of Listings

Number(s)	Title	Topline?
16.2.5.7.1	Columbia-Suicide Severity Rating Scale (C-SSRS) categorical results	
16.2.5.7.2	Young Mania Rating Scale (YMRS) categorical results	
16.2.5.7.3	Hamilton Depression Rating Scale [HDRS-17] categorical results	
16.2.5.7.4	Short Form Health Survey [SF-36] dimension results	
16.2.5.8.1	Columbia-Suicide Severity Rating Scale (C-SSRS) individual question results	
16.2.5.8.2	Young Mania Rating Scale (YMRS) individual question results	
16.2.5.8.3	Hamilton Depression Rating Scale [HDRS-17] individual question results	
16.2.5.8.4	Short Form Health Survey [SF-36] individual question results	
16.2.5.9	Vital signs	
16.2.5.10	Electrocardiograms	
16.2.6.1.[1-5]	Laboratory measurements, continuous measures [hematology, clinical chemistry, serology, urinalysis, pregnancy]	
16.2.6.2.[1-5]	Laboratory measurements, categorical measures [hematology, clinical chemistry, serology, urinalysis, pregnancy]	
16.2.7	Dosing	
16.2.8.1.1	Pharmacokinetic concentration, plasma	Y
16.2.8.1.2	Pharmacokinetic concentration, whole brain and brain regions	Y
16.2.8.2.1	Pharmacokinetic parameters, plasma	Y
16.2.8.2.2	Pharmacokinetic parameters, whole brain and brain regions	Y
16.2.9	Software versions of R and libraries used for analysis	