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

Detailed Protocol Date: 04 November 2025

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

Sponsor Protocol Number:	AL001-ALZ03
Investigational Product:	AL001 (lithium salicylate/L-proline cocrystal)
Phase of Development:	Phase 1 (Healthy Subjects)
Study Sponsor:	Alzamend Neuro, Inc. 3480 Peachtree Road NE Second Floor, Suite 103 Atlanta, GA 30326 Tel: (844) 722-6333
MGB IRB Protocol Number:	2024P003031
Principal Investigator:	Ovidiu Andronesi, MD, PhD

COMPLIANCE

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and all other applicable regulatory requirements.

Sponsor Protocol Version	Date
1.0 (Final)	12 September 2024
2.0 (Amendment 01)	22 April 2025
3.0 (Amendment 02)	03 September 2025
4.0 (Amendment 03)	04 November 2025

PROTOCOL APPROVAL – SPONSOR'S SIGNATURE PAGE

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
MGB IRB Protocol Number	2024P003031
Sponsor Protocol Number	AL001-ALZ03
Sponsor Protocol Version	4.0 (Amendment 03)
Sponsor Protocol Date	04 November 2025

Protocol accepted and approved by:

Stephan Jackman
Chief Executive Officer
Alzamend, Neuro, Inc.
3480 Peachtree Road NE
Second Floor, Suite 103
Atlanta, GA 30326

_____ _____

Stephan Jackman, CEO Date (dd/mm/yyyy)

INVESTIGATOR'S SIGNATURE PAGE

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
MGB IRB Protocol Number	2024P003031
Sponsor Protocol Number	AL001-ALZ03
Sponsor Protocol Version	4.0 (Amendment 03)
Sponsor Protocol Date	04 November 2025

I have read and understood all sections of the above referenced study protocol and the Investigator's Brochure for AL001.

I agree to supervise all aspects of the protocol at my clinical research study site(s) and to conduct the clinical investigation in accordance with Good Clinical Practice (GCP) guidelines, the International Council for Harmonisation (ICH) regulations and United States IND regulations in 21 CFR 312. I will not make changes to the protocol before consulting with the Study Sponsor (Alzamend Neuro, Inc.) or implement protocol changes without Institutional Review Board (IRB) approval except to eliminate an immediate risk to subjects. I agree to administer investigational treatment only to study subjects under my personal supervision or the supervision of a Sub-Investigator.

I will not supply the study drugs to any person not authorized to receive it. Confidentiality will be protected. Individually identifiable health information will not be disclosed to third parties or appear in any study reports or publications.

Ovidiu Andronesi, MD, PhD
Principal Investigator

_____ _____

Signature of Principal Investigator Date (dd/mm/yyyy)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANOVA	analysis of variance
AST	aspartate aminotransferase
BD	bipolar disorder
BD1	bipolar I disorder
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus SARS-CoV2
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
DMP	Data Management Plan
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLM	General Linear Model
GMP	Good Manufacturing Practice
HbA1c	Hemoglobin A1c
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein

Abbreviation	Definition
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	investigational product
IR	immediate-release
IRB	Institutional Review Board
LDL	low density lipoprotein
mEq	milliequivalent
mEq/L	milliequivalents per liter
mg	milligram
mg/dL	millgrams per deciliter
mL	milliliters
MAD	multiple ascending dose
MDD	Major Depressive Disorder
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MTD	maximum tolerated dose
mmHg	millimeters of mercury
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NDA	New Drug Application
OTC	over-the-counter
pH	Potential Hydrogen: the logarithm, on the base 10, of the reciprocal of the hydrogen ion concentration
PI	Principal Investigator
PK	pharmacokinetic
PTSD	Post-Traumatic Stress Disorder
QA	quality assurance
RLD	reference listed drug
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation

Abbreviation	Definition
SOC	System Organ Class
TDD	total daily dose
TDM	therapeutic drug monitoring
TEAE	treatment-emergent adverse event
TID	three times a day (*"ter in die"*)
TSH	Thyroid-stimulating hormone
UAE	unexpected adverse event
USA	United States of America
USP	United States Pharmacopeia

SUMMARY OF CHANGES

SPONSOR PROTOCOL AMENDMENT 01 – SUMMARY OF CHANGES

Description of Change Made	Section / Location	Rationale
Addition of MGB IRB Protocol Number	Title Page; Sponsor's and Investigator's Signature Pages	Addition by Sponsor
Addition/Removal of Acronyms	List of Abbreviations	Updates by Sponsor
Addition of MGB IRB Protocol Number and PI Name	Study Synoposis	Addition by Sponsor
Addition of another primary endpoint to the lithium brain/plasma pharmacokinetic analysis	Study Synoposis: Endpoints for AL001 and Lithium Carbonate Plasma and Brain Lithium PK, AL001 Plasma Salicylate PK, Pharmacodynamics, and Safety; Section 8.6.3.1	Based on discussions with Human Predictions
Addition of exploratory pharmacodynamics endpoints	Study Synoposis: Endpoints for AL001 and Lithium Carbonate Plasma and Brain Lithium PK, AL001 Plasma Salicylate PK, Pharmacodynamics, and Safety; Section 2; Section 8.6.3.1	Based on discussions with the Principal Investigator and the MGH team
Addition of Screened Analysis Set and Pharmacodynamics Analysis Set to Populations for Statistical Analysis	Study Synoposis: Statistical Analysis and Section 8.2	Addition by Sponsor
Addition of Dr. Henry (Sub-Investigator/On-Call Medical Doctor), Monitor for Hire (Clinical Monitoring); Updates to Medical Monitors, Data Management Facilities, and Sponsor's contact information	Investigator and Study Administrative Structure; Section 6.11	Updates by Sponsor
Changed Alcohol screening to be in urine only (removed serum testing)	Study Synoposis: Study Activities and within Section 5.6 under specific study days	Decision to test in urine based on discussions with Sponsor and MGH team
Addition of, "Salicylate bioasssays will only be conducted following AL001 treatments."	Study Synoposis: Study Activities	Clarification of Salicylate assay timing
Updates to PK Blood draw times during 24 hours sampling period	Study Synoposis: Study Activities	Updates by Sponsor based on discussion with the MGH team
Updates to batch numbers and information reagarding IP and Reference products	Study Synoposis: Investigational Product and Reference Product; Section 5.2 Study Medications	Updates by Sponsor

Description of Change Made	Section / Location	Rationale
Removal of uncontrolled hypertension and fever prior to the first dose as an I/E criteria	Study Synoposis: Exclusion Criteria and Section 4.1.2	Updates based on discussion between Sponsor and MGH team. Hypertension and fever will still be checked prior to the first dose (and treated as an AE, if applicable)
Addition of language to allow blood pressure and temperature to be retaken to ensure accuracy at the Screening visit and on Day -1 (P1) as part of I/E criteria evaluation (prior to randomization)	Sections 5.6.1.2 and 5.6.2.1	Updates based on discussion between Sponsor and MGH team
Updates to Exclusion Criteria timing for xanthine consumption and grapefruit, pomelo, and Seville orange products and juices prior to check in Day -1 (P1)	Study Synoposis: Exclusion Criteria and Section 4.1.2	Updates based on discussions between Sponsor and MGH team
Addition of specifics to study subject identifier	Section 4: Study Population and Recruitment	Updates by Sponsor
Updates to procedures for missed IP and Reference product dosages	Section 5.2 Study Medications	Updates based on discussion between Sponsor and MGH team
Addition of a virtual informed consent visit (Visit #01a) to the screening period and language noting that subjects on any medications must wait at least 14 days prior to the in-person screening visit (Visit #01b)	Section 5.6.1; SOE Table	Updates based on discussion between Sponsor and MGH team
Addition of body weight measurements collection at Day -1 (P1), Day 15 (P1), Day -1 (P2), and Day 23 (P2)	Section 5.6.2.1, Section 5.6.2.3, Section 5.6.2.5 and Section 5.6.3; SOE Table	Updates based on discussion between Sponsor and MGH team for HDRS-17 assessment
Addition of Randomization language/procedures on Day -1 (P1)	Section 5.6.1.2.	Addition by Sponsor based on discussion with MGH team
Update timeframe for telephone check-in with subjects during washout period	Section 5.6.2.4	Updated by Sponsor based on discussion with MGH team
Updates to details and descriptions in the Schedule of Activities	Schedule of Activities	Updated per Sponsor, based on conversations and input by MGH on Statistical

Description of Change Made	Section / Location	Rationale
		Analysis plan and laboratory results
Updates to SAE Reporting procedures	Section 6.11	Based on discussion between Sponsor and MGH team
Addition of the Study Treatment Sequence Table	Section 8.9	Addition by Sponsor
Updates to the amount of time the site has to transcribe information from source to EDC when transcription in real time is not possible	Section 10.2	Based on MGH team's request
Updates to language clarity and spelling	Throughout document	Clarification of protocol language and procedures

SPONSOR PROTOCOL AMENDMENT 02 – SUMMARY OF CHANGES

Description of Change Made	Section / Location	Rationale
Addition of temporal artery temperature readings	Throughout document	Updated per procedures and equipment available within MGH
Addition of re-testing safety laboratory tests (if the value appears to be significantly out of range) at the discretion of the investigator	Througout document	Based on MGH team's request
Addition of NP Sub-Investigators assessing the relation of adverse events to the study drug	Section 6.4	Based on roles and study staffing
Addition of fasting requirements (10 hours) for study visits with safety laboratory testing	Section 5.7.7	Based on MGH team's request – allows for accurate laboratory results
Harmonization of study stopping rules with Data and Safety Monitoring Plan	Section 6.13	Harmonization of protocols across study documentation
Addition of a respiratory belt used when MRI scanning	Throughout relevant sections	Based on MGH team's request
Updated Alcohol screening to be in saliva, urine, or blood	Study Synoposis: Study Activities and within Section 5.7.9 (added)	Decision to test in saliva, urine, or blood based on MGH team's request and discussions with Sponsor
Addition of ±15-minute window for PK sample collection times. This has been updated from the previously established ±10-minute window	Study synoposis, Schedule of Events, Section 5.6.2.6.3, Section 5.7.13	Based on MGH team's request
Addition of additional neuroimaging sessions, when needed, based on the determination of the Investigator and with Sponsor's approval	Section 5.7.13	Based on MGH Team's request
Addition of snack with Lunch or Dinner, if subject is still hungry after eating initial meal	Section 5.6.2.2 and Section 5.6.2.6	Based on discussion with Sponsor and MGH team
Option of HCG Testing in serum if urine is not available at the time of testing	Throughout relevant sections	Based on discussion with Sponsor and MGH team

SPONSOR PROTOCOL AMENDMENT 03 – SUMMARY OF CHANGES

Description of Change Made	Section / Location	Rationale
Fixing spelling, grammar, formatting and wording of sections and headers	Synopsis and throughout the document	For clarity and cohesiveness with the rest of the document
Updating that randomization occurs on Day -1	Synopsis	For harmonization with the rest of the protocol
Updating Exclusion Criteria #18 to read as "Unwillingness" rather than "Willingness"	Synopsis and Section 4.1.2	The way previously written the answer would need to be Yes, however, Exclusion Criteria should always be answered as No
Update to Exclusion Criteria #14 to read as, "Current and during lithium treatment hyponatremia, defined as serum sodium laboratory value outside the standard reference range"	Synopsis and Section 4.1.2	Updated based on clincal judgement from MGH
Updates to Exclusion Criteria #16 to include treatment with Acetaminophen TID.	Synopsis and Section 4.1.2	Updated based on clincal judgement from MGH
Updates to Exclusion Criteria #27 to note "non-removable" medical devices.	Synopsis and Section 4.1.2	The way it was written previously alluded to the fact that removable medical devices were exclusionary
Clarification of the restriction timelines for Xanthine consumption	Synopsis and Section 4.1.2	Clarification needed for subject adherence
Updates to visit window to be +/- 2 days for the In-Clinic Follow-up – Visit #34; Day 23 (P2)	Table 3	Allows for more scheduling flexibility
Updates to language surrounding fasting requirements	Global Update	Updated by Alzamend Team
Updates to language regarding snacks provided at meal time.	Global Update	Updated by Alzamend Team
Clarified langiage surrounding salicylate PK sample collection during the Lithium Carbonate Treament Period	Global Update	Updated by Alzamend Team
Addition of total blood draw volume (603mL)	In relevant sections	Updated by Alzamend Team
Addition of rationale for dose of AL001 given	Section 5.1	To aid in explanation of safety profile for the study drug
Added description for the Health Status Questionnaire	Section 5.7.14	To correct missing information for this questionnaire used in the trial

STUDY SYNOPSIS

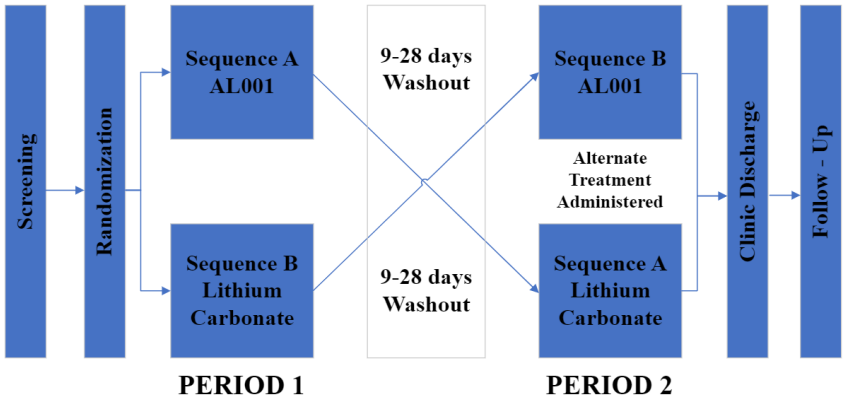
Name of Sponsor/ Company:	Alzamend Neuro, Inc.
Name of Investigational Product:	AL001 (lithium salicylate/L-proline cocrystal)
FDA IND Number:	145442
Indication:	Mild-to-moderate Alzheimer's disease (AD) Stages 2, 3, or 4 per the Food and Drug Administration (FDA) classification
Title of Study:	A Randomized, 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
Sponsor Protocol Number:	AL001-ALZ03
MGB IRB Protocol Number:	2024P003031
Principal Investigator:	Ovidiu Andronesi, MD, PhD
Study Development Phase:	Phase 1 (Healthy Subjects)
Study Deployment and Purpose:	This is a Phase 1 feasibility study to explore AL001 compared to marketed lithium salts dosing requirements. This study, in healthy adult subjects, is intended to be combined/compared for dosing requirements with Phase 2a aggregate data to be obtained for the following additional subject populations: bipolar disorder type 1 (BD1), major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and Alzheimer's disease (AD). Brain is the target organ for therapeutic lithium pharmacologic effects. Based on studies in rodents, AL001 is a lithium delivery system anticipated to enhance lithium absorption and/or persistence in brain tissues thereby potentially resulting in systemic lithium dose-sparing properties and/or enhanced efficacy and safety. Quantitation of differences in brain, brain structures, and plasma lithium concentrations can be expected to permit assessment of the lithium dose-sparing properties of AL001.

	These measures may permit targeting of relative systemic lithium doses in future efficacy/safety trials, and exploration of mechanism-of-action differences between AL001 and lithium carbonate. The purpose of this study is: • To assess lithium brain/plasma pharmacokinetics (PK) of the AL001 oral capsule relative to a marketed lithium carbonate capsule in healthy adult subjects for the purpose of determining potential clinically safe and effective AL001 dosing in future studies. • To characterize AL001 lithium and salicylic acid steady-state plasma PK, and lithium relative to a marketed lithium carbonate capsule. • To characterize differences in brain and brain structure(s) PK behaviors such as absorption and persistence between AL001 capsule and a marketed lithium carbonate capsule. • To characterize safety and tolerability of the tested formulations under the conditions of this study (38% below the pre-determined maximum tolerated dose [MTD] for AL001, at a dose ½ of a usual lithium starting dose of lithium carbonate for treatment of BD1, equivalent to 150 mg lithium carbonate TID).
Endpoints for AL001 and Lithium Carbonate Plasma and Brain Lithium PK, AL001 Plasma Salicylic Acid PK, and Safety	**<u>Primary endpoints for AL001 and lithium carbonate plasma and brain lithium PK are as follows:</u>** • Plasma $AUC_{tau\ ss}$ = Area under the plasma concentration versus time curve from time zero to the end of the 24-hour 3-dose interval at steady-state • Brain $AUC_{tau\ ss}$ = Area under the brain concentration versus time curve from time zero to the end of the 24-hour 3-dose interval at steady-state • Plasma $C_{max\ ss}$ = Maximum plasma concentration at steady-state • Brain $C_{max\ ss}$ = Maximum brain concentration at steady-state • Plasma $t_{max\ ss}$ = Time to reach the maximum plasma concentration at steady-state • Brain $t_{max\ ss}$ = Time to reach the maximum brain concentration at steady-state

	• Plasma $C_{min\ ss}$ = Minimum plasma concentration at steady-state (if at end-of-24 hour dosing interval: C_{trough}) • Brain $C_{min\ ss}$ = Minimum brain concentration at steady-state-(if at end-of-24 hour dosing interval: C_{trough}) • Plasma $t_{min\ ss}$ = Time to reach the minimum plasma concentration at steady-state over 24 hours • Brain $t_{min\ ss}$ = Time to reach the minimum brain 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 swing 24 h = [($C_{max\ ss}$ - $C_{min\ ss}$)/ $C_{min\ ss}$] • 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) • Steady-state conditions will be assessed by applying linear regression of 3 trough analyte plasma concentrations

	presenting on Days 13, 14 and 15, or by other appropriate method(s). • Individual brain structure (e.g., 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 documented as accurate and precise. • Individual brain structure (e.g., hypothalamus, frontal cortex) $AUC_{tau\ ss}$ to total brain $AUC_{tau\ ss}$ ratios will be calculated when documented as accurate and precise. **Exploratory endpoints for AL001 plasma salicylic acid PK are as follows:** Analysis of endpoints for AL001 plasma salicylic acid PK will be the same as the endpoints for AL001 plasma lithium PK (see above). **Exploratory pharmacodynamics endpoints:** Magnetic resonance spectroscopy (MRS) techniques will be also applied to explore brain metabolism, including possible metabolic similarities/differences between treatments. **Safety endpoints are as follows:** • Adverse events (AEs)/serious adverse events (SAEs) • Vital signs (blood pressure, pulse rate, and temporal artery body temperature) • 12-lead electrocardiogram (ECG) • Physical examination • Safety laboratory tests (standard hematology, blood chemistry [clinical chemistry], and urinalysis) • Prevalence of plasma lithium concentrations above 1.2 mEq/L • Prevalence of plasma salicylic acid concentrations above 30 mg/dL
Study Rationale:	Lithium salts are marketed for treatment of patients suffering from bipolar disorder (BD). AL001 is a lithium, salicylate/L-proline crystal-engineered lithium delivery system that in non-clinical studies was shown to enhance and prolong the PK profile of

	lithium in the brain with enhanced efficacy potential in AD rodent models compared to lithium carbonate. This may permit lower lithium systemic exposures during treatment of this historically narrow therapeutic index drug, resulting in enhanced efficacy and safety for treatment of human neurological diseases via a broader therapeutic index. In Alzamend Study AL001-ALZ01, a single AL001 dose of 1050 mg, equivalent in lithium content to 150 mg lithium carbonate, was found to be well tolerated. AL001 1050 mg single dose (5 x 210 mg capsules) evidenced an immediate-release (IR) lithium PK profile that is systemically bioequivalent to a dose-normalized lithium carbonate 300 mg IR capsule. The sample size for the current study is a minimum of 6 subjects. This is not based on any available statistical data for human brain lithium PK. The healthy subject data collected during this study are expected to be combined/compared with analogous results from BD1 subjects, MDD subjects, PTSD subjects, and AD subjects to complete an aggregate total of 30 subjects under multiple INDs. The current study will explore translation of preclinical-observed lithium dose-sparing properties of AL001 compared to lithium salts by assessing the potential for reduced systemic AL001 lithium dose adjustments. Such adjustments may be possible due to enhanced brain lithium PK/bioavailability properties, permitting reduced systemic AL001 lithium doses/exposure. These risk-mitigated lithium doses may then be deployed in efficacy and safety clinical trials to avoid the untoward systemic exposures currently imposed by marketed BD1 lithium products. The need for lithium therapeutic drug monitoring (TDM), as is currently practiced, may thereby be avoided for AL001 formulations.
Study Design:	Historically collected data guided the design of the current study, including the appropriate investigational product (AL001 capsules) and reference product (Lithium Carbonate capsule) doses. Alzamend Study AL001-ALZ01 demonstrated dose-normalized lithium bioequivalence between a single dose of AL001 capsules and a marketed lithium carbonate capsule. Alzamend's multiple-ascending dose (MAD) Study AL001-ALZ02 determined the MTD of AL001 in healthy non-elderly and elderly subjects, and subjects with AD. The determined MTD was observed to be AL001 1680 mg (8 x 210 mg capsules) given three times daily (TID)(total daily dose [TDD] 5040 mg) providing lithium at a lithium carbonate equivalent dose of 240 mg TID (TDD 720 mg), or a lithium citrate syrup, USP (8 mEq/5mL) equivalent dose of 4

	mL; each of these formulations as dosed provide lithium 6.4 mEq TID (TDD 19.2 mEq). A lithium dose 38% below the MTD will be deployed in the current study to facilitate the safety of subjects: AL001 1050 mg (5 x 210 mg capsules) given TID (TDD 3150 mg). This provides lithium at a lithium carbonate equivalent dose of 150 mg TID (TDD 450 mg). A reference listed drug (RLD) lithium carbonate 150 mg capsule will serve as the reference product given TID. Each of these formulations provides lithium 4 mEq TID (TDD 12 mEq). The dose ratio for lithium content of AL001 to lithium carbonate is 7:1. The current study (AL001-ALZ03) design will employ a randomized, balanced, 14-day multiple-dose, open-label, two-treatment, two-period, two-sequence, crossover approach with investigational/reference equivalent lithium doses. Study treatments will be AL001 capsule (investigational) and a lithium carbonate marketed capsule (reference) each dosed with equivalent 4 mEq TID lithium content (TDD 12 mEq). Both investigational and reference products will be dosed TID (8 AM, 2 PM, 8 PM) under fasted conditions (at least 10 hours before the first daily dose; for the second and third daily doses, at least 1 hour before or 4 hours after meals) for 14 days. ^{7}Li magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) of brain lithium distribution will be employed. The Study Flow Chart (Study Schema) is presented in the figure below.  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).
Study Populations:	Six (6) healthy male and female subjects between the age of 18 and 64 years, inclusive, completing both study drug treatment periods with evaluable results.

Study Activities:	Subjects must meet the eligibility criteria and be able to fulfill the study requirements and execute informed consent. **Screening Period** The screening period will take place up to 28 days prior to dosing of the first study drug to determine subject eligibility. After signing informed consent, the procedures described in the Schedule of Activities (Table 3) will be performed (including vital signs, 12-lead ECG, physical examination, safety laboratory tests, urine drug screening, an ethanol test, and baseline MRI). **Treatment Periods, separated by a Washout Period** There will be 2 drug treatment confinement periods (Treatment Period 1 and Treatment Period 2) separated by a washout period (of at least 9 days). Each treatment confinement period will require subjects' participation for 16 days. During each treatment confinement period, subjects will be housed at the study site starting on Day -1 for treatment period study initiation. Subjects will be admitted to the study site at least 16 hours before initial drug administration on Day 1. Procedures described in the Schedule of Activities (Table 3) will be performed during subjects' confinement (Day -1 to Day 15). Treatment Period 1 Days will be identified as (P1), e.g., "Day 1 (P1)". Treatment Period 2 Days will be identified as (P2), e.g., "Day 1 (P2)". Washout days will be identified as "Day 15 (P1)" to "Day 'X' (P1)" since the washout period can vary. Subjects will be randomized into 2 cohorts, identifying their treatment sequence as "A" (AL001 followed by lithium carbonate), or "B" (lithium carbonate followed by AL001), in a 1:1 ratio. Randomization will be conducted on Day -1 (P1), at which time subjects will be assigned to one of the two possible treatment sequences (in a 2x2 study design). After the washout period, subjects will return to the study site to be subsequently dosed with the alternative treatment. (Figure 1) A sufficient number of subjects will be enrolled to fully complete the 6-subject study population target. Drug treatments will be administered according to the randomization plan with approximately 237 mL of non-carbonated water under fasted conditions (at least 10 hours before the first daily dose; for the second and third daily doses, at least 1 hour before or 4 hours after meals) TID at 8 AM, 2 PM, and 8 PM (6 hours apart, within ±10 minutes) starting on Day 1. Additional

	non-carbonated water will be permitted if necessary to complete dosing requirements. Subjects will be seated or in ambulatory posture for 1 hour post-dose for each dose on Days 13 (P1), 14 (P1), 13 (P2), and 14 (P2), except when not feasible such as during neuroimaging procedures. They will be encouraged to be seated or in ambulatory posture for 1 hour post-dose for all other doses. Standardized meals and an optional snack will be provided to subjects. Non-carbonated water is allowed throughout the day as desired except for 1 hour before and 1 hour after drug administration. On Days 13, 14 and 15 of each treatment confinement period, subjects will undergo intensive blood samples collection for lithium and salicylic acid plasma PK assessments, as well as lithium brain neuroimaging PK assessments. There will be no subsequent 8AM dose on Day 15 (P1), the start of the washout period, or on Day 15 (P2). Subjects will be discharged from the study site during the washout period. Washout period will be a minimum of 9 days (+19 days; maximum 28 days) between each drug treatment period. ***PK Blood Sampling and ^{7}Li-MRI-MRS During Each Treatment Period*** Blood samples for establishing each treatment period's baseline lithium and salicylic acid plasma PK values will be obtained on Day 1 (P1) and Day 1 (P2) prior to the 8 AM dosing. Following lithium carbonate capsule treatment and during lithium carbonate intensive PK blood sampling activities, blood samples for salicylic acid plasma PK bioassay will not be collected; salicylic acid plasma PK bioassay will only be conducted following AL001 treatment. For the intensive PK blood sampling (30 samples for each analyte [lithium and salicylic acid]; 60 total samples from Days 13-15 of AL001 treatment period and 30 total samples from Days 13-15 of lithium carbonate treatment period), blood samples will be collected at pre-dose (or 0 h, i.e., within 0.25 hour prior to the 8 AM drug administration on Day 13 (P1), Day 13 (P2), Day 14 (P1) and Day 14 (P2); and at 0.5, 1, 1.5, 2, 3, 4, 5, 6 (before the 2 PM dose), 6.5, 7, 8, 9, 10, 11, 12 (before the 8 PM dose), 12.5, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 hours after the initial 8 AM dose given on Days 14 (P1) and 14 (P2). A ±15-

	minute window for deviation from nominal times will be allowed for collection of PK blood samples. Actual dosing and PK blood sampling times will be recorded for accurate/precise PK analyses. All PK measures/parameter calculations will be based on actual times of sample/data collection. Additional blood samples for plasma PK bioassays may be obtained at the discretion of the Investigator during the trial, particularly to assess the relationship to possible lithium and/or salicylic acid related AEs. These "safety samples" could be sent expedited to a local laboratory with remaining aliquots saved for the bioanalytical laboratory. If there is an early termination from the study of a study subject, blood samples for lithium and salicylic acid plasma PK concentrations will be collected for safety assessments, if possible. The total volume of blood drawn including the volume necessary for the laboratory tests will be up to 603 mL (excluding the ET visit). Specifics regarding blood volumes obtained can be found in the study's lab manual. Adequate blood samples will be collected for both lithium and salicylic acid plasma validated bioassays, with priority given to blood samples for lithium bioassay. These blood samples will be processed at the clinical study site(s) and plasma aliquots shipped to the designated bioanalytical laboratory. Bioassays for lithium and salicylic acid PK concentrations in plasma will be validated as per FDA guidance: • https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf. Lithium brain distribution and mass will be characterized by using ^{7}Li-MRI-MRS on Days 14 (P1) and 14 (P2) at pre-dose (or "0 h", i.e., within 1 hour prior to drug administration) and at 3, 6, 8, 12, 16, 20, 24 hours after the initial 8 AM dose to conduct individual brain structures and whole brain lithium neuroimaging bioassays. A ±20-minute window for deviation from nominal times for lithium neuroimaging will be allowed. Coordination between lithium neuroimaging requirements will give priority to timely collection of PK blood samples, with all PK measures/parameter calculations based on actual times of sample/data collection. If neuroimaging cannot be conducted, PK blood sampling will be continued.

	The lithium brain bioassay method will be validated using a head phantom model prior to clinical deployment. (Iida 2013; Stout 2020) All procedures will be repeated for treatments in the cross-over period of the study. At select imaging timepoints, a respiratory belt may be used to track subject's breathing motion during scanning. Study procedures may be repeated at the discretion of the Investigator to ensure the integrity of the data, subject safety, or to address protocol deviations. The decision to repeat any procedure will be based on clinical judgment and the specific circumstances surrounding the subject's involvement in the study. **Follow-up Period (Post-Treatment Period 2)** During the follow-up period, a safety follow-up clinic visit will occur on Day 23 (P2) ±2 days and a telephone safety follow-up visit will occur on Day 42 (P2) ±2 days after the last dose of Period 2. **Safety Monitoring** Subjects will be carefully monitored for safety throughout the trial. Lithium and salicylate potential adverse events are well characterized and are described below. **Lithium:** Commonly reported and often tolerable side effects of lithium are: headache, mild to moderate nausea and/or vomiting, diarrhea, dizziness, drowsiness, changes in appetite, hand tremors, dry mouth, increased thirst, increased urination, thinning of hair or hair loss, and acne-like rash. Signs of lithium toxicity include severe nausea and vomiting, severe hand tremors, confusion, vision changes, and unsteadiness while standing or walking; rarely-diabetes insipidus. **Salicylate:** Commonly reported and often tolerable side effects of salicylate include dyspepsia, tinnitus, heartburn, epigastric distress and/or nausea; less frequently these present as mild to moderate vomiting, anorexia, or abdominal pain. Signs of salicylate toxicity include severe vomiting, severe gastrointestinal bleeding, and tinnitus/hearing loss. These are generally dose and treatment duration related.
Planned Number of Subjects:	Planned for inclusion are 6 subjects completing both drug treatment periods with evaluable results. It is anticipated that analogous study methods as deployed for this healthy subject study will permit pooling and comparisons of PK

	data from the following subject populations: BD1, MDD, PTSD, and AD subjects (6 completing subjects [with evaluable results] each, total completing aggregate study population: 30 subjects).
Investigational Product:	***Name:*** AL001 Immediate-Release Capsules, 210 mg ***Dosage form/Route of administration:*** Capsule / Oral ***Regimen:*** Multiple doses of AL001 1050 mg (5 x 210 mg capsules) given TID (TDD 3150 mg) for 14 days ***Lot/Batch No.:*** B230078
Reference Product:	***Name:*** Lithium Carbonate Capsules USP, 150 mg ***Dosage form/Route of administration:*** Capsule / Oral ***Regimen:*** Multiple doses of Lithium Carbonate 150 mg (1 x 150 mg capsule) given TID (TDD 450 mg) for 14 days ***Lot/Batch No.:*** 464253A
Study Duration and Subject Confinement:	The total duration of the trial for each subject will be approximately 16 weeks: a 4-week maximum screening period (may take place across multiple days), 2 x 16-day treatment confinement periods with a 9-28 days wash-out period (not confined at study site) in between drug treatments, and a 4-week follow-up period after the 2nd treatment confinement period.
Subject Recruitment/ Participation:	Six healthy adult subjects will be recruited initially; others will be added as needed to complete six subjects with evaluable results from both drug treatment periods. Informative IRB-approved brochures and/or flyers will be made available to interested candidates. Candidate subjects will be informed about the study and allowed to discuss and ask questions about the requirements and procedures related to the study before providing informed consent. Subjects will be monitored for suicidality throughout the study. There will be two (2) drug treatment periods separated by a washout period. For Treatment Period 1, subjects will be admitted to the study site at least 16 hours before dosing, on Day -1 (P1) and will be confined until discharge on Day 15 (P1). There will be a 9- to 28-days washout period between the treatments. For Treatment Period 2, subjects will be admitted to the study site at least 16 hours before dosing, on Day -1 (P2), and will be confined until discharge on Day 15 (P2). Subjects will be asked to return to the clinic on Day 23 (P2) ± 2 days (i.e., 9 days after last dose) for a safety Follow-up visit

	and will have a follow-up telephone call on Day 42 (P2) ± 2 days. Subjects will then be dismissed from the study.
Inclusion Criteria:	1) Healthy subjects ≥ 18 and < 65 years old who are in reasonably good physical and psychological health, as determined by the Investigator's review of medical and surgical history, physical examination (including neurological examination), 12-lead ECG, vital signs, and clinical laboratory tests. 2) Assessment of subject's mental health status will be conducted to avoid enrolling subjects who are on the verge of a manic or depressive episode. Affective stability, defined by a Young Mania Rating Scale (YMRS) rating of < 8 and a Hamilton Depression Rating Scale (HDRS-17) rating of ≤ 7 at the Screening visit and on Day -1 (P1). Assessment of subject's suicidal ideation and behavior (SI/B) using the Columbia-Suicide Severity Rating Scale (C-SSRS) will be conducted to avoid enrolling subjects with concerning results, defined as a lifetime history of a suicide attempt, past year level 4 or higher suicidal ideation on the C-SSRS, or past month suicidal ideation of any kind. The "Lifetime/Recent" version will be used at screening and the "Since Last Visit" version will be used subsequently. 3) Able to understand and follow instructions during the study as determined by the Investigator. 4) Willing to follow study procedures. 5) Willing and able to adhere to study restrictions and to be confined at the clinical research center per protocol requirements. 6) Any gender, race, or ethnicity. 7) Able to understand and provide written informed consent. 8) Males (non-vasectomized and vasectomized) must agree to use barrier contraception during the study until after Treatment Period 2 in-clinic follow-up visit on Day 23 (P2). 9) Females must meet one of the following criteria: Is of childbearing potential and agrees to use an acceptable contraceptive method. Acceptable contraceptive methods include:

	a) Abstinence from heterosexual intercourse from the Screening visit through to at least 30 days after the last dose of the second study drug on Day 14 (P2). b) One of the following *highly-effective* contraceptive methods, used from at least 28 days prior to the Screening visit through to at least 30 days after the last dose of the second study drug on Day 14 (P2). i. Systemic contraceptives (combined birth control pills, injectable/implant/insertable hormonal birth control products, or transdermal patch). ii. Intrauterine device (with or without hormones). iii. Male partner vasectomized at least 6 months prior to the Screening visit. c) One of the following double-barrier contraceptive methods, used from the Screening visit through to at least 30 days after the last dose of the second study drug on Day 14 (P2): i. Male condom used simultaneously with diaphragm plus spermicide. ii. Male condom used simultaneously with cervical cap plus spermicide. Or Is of non-childbearing potential, defined as surgically sterile (i.e., has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation), or is in a postmenopausal state (i.e., at least 1 year without menses prior to the Screening visit). 10) Able to communicate in English, including speaking, reading, and writing. 11) Body mass index (BMI) within 18.0 to 30.0 kg/m^2, inclusive, and body weight of at least 50 kg at the time of Screening. 12) ECG recording, after at least 5 minutes of rest in a supine position without clinically significant abnormalities as determined by the Investigator.
Exclusion Criteria:	1) Clinically significant abnormalities detected by medical history, physical examination, vital sign measurements, ECG findings, or clinical laboratory findings (as determined by the Investigator) that may affect the safety or successful participation of the subject. Specifically, evidence of

	clinically significant hematological, renal, endocrine, pulmonary, cardiovascular, dermatologic, muscular, or allergic disease or disorder (including drug allergies, but *excluding* untreated, asymptomatic, seasonal allergies at time of dosing) that may affect the safety or successful participation of the subject. Any history of drug hypersensitivity, asthma (with the exception of childhood asthma), urticaria or other severe allergic diathesis. 2) Presence or history of any disorder that may prevent the successful completion of the study. 3) Other severe acute, chronic, or historical medical or psychiatric condition or laboratory abnormality or social circumstance that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study. 4) History of seizure disorder and/or severe head trauma (other than a single childhood febrile seizure). 5) History or presence of gastrointestinal disease including chronic gastritis, peptic ulcers, inflammatory bowel disease, hemorrhagic gastritis, or duodenitis. 6) History or presence of acute or chronic liver disease as determined by the Investigator. 7) Any surgical or medical condition that may interfere with the absorption, distribution, metabolism, or excretion of the study treatments. 8) Any history of frequent headache or migraine. 9) Kidney disease (eGFR < 60 mL/minute/1.73 m^2). 10) Uncontrolled tachy/brady arrhythmias, atrial fibrillation, or coronary heart failure. 11) Systemic related exclusions: a) Active cancer (except squamous cell and basal skin cancers) requiring chemo- or radiation therapy. b) Positive test results for HIV, HBV, or HCV (unless quantitative PCR negative for HCV) at Screening.

	c) Uncontrolled hypertension with a sustained blood pressure >160/100 mmHg at Screening or at check-in on Day -1 (P1). d) Fever (body temperature >101.4°F [38.5°C]), acute upper respiratory, or any other infections at Screening or at check-in on Day -1 (P1). 12) Psychiatric or neurological illnesses (e.g., depression, schizophrenia or other psychotic syndromes, Parkinson's disease and related movement disorders, seizure disorder, and myasthenia gravis). 13) Treatment with haloperidol, antipsychotics, monoamine oxidase inhibitors, neuromuscular blocking agents. Subjects who have ever received immunosuppressant treatment (excluding topical or oral corticosteroids taken 1 year and 5 years before Screening, respectively). 14) Current and during lithium treatment hyponatremia, defined as serum sodium laboratory value outside the standard reference range. 15) The use of any medication on a chronic basis with the exception of hormonal contraceptives for females of childbearing potential. An appropriate drug free period will be required for prescription or over-the-counter (OTC) drugs to washout, particularly of any especially long half-life drugs (see exclusion criteria 16 and 17 below for relevant details). 16) The use of any medication (OTC, prescription medication, vitamins, and herbal supplements) within 14 days prior to the Screening visit and 14 days prior to Day -1 (P1) – or at least 6 times the respective elimination half-life rather than 14 days, whichever is longer – through the completion of the second study drug treatment on Day 14 (P2). Contraception may be continued. Acetaminophen may be concomitantly used at the discretion of the Investigator (up to 1000 mg TID). Non-medicated opthalmic products (for lubrication and comfort) may also be permitted at the discretion of the Investigator. (Section 5.7.17) 17) Prescribed or OTC use of a salicylate-containing product other than low dose aspirin for cardioprotection (e.g., aspirin, magnesium salicylate, bismuth sub-salicylate, salicylazosulfapyridine [sulfasalazine]) from 1 week before first dose of the first study drug on Day 1 (P1) to 1 week after

	last dosing of the second study drug on Day 14 (P2); any other prescribed anticoagulant medication. (Section 5.7.17) 18) Unwilling to refrain from consumption of poppy seeds or quinine (tonic water) 48 hours prior to check-in on Day -1 (P1) and throughout the course of the study. 19) Aspirin/nasal polyposis/asthma syndrome. 20) Female who is breastfeeding. 21) Female who is pregnant according to the pregnancy test at Screening or on Day -1 (P1); female planning to become pregnant during the study. 22) History of adverse or hypersensitivity reaction to lithium, aspirin, salicylate, L-proline, or any investigational or reference article excipient. 23) Drug/alcohol abuse: a) History of drug abuse (barbiturate, amphetamine, benzodiazepine, cocaine, opiates and cannabis) within the last 12 months or a positive urine drug screen at Screening or Day -1 (P1). b) Admitted alcohol abuse or history of alcohol use that may interfere with the subject's ability to comply with the protocol requirements or positive ethanol (alcohol) test at Screening or Day -1 (P1). c) More than moderate current alcohol consumption. Subjects will be advised to consume no more than 2 units of alcohol per day and completely abstain from 72 hours prior to any study visit (1 unit is equal to approximately 10 g of pure alcohol, [250 mL] of beer [5%], 1 small glass [100 mL] of wine [12%], or 35 mL of spirits [35%]). 24) Demonstrating excess xanthine consumption (e.g., ingests more than 5 cups of coffee or equivalent per day). Also, subject is not willing to refrain from xanthine products for 48 hours prior to check-in on Day -1 (P1) until discharge from Period 2 treatment on Day 15 (P2). The subject is not willing to refrain from grapefruit, pomelo, Seville orange products or juice within 14 days prior to check-in on Day -1 (P1) until discharge from Period 2 treatment on Day 15 (P2). Exceptions may be made on a case-by-base basis following agreement by the Principal Investigator and the Sponsor. 25) Participation in a clinical trial and receipt of an investigational medication within 30 days or 5 half-lives (if known),

	whichever is greater, prior to the first dose of the current study drug. 26) History of untreated thyroid dysfunction (due to potential lithium drug-disease interaction). 27) Screening MRI-related exclusion criteria: intracranial mass, evidence of other anatomical findings that might affect safety or causes of cognitive/behavioral impairment as assessed by a qualified neurologist. Subjects must not have any implantable medical device (e.g., aneurysm clip, vagus nerve stimulator, cardiac pacemaker) or be reliant on a non-removable medical device (e.g., insulin pump) unless that device is certified as MRI compatible. Known intolerability to MRI neuroimaging procedures. 28) Subjects with any past apparent suicide attempt or suicidal behavior, including those with a lifetime history of suicide attempt(s) or a past year level 4 or higher SI/B (C-SSRS) or past month SI/B (C-SSRS) of any kind.
Statistical Analysis:	**<u>Sample Size</u>** The objective of this study is to estimate relative bioavailability of PK parameters of the AL001 capsule as compared to a marketed lithium carbonate capsule and precision of the estimate. A sample size of 6 completing subjects with evaluable results is selected. The sample size is not based upon any available statistical data for human brain lithium pharmacokinetics. The number of subjects is also not based on statistical power considerations. The estimate of the within-subject standard deviation of log transformed AUC of 0.065, as observed in Alzamend study AL001-ALZ01, was used in calculation of precision. The following table provides probable confidence limits and confidence width for several possible absolute bioavailability estimates, based upon AUC, including the hypothesized value of 95%. If the absolute bioavailability estimate is 95%, the 95% confidence interval will be no wider than (83.6%, 108.3%) with tolerance probability of 80%. Minimum relative precision, defined as the relative distance of the lower confidence limit from the estimate, is 12%. Probable Confidence Intervals for Several Absolute Bioavailability Estimates based on AUC are:

Bioavailability Estimate	Lower Limit of Probable CI	Upper Limit of Probable CI	Probable CI Width
40%	35.2%	45.6%	10.4%
50%	44.0%	57.0%	13.0%
60%	52.8%	68.4%	15.6%
70%	61.6%	79.8%	18.2%
80%	70.4%	91.2%	20.8%
90%	79.2%	102.6%	23.4%
95%	83.6%	108.3%	24.7%

Probable Confidence Intervals for Several Absolute Bioavailability Estimates based on C_{max} are:

Bioavailability Estimate	Lower Limit of Probable CI	Upper Limit of Probable CI	Probable CI Width
40%	30.8%	52.0%	21.2%
50%	38.5%	65.0%	26.5%
60%	46.2%	78.0%	31.8%
70%	53.9%	91.0%	37.1%
80%	61.6%	104.0%	42.4%
90%	69.3%	117.0%	47.7%
95%	73.2%	123.5%	50.4%

The estimate of the with-in subject standard deviation of log transformed C_{max} of 0.135, as observed in Alzamend study AL001-ALZ01, was used in the calculation of precision.

Both the investigational product and the reference product are expected to provide at least 95% lithium bioavailability *per os* due to their highly soluble, highly permeable properties.

Disposition of Subjects

The number of subjects in each analysis set will be summarized by sequence-cohort and by treatment group. In addition, the number of subjects in the Randomized and Safety Analysis Sets who complete the clinical trial and those who prematurely discontinue, including the reason for premature discontinuation, will be

summarized by treatment group for each randomized cohort and overall.

Demographic & Baseline Characteristics

Descriptive statistics for demographic (e.g., age, race, and sex) and baseline characteristics (e.g., body height, body weight, BMI) will be presented by treatment group for each cohort and overall.

Populations for Analysis

Screened Analysis Set: The Screened Analysis Set will include all subjects who have signed the inform consent form.

Randomized Analysis Set: The Randomized Analysis Set will include all subjects who are randomized within one of the sequence cohorts.

Safety Analysis Set: The Safety Analysis Set will include all subjects in the Randomized Analysis Set who receive any dose of study drug. This analysis set will be utilized for all safety analyses.

Pharmacokinetic Analysis Set: For the purpose of relative bioavailability/bioequivalence testing, the PK Analysis Set will include all subjects in the Safety Analysis Set who receive AL001 capsules or lithium carbonate capsules and have at least one complete plasma or brain structures/whole brain PK profile.

Pharmacodynamics Analysis Set: For the purpose of relative bioavailability/bioequivalence testing, the Pharmacodynamics Analysis Set will include all subjects in the Safety Analysis Set who receive AL001 capsules or lithium carbonate capsules and have at least one complete plasma or brain structures/whole brain PK profile.

General Considerations

Demographic and baseline characteristics (including age, sex, weight, etc.) will be summarized descriptively using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Continuous variables will be summarized using the number of observations, mean, standard deviation, minimum, median, and maximum. PK variables will also be summarized using the geometric mean (i.e., the mean calculated on the $\log_e$ scale transformed back to the original scale). Categorical variables will be summarized using frequencies and the corresponding percentage.

	Pharmacokinetics A non-compartmental analysis with linear trapezoidal AUC_{tau} approximations will be used for PK analyses. Plasma concentrations of lithium and salicylic acid, lithium brain structures/whole brain measured and PK values, individual subject derived PK measures/parameters are to be listed by subject identifier, nominal and actual times of sampling, and summarized by nominal time point and by treatment including number of observations (N), arithmetic mean (mean), standard deviation (SD), geometric mean, minimum (min), median, maximum (max), and coefficient of variation (CV%) for AL001 capsule and lithium carbonate capsule treatments. Lithium statistical analysis for measures/parameters will be performed to compare AL001 capsule to a lithium carbonate capsule with a mixed model analysis of variance (ANOVA) using General Linear Model (GLM) procedure for the following PK measures/parameters; the two-sided 90% CI of the ratio of geometric means will be calculated for the above listed endpoints for AL001 and lithium carbonate plasma and brain structures/whole brain lithium PK. Details can be found in the Pharmacokinetic Analysis Plan and the Statistical Analysis Plan (SAP). The relative bioavailability and other comparisons between AL001 capsule and lithium carbonate capsule will use PK and statistical conventions consistent with FDA guidance for bioequivalence testing: (see links below) • https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-approaches-establishing-bioequivalence • https://www.fda.gov/files/drugs/published/Bioavailability-and-Bioequivalence-Studies-Submitted-in-NDAs-or-INDs-%E2%80%94-General-Considerations.pdf • https://www.fda.gov/media/121311/download ANOVA model: Repeated measures with fixed factors: sequence, period and treatment; Random factor: subject (nested within sequence). Measures will be $\log_e$ transformed with 90% confidence interval (CI) for the differences between treatments. These will be calculated on the $\log_e$ scale and then transformed back to the original scale. If the 90% CI on the original scale is contained within the interval of 80.0% to 125.0%, then equivalence will be concluded.

	In order to assess whether PK steady-state has been approximately achieved, descriptive statistics for 3 trough measurements of lithium and salicylic acid will be presented for Day 13 (8 AM), Day 14 (8 AM) and Day 15 (8 AM, the 24-hour sample for the last dosing day) of each study drug treatment period (P1 and P2); these will be presented and a linear regression method will be applied to determine statistical similarity. Alternative approaches to estimate achievement of steady-state conditions may be used, as appropriate. **Pharmacodynamics** Magnetic resonance spectroscopy (MRS) techniques will be also applied to explore brain metabolism, including possible metabolic similarities/differences between treatments. **Safety** Prevalence of plasma lithium concentrations above 1.2 mEq/L and plasma salicylic acid concentrations above 30 mg/dL will be documented. Baseline for each safety parameter is defined as the last value collected prior to the first dose of each study drug. In order to evaluate the safety and tolerability of AL001 capsule and lithium carbonate capsule under the conditions of this study, descriptive statistics will be presented by treatment group for each sequence cohort and overall for the following: • Proportion of subjects with treatment-emergent adverse events (TEAEs) • Proportion of subjects with serious adverse events (SAEs) • Proportion of subjects with TEAEs that lead to premature discontinuation • Change from baseline for each safety laboratory test • Proportion of subjects with abnormal values for each safety laboratory test • Change from baseline for each ECG parameter • Proportion of subjects with abnormal values for each ECG parameter Planned summaries of safety endpoints will be provided in detail in the Statistical Analysis Plan (SAP).

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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1. INTRODUCTION

1.1. Background

Alzamend Neuro, Inc. is developing a proprietary technology: a lithium, salicylate, and L-proline crystal-engineered lithium delivery system for treatment of mild and moderate Alzheimer's disease (AD) and for other neurodegenerative, neurological and neuropsychiatric conditions. Crystal engineered lithium is a novel formulation that, based on preclinical data in the mouse, may favorably alter lithium brain pharmacokinetics (penetration through the blood-brain barrier and persistence) in humans. This may serve to reduce systemic exposure and the potential for adverse events (AEs). This novel lithium technology will be referred to as AL001 in this clinical study protocol. Lithium salts in solid and liquid dosage forms are marketed for treatment of patients suffering from bipolar I disorder (BD1). (FDA Lithium Carbonate Label)

The current study will explore translation of preclinical-observed lithium dose-sparing properties of AL001 compared to lithium salts by assessing the potential for reduced systemic AL001 lithium dose adjustments. Such adjustments may be possible due to enhanced brain lithium pharmacokinetics (PK)/ bioavailability properties, permitting reduced systemic AL001 lithium doses/exposure. These risk-mitigated lithium doses may then be deployed in efficacy and safety clinical trials to avoid the untoward systemic exposures currently imposed by marketed BD1 lithium products. The need for lithium therapeutic drug monitoring (TDM), as is currently practiced, may thereby be avoided for AL001 formulations.

The AL001-ALZ03 study is designed to quantitate differences in lithium brain-to-plasma exposure in healthy adult subjects between AL001 capsule and a marketed lithium carbonate capsule for the purpose of contributing to an aggregate database of analogously studied brain-plasma assessments that include data from healthy subjects and multiple additional neurodegenerative, neurological and neuropsychiatric disorders. Currently, AL001 is targeted for treatment of AD, BD1, major depressive disorder (MDD), and post-traumatic stress disorder (PTSD). It is anticipated that this study design may help target appropriate AL001 lithium systemic dosing for these indications in future studies. Using this study design, comparable target organ (brain) lithium concentrations may be quantitated between AL001 capsule, a marketed lithium carbonate capsule and, by equivalence, lithium citrate syrup, USP, to guide reduction in AL001 lithium oral dose amounts and, therefore, reduction in systemic lithium exposure for a comparable efficacy outcome.

1.2. Purpose of Current Study

The purpose of the current study is to investigate the potential dose-sparing properties of AL001 capsule compared to a marketed lithium carbonate capsule for targeting of systemic doses in efficacy/safety clinical trials involving subjects with neurodegenerative, neurological and neuropsychiatric conditions. This study will characterize plasma and brain lithium concentrations in healthy adult subjects. It is designed to complement (with healthy subject comparative values) analogous studies of BD1 subjects, MDD subjects, PTSD subjects, and AD subjects (under multiple INDs for AL001). This study's sample size (a total of 6 subjects who completed both drug treatments with evaluable results) is not based on any available statistical data for human

brain lithium PK. The acquired healthy subject data is expected to be combined/compared with analogous results from BD1 subjects, MDD subjects, PTSD subjects, and AD subjects (6 subjects each) to complete an aggregate study population of 30 subjects.

Alzamend Study AL001-ALZ01 was a first-in-human clinical trial involving healthy subjects. This initial study compared AL001 immediate-release capsule to a well characterized and marketed lithium carbonate immediate-release capsule. AL001 was found to be dose-normalized bioequivalent for lithium in plasma to lithium carbonate. A subsequent multiple-ascending dose (MAD) clinical study AL001-ALZ02 identified the maximum tolerated dose (MTD) of AL001 in healthy non-elderly and elderly subjects and in subjects with AD as: AL001 1680 mg (8 x 210 mg capsules) given TID, total daily dose (TDD) 5040 mg. This provides lithium at a lithium carbonate equivalent dose of 240 mg TID (TDD 720 mg), or a lithium citrate syrup, USP (8 mEq/5mL) equivalent dose of 4 mL; each of these formulations, as dosed, provide lithium 6.4 mEq TID, or a TDD of 19.2 mEq.

A lithium dose 38% below the MTD will be deployed in the current study to facilitate the safety of subjects: AL001 1050 mg (5 x 210 mg capsules) given TID (TDD 3150 mg). This provides lithium at a lithium carbonate equivalent dose of 150 mg TID (TDD 450 mg). A reference listed drug (RLD) lithium carbonate 150 mg capsule will serve as the reference product given TID (TDD 450 mg). Each of these formulations provides lithium 4 mEq TID, or a TDD of 12 mEq. The dose ratio for lithium content of AL001 to lithium carbonate is 7:1.

The two essential (primary) study purposes are, therefore:

1) To evaluate the safety and tolerability of AL001 under multiple-dose, steady-state conditions in healthy adult subjects under the conditions of this study.

2) To explore the potential lithium dose-sparing properties of AL001 capsule compared to a marketed lithium carbonate capsule for targeting of systemic doses in future efficacy/ safety trials.

2. STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To evaluate differences in brain and/or brain structure lithium PK relative to plasma PK for AL001 capsule compared to 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.
Primary	
To evaluate the safety and tolerability of AL001 under multiple-dose, steady-state conditions in healthy adult subjects under the conditions of this study.	• Vital signs (blood pressure, heart rate, and temporal artery body temperature) • 12-lead electrocardiogram (ECG) • Physical examination • Safety laboratory tests (hematology, chemistry [including TSH, vitamin B12, and Mg], 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 salicylic acid PK under the conditions of this study.	Analysis of exploratory endpoints for AL001 plasma salicylic acid 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.

3. INVESTIGATIONAL PLAN AND STUDY DESIGN

3.1. Overall Study Design

The current study was designed based on results of earlier clinical studies. Alzamend Study AL001-ALZ01 demonstrated dose-normalized lithium bioequivalence between AL001 capsule and a marketed lithium carbonate capsule. Alzamend Study AL001-ALZ02 determined the MTD of AL001 in healthy non-elderly and healthy elderly subjects, and subjects with AD. Based on the results of Study AL001-ALZ02 , the current study (AL001-ALZ03) will employ a randomized, balanced, open-label, 14-day multiple-dose, two-treatment (AL001 capsule and a marketed lithium carbonate capsule), two-period, two-sequence, crossover design.

Study treatments will be AL001 210 mg capsule (investigational product) dosed at 1050 mg TID (5 x 210 mg capsules) and a marketed lithium carbonate 150 mg capsule (reference product) dosed TID. Both investigational and reference products will be dosed orally for 14 days while subjects are confined at the study site. ^{7}Li magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) of brain lithium distribution/pharmacokinetics will be employed on Days 14 to 15 of each study drug treatment period.

A Study Schema representing the crossover drug treatment periods is presented in Figure 1. The study consists of 5 periods (refer to the schedule of activities in Section 5.6 and Table 3 for greater detail):

- **Screening Period** – up to 28 days prior to dosing of the first study drug treatment.

  Activities to be performed during this period include: obtain informed consent; evaluate inclusion/exclusion criteria; collect demographic information; collect medical/surgical history and prior/concomitant medications; conduct a physical examination (including a brief neurological examination); collect body height/weight measurements; collect vital signs (blood pressure, heart rate, and temporal artery body temperature); 12-lead ECG; collect biological samples for safety laboratory assessments; HIV/HBV/HCV screen; urine drug screening; ethanol (alcohol) test; plasma pregnancy test (for females of childbearing potential); brain MRI including lithium baseline and tolerability assessment.

- **Two Treatment Periods, separated by a Washout Period** – 16 days x 2 with a ≥9 (+19; maximum 28)-day washout between study drug treatment periods:

  There will be 2 drug treatment periods separated by a washout period. Period 1 Days will be identified as (P1), e.g., Day 1 (P1). Period 2 Days will be identified as (P2), e.g., Day 1 (P2). Washout days will be identified as Day 15 (P1) to Day "X" (P1) since the washout period can vary.

  Subjects will be admitted to the study site on Day -1 of each study drug treatment period for check-in. Subjects will remain confined until discharged on Day 15. The first study dose of each period will be administered on the morning of Day 1 and continued for 14 days. A pre-initial dose blood sample will be obtained for lithium and salicylic acid

bioassays on Day 1 of each drug treatment. Safety and plasma/brain PK data collection procedures will be subsequently conducted on Days 13-15. Subjects will receive 14 days of TID dosing with assigned study medication from Days 1 to 14, with completion of treatment period requirements on Days 15 of each study drug treatment period. Trough (C_{min}) blood samples for lithium (AL001 and lithium carbonate) and salicylic acid (AL001 only) bioassays will be obtained prior to the first dose on Day 13 followed by intensive blood sampling to be obtained over 24 hours starting from just before the first daily dose on Day 14. Neuroimaging over 24 hours for brain and brain structure lithium concentration measurements will be obtained concurrently with the intensive blood sampling on Day 14, ending on Day 15 of each study drug treatment period. If neuroimaging cannot be conducted, blood sampling will be continued. Subjects will be discharged on Day 15 of each period.

- **Follow-up Period** – 4 weeks

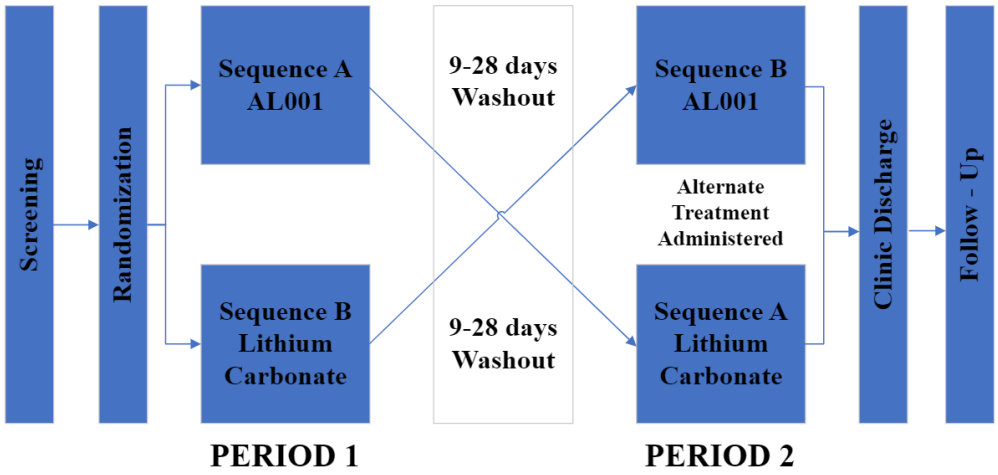
  Subjects will be followed up after discharge from the study site on Day 15 (P2) with a post-treatment clinic visit on Day 23 (P2) ±2 days and a post-treatment telephone call on Day 42 (P2) ±2 days.

Each subject will participate in the study for approximately 16 weeks.

The study schema is presented in Figure 1.

The schedule of activities of the study is described in Table 3 and Section 5.6

Figure 1: Study Schema



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).

PK measurements from 0-24 hours will be obtained to definitively characterize PK diurnal variation under steady-state conditons, particularly in plasma relative to brain and brain structures.

Circadian changes in pharmacokinetics and pharmacodynamics (drug target) are two essential sources of time-varying drug effects. Pharmacokinetics determines the drug concentrations (exposure) in target tissues/organs, thereby impacting drug efficacy and toxicity. Chronopharmacokinetics is defined as dosing-time dependent and predictable rhythmic variations in parameters used to characterize the pharmacokinetics (or the bioavailability) of a drug. (Erkekoglu 2012)

3.2. Discussion of Study Design, including the Choice of Control Group

3.2.1. Choice of Study Design

The randomized crossover design is often deployed for PK comparisons between test articles to utilize the statistical discrimination characteristics of paired (same-subject) comparisons. Plasma and brain lithium PK are to be studied under steady-state conditions so that the results can be optimally relevant clinically. It is expected that lithium will be administered chronically for targeted neurodegenerative, neurological and neuropsychiatric indications.

3.2.2. Choice of Control Group, Dosing, and Safety

The MTD in healthy non-elderly subjects, healthy elderly subjects, and subjects with AD was determined in clinical study AL001-ALZ02 and will be reduced by 38% in the current study as safe and suitable. Lithium content from the lithium carbonate comparator will be the same as for AL001, at a dose of 150 mg TID for 14 days. Primary PK endpoints are objective measures and therefore inclusion of a placebo control group or blinding of study personnel and/or subjects is not appropriate for this study.

4. STUDY POPULATION AND RECRUITMENT

The study population will be comprised of 6 healthy adult subjects between the age of ≥ 18 and < 65 years who are willing to adhere to the study requirements/restrictions, understand, and sign the informed consent and meet the inclusion and exclusion criteria.

Subjects will be recruited from the surrounding community, the study site's database, a physician referral network and/or other appropriate venues. Potential subjects will be made aware of the opportunity to participate in this study via informative IRB-approved brochures and/or flyers. Subjects will be allowed to discuss and ask questions about the requirements and procedures related to the study before providing informed consent. Subjects will be encouraged to discuss the study with their healthcare provider. Subjects will be assigned a unique Subject Screening Number (e.g., HC01) after providing informed consent.

4.1. Inclusion/Exclusion Criteria

4.1.1. Inclusion Criteria

1) Healthy subjects ≥ 18 and < 65 years old who are in reasonably good physical and psychological health as determined by the Investigator's review of medical and surgical history, physical examination (including neurological examination), 12-lead ECG, vital signs, and clinical laboratory tests.

2) Assessment of subject's mental health status will be conducted to avoid enrolling subjects who are on the verge of a manic or depressive episode. Affective stability, defined by a Young Mania Rating Scale (YMRS) rating of < 8 and a Hamilton Depression Rating Scale (HDRS-17) rating of ≤ 7 at the Screening visit and on Day -1 (P1). Assessment of subject's suicidal ideation and behavior (SI/B) using the Columbia-Suicide Severity Rating Scale (C-SSRS) will be conducted to avoid enrolling subjects with concerning results, defined as a lifetime history of a suicide attempt, past year level 4 or higher suicidal ideation on the C-SSRS, or past month suicidal ideation of any kind. The "Lifetime/Recent" version will be used at screening and the "Since Last Visit" version will be used subsequently.

3) Able to understand and follow instructions during the study as determined by the Investigator.

4) Willing to follow study procedures.

5) Willing and able to adhere to study restrictions and to be confined at the clinical research center per protocol requirements.

6) Any gender, race, or ethnicity.

7) Able to understand and provide written informed consent.

8) Males (non-vasectomized and vasectomized) must agree to use barrier contraception during the study until after Treatment Period 2 in-clinic follow-up visit on Day 23 (P2).

9) Females must meet one the of the following criteria:

   Is of childbearing potential and agrees to use an acceptable contraceptive method. Acceptable contraceptive methods include:

   a. Abstinence from heterosexual intercourse from the Screening visit through to at least 30 days after the last dose of the second study drug on Day 14 (P2).

   b. One of the following *highly-effective* contraceptive methods, used from at least 28 days prior to the Screening visit through to at least 30 days after the last dose of the second study drug on Day 14 (P2).

      i. Systemic contraceptives (combined birth control pills, injectable/implant/ insertable hormonal birth control products, or transdermal patch).

      ii. Intrauterine device (with or without hormones).

      iii. Male partner vasectomized at least 6 months prior to the Screening visit.

   c. One of the following double-barrier contraceptive methods, used from the Screening visit through to at least 30 days after the last dose of the second study drug on Day 14 (P2):

      i. Male condom used simultaneously with diaphragm plus spermicide.

      ii. Male condom used simultaneously with cervical cap plus spermicide.

   Or

   Is of non-childbearing potential, defined as surgically sterile (i.e., has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation), or is in a postmenopausal state (i.e., at least 1 year without menses prior to the Screening visit).

10) Able to communicate in English, including speaking, reading, and writing.

11) Body mass index (BMI) within 18.0 to 30.0 kg/m^2, inclusive, and body weight of at least 50 kg at the time of Screening.

12) ECG recording, after at least 5 minutes of rest in a supine position without clinically significant abnormalities as determined by the Investigator.

4.1.2. Exclusion Criteria

1) Clinically significant abnormalities detected by medical history, physical examination, vital sign measurements, ECG findings, or clinical laboratory findings (as determined by the Investigator) that may affect the safety or successful participation of the subject. Specifically, evidence of clinically significant hematological, renal, endocrine, pulmonary, cardiovascular, dermatologic, muscular, or allergic disease or disorder (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing) that may affect the safety or successful participation of the subject. Any history of drug

hypersensitivity, asthma (with the exception of childhood asthma), urticaria or other severe allergic diathesis.

2) Presence or history of any disorder that may prevent the successful completion of the study.

3) Other severe acute, chronic, or historical medical or psychiatric condition or laboratory abnormality or social circumstance that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

4) History of seizure disorder and/or severe head trauma (other than a single childhood febrile seizure).

5) History or presence of gastrointestinal disease including chronic gastritis, peptic ulcers, inflammatory bowel disease, hemorrhagic gastritis, or duodenitis.

6) History or presence of acute or chronic liver disease as determined by the Investigator.

7) Any surgical or medical condition that may interfere with the absorption, distribution, metabolism, or excretion of the study treatments.

8) Any history of frequent headache or migraine.

9) Kidney disease (eGFR < 60 mL/minute/1.73 m^2).

10) Uncontrolled tachy/brady arrhythmias, atrial fibrillation, or coronary heart failure.

11) Systemic related exclusions:

    a) Active cancer (except squamous cell and basal skin cancers) requiring chemo- or radiation therapy.

    b) Positive test results for HIV, HBV, or HCV (unless quantitative PCR negative for HCV) at Screening.

    c) Uncontrolled hypertension with a sustained blood pressure >160/100 mmHg at Screening or at check-in on Day -1 (P1).

    d) Fever (body temperature >101.4°F [38.5°C]), acute upper respiratory, or any other infections at Screening or at check-in on Day -1 (P1).

12) Psychiatric or neurological illnesses (e.g., depression, schizophrenia or other psychotic syndromes, Parkinson's disease and related movement disorders, seizure disorder, and myasthenia gravis).

13) Treatment with haloperidol, antipsychotics, monoamine oxidase inhibitors, neuromuscular blocking agents. Subjects who have ever received immunosuppressant treatment (excluding topical or oral corticosteroids taken 1 year and 5 years before Screening, respectively).

14) Current and during Lithium treatment hyponatremia, defined as serum sodium laboratory value outside the standard reference range.

15) The use of any medication on a chronic basis with the exception of hormonal contraceptives for females of childbearing potential. An appropriate drug free period will be required for prescription or over-the-counter (OTC) drugs to washout, particularly of any especially long half-life drugs (see exclusion criteria 16 and 17 below for relevant details).

16) The use of any medication (OTC, prescription medication, vitamins, and herbal supplements) within 14 days prior to the Screening visit and 14 days prior to Day -1 (P1) – or at least 6 times the respective elimination half-life rather than 14 days, whichever is longer – through the completion of the second study drug treatment on Day 14 (P2). Contraception may be continued. Acetaminophen may be concomitantly used at the discretion of the Investigator (up to 1000 mg TID). Non-medicated opthalmic products (for lubrication and comfort) may also be permitted at the discretion of the Investigator. (Section 5.7.17)

17) Prescribed or OTC use of a salicylate-containing product other than low dose aspirin for cardioprotection (e.g., aspirin, magnesium salicylate, bismuth sub-salicylate, salicylazosulfapyridine [sulfasalazine]) from 1 week before first dose of the first study drug on Day 1 (P1) to 1 week after last dosing of the second study drug on Day 14 (P2); any other prescribed anticoagulant medication. (Section 5.7.17)

18) Unwilling to refrain from consumption of poppy seeds or quinine (tonic water) 48 hours prior to check-in on Day -1 (P1) and throughout the course of the study.

19) Aspirin/nasal polyposis/asthma syndrome.

20) Female who is breastfeeding.

21) Female who is pregnant according to the pregnancy test at Screening or on Day -1 (P1); female planning to become pregnant during the study.

22) History of adverse or hypersensitivity reaction to lithium, aspirin, salicylate, L-proline, or any investigational or reference article excipient.

23) Drug/alcohol abuse:

    a) History of drug abuse (barbiturate, amphetamine, benzodiazepine, cocaine, opiates and cannabis) within the last 12 months or a positive urine drug screen at Screening or Day -1 (P1).

    b) Admitted alcohol abuse or history of alcohol use that may interfere with the subject's ability to comply with the protocol requirements or positive ethanol (alcohol) test at Screening or Day -1 (P1).

c) More than moderate current alcohol consumption. Subjects will be advised to consume no more than 2 units of alcohol per day and completely abstain from 72 hours prior to any study visit (1 unit is equal to approximately 10 g of pure alcohol, [250 mL] of beer [5%], 1 small glass [100 mL] of wine [12%], or 35 mL of spirits [35%]).

24) Demonstrating excess xanthine consumption (e.g., ingests more than 5 cups of coffee or equivalent per day). Also, subject is not willing to refrain from xanthine products for 48 hours prior to check-in on Day -1 (P1) until discharge from Period 2 treatment on Day 15 (P2). The subject is not willing to refrain from grapefruit, pomelo, Seville orange products or juice within 14 days prior to check-in on Day -1 (P1) until discharge from Period 2 treatment on Day 15 (P2). Exceptions may be made on a case-by-base basis following agreement by the Principal Investigator and the Sponsor.

25) Participation in a clinical trial and receipt of an investigational medication within 30 days or 5 half-lives (if known), whichever is greater, prior to the first dose of the current study drug.

26) History of untreated thyroid dysfunction (due to potential lithium drug-disease interaction).

27) Screening MRI-related exclusion criteria: intracranial mass, evidence of other anatomical findings that might affect safety or causes of cognitive/behavioral impairment as assessed by a qualified neurologist. Subjects must not have any implantable medical device (e.g., aneurysm clip, vagus nerve stimulator, cardiac pacemaker) or be reliant on a non-removable medical device (e.g., insulin pump) unless that device is certified as MRI compatible. Known intolerability to MRI neuroimaging procedures.

28) Subjects with any past apparent suicide attempt or suicidal behavior, including those with a lifetime history of suicide attempt(s) or a past year level 4 or higher SI/B (C-SSRS) or past month SI/B (C-SSRS) of any kind.

5. STUDY TREATMENT

5.1. Rationale for AL001 Dose Selected for Study

Lithium has been well characterized for safety and is approved /marketed in multiple formulations for treatment of BD1. A single-dose relative bioavailability study (Study AL001-ALZ01) was completed demonstrating that AL001 1050 mg (5 x 210 mg capsules) is dose-normalized bioequivalent for lithium content in plasma to a lithium carbonate 300 mg marketed capsule immediate-release formulation. A MAD study (Study AL001-ALZ02) was completed that identified the AL001 MTD in healthy non-elderly subjects, healthy elderly subjects, and subjects with AD. (Table 1) The MTD was identified based on a benign safety profile and lithium/ salicylate exposures that do not require TDM in subjects with eGFR ≥ 60 mL/min/1.73m^2.

Table 1: Maximum Tolerated Dose of AL001 for Healthy Non-Elderly Subjects, Healthy Elderly Subjects, and Subjects with Alzheimer's Disease in Completed Multiple Ascending Dose Study AL001-ALZ02

Daily Lithium Dosing Level	No. of AL001 210 mg Capsules	AL001 Daily Dose Administered for 14 days
720 mg lithium carbonate equivalent	8 capsules TID	1680 mg TID = 5040 mg daily

To mitigate risk to subjects, the selected dose for this study will be 38% below the pre-determined MTD for AL001. This is ½ of a usual lithium starting dose of lithium carbonate for treatment of BD1, equivalent to 150 mg lithium carbonate TID. The AL001 dose for this study is 5 x 210 mg capsules given TID (TDD 3150 mg containing 12 mEq lithium). The reference product will be a marketed lithium carbonate 150 mg capsule given TID (TDD 450 mg containing 12 mEq lithium). This dose is judged to be fit-for-purpose to achieve the goals of the current PK study.

5.2. Study Medications

Investigational Treatment

Doses of AL001 are manufactured in 210 mg 0 size capsules. The rationale for the number of AL001 capsules administered at each dose is based on AL001 equivalent lithium content to a bioequivalent marketed lithium carbonate capsule and a dose 38% below the MTD characterized in Alzamend's clinical study AL001-ALZ02. Dosing of AL001 in the current study will be 1050 mg (5 x 210 mg capsules) TID at 8AM, 2PM, and 8PM (6 hours apart, within ±10 minutes) under fasted conditions (at least 10 hours before the first daily dose; for the second and third daily doses, at least 1 hour before or 4 hours after meals) for 14 days.

Reference Treatment

A marketed RLD lithium carbonate capsule will be supplied from the manufacturer and dosed at 150 mg TID, TDD 450 mg. This reference product will be dosed at 8 AM, 2 PM, and 8 PM (6 hours

apart, within ±10 minutes) under fasted conditions (at least 10 hours before the first daily dose; for the second and third daily doses, at least 1 hour before or 4 hours after meals) for 14 days.

Table 2: Description of Study Medications

Drug Code:	Investigational Product	Reference Product
Formulation:	AL001 Immediate-Release Capsules 210 mg	Lithium Carbonate Capsules, USP 150 mg
Manufacturer:	Alcami Corporation 1519 North 23rd Road Wilmington, NC 28405	Hikma Pharmaceuticals USA Inc. 200 Connell Drive Berkeley Heights, NJ 07922
Batch No.:	B230078	464253A
Manufacturing Date:	2023-MAR-07	N/A
Expiry Date:	N/A	2027-JUL-31

Missed Study Medication Dosing

In the event that a study dose of either the investigational product (AL001) or the reference product (Lithium Carbonate) is missed, the following will occur:

- If missed within 1 hour 30 minutes of scheduled dosing, the dose will still be administered. Normal dosing schedule will be followed thereafter. This timing deviation will be noted within the subject records.
- If dosing is beyond 1 hour 30 minutes of the scheduled dosing time, that dose will be skipped. This missed dose will be noted within the subject records. The medical monitors and Sponsor will be notified of this missed dose, particularly if the missed dose occurs on Day 13 or 14 of each treatment period.

The modest drug doses within this protocol allow for some flexibility in the timing of doses, while still maintaining adequate safety margins.

5.3. Study Randomization and Blinding

The subjects will be assigned a unique Subject Screening Number (e.g., HC01) upon signing the informed consent at the Informed Consent Visit, and a unique Subject Randomization Number (e.g, RA101) upon meeting study eligibility criteria on Day -1 (P1). Both numbers will be allocated sequentially by the Investigator or authorized study staff. Neither number will be reused once they are assigned to a subject. Management of Subject Randomization Number, including availability of extra numbers to compensate for subjects' replacement and/or additional recruitment will be managed by the study's MGH statistician.

Enrolled subjects will be equally randomized to one of two treatment sequences (see Table 9).

This is an open label study and neither subjects nor investigative staff will be blinded.

5.4. Accountability of Study Medications

Study medications must be received by the pharmacist or other designated person at the study site. Once received, these medications must be handled and stored safely and properly according to label instructions, and kept in a secured location to which only the Investigator and their designee(s) have access. Study medications are to be dispensed only in accordance with the protocol.

Medication labels will include storage conditions; management of individual subject dosing and labelling will be the responsibility of the study site. The Investigator must maintain an accurate record of the shipment and dispensing of study medications in a drug accountability log. Monitoring of drug accountability will be performed by a Clinical Research Associate (CRA) during site visits and at the completion of the trial. At the conclusion of the study, or as appropriate during the course of the study, the Investigator will destroy all unused study medications, packaging, drug labels according to instructions in the study's Pharmacy Manual. A copy of the completed drug accountability log will be retained.

For specific instructions on study medications shipment receipt procedures, including selection and storage of reserve (retained) samples in accordance with FDA regulations, please refer to the Pharmacy Manual.

5.5. Instructions for Administering Study Medication

For all subjects, doses of AL001 capsules or lithium carbonate capsules will be administered TID for 14 days at 8AM, 2PM and 8PM (6 hours apart, within ±10 minutes) under fasted conditions (at least 10 hours before the first daily dose; for the second and third daily doses, at least 1 hour before or 4 hours after meals) while confined at the study site. Study medication will be administered with approximately 237 mL of non-carbonated water, starting in the morning of Day 1 of each study drug treatment period. Additional non-carbonated water will be permitted if necessary to complete dosing requirements. Subjects will have been fasting overnight for at least 10 hours before the first daily dose. A mouth check will be performed by the study staff to ensure all the capsules were ingested.

Subjects will be seated or in ambulatory posture for 1 hour post-dose for each dose on Days 13 (P1), 14 (P1), 13 (P2) and 14 (P2) except when not feasible such as due to neuroimaging procedures on Days 14 (P1) and 14 (P2). On all other dosing days, subjects will be encouraged to be seated or in ambulatory posture for 1 hour post-dose.

Meals and snack times will be standardized as to content and timing for all subjects when present at the study site to permit dosing under fasted conditions.

5.6. Schedule of Activities

The study consists of 5 periods: screening period, two treatment periods separated by a washout period, and a follow-up period. An overview of the activities/procedures to be performed for each subject during these study periods is described below and in Table 3.

Since this is a randomized crossover study, there are 2 drug treatment periods separated by a washout period. Each treatment period will require subjects' participation for 16 days. During each treatment period, subjects will be housed at the study site starting on Day -1 for study initiation. On Days 13, 14 and 15 of each treatment period, subjects will undergo intensive blood draws for lithium plasma PK analysis (for both AL001 and lithium carbonate treatments) and salicylic acid plasma PK analysis (for AL001 treatment only), and lithium brain neuroimaging PK assessments (for both AL001 and lithium carbonate treatments). Subjects will be discharged from the study site during the washout period. Washout period will be a minimum of 9 days (+19 days; maximum 28 days) between each treatment period.

Period 1 Days will be identified as (P1); e.g., Day 1 (P1). Period 2 Days will be identified as (P2); e.g., Day 1 (P2). Washout days will be identified as Day 15 (P1) to Day "X" (P1) since the washout period can vary.

Visit #s may be used to track activities/procedures performed for documentation in the EDC system. Visit #s are aligned with constituent study days. After each study visit, all information collected from the subject must be transcribed from the source document into the EDC system in real time whenever possible, or within the timeframe specified in the study's Data Management Plan (DMP) if transcription in real time is not possible.

Study procedures may be repeated at the discretion of the Investigator to ensure the integrity of the data, subject safety, or to address protocol deviations. The decision to repeat any procedure will be based on clinical judgment and the specific circumstances surrounding the subjects's involvement in the study.

5.6.1. Screening Period – Visits #01a & 01b; between Day -28 (P1) to Day -1 (P1)

The screening period will take place up to 28 days prior to dosing of the first study drug to determine subject eligibility. Interested candidates who are on any medications (e.g., OTC, prescription medication, vitamins, and herbal supplements) must wait at least 14 days after providing informed consent before starting the in-person screening (or at least 6 times the respective elimination half-life [if known] rather than 14 days, whichever is longer).

Before any screening activity is initiated, the potential subject will need to sign the informed consent form (ICF) indicating their understanding and willingness to participate in the study. After signing the ICF, a unique Subject Screening Number (e.g., HC01) will be assigned to the subject and Screening tests and procedures will be initiated and completed by Day -1 (P1) – Visit #02.

5.6.1.1. Visit #01a; Informed Consent Visit (Virtual)

The following activities/procedures will be completed during this remote (virtual) visit:

- Obtain subject signed and dated written informed consent prior to any Screening procedures.
- Assign the next sequential Subject Screening Number to the subject.
- Collect demographic information.
- Collect medical and surgical history.
- Collect prior medications (taken up to 60 days prior to signing informed consent) and concomitant medications information.

5.6.1.2. Visit #01b; In-person Screening Visit

The following activities/procedures will be completed during the visit (***note**: this visit may take place over multiple days*):

- Evaluate inclusion/exclusion criteria.
- Record any AEs.
- Collect concomitant medications information.
- Conduct a physical examination (including a brief neurological examination).
- Collect body height/body weight measurements.
- Collect vital sign measurements (blood pressure, heart rate, and temporal artery body temperature) with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements.
    - If the PI or other Sub-Investigator(s) thinks there may be a "white coat effect" on the blood pressure result, the blood pressure measurement can be redone after the subject is given the chance to sit and relax for five minutes.
    - If the subject's body temp is > 101.4°F, their temperature will be retaken to ensure accuracy.
- Collect 12-lead ECG measurements with the subject resting in a supine position for at least 5 minutes and prior to any blood collection procedures.
- Collect blood and urine samples for safety laboratory tests (chemistry [including Lipid Panels, TSH and Vitamin B12]; hematology [including HbA1c]; urinalysis). See Table 4 for more details. *The subject should be fasting for at least 10 hours prior to this visit for accurate safety laboratory results.*

- These safety laboratory tests may be repeated at the discretion of the Investigator if the initial values are outside the clinical laboratory's reference range.

- Collect blood sample for serology (HIV/Hepatitis B and C) screen.
- Collect blood sample for plasma pregnancy test (for females of childbearing potential only).
- Collect urine sample for drug screening.
- Collect saliva, urine, or blood sample for ethanol (alcohol) test.
- Conduct C-SSRS, YMRS, and HDRS-17 assessments.
- Conduct brain MRI (including lithium baseline measurements and MRI tolerability assessment). *Subjects may undergo multiple MRI procedures to ensure that they are adequately acclimatized to fulfill study requirements.*

5.6.2. Treatment Periods 1 and 2, separated by a Washout Period

The treatment periods for each subject comprises 14 days of TID dosing (x2), with either AL001 capsules (Investigational) or lithium carbonate capsule (Reference) under fasted conditions (at least 10 hours before the first daily dose; for the second and third daily doses, at least 1 hour before or 4 hours after meals). The first dose of the randomized treatment (Investigational or Reference) will be administered in the morning of Day 1 (P1) – Visit #03. Subsequently, the first dose of the alternate treatment will be administered on Day 1 (P2) – Visit #19. Subjects are discharged between drug treatment periods. Each treatment period will require subjects' participation for 16 days.

5.6.2.1. Check-in for Treatment Period 1 – Visit #02; Day -1 (P1)

Subjects will be admitted to the study site at least 16 hours before initial drug administration on Day 1 (P1) – Visit #03.

The following activities/procedures will be completed during the visit:

- Admit the subject to the study site by 4PM; at least 16 hours before initial drug administration.
- Reevaluate inclusion/exclusion criteria.
- Record any AEs.
- Collect concomitant medications information.
- Collect body weight measurements.
- Collect vital sign measurements (blood pressure, heart rate, and temporal artery body temperature) with the subject in a seated position for 5 minutes. If possible, the same arm should be used for all measurements.

- If the PI or other Sub-Investigator(s) thinks there may be a "white coat effect" on the blood pressure result, the blood pressure measurement can be redone after the subject is given the chance to sit and relax for five minutes.
- If the subject's body temp is > 101.4°F, their temperature will be retaken to ensure accuracy.

- Collect blood and urine samples for safety laboratory tests (chemistry [excluding Lipids Panel, TSH, and Vitamin B12]; hematology [excluding HbA1c]; urinalysis). See Table 4 for more details. *The subject should be fasting for at least 10 hours prior to this visit for accurate safety laboratory results.*
  - These safety laboratory tests may be repeated at the discretion of the Investigator if the initial values are outside the clinical laboratory's reference range.
  - *For subjects who are screened within 5 days of check-in [on Day -6 (P1) to Day -2 (P1)], above safety laboratory tests will not be performed at all on this visit.*
- Collect urine sample for drug screening.
- Collect saliva, urine, or blood sample for ethanol (alcohol) test.
- Collect urine sample for urine pregnancy test (for females of childbearing potential only).
  - If urine sample is not available, then collect blood sample for plasma pregnancy test (for females of childbearing potential only).
- Conduct C-SSRS, YMRS, and HDRS-17 assessments.
- Conduct a health status questionnaire (SF-36).
- Assign the next sequential Subject Randomization Number to the subject, which will specify the subject's drug treatment sequence in the study (see Table 9 for study treatment sequence).
  - Subject Randomization should occur only after all the safety lab tests results are back and subject's continued eligibility to participate in the study has been confirmed.
- Provide subject with a meal (dinner).

5.6.2.2. Treatment Dosing Period 1 – Visits #03 to 16; Day 1 (P1) to Day 14 (P1)

The first daily dose of study medication (Period 1's assigned treatment) will be administered in the morning at 8 AM with afternoon and evening doses administered at 2 PM and 8 PM (6 hours apart, ±10 minutes for all doses). Subjects will be confined to the study site for all doses and discharged on Day 15 (P1) – Visit #17, or early termination – Visit #ET.

For specific instructions regarding study subject's fasted study drug administration (Section 5.7.11) and standardized meals (Section 5.7.12) during the confinement period, please refer to those respective sections.

5.6.2.2.1. Visit #03; Day 1 (P1)

The following activities/procedures will be completed during the visit:

- Before the first dosing (8 AM)
  - Confirm subject continues to be appropriate for study participation.
  - Record any AEs.
  - Collect concomitant medications information.
  - Collect vital sign (pre-dose) measurements (blood pressure, heart rate, and temporal artery body temperature) within 1 hour before dose with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements.
  - Collect 12-lead ECG measurements with the subject resting in a supine position for at least 5 minutes and prior to any blood collection procedures.
  - Collect baseline PK blood samples for assessment of lithium and salicylic acid levels (for both AL001 and lithium carbonate treatments based on randomization).
- Study Drug Dose Administration (8 AM, 2 PM, 8 PM; ±10 minutes for all doses). Subjects will be encouraged to be seated or in ambulatory posture for 1 hour post-dose.
- Provide subjects with standardized meals as necessary.
- After the third dosing (8 PM)
  - Wait 1 hour (±10 minutes), then conduct 12-lead ECG (repeat) with the subject resting in a supine position for at least 5 minutes.

Note: Please also see *Additional procedures during Treatment Period 1* (Section 5.6.2.2.4).

5.6.2.2.2. Visits #04 to 14; Day 2 (P1) to Day 12 (P1)

The following activities/procedures will be completed during the visit:

- Before the first daily dosing (8 AM)
  - Confirm subject continues to be appropriate for study participation.
  - Record any AEs.
  - Collect concomitant medications information.
  - Collect vital sign (pre-dose) measurements (blood pressure, heart rate, and temporal artery body temperature) within 1 hour before dose with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements.
- Study Drug Dose Administration (8 AM, 2 PM, 8 PM; ±10 minutes for all doses). Subjects will be encouraged to be seated or in ambulatory posture for 1 hour post-dose.

- Provide subject with standardized meals as necessary.

Note: Please also see *Additional procedures during Treatment Period 1* (Section 5.6.2.2.4).

5.6.2.2.3. Visits #15 & 16; Day 13 (P1) & Day 14 (P1)

The following activities/procedures will be completed during the visit:

- Before the first daily dosing (8 AM)
  - Confirm subject continues to be appropriate for study participation.
  - Record any AEs.
  - Collect concomitant medications information.
  - Collect vital sign (pre-dose) measurements (blood pressure, heart rate, and temporal artery body temperature) within 1 hour before dose with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements.
  - Collect 12-lead ECG measurements with the subject resting in a supine position for at least 5 minutes and prior to any blood collection procedures.
  - *On the morning of Visit #16; Day 14 (P1):* An intravenous catheter (IV) may be placed in the subject's arm to perform the multiple PK blood draws. In instances where blood sample is unable to be obtained from the IV, blood will be drawn using venipuncture phlebotomy processes.
  - Collect (pre-dose) blood samples for assessment of lithium and salicylic acid levels within 15 minutes before dose.
    - For lithium carbonate capsule treatment, salicylic acid bioassay in plasma will not be collected during lithium intensive blood sampling activities.
- Additional procedure before the first dosing (8 AM) on Visit #16; Day 14 (P1)
  - Conduct brain MRI (pre-dose) within 1 hour before dose.
- Study Drug Dose Administration (8 AM, 2 PM, 8 PM; ±10 minutes for all doses). Subjects will be seated or in ambulatory posture for 1 hour post-dose for each dose, except when not feasible such as due to neuroimaging procedures on Day 14 (P1).
- Additional procedures after the first dosing (8 AM) on Visit #16; Day 14 (P1)
  - Collect blood samples (post-1st daily dose) for lithium PK analysis (for subjects assigned to either AL001 and lithium carbonate treatments) and salicylic acid PK analysis (for subjects assigned to AL001 treatment only). Blood sampling will occur at 0.5, 1, 1.5, 2, 3, 4, 5, 6 (before the 2 PM dose), 6.5, 7, 8, 9, 10, 11, 12 (before the 8 PM dose), 12.5, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 hours after the initial 8 AM dose. A ±15-minute window for deviation from nominal times will be allowed

for collection of PK blood samples. Actual dosing and PK blood sampling times will be recorded for accurate/precise PK analyses.

- Conduct brain MRI (post-1st daily dose) at 3, 6, 8, 12, 16, 20, 24 hours after the initial morning dose. A ±20-minute window for deviation from nominal times for lithium neuroimaging will be allowed.
- Coordination between lithium neuroimaging requirements will give priority to timely collection of PK blood samples when feasible. If neuroimaging cannot be conducted, PK blood sampling will be continued.

- Provide subjects with standardized meals as necessary.

Note: Please also see *Additional procedures during Treatment Period 1* (Section 5.6.2.2.4).

5.6.2.2.4. Additional procedures during Treatment Period 1

- Conduct C-SSRS assessments *at least twice* between Day 1 (P1) and Day 15 (P1) at times regarded as most clinically meaningful/useful.
- Other blood samples may be requested by the Investigator to determine the relationship between lithium and/or salicylic acid plasma drug concentrations and AEs, and to guide subject care accordingly (these are additional "safety samples" for Therapeutic Drug Monitoring). These PK "safety samples" could be sent for expedited assay and remaining aliquots of these Investigator-requested samples retained at the study site for later shipment to the designated bioanalytical laboratory if appropriate (i.e., if a local laboratory was used for rapid reporting rather than the designated bioanalytical laboratory).
- Additional blood, urine, and/or saliva sample collection for re-testing of safety laboratory tests initially found to be outside of the clinical laboratory's reference range may be requested by the Investigator to ensure the subject's continued eligibility and safety throughout the study.

5.6.2.3. Clinic Discharge for Treatment Period 1 – Visit #17; Day 15 (P1)

There will be no subsequent 8 AM dose on Day 15 (P1), the start of the washout period. Prior to the subject's discharge from study site, the following activities/procedures will be completed:

- Confirm subject continues to be appropriate for study participation.
- Record any AEs.
- Collect concomitant medications information.
- Conduct a physical examination (including a brief neurological examination).
- Collect body weight measurements.

- Collect vital sign measurements (blood pressure, heart rate, and temporal artery body temperature) with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements.
- Collect 12-lead ECG measurements with the subject resting in a supine position for at least 5 minutes and prior to any blood collection procedures.
- Collect blood and urine samples for safety laboratory tests (chemistry [including Lipids Panel and TSH, but not Vitamin B12]; hematology [excluding HbA1c]; urinalysis). See Table 4 for more details. *The subject should be fasting for at least 10 hours prior to this visit for accurate safety laboratory results.*
    - These safety laboratory tests may be repeated at the discretion of the Investigator if the initial values are outside the clinical laboratory's reference range.
- Conduct C-SSRS, YMRS, and HDRS-17 assessments.
    - If at least two C-SSRS assessments were conducted between Day 1 (P1) and Day 14 (P1), then it is unnecessary to conduct another C-SSRS assessment on Day 15 (P1).
- Provide subject with a meal (breakfast) as necessary prior to discharge from the study site.

5.6.2.4. Washout Period – Visits # W01 and W02 (or more); Day 15 (P1) to Day "X" (P1), since the washout period can vary (9 to 28 days).

Subjects will be interviewed, by telephone, a minimum of 2 times during the washout period. The first washout telephone call (visit) will take place 3 days (±2 days) after Treatment 1 discharge from the study site. The second washout telephone call (visit) will take place 9 days (±2 days) after Treatment 1 discharge from the study site. Each washout period telephone call (visit) will include the following:

- Confirm subject continues to be appropriate for study participation.
- Record any AEs.
- Collect concomitant medications information.
- Conduct a health status questionnaire (SF-36).
- Conduct C-SSRS assessment.

In the event the washout period extends beyond 14 days after Treatment 1 discharge, up to two (2) additional follow-up telephone calls may take place (at 16 days [±2 days] and at 23 days [±2 days] after Treatment 1 discharge).

5.6.2.5. Check-in for Treatment Period 2 – Visit #18; Day -1 (P2)

Subjects will be admitted to the study site at least 16 hours before initial drug administration on Day 1 (P2) – Visit #19.

The following activities/procedures will be completed during the visit:

- Confirm subject continues to be appropriate for study participation.
- Admit the subject to the study site by 4 PM; at least 16 hours before initial drug administration.
- Record any AEs.
- Collect concomitant medications information.
- Collect body weight measurements.
- Collect vital sign measurements (blood pressure, heart rate, and temporal artery body temperature) with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements.
- Collect blood and urine samples for safety laboratory tests (chemistry [excluding Lipids Panel, TSH, and Vitamin B12]; hematology [excluding HbA1c]; urinalysis). See Table 4 for more details. *The subject should be fasting for at least 10 hours prior to this visit for accurate safety laboratory results.*
    - These safety laboratory tests may be repeated at the discretion of the Investigator if the initial values are outside of the clinical laboratory's reference range.
- Collect urine sample for drug screening.
- Collect saliva, urine, or blood sample for ethanol (alcohol) test.
- Collect urine sample for urine pregnancy test (for females of childbearing potential only).
    - If urine sample is not available, then collect blood sample for plasma pregnancy test (for females of childbearing potential only).
- Conduct C-SSRS, YMRS, and HDRS-17 assessments.
- Provide subject with a meal (dinner).

5.6.2.6. Treatment Dosing Period 2 – Visits #19 to 32; Day 1 (P2) to Day 14 (P2)

The first daily dose of study medication (Period 2's assigned treatment) will be administered in the morning at 8 AM with afternoon and evening doses administered at 2 PM and 8 PM (6 hours apart, ±10 minutes for all doses). Subjects will be confined to the study site for all doses and discharged on Day 15 (P2) – Visit #33, or early termination – Visit #ET.

For specific instructions regarding study subject's fasted study drug administration (Section 5.7.11) and standardized meals (Section 5.7.12) during the confinement period, please refer to those respective sections.

5.6.2.6.1. Visit #19; Day 1 (P2)

The following activities/procedures will be completed during the visit:

- Before the first dosing (8 AM)
  - Confirm subject continues to be appropriate for study participation.
  - Record any AEs.
  - Collect concomitant medications information.
  - Collect vital sign (pre-dose) measurements (blood pressure, heart rate, and temporal artery body temperature) within 1 hour before dose with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements
  - Collect 12-lead ECG measurements with the subject resting in a supine position for at least 5 minutes and prior to any blood collection procedures.
  - Collect baseline PK blood samples for assessment of lithium and salicylic acid levels (for both AL001 and lithium carbonate treatments based on randomization).
- Study Drug Dose Administration (8 AM, 2 PM, 8 PM; ±10 minutes for all doses). Subjects will be encouraged to be seated or in ambulatory posture for 1 hour post-dose.
- Provide subject with standardized meals as necessary.
- After the third dosing (8 PM)
  - Wait 1 hour (±10 minutes), then conduct 12-lead ECG (repeat) with the subject resting in a supine position for at least 5 minutes.

Note: Please also see *Additional procedures during Treatment Period 2* (Section 5.6.2.6.4).

5.6.2.6.2. Visits #20 to 30; Day 2 (P2) to Day 12 (P2)

The following activities/procedures will be completed during the visit:

- Before the first daily dosing (8 AM)
  - Confirm subject continues to be appropriate for study participation.
  - Record any AEs.
  - Collect concomitant medications information.
  - Collect vital sign (pre-dose) measurements (blood pressure, heart rate, and temporal artery body temperature) within 1 hour before dose with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements.
- Study Drug Dose Administration (8 AM, 2 PM, 8 PM; ±10 minutes for all doses). Subjects will be encouraged to be seated or in ambulatory posture for 1 hour post-dose.

- Provide subject with standardized meals as necessary.

Note: Please also see *Additional procedures during Treatment Period 2* (Section 5.6.2.6.4).

5.6.2.6.3. Visits #31 & 32; Day 13 (P2) & Day 14 (P2)

The following activities/procedures will be completed during the visit:

- Before the first daily dosing (8 AM)
  - Confirm subject continues to be appropriate for study participation.
  - Record any AEs.
  - Collect concomitant medications information.
  - Collect vital sign (pre-dose) measurements (blood pressure, heart rate, and temporal artery body temperature) within 1 hour before dose with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements.
  - Collect 12-lead ECG measurements with the subject resting in a supine position for at least 5 minutes and prior to any blood collection procedures.
  - *On the morning of Visit #32; Day 14 (P2):* An intravenous catheter (IV) may be placed in the subject's arm to perform the multiple PK blood draws. In instances where blood sample is unable to be obtained from the IV, blood will be drawn using venipuncture phlebotomy processes.
  - Collect (pre-dose) blood samples for assessment of lithium and salicylic acid levels within 15 minutes before dose.
    - For lithium carbonate capsule treatment, salicylic acid bioassay in plasma will not be collected during lithium intensive blood sampling activities.
- Additional procedure before the first dosing (8 AM) on Visit #32; Day 14 (P2)
  - Conduct brain MRI (pre-dose) within 1 hour before dose.
- Study Drug Dose Administration (8 AM, 2 PM, 8 PM; ±10 minutes for all doses). Subjects will be seated or in ambulatory posture for 1 hour post-dose for each dose, except when not feasible such as due to neuroimaging procedures on Day 14 (P2).
- Additional procedures after the first dosing (8 AM) on Visit #32; Day 14 (P2)
  - Collect blood samples (post-1st daily dose) for lithium PK analysis (for subjects assigned to either AL001 and lithium carbonate treatments) and salicylic acid PK analysis (for subjects assigned to AL001 treatment only) Blood sampling will occur at 0.5, 1, 1.5, 2, 3, 4, 5, 6 (before the 2 PM dose), 6.5, 7, 8, 9, 10, 11, 12 (before the 8 PM dose), 12.5, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 hours after the initial 8 AM dose. A ±15-minute window for deviation from nominal times will be allowed for

collection of blood samples. Actual dosing and PK blood sampling times will be recorded for accurate/precise PK analyses.

- Conduct brain MRI (post-1st daily dose) at 3, 6, 8, 12, 16, 20, 24 hours after the initial morning dose. A ±20-minute window for deviation from nominal times for lithium neuroimaging will be allowed.
- Coordination between lithium neuroimaging requirements will give priority to timely collection of PK blood samples when feasible. If neuroimaging cannot be conducted, PK blood sampling will be continued.

- Provide subject with standardized meals as necessary.

Note: Please also see *Additional procedures during Treatment Period 2* (Section 5.6.2.6.4).

5.6.2.6.4. Additional procedures during Treatment Period 2

- Conduct C-SSRS assessments *at least twice* between Day 1 (P2) and Day 15 (P2) at times regarded as most clinically meaningful/useful.
- Other blood samples may be requested by the Investigator to determine the relationship between lithium and/or salicylic acid plasma drug concentrations and AEs, and to guide subject care accordingly (these are additional "safety samples" for Therapeutic Drug Monitoring). These PK "safety samples" could be sent for expedited assay and remaining aliquots of these Investigator-requested samples retained at the study site for later shipment to the designated bioanalytical laboratory if appropriate (i.e., if a local laboratory was used for rapid reporting rather than the designated bioanalytical laboratory).
- Additional blood, urine, and/or saliva sample collection for re-testing of safety laboratory tests initially found to be outside of the clinical laboratory's reference range may be requested by the Investigator to ensure the subject's continued eligibility and safety throughout the study.

5.6.2.7. Clinic Discharge for Treatment Period 2 – Visit #33; Day 15 (P2)

There will be no subsequent 8 AM dose on Day 15 (P2). Prior to the subject's discharge from study site, the following activities/procedures will be completed:

- Confirm subject continues to be appropriate for study participation.
- Record any AEs.
- Collect concomitant medications information.
- Conduct a physical examination (including a brief neurological examination).
- Collect body weight measurements.

- Collect vital sign measurements (blood pressure, heart rate, and temporal artery body temperature) with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements.
- Collect 12-lead ECG measurements with the subject resting in a supine position for at least 5 minutes and prior to any blood collection procedures.
- Collect blood and urine samples for safety laboratory tests (chemistry [including Lipids Panel and TSH, but not Vitamin B12]; hematology [excluding HbA1c]; urinalysis). See Table 4 for more details. *The subject should be fasting for at least 10 hours prior to this visit for accurate safety laboratory results.*
  - These safety laboratory tests may be repeated at the discretion of the investigator if the initial values are outside the clinical laboratory's reference range.
- Collect urine sample for urine pregnancy test (for females of childbearing potential only).
  - If urine sample is not available, then collect blood sample for plasma pregnancy test (for females of childbearing potential only).
- Conduct C-SSRS, YMRS, and HDRS-17 assessments.
  - If at least two C-SSRS assessments were conducted between Day 1 (P2) and Day 14 (P2), then it is unnecessary to conduct another C-SSRS assessment on Day 15 (P2).
- Provide subject with a meal (breakfast) as necessary prior to discharge from the study site.

5.6.3. Follow-up Period

The safety follow-up period will begin after the subject has been discharged from the study site on Day 15 (P2). This period consists of an in-clinic follow-up on Day 23 (P2) ±2 days and a telephone call follow-up on Day 42 (P2) ±2 days.

5.6.3.1. In-Clinic Follow-up – Visit #34; Day 23 (P2) ±2 days

The following activities/procedures will be completed during the visit:

- Confirm subject continues to be appropriate for study participation.
- Record any AEs.
- Collect concomitant medications information.
- Conduct a physical examination (including a brief neurological examination).
- Collect body weight measurements.

- Collect vital sign measurements (blood pressure, heart rate, and temporal artery body temperature) with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements.
- Collect 12-lead ECG measurements with the subject resting in a supine position for at least 5 minutes and prior to any blood collection procedures.
- Collect blood and urine samples for safety laboratory tests (chemistry [including Lipids Panel, TSH and Vitamin B12]; hematology [including HbA1c]; urinalysis). See Table 4 for more details. *The subject should be fasting for at least 10 hours prior to this visit for accurate safety laboratory results.*
- Collect urine sample for urine pregnancy test (for females of childbearing potential only).
    - If urine sample is not available, then collect blood sample for plasma pregnancy test (for females of childbearing potential only).
- Conduct C-SSRS, YMRS, and HDRS-17 assessments.
- Conduct a health status questionnaire (SF-36).

5.6.3.2. Telephone Call Follow-up – Visit #35; Day 42 (P2) ±2 days

The following activities/procedures will be completed during the visit:

- Confirm subject continues to be appropriate for study participation.
- Record any AEs.
- Collect concomitant medications information.
- Conduct a health status questionnaire (SF-36).
- Conduct C-SSRS assessment.
- Discharge the subject from the study.

5.6.4. Early Termination

If the subject is terminated early from the study, the Investigator should make every effort to complete the following activities/procedures prior to subject discharge:

- Record any AEs.
- Collect concomitant medications information.
- Conduct a physical examination (including a brief neurological examination).
- Collect body weight measurements.

- Collect vital sign measurements (blood pressure, heart rate, and temporal artery body temperature) with the subject in a seated position for 5 minutes. If possible, the same arm will be used for all measurements
- Collect 12-lead ECG measurements with the subject resting in a supine position for at least 5 minutes and prior to any blood collection procedures.
- Collect blood and urine samples for safety laboratory tests (chemistry [including Lipids Panel, TSH and Vitamin B12]; hematology [including HbA1c]; urinalysis). See Table 4 for more details. *The subject should be fasting for at least 10 hours prior to this visit for accurate safety laboratory results.*
- Collect urine sample for urine pregnancy test (for females of childbearing potential only).
    - If urine sample is not available, then collect blood sample for plasma pregnancy test (for females of childbearing potential only).
- Collect blood samples for lithium and salicylic acid PK/safety analysis.
- Conduct C-SSRS, YMRS, and HDRS-17 assessments.
- Conduct a health status questionnaire (SF-36).
- Discharge the subject from the study.

Table 3: Schedule of Activities

Note: Since this is a randomized crossover trial, there are 2 treatment confinement periods with a 9-28 days washout period between confinement periods. Subjects are discharged between treatment confinement periods. Each treatment confinement period is represented in the schedule of activities below as having a Day -1 admission day, dosing Days 1 to 14 while confined, and clinic discharge on Day 15. The follow-up period includes Days 23 and 42 of the 2nd drug treatment period only. Because the number of days needed for each subject's washout period can vary, days are identified according to period 1 or 2, e.g., Day 1 (P1) or Day 1 (P2). Washout Days are identified as Day 15 (P1) to Day "X" (P1). **Visit #s may be used to track activities performed for documentation in the electronic data capture (EDC) system. Visit #s are aligned below with corresponding study days.**

		Confinement Period 1						Confinement Period 2					Follow-Up		
	Screening	In-Patient Admission	Treatment			Clinic Discharge	Washout Period (Telephone Call)	In-Patient Admission	Treatment			Clinic Discharge	In-Clinic	Telephone Call	Early Termination
Study Procedures	**Visits #01a & 01b** Day -28 to Day -1 (P1)	**Visit #02** Day -1 (P1)	**Visit #03** Day 1 (P1)	**Visits #04 to 14** Days 2 to 12 (P1)	**Visits #15 & 16** Days 13 & 14 (P1)	**Visit #17** Day 15 (P1)	**Visits #W01 & W02** Day 15 (P1) to Day X (P1) *(variable, 9-28 days)*	**Visit #18** Day -1 (P2)	**Visit #19** Day 1 (P2)	**Visits #20 to 30** Days 2 to 12 (P2)	**Visits #31 & 32** Days 13 & 14 (P2)	**Visit #33** Day 15 (P2)	**Visit #34** Day 23 (P2) ±2 days	**Visit #35** Day 42 (P2) ±2 days	**Visit #ET**
Informed Consent[1]	x														
Medical and Surgical History[1]	x														
Demographic Information[1]	x														
Inclusion/Exclusion Criteria	x	x													
Adverse Event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Examination	x					x						x	x		x
Body Height / Body Weight[2]	x	x				x		x				x	x		x

Study Procedures	Screening	Confinement Period 1					Washout Period (Telephone Call)	Confinement Period 2					Follow-Up		Early Termination
		In-Patient Admission	Treatment			Clinic Discharge		In-Patient Admission	Treatment			Clinic Discharge	In-Clinic	Telephone Call	
	Visits #01a & 01b Day -28 to Day -1 (P1)	**Visit #02** Day -1 (P1)	**Visit #03** Day 1 (P1)	**Visits #04 to 14** Days 2 to 12 (P1)	**Visits #15 & 16** Days 13 & 14 (P1)	**Visit #17** Day 15 (P1)	**Visits #W01 & W02** Day 15 (P1) to Day X (P1) *(variable, 9-28 days)*	**Visit #18** Day -1 (P2)	**Visit #19** Day 1 (P2)	**Visits #20 to 30** Days 2 to 12 (P2)	**Visits #31 & 32** Days 13 & 14 (P2)	**Visit #33** Day 15 (P2)	**Visit #34** Day 23 (P2) ±2 days	**Visit #35** Day 42 (P2) ±2 days	**Visit #ET**
Vital Signs[3]	x	x	x	x	x	x		x	x	x	x	x	x		x
12-lead ECG[4]	x		x		x	x			x		x	x	x		x
Safety Laboratory Tests[5]	x	x				x		x				x	x		x
Serology (HIV/HBV/HCV)[6]	x														
Plasma Pregnancy Test *(Female of childbearing potential only)*	x														
Urine Pregnancy Test *(Female of childbearing potential only)* [7]		x						x				x	x		x
Urine Drug Screening	x	x						x							
Ethanol (Alcohol) Test[8]	x	x						x							
Admission[9]		x						x							
Randomization		x													
Clinic Confinement		x	x	x	x			x	x	x	x				
Fasted Drug Administration (all doses) [10]			x	x	x				x	x	x				

Study Procedures	Screening	Confinement Period 1					Washout Period (Telephone Call)	Confinement Period 2					Follow-Up		Early Termination
		In-Patient Admission	Treatment			Clinic Discharge		In-Patient Admission	Treatment			Clinic Discharge	In-Clinic	Telephone Call	
	Visits #01a & 01b Day -28 to Day -1 (P1)	**Visit #02** Day -1 (P1)	**Visit #03** Day 1 (P1)	**Visits #04 to 14** Days 2 to 12 (P1)	**Visits #15 & 16** Days 13 & 14 (P1)	**Visit #17** Day 15 (P1)	**Visits #W01 & W02** Day 15 (P1) to Day X (P1) *(variable, 9-28 days)*	**Visit #18** Day -1 (P2)	**Visit #19** Day 1 (P2)	**Visits #20 to 30** Days 2 to 12 (P2)	**Visits #31 & 32** Days 13 & 14 (P2)	**Visit #33** Day 15 (P2)	**Visit #34** Day 23 (P2) ±2 days	**Visit #35** Day 42 (P2) ±2 days	**Visit #ET**
Lithium Neuroimaging/MRI-MRSs[11, 13]	x				x	x					x	x			
Pharmacokinetic Blood Samples Collection[12, 13]			x		x	x			x		x	x			x
Meals[14]		x	x	x	x	x		x	x	x	x	x			
Discharge[15]						x						x			x
Health Status Questionnaire (SF-36)		x					x						x	x	x
C-SSRS[16]	x	x	o	o	o	o	x	x	o	o	o	o	x	x	x
YMRS/HDRS-17[17]	x	x				x		x				x	x		x

1 Informed consent may be obtained via a virtual visit (Visit 1a) at least 14 days prior to the in-person screening visit (Visit 1b). After receiving informed consent, subject's demographic information, medical and surgical history, prior medications (taken up to 60 days before signing informed consent), and conconmitant medications information will be collected at this virtual visit.

2 Body height measurements will be recorded at Screening only. Body weight measurements will be recorded at Screening, Day -1 (P1), Day 15 (P1), Day -1 (P2), Day 15 (P2), and Day 23 (P2), or ET.

3 Vital signs will include blood pressure, heart rate and temporal artery body temperature on all study days while in-house. On dosing days, vital signs will be measured within 1 hour prior to the initial daily dose (8 AM). Subject's vital signs should be recorded after 5 minutes in a seated position. If possible, the same arm will be used for all measurements.

4 On Day 1 (P1) and Day 1 (P2), ECGs will be conducted prior to the first dose (8 AM) and 1 hour (±10 minutes) after the third dose (8PM). On Day 13 (P1), Day 14 (P1), Day 13 (P2), and Day 14 (P2), ECGs will be performed prior to first daily dose (8 AM). On Days 15 (P1) and Day 15 (P2), or ET, ECGs will be performed prior to discharge. Collect ECG measurements with the subject resting in a supine position for at least 5 minutes and prior to any blood collection procedures.

5 Safety laboratory tests (chemistry, hematology, and urinalysis) will be performed at Screening and on Day -1 (P1), Day 15 (P1), Day -1 (P2), Day 15 (P2), and Day 23 (P2), or ET. For subjects who are screened within 5 days of check-in – on Day -6 (P1) to Day -2 (P1) – safety laboratory tests will not be performed on Day -1 (P1). Lipids panel (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides) will be performed at Screening and on Day 15 (P1), Day 15 (P2), and Day 23 (P2), or ET. HbA1c, TSH, and Vitamin B12 will be performed at Screening and Day 23 (P2), or ET. An additional TSH will be performed on Day -1 (P2). The total volume of blood drawn, including the volume necessary for the lithium and salicylic acid plasma bioassays, will be up to 603 mL (excluding the ET visit). Refer to Table 4 for the complete list of safety laboratory assessments. The subject should be fasting for at least 10 hours prior to these visits for accurate safety laboratory results. Safety laboratory tests may be re-tested at the request of the investigator for assessment of safety and eligibility.

6 An HIV 1/2 Ag/Ab test will be used to detect antibodies to the HIV 1/2 and the HIV1 p24 antigen. HIV-1 and HIV-2 Antibody Confirmation and Differentiation testing will automatically be performed when the HIV 1/2 Ag/Ab test is reactive. If the HCV antibody test returns a positive result, a quantitative PCR viral load test will be ordered.

7 If urine sample is not available, then collect blood sample for plasma pregnancy test.

8 The ethanol test may be performed with saliva, urine, or blood. Refer to the study laboratory manual for details.

9 Subjects will be admitted to the clinical research study site at least 16 hours prior to the initial study drug administration.

10 Doses of AL001 capsules or lithium carbonate capsules will be administered TID for 14 days at 8 AM, 2 PM and 8 PM (within ±10 minutes) under fasted conditions (at least 10 hours before the first daily dose; for the second and third daily doses, at least 1 hour before or 4 hours after meals) while confined at the study site. Subjects will have been fasting overnight for at least 10 hours before the first daily dose. Study medication will be administered with approximately 237 mL of non-carbonated water starting in the morning of Day 1(P1) and Day 1 (P2). Additional non-carbonated water will be permitted if necessary to complete dosing requirements. A mouth check will be performed by the study staff to ensure the subject swallowed all the capsules. On Day 13 (P1), Day 14 (P1), Day 13 (P2), and Day 14 (P2), subjects will be seated or in ambulatory posture for 1 hour post-dose when feasible since, for example, neuroimaging procedures on Day 14 (P1) and Day 14 (P2) may obviate such postures. On all other dosing days, subjects will be encouraged to be seated or in ambulatory posture for 1 hour post-dose.

11 Lithium and diagnostic MRI-MRS will be conducted at Screening Visit. Lithium brain distribution and lithium concentration/mass will be characterized using ^{7}Li-MRI-MRS on Day 14 (P1) and Day 14 (P2) at pre-dose (or 0 h, i.e., within 1 hour prior to the 8 AM drug administration) and at 3, 6, 8, 12, 16, 20, 24 hours after the initial morning dose. A ±20-minute window for deviation from nominal times for lithium neuroimaging will be allowed. At select imaging timepoints, a respiratory belt may be used to track subject's breathing motion during scanning.

12 Blood samples for establishing each treatment period's baseline lithium and salicylic acid plasma PK values will be obtained on Day 1 (P1) and Day 1 (P2) prior to the 8 AM dosing. Following lithium carbonate treatment and during lithium carbonate intensive PK blood sampling activities, blood samples for salicylic acid plasma PK bioassay will not be collected; salicylic acid plasma PK bioassay will only be conducted following AL001 treatment. For the intensive PK blood sampling (30 samples for each analyte [lithium and salicylic acid]; 60 total samples from Days 13-15 of AL001 treatment period and 30 total samples from Days 13-15 of lithium carbonate treatment period), blood samples will be collected at pre-dose (or 0 h, i.e., within 0.25 hour prior to the 8 AM drug administration) on Day 13 (P1), Day 14 (P1), Day 13 (P2), and Day 14 (P2); and at 0.5, 1, 1.5, 2, 3, 4, 5, 6 (before the 2 PM dose), 6.5, 7, 8, 9, 10, 11, 12 (before the 8 PM dose), 12.5, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 hours after the initial 8 AM dose given on Day 14 (P1) and Day 14 (P2). A ±15-minute window for deviation from nominal times will be allowed for collection of PK blood samples. Actual dosing and PK blood sampling times will be recorded for accurate/precise PK analyses. All PK measures/parameter calculations will be based on actual times of sample/data collection. Additional blood samples for plasma PK bioassays may be obtained at the discretion of the Investigator during the trial, particularly to assess the relationship to possible lithium and/or salicylic acid related AEs. These "safety samples" could be sent expedited to a local laboratory with remaining aliquots saved for the bioanalytical laboratory. If there is an early termination from the study of a study subject, blood samples for lithium and salicylic acid plasma PK concentrations will be collected for safety assessments, if possible. The total volume of blood drawn, including the volume necessary for the safety laboratory tests, will be up to 603 mL (excluding the ET visit). Specifics regarding blood volumes to be obtained can be found in the study's lab manual. Adequate blood samples must be collected for both lithium and salicylic acid plasma validated bioassays, with priority given to blood samples for lithium bioassay. These blood samples will be processed at the clinical study site(s) and plasma aliquots shipped to the designated bioanalytical laboratory.

13 Coordination between lithium neuroimaging requirements will give priority to timely collection of PK blood samples when feasible, with all pharmacokinetic measure/parameter calculations based on actual times of sample/data collection. If neuroimaging cannot be conducted, PK blood sampling will be continued.

14 Standardized meals during confinement should include breakfast (at least 1 hour after first dose), lunch (at least 1 hour after second dose), dinner (at least 1 hour after third dose), and an optional (one) snack (if time permits and a 10-hour fast before the first morning dose the next day is respected). All meals and the optional (one) snack will be timed to ensure all doses are administered at least 1 hour before food ingestion or 4 hours after meals, 6 hours apart. Subjects are to receive standardized meals scheduled at approximately the same time each day while at the study site. One snack is allowed per day, which may be consumed with any meal, but does not have to be consumed at all if the subject does not require it. Non-carbonated water is allowed throughout the day as desired except for 1-hour before and 1-hour after drug administration. On Day -1 (P1) and Day -1 (P2), dinner (non-standardized) will be provided to study subjects. On Day 15 (P1) and Day 15 (P2), breakfast (non-standardized) will be provided to study subjects prior to their discharge from the study site.

15 Discharged on Day 15 (P1) and Day 15 (P2), or ET after completion of procedures.

16 The C-SSRS will be used to assess suicidal ideation and behavior (SI/B) at Screening, Day -1 (P1), Day -1 (P2); at least twice during each drug treatment period (P1 and P2) at times regarded as most clinically meaningful/useful; Day 15 (P1), Day 15 (P2), Day 23 (P2), Day 42 (P2); or ET. If at least two C-SSRS assessments were conducted between Day 1 and Day 14 in a treatment period, then it is unnecessary to conduct another C-SSRS assessment on Day 15 of that same treatment period. The C-SSRS will also be used to assess SI/B at least twice during the washout period (via telephone) at times regarded as most clinically meaningful/useful. Note “o” denotes when C-SSRS could be completed throughout each treatment period to assess SI/B to meet the minimum requirement of at minimum two assessments during each drug treatment period at times regarded as most clinically meaningful/useful.

17 The YMRS and HDRS-17 will be conducted at the following visits: Screening, Day -1 (P1), Day 15 (P1), Day -1 (P2), Day 15 (P2), and Day 23 (P2), or ET.

5.7. Study Procedures and Assessments

5.7.1. Informed Consent

Informed consent is the process of ensuring that potential subjects fully understand what will and may happen to them while participating in a research study. The informed consent form (ICF) documents that the subject:

1) has been informed about the study drug, study schedule, requirements, potential risks, benefits, and alternatives to participation, and

2) is willing to participate in the study.

Informed consent encompasses all written or verbal study information that the Investigator and/or study staff provides to the potential subject before and during the trial. Study staff will obtain informed consent from each subject prior to performing any study procedures according to study site's policies and procedures, and applicable regulations.

The informed consent process continues throughout the study. Key study concepts should be reviewed periodically with the subject and the review should be documented. At each study visit, study staff should consider reviewing the procedures and requirements for that visit and for the remaining visits. Additionally, if any new information becomes available that might affect the subject's decision to stay in the trial, this information will be shared with the subject. The ICF will be revised accordingly, submitted to the IRB for approval, and the subject will be asked to sign a new consent form.

Prior to implementing this study, the protocol and study-specific protocol consent form must be approved by an IRB. The study-specific consent form describes the study medications and all aspects of study participation, including Screening and enrollment procedures.

The Principal Investigator (PI) is responsible for developing the site-specific ICF. The Sponsor is allowed to review the draft ICF. The consent form must be developed in accordance with local IRB requirements and the principles of informed consent as described in Title 45, Code of Federal Regulations (CFR) Part 46 and Title 21 CFR, Part 50, and in the International Council for Harmonisation (ICH) E6, Good Clinical Practice: Consolidated Guidance 4.8.

5.7.2. Medical History and Demographic Information

Medical history, including surginal history and prior/concomitant medications, along with demographic information will be collected and recorded on the eCRF. Demographics will include information related to the subject's sex, age, race, and ethnicity.

5.7.3. Adverse Events

An adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, and occurs after the subject is given the first dose of study drug. Any AE that occurs prior to the first dose is part of the subject's medical history.

Subjects will be encouraged to spontaneously report any AE. Study personnel will ask open-ended questions to obtain information about AEs at every visit. Date and time of onset and resolution (if applicable) of the AE will be documented.

For full details on AE definitions and reporting see **Section 6**.

5.7.4. Physical Examination

A physical examination will be performed by a medically qualified and licensed individual as scheduled in Table 3. The physical examination will include a general review of the following body systems (at minimum): general appearance; head, eyes, ears, nose, and throat (HEENT); neck and thyroid; cardiovascular, respiratory, gastrointestinal, and neurological functions; skin; extremities.

Any clinically significant abnormalities at screening will be recorded in the eCRF. Any clinically significant abnormalities after the first study drug administration will be recorded as treatment-emergent adverse events (TEAEs).

5.7.5. Vital Signs

Vital sign parameters collected will include blood pressure, heart rate, and temporal artery body temperature (via digital medical grade thermometer) and will be measured after 5 minutes in a seated position as scheduled in Table 3. If possible, the same arm will be used for all measurements. On Days 1 to 14 of both study drug treatment periods, pre-dose vital sign measurements will be performed within 1 hour prior to the 8 AM dose.

5.7.6. 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed at the Screening visit and during the study as scheduled in Table 3. A ±10-minute window will be allowed for the 1-hour post third dose ECG measurement performed on Day 1 (P1) and Day 1 (P2). The ECG measurements will be performed after subjects are resting in supine position for at least 5 minutes and prior to any blood collection procedures. Individual parameters including heart rate, PR, QT, QTcF, QRS, and RR intervals will be collected. Repeat ECGs (if deemed necessary) should be performed at least 5 minutes apart.

A standard electrocardiograph machine will be used to record ECGs.

5.7.7. Clinical Safety Laboratory Tests

Laboratory evaluations will be performed as scheduled in Table 3. The laboratory evaluations to be conducted are presented in Table 4 and include a chemistry panel, hematology, serology, toxicology, and urinalysis. Female subjects of childbearing potential will also be tested for pregnancy.

Study subjects should be fasting for at least 10 hours prior to safety laboratory tests for accurate safety laboratory analysis/results. This includes the assessments done at Screening, Day -1 (P1), Day 15 (P1), Day -1 (P2), Day 15 (P2), Day 23 (P2), and when applicable, Early Termination visit.

The Investigator or appropriate designee will assess each abnormal value to determine if it is clinically significant. Prior to dosing on Day 1 of each study drug treatment period, a blood Na value must be at or above the lower laboratory normal value. Post-dose clinically significant laboratory values or values greater than 3x upper limit of normal will be reported as AEs, if applicable, as judged by the Investigator or designee. For each value reported as an AE, the Investigator must establish relationship to study medication.

Table 4: Safety Laboratory Assessments

Hematology	**Chemistry Panel**
Complete blood count including: Red blood cells (RBCs), hemoglobin, hematocrit, reticulocytes, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count White blood cell (WBC) count with differential including (absolute and percentage): neutrophils, lymphocytes, monocytes, eosinophils, basophils, band neutrophils HbA1c[a]	Albumin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) Blood Urea Nitrogen (BUN) or Urea Bicarbonate Creatinine (including eGFR calculated using the CKD-EPI refit equation) Electrolytes (Na, K, Cl, Ca, P, Mg) Glucose (fasting) Lactate dehydrogenase (LDH) Total bilirubin Direct bilirubin Total cholesterol[b] high-density lipoprotein (HDL)[b] low-density lipoprotein (LDL)[b] Triglycerides[b] TSH[a] Vitamin B12[a]
Serology[c]	**Female Subjects of Childbearing Potential Only**
HIV, HBV, HCV	Serum HCG pregnancy[d] Urine HCG pregnancy[d]
Urinalysis	**Toxicology**
Urobilinogen[e] Glucose Ketones Bilirubin Protein Nitrite Leukocytes Blood pH Specific gravity	Cannabinoids Opiates Barbiturates Amphetamines Cocaine Benzodiazepines Ethanol (Alcohol)[f]

a HbA1c, TSH, and Vitamin B12 will be performed on the following visits: Screening and Day 23 (P2), or ET (early termination). An additional TSH will be performed on Day -1 (P2).

b Lipid panel (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides) will be performed on the following visits: Screening, Day 15 (P1), Day 15 (P2), and Day 23, or ET.

c An HIV 1/2 Ag/Ab test will be used to detect antibodies to the HIV 1/2 and the HIV1 p24 antigen. HIV-1 and HIV-2 Antibody Confirmation and Differentiation testing will automatically be performed when the HIV 1/2 Ag/Ab test is reactive. If an HCV antibody test returns a positive result, a quantitative PCR viral load test will be ordered.
d For female subjects of childbearing potential only, a plasma pregnancy test will be performed at Screening; a urine pregnancy test will be performed on Day -1(P1), Day -1(P2), Day 15 (P2), and Day 23 (P2); or ET. If urine sample is not available, then collect blood sample for plasma pregnancy test.
e Urobilinogen may be measured via a urine dipstick test at the site if the local laboratory does not include it in their urinalysis panel.
f The ethanol (alcohol) test may be performed with saliva, urine, or blood. Refer to the study laboratory manual for details.

A positive pregnancy test after the subject has been dosed with a study drug will be recorded as an AE, and the subject will be terminated from the study (see Section 6.10).

Additional blood, urine, and/or saliva sample collection for re-testing of safety laboratory tests initially found to be outside the clinical laboratory's reference range may be requested by the Investigator to ensure the subject's continued eligibility and safety throughout the study.

5.7.8. Urine Drug Screening

At the Screening visit, Day -1 (P1), and Day -1 (P2), a urine sample will be collected to complete a urine drug screening which will include testing for illicit drugs (not prescribed medications) including cannabinoids, opiates, barbiturates, amphetamines, cocaine, and benzodiazepines.

5.7.9. Ethanol (Alcohol) Test

An ethanol (alcohol) test using either saliva, urine, or blood sample will also be conducted at Screening, on Day -1 (P1), and on Day -1 (P2).

5.7.10. Randomization

For inclusion of subjects in sequence within the cohort, standard methods of a computer-assisted randomization system will be used.

5.7.11. Study Drug Administration

For all subjects, doses of AL001 capsules or lithium carbonate capsules will be administered TID for 14 days at 8 AM, 2 PM and 8 PM (6 hours apart, within ±10 minutes) under fasted conditions (at least 10 hours before the first daily dose; for the second and third daily doses, at least 1 hour before or 4 hours after meals) while confined at the study site. Study medication will be administered with approximately 237 mL of non-carbonated water, starting in the morning of Day 1 of each study drug treatment period. Additional non-carbonated water will be permitted if necessary to complete dosing requirements. A mouth check will be performed by the study staff to ensure all capsules were ingested.

Subjects will be seated or in ambulatory posture for 1 hour post-dose for each dose on Day 13 (P1), Day 14 (P1), Day 13 (P2) and Day 14 (P2) except when not feasible such as due to neuroimaging procedures on Day 14 (P1) and Day 14 (P2). On all other dosing days, subjects will be encouraged to be seated or in ambulatory posture for 1 hour post-dose.

5.7.12. Standardized Meals

Standardized meals during confinement should include breakfast (at least 1 hour after first dose), lunch (at least 1 hour after second dose), dinner (at least 1 hour after third dose), and an optional (one) snack (if time permits and a 10 hour fast before the first morning dose the next day is respected). All meals and the optional (one) snack will be timed to ensure all doses are administered at least 1 hour before food ingestion or 4 hours after meals, 6 hours apart. Subjects are to receive standardized meals scheduled at approximately the same time each day while at the study site. One snack is allowed per day, which may be consumed with any meal, but does not have to be consumed at all if the subject does not require it. Non-carbonated water is allowed throughout the day as desired except for 1 hour before and 1 hour after drug administration.

On Day -1 (P1) and Day -1 (P2), dinner (non-standardized) will be provided to study subjects.

On Day 15 (P1) and Day 15 (P2), breakfast (non-standardized) will be provided to study subjects prior to their discharge from the study site.

5.7.13. Pharmacokinetics Blood Samples Collection and Lithium Neuroimaging

Blood samples for establishing each treatment period's baseline lithium and salicylic acid plasma PK values will be obtained on Day 1 (P1) and Day 1 (P2) prior to 8 AM dosing.

Following lithium carbonate capsule treatment and during lithium carbonate intensive PK blood sampling activities, blood samples for salicylic acid plasma PK bioassay will not be collected; salicylic acid plasma PK bioassay will only be conducted following AL001 treatment.

For the intensive PK blood sampling (30 samples for each analyte [lithium and salicylic acid]; 60 total samples from Days 13-15 of AL001 treatment period and 30 total samples from Days 13-15 of lithium carbonate treatment period), blood samples will be collected at pre-dose (or 0 h, i.e., within 0.25 hour prior to the 8 AM drug administration on Days 13 (P1), 13 (P2), 14 (P1) and 14 (P2) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6 (before the 2 PM dose), 6.5, 7, 8, 9, 10, 11, 12 (before the 8 PM dose), 12.5, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 hours after the initial 8 AM dose given on Day 14 (P1) and Day 14 (P2). A ±15-minute window for deviation from nominal times will be allowed for collection of PK blood samples.

Actual dosing and PK blood sampling times will be recorded for accurate/precise PK analyses. All PK measures/parameter calculations will be based on actual times of sample/data collection.

Additional blood samples for plasma PK bioassays may be obtained at the discretion of the Investigator during the trial, particularly to assess the relationship to possible lithium and/or salicylic acid related AEs. These "safety samples" could be sent expedited to a local laboratory with remaining aliquots saved for the bioanalytical laboratory.

If there is an early termination from the study of a study subject, blood samples for lithium and salicylic acid plasma PK concentrations will be collected for safety assessments, if possible.

The total volume of blood drawn, including the volume necessary for the laboratory tests, will be up to 603 mL (excluding the ET Visit). Specifics regarding blood volumes obtained can be found in the study's lab manual.

Adequate blood samples must be collected for both lithium and salicylic acid plasma validated bioassays, with priority given to blood samples for lithium bioassay. These blood samples will be processed at the clinical site(s) and plasma aliquots shipped to designated bioanalytical laboratory.

Bioassays for lithium and salicylic acid PK concentration in plasma will be validated as per FDA guidance:

- https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf.

Lithium brain distribution and mass will be characterized by using ^{7}Li-MRI-MRS on Day 14 (P1) and Day 14 (P2) at pre-dose (or 0 h, i.e., within 1 hours prior to drug administration) and at 3, 6, 8, 12, 16, 20, 24 hours after the initial morning dose to conduct individual brain structures and whole brain lithium neuroimaging bioassays. A ±20-minute window for deviation from nominal times for lithium neuroimaging will be allowed. At select imaging timepoints, a respiratory belt may be used to track subject's breathing motion during scanning. This will aid in motion correction of images during MRI data analysis.

Coordination between lithium neuroimaging requirements will give priority to timely collection of PK blood samples, with all PK measures/parameter calculations based on actual times of sample/data collection. If neuroimaging cannot be conducted, PK blood sampling will be continued.

In instances where an additional lithium neuroimaging scan session is needed for accurate data collection (based on the determination of the Investigator and with Sponsor's approval), the subject will be invited to participate in an additional lithium neuroimaging scan session.

The lithium neuroimaging method will be validated using a head phantom model prior to clinical deployment. (Iida 2013; Stout 2020)

All procedures will be repeated for treatments in the cross-over period of the study.

5.7.13.1. Bioanalytical Methods: Lithium and Salicylic Acid Including Expedited Deployments

Bioassays for lithium and salicylic acid plasma concentrations are to be validated and deployed in compliance with FDA guidances and conventions by qualified and experienced bioanalytical laboratories. Expedited lithium and/or salicylic acid bioassays that are clinically indicated and therefore requested by the Investigator(s) may be conducted by a local clinical laboratory or expedited by the study's designated bioanalytical laborarory. In the former case, remaining aliquots of these samples will be saved and sent to the study's designated bioanalytical laboratory for redundant/comparative assessments.

5.7.14. Mental Health Status Assessments (C-SSRS/YMRS/HDRS-17)

Assessment of subject's suicidal ideation and behavior (SI/B) using the Columbia-Suicide Severity Rating Scale (C-SSRS) will be conducted to avoid enrolling subjects with concerning results, defined as a lifetime history of a suicide attempt, past year level 4 or higher suicidal ideation on the C-SSRS, or past month suicidal ideation of any kind. The "Lifetime/Recent" version will be used at screening and the "Since Last Visit" version will be used subsequently.

Assessment of subject's mental health status using the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HDRS-17) will be conducted to avoid enrolling subjects who are on the verge of a manic or depressive episode. These tests will also be administered during this study to monitor subjects mental health status. Refer to Table 3 for specific timepoints.

5.7.15. Health Status Questionnaire (SF-36)

The Short Form Health Survey (SF-36) will serve as a secondary endpoint to evaluate the broader impact of the investigational intervention on study subject's perceived health status. It will be administered during this study to enable longitudinal tracking of health-related quality of life (HRQoL). The inclusion of this instrument aligns with regulatory guidance emphasizing the importance of study subject-centered outcomes and supports the protocol's objective to quantify therapeutic benefit in terms that matter to study subjects.

5.7.16. COVID-19 Testing

A COVID-19 testing schedule during the study, if any, can be appropriately determined at the discretion of the Investigator, based on guidelines from local health departments. This applies also to any other emergent infectious diseases/ health-related precautions.

5.7.17. Prohibited Medications and Foods

Subjects will be prohibited from taking any medication (OTC, prescription medication, vitamins, and herbal supplements) from 14 days prior to Day -1 (P1) (or at least 6 times the respective elimination half-life rather than 14 days, whichever is longer) through completion of the study on Day 42 (P2). Contraception may be continued. Acetaminophen may be concomitantly used at the discretion of the Investigator (up to 1000 mg TID). Non-medicated opthalmic products (for lubrication and comfort) may also be permitted at the discretion of the Investigator.

Prescribed or OTC use of any salicylate-containing product is prohibited, except for low dose aspirin for cardioprotection (e.g., aspirin, bismuth sub-salicylate, magnesium salicylate, salicylazosulfapyridine [sulfasalazine]), from 1 week before first dose of the first study drug treatment to 1 week after last dosing of the second study drug treatment. The use of any other prescribed anticoagulant medication is prohibited.

The following foods and drinks are prohibited during the course of this trial:

- Avoid consuming alcohol for at least 72 hours before each study treatment period
- Avoid eating poppy seeds or drinking Quinine (tonic water) for at least 48 hours before Treatment Day 1 until the end of the study, including the washout period

- Avoid eating or drinking caffeine-containing products for at least 48 hours before Treatment Day 1 until the end of the study, including the washout period
- Avoid eating or drinking grapefruits, pomelos, or Seville Orange products and juices at least 14 days before Treatment Day 1 until the end of the study, including the washout period

Violation of any restriction will be evaluated by the Investigator and Sponsor on a case-by-case basis to determine a subject's eligibility for enrollment or continuation in the study.

5.7.18. Removal of Subjects from Therapy or Assessment

5.7.18.1. Discontinuation of Individual Subjects

Under certain circumstances, an individual subject may be terminated from participation in this study. Specific events that will result in early termination (ET) include, but are not limited to:

- Subject refuses further participation (i.e., withdraws consent).
- Subject is non-compliant.
- Subject relocates and remote Follow-up is not possible.
- Investigator determines that the subject is lost to follow-up.

5.7.18.2. Subject Withdrawal from Study

Subjects are free to withdraw from the study at any time for any reason. The Investigator or the Sponsor/Sponsor's medical designee may withdraw a subject from the study if he/she believes it is in the best interests of the study or the subject. Reasons for withdrawal include, but are not limited to, any of the following:

- Protocol violation occurs.
- Serious or intolerable AE occurs.
- Clinically significant change in a vital sign, physical examination, or laboratory parameter occurs that poses a safety risk to the subject.
- Difficulties with blood collection.
- Subject requests to be discontinued from the study.
- Sponsor or Investigator terminates the study.

All subjects experiencing adverse reactions should be followed until the AE has resolved, stabilized, or no longer deemed clinically significant, as judged by the Investigator. Appropriate supportive and/or definitive therapy will be administered as required.

Subjects withdrawn from this study cannot re-enroll. Subjects who discontinue for a non-safety related reason may be replaced upon request by the Sponsor. Reason for withdrawal from study and the presence of any AEs must be ascertained and documented by the Investigator who must

consult with the Medical Monitors and document the subject's withdrawal from the study in the EDC form and note in the medical records. Should the subject agree to be followed for safety information, this should be documented in the medical records.

At the time of withdrawal, the subject should, if possible, have the early termination visit assessments performed. To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially safety status at study closure.

5.7.19. Discontinuation of Entire Study

The Sponsor and the Investigator reserve the right to terminate the study voluntarily at any time. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of each subject's interests and safety. The Investigator must inform the IRB of the study termination. Study Stopping rules are listed in **Section 6.13.**

5.8. Treatments

5.8.1. Identity of Investigational Product(s)

5.8.1.1. Formulation

AL001 Capsule

Lithium will be prepared as a proline and salicylate engineered crystal to optimize delivery. AL001 is a white crystalline powder which will be incorporated into a capsule dosage form (each capsule contains 210 mg of AL001). The empirical formula of AL001 is $C_{12}H_{14}LiNO_5$ and molecular weight is 259.19 g/mol. The quantitative composition of the oral dosage form of AL001 is presented in Table 5. L-Proline and salicylate are inactive ingredients to facilitate lithium delivery.

Table 5: Quantitative Composition of AL001

Ingredient	Amount per Gram (g)
Lithium	27 mg
Salicylate	529 mg
L-proline	444 mg

Lithium Carbonate Capsule

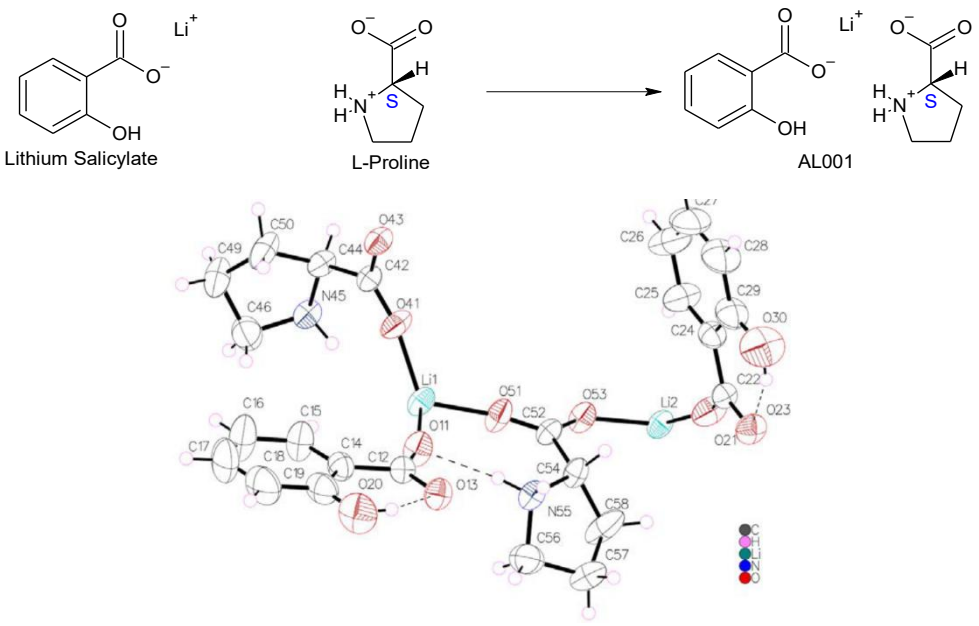
A marketed RLD lithium carbonate capsule formulation will be used as the reference product.

5.8.1.2. Chemical Structure

AL001

Colorless crystals of AL001 are produced from lithium salicylate and L-proline (Figure 2) as described in the Investigator's Brochure.

Figure 2: AL001 Chemical Reaction Diagram and Cocrystal Structure



Source: Alzamend Neuro

5.8.2. Packaging, Labelling, and Dispensing

The study medications will be labelled according to national regulations and/or guidelines. Labelling will be performed under conditions that are compliant with Good Manufacturing Practice (GMP). The labels attached to each packaging bottle will specify that the drug is for Investigational Use only. Drugs will be packaged in bulk.

5.8.3. Storage and Disposition of Study Medications

All study medications will be stored at USP controlled room temperature (20 to 25°C) under the supervision of the research pharmacist or other designated study staff. The study site should maintain a daily temperature log documenting storage conditions. Any excursions from the allowable temperature range should be reported to the Sponsor or designee promptly. The temperature logs will be reviewed by the CRA at each visit. At the completion of the study, all unused study medications will be inventoried by the CRA and returned to the Sponsor (or designee) or disposed by the site in accordance with the Sponsor's written instructions.

5.8.4. Selection and Timing of Treatments and Groups for Each Subject

Subjects will be randomly assigned to sequence cohorts at a ratio of 1:1 without any study deployment modifications. Refer to Figure 1, Study Schema.

5.8.5. Treatment Adherence

Treatment adherence, including refused or otherwise unused study medication, will be reviewed and documented for relationships to demographics, tolerability, PK, AEs, and any observed behavioral factors.

5.8.6. Drug Accountability Log

The Investigator, research pharmacist, or designee must maintain an accurate record of the receipt of the study medications shipment, including the date received and lot or batch numbers. In addition, an accurate record of dispensed study medication must be kept in a drug accountability log, specifying the Subject Screening Number, Subject Randomization Number, date, lot or batch numbers of AL001 capsules or lithium carbonate capsules dispensed, and the number of AL001 capsules or lithium carbonate capsules dispensed to each subject at each dose.

Monitoring of drug accountability will be performed by a CRA during site visits and at the completion of the trial. At the conclusion of the study, or as appropriate during the course of the study, the Investigator will destroy all unused study medications, packaging, drug labels according to instructions in the study's Pharmacy Manual. A copy of the completed drug accountability log will be retained.

6. ADVERSE EVENTS

6.1. Safety Monitoring

Subject's will be carefully monitored for safety throughout the trial. Lithium and salicylate potential adverse events are well characterized and are described below.

Lithium: Commonly reported and often tolerable side effects of lithium are: headache, mild to moderate nausea and/or vomiting, diarrhea, dizziness, drowsiness, changes in appetite, hand tremors, dry mouth, increased thirst, increased urination, thinning of hair or hair loss, and acne-like rash.

Signs of lithium toxicity include severe nausea and vomiting, severe hand tremors, confusion, vision changes, and unsteadiness while standing or walking; rarely-diabetes insipidus.

Salicylate: Commonly reported and often tolerable side effects of salicylate include dyspepsia, tinnitus, heartburn, epigastric distress and/or nausea; less frequently these present as mild to moderate vomiting, anorexia, or abdominal pain.

Signs of salicylate toxicity include severe vomiting, severe gastrointestinal bleeding, and tinnitus/hearing loss. These are generally dose and treatment duration related.

6.2. Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a study product/procedure(s) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational study product/procedure(s), whether or not related to the investigational study product/procedure(s).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition (including the physical examination), or abnormal results of diagnostic procedures (including laboratory test abnormalities).

Events should also be considered AEs and documented in source documents if they:

- Result in discontinuation from the study.
- Require treatment or any other therapeutic intervention.
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality).
- Are associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact.

An AE is not:

- A surgical procedure.

- A situation where an untoward event did not occur (e.g., an elective hospitalization).
- The disease being studied, unless progression is more severe than anticipated. (Does not apply for the current study of healthy subjects.)
- Lack of efficacy. (Does not apply for the current study of healthy subjects.)
- Baseline conditions that have not worsened in severity or frequency.
- The puncture from venipunctures.

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to believe the drug caused the event. Suspected adverse drug reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Clinically Significant Laboratory Changes: It is the Investigator's responsibility to review the results of all laboratory tests as they become available. For each abnormal result, the Investigator or appointed delegate (i.e., Sub-Investigators) needs to ascertain whether the abnormality presents a clinically significant change from baseline. If the change is due to the expected course of the subject's underlying disease (e.g., elevated cholesterol in a study of dyslipidemia), it is not considered an AE unless the abnormality is more severe than expected. An abnormal laboratory test result may be confirmed by repeat testing or other diagnostic tests before being considered an AE. If the laboratory abnormality is a significant change from baseline for the subject, then it should be considered an AE. Repeat laboratory testing will be performed to monitor the abnormal value until it returns within the normal range

6.3. Serious Adverse Event

As defined by the CFR, a serious adverse event (SAE) is any adverse experience that results in any of the following outcomes:

- Death.
- Life-threatening adverse drug experience defined as any adverse drug experience that, in the opinion of the Investigator, places the subject at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.
- An in-patient hospitalization (outside of that specified by the study protocol) or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity, defined as "A substantial disruption of a person's ability to conduct normal life functions".

- Congenital anomaly/birth defect (in the offspring of a subject).
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they jeopardize the subject or subjects and require medical or surgical intervention to prevent one of the outcomes in this definition. Examples of such medical events include but are not restricted to allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

SAEs are required to be reported by the Investigator to the Sponsor within 24 hours after learning of the event (see Section 6.11).

6.4. Adverse Event Severity

AEs will be graded according to the NCI-CTCAE version 5.0 (Table 6).

Table 6: NCI-CTCAE Severity Grading Guideline

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

Every effort will be made to obtain an adequate evaluation of the severity.

6.5. Relationship to Study Drug

The Investigator must assign a relationship of each AE to the investigational product (IP). The Investigator or appointed delegate (i.e., Sub-Investigators) will use clinical judgment to assess a plausible biologic mechanism for a temporal relationship between the onset of the event in relation to receipt of the IP, and the Investigator may determine possible alternate etiologies including underlying disease, concurrent illness or concomitant medications. The following guidelines should be used by Investigators to assess the relationship of an AE to study product administration:

- NOT RELATED: No relationship to study product. Applies to those events for which evidence exists that there is an alternate etiology.
- UNLIKELY RELATED: The temporal association between the study product and AE is such that study treatment is not likely to have any reasonable association with the AE.

- POSSIBLY RELATED: An association between the event and the administration of study product cannot be ruled out. There is a reasonable temporal association, but there may also be an alternative etiology such as the subject's clinical status or underlying factors including other therapy.
- PROBABLY RELATED: The AE follows a reasonable temporal sequence from the time of study product administration, and cannot be reasonably explained by the known characteristics of the subject's clinical state.
- DEFINITELY RELATED: An association exists between the receipt of study product and the event. An association to other factors has been ruled out.

Hospitalization for elective surgery related to a pre-existing condition, routine clinical procedures, or social reasons that did not increase in severity or frequency after beginning the study are not considered to be AEs, but must be recorded in the source documents. If the hospitalization is due to a pre-existing condition or was planned prior to the start of the study, the condition that led to the hospitalization should be recorded in the electronic Case Report Form (eCRF) Medical History form. If the hospitalization arises from a pre-existing condition that did not worsen and the hospitalization was planned after the start of the study, the condition that led to hospitalization should be recorded in the AE page of the eCRF. In both cases, the condition that led to hospitalization should be recorded, and the relationship to IP will be recorded as "Not Related".

6.6. Unexpected Adverse Event

As defined by 21 CFR 312.32 (a), an unexpected adverse drug experience is:

"An AE or suspected adverse reaction is considered 'unexpected' if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. 'Unexpected' as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation". The expectedness will be assessed by the Sponsor for all AEs and will be reported in the final report.

New or unresolved AEs are to be followed until they are resolved or a stable medical condition is reached. Unexpected/unsolicited AEs with onset within 30 days of the last dose of AL001 capsules or lithium carbonate capsule will be captured and monitored until resolution.

6.7. Other Adverse Events

Other AEs may be identified by the Investigator during the evaluation of the safety data. Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from the study will be classified as other AEs. For each other AE, a narrative may be written and included in the Clinical Study Report (CSR). The Sponsor or

Clinical Research Organization (CRO) will include narratives in the CSR for all SAEs and AEs causing discontinuation.

6.8. Adverse Event Collection Period

The Investigator(s) will seek information on AEs at each subject contact via a general, non-leading question. All AEs, whether spontaneously reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the Adverse Event eCRF.

A treatment-emergent AE (TEAE) is defined as any event not present prior to the first dose of study drug or any event already present that worsens in either intensity or frequency following exposure to the treatment. Non-treatment emergent AEs occur after informed consent has been obtained but before first dose of study drug. These non-treatment emergent AEs should be documented in the subject's medical history.

After informed consent has been obtained but prior to dosing of any IP, all non-treatment emergent AEs should be recorded on the eCRF throughout the study treatment period post Screening. Subjects are dosed after this period, therefore Investigators should report any deaths, SAEs, or AEs suspected to be caused by the IP.

6.9. Adverse Event Reporting

After the first dose of study drug is given to every subject, the Medical Monitors should evaluate every AE and adverse reaction to determine if it meets the requirements for expedited reporting. The Sponsor, or if designated, the CRO, will report all AEs, SAEs, and unexpected adverse events (UAEs) observed in this clinical trial to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports).

6.10. Reporting of Pregnancy

Pregnancy in a female study subject shall be reported to the Sponsor within 24 hours of the knowledge of its occurrence by an Investigator or delegate (for pregnancies occurring during the course of the study or immediately following the end of the study). Because of the possibility the fetus/embryo could have been exposed to the study drug through the parent and for the subject's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

The pregnancy will be recorded and reported by the clinical site to the Sponsor. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the study drug and will include an assessment of the possible causal relation between the study drug and any pregnancy outcome. Any SAE experienced during pregnancy will be reported on an SAE Report Form.

6.11. SAE Reporting

Any SAE that occurs after the first dose is administered until the last visit must be reported to the Medical Monitors whether or not it is judged to be related to the study drug.

If the Investigator determines that the event is an SAE, the following procedures will be followed:

- The Investigator will report the SAE directly to the Medical Monitors by telephone within 24 hours of when the Investigator becomes aware of the SAE.
- An initial written report must also follow within 24 hours (via email).
- The Investigator will provide, at a minimum, the protocol number, subject's initials, Subject Screening Number, date of the SAE, event term and relationship to investigational product or reference product. The initial SAE report form should be submitted with any supporting data. All supporting information must redact subject names and other identifying information before submission.
- An interim written report and a final written report must be submitted in a timely manner after the initial written report.

An SAE requiring immediate notification should be in the form of a telephone call and a follow-up email. The Medical Monitors contact information are listed below in Table 7.

Table 7: Medical Monitors Contact for Reporting Serious Adverse Events

Medical Monitors	Michael Murphy, MD, PhD Phone: (617) 855-3972 Email: mmurphy@mgh.harvard.edu Susie Huang, MD, PhD Phone: (617) 935-3257 Email: susie.huang@mgh.harvard.edu

The study site has the responsibility to notify the Sponsor in writing of any UAE (where causality is possibly related or greater) and/or SAE within 24 hours of the event.

The IRB should also be notified of the SAE by the site within the timeframes described below:

- Unexpected adverse events (UAEs) qualifying as SAEs should be reported to the IRB within 24 hours of the Investigator becoming aware of the event.
- Any other UAE should be reported to the IRB within 5 working days of the Investigator becoming aware of the event.

An initial report followed promptly by a complete report will be sent to the Sponsor and the Medical Monitors for any UAEs where causality is possibly related or greater and for all SAEs; copies of the reports will be forwarded to the IRB when necessary.

6.12. Adverse Event Follow-Up

The subject will be observed and monitored carefully until:

- Event resolves, or
- Event/condition has stabilized (e.g., in the case of persistent impairment), or
- Event returns to baseline, if a baseline assessment is available.

The Investigator and Medical Monitors will determine if additional follow-up is required. Follow-up information relating to an SAE must be submitted as soon as additional data related to the event are available. All efforts must be taken to obtain follow-up information promptly.

Follow-up information may consist of:

- A hospital discharge summary for the subjects who are hospitalized. If possible, the discharge summary should be obtained when it becomes available.
- A copy of the autopsy report, if a death occurs and an autopsy is performed, should be obtained if possible when it becomes available.

Any SAEs that are ongoing at end of the study should be followed as described above until resolution. Data obtained after end of the study should be recorded on the source documents and submitted to the Safety Team (Medical Monitors and IRB) and the Sponsor on an SAE report form. For ongoing SAEs, the Investigator must submit follow-up SAE reports regarding the subject's subsequent course until the case is closed. It is not until the case is closed that the subject will be officially discharged from the study.

6.13. Study Stopping Rules/Benchmarks

The study will be stopped for individual subjects based on discretion from the Sponsor and the Principal Investigator, if there is evidence of lithium and/or salicylate toxicity including:

- Lithium toxicity:
  - Gastrointestinal: progressive diarrhea or vomiting.
  - Central nervous system: muscle weakness, lack of coordination, drowsiness or lethargy progressing to dizziness, ataxia, tinnitus, blurred vision, dysarthria, coarse tremor, and muscle twitching.
- Salicylate toxicity:
  - Gastrointestinal: progressive nausea/vomiting.
  - Central Nervous System: diaphoresis, tinnitus, vertigo, hyperventilation, and hyperactivity. As toxicity progresses, agitation, delirium, hallucinations, convulsions, lethargy, and stupor may occur.

The study may also be stopped for the following reasons:

- The study will be stopped for individual subjects if there are voluntary withdrawals or Investigator concerns for any reason.
- The study will be stopped upon early termination by the Investigator due to assessed drug intolerance/adverse events.
- The study will be stopped if FDA, IRB, or other regulatory bodies deem the study unsafe or unwarranted.

6.14. Drug Interaction Monitoring

Drug-drug interactions have been identified for lithium. Careful safety monitoring is required when there are concomitant treatments.

The following table is provided to enhance awareness of these interactions.

Table 8: Medicines That May Interact with Lithium

Interactions that may increase lithium concentrations	
Selective serotonin re-uptake inhibitors (SSRIs)	
Non-steroidal anti-inflammatory drugs (NSAIDs)	
Angiotensin-converting enzyme (ACE) inhibitors	
Angiotensin-II receptor antagonists	
Diuretics: thiazides, spironolactone, furosemide	
Other: metronidazole, tetracyclines, topiramate, medicines that affect electrolyte balance	
Interactions that may cause or aggravate neurotoxicity	
Xanthines: theophylline, caffeine	
Sodium bicarbonate and sodium chloride containing products	
Other: psyllium or ispaghula husk, urea, mannitol, acetazolamide	
Interactions that may cause or aggravate neurotoxicity	
Antipsychotics: haloperidol, risperidone, clozapine, phenothiazines	In rare cases: confusion, disorientation, lethargy, tremor, extrapyramidal symptoms, myoclonus.
SSRIs, sumatriptan, tricyclic antidepressants	Associated with episodes of neurotoxicity and may precipitate serotonin syndrome. Either presentation justifies immediate discontinuation of treatment. Lithium can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, triptans, tricyclic antidepressants, fentanyl, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs. Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor,

	rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).
Calcium channel blockers	May lead to ataxia, confusion and somnolence, reversible after discontinuation of the medicine.
Carbamazepine, phenytoin	May lead to dizziness, somnolence, confusion, cerebellar symptoms.
Methyldopa	A drug interaction that exaggerates the action of lithium at the central nervous system neuron or enhances lithium uptake by the brain has been proposed as theoretically concerning.
Other interactions	
Neuromuscular blocking agents	Lithium may prolong the effects of these agents.
Iodine	May act synergistically with lithium to produce hypothyroidism.
Other: baclofen, cotrimoxazole, cyclovir, prostaglandin-synthetase inhibitors	Case reports of interactions with lithium. Clinical significance uncertain.

Source: Medsafe NZ and FDA Lithium Carbonate Label

7. PROTOCOL DEVIATIONS

This study is intended to be conducted as described in this protocol. Waivers to the inclusion/exclusion criteria will be considered on a case-by-case basis. In the event of other significant deviations from the protocol due to an emergency, accident, or mistake, the Investigator or designee must notify the Medical Monitors by submitting a form via e-mail that documents the deviation for approval for the subject to continue participation in the study.

Significant deviations that require review by the Medical Monitors include deviations from inclusion/exclusion criteria, use of prohibited medications or therapies after subject enrollment, significant non-compliance, or treatment (dosage) error. In addition, all deviations will be captured in the EDC and/or Clinical Trial Management System tracking system.

8. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

8.1. Sample Size

The objective of this study is to estimate relative bioavailability of PK parameters of AL001 capsule as compared to marketed lithium carbonate capsule and precision of the estimate.

A sample size of 6 completing subjects with evaluable results is selected. The sample size is not based upon any available statistical data for human brain lithium PK. The number of subjects is also not based on statistical power considerations. The estimate of the within-subject standard deviation of log transformed AUC of 0.065, as observed in Alzamend study AL001-ALZ01, was used in calculation of precision. The following table provides probable confidence limits and confidence width for several possible absolute bioavailability estimates, based upon AUC, including the hypothesized value of 95%. If the absolute bioavailability estimate is 95%, the 95% confidence interval will be no wider than (83.6%, 108.3%) with tolerance probability of 80%. Minimum relative precision, defined as the relative distance of the lower confidence limit from the estimate is 12%.

Probable Confidence Intervals for Several Absolute Bioavailability Estimates based on AUC are:

Bioavailability Estimate	Lower Limit of Probable CI	Upper Limit of Probable CI	Probable CI Width
40%	35.2%	45.6%	10.4%
50%	44.0%	57.0%	13.0%
60%	52.8%	68.4%	15.6%
70%	61.6%	79.8%	18.2%
80%	70.4%	91.2%	20.8%
90%	79.2%	102.6%	23.4%
95%	83.6%	108.3%	24.7%

Probable Confidence Intervals for Several Absolute Bioavailability Estimates based on C_{max} are:

Bioavailability Estimate	Lower Limit of Probable CI	Upper Limit of Probable CI	Probable CI Width
40%	30.8%	52.0%	21.2%
50%	38.5%	65.0%	26.5%
60%	46.2%	78.0%	31.8%
70%	53.9%	91.0%	37.1%
80%	61.6%	104.0%	42.4%
90%	69.3%	117.0%	47.7%
95%	73.2%	123.5%	50.4%

The estimate of the within subject standard deviation of log transformed C_{max} of 0.135, as observed in Alzamend study AL001-ALZ01, was used in calculation of precision.

Both the investigational product and the reference product are expected to provide at least 95% lithium bioavailability *per os* due to their highly soluble, highly permeable properties.

8.2. Populations for Analysis

Screened Analysis Set: The Screened Analysis Set will include all subjects who have signed the inform consent form.

Randomized Analysis Set: The Randomized Analysis Set will include all subjects who are randomized within one of the sequence cohorts.

Safety Analysis Set: The Safety Analysis Set will include all subjects in the Randomized Analysis Set who receive any dose of study drug. This analysis set will be utilized for all safety analyses.

Pharmacokinetic Analysis Set: For the purpose of relative bioavailability/bioequivalence testing, the PK Analysis Set will include all subjects in the Safety Analysis Set who receive AL001 capsule or lithium carbonate capsule and have at least one complete plasma or brain/brain structure pharmacokinetic profile.

Pharmacodynamics Analysis Set: For the purpose of relative bioavailability/bioequivalence testing, the Pharmacodynamics Analysis Set will include all subjects in the Safety Analysis Set who receive AL001 capsule or lithium carbonate capsule and have at least one complete plasma or brain/brain structure pharmacokinetic profile.

8.3. General Considerations

Lithium and salicylic acid PK in blood (plasma) are well characterized for relationship to efficacy and safety in the medical literature and in the labelling of multiple marketed products. For the current study, documentation of lithium and salicylic acid plasma data and plasma PK summary statistics can serve to confirm consistency of results to the extant literature. The statistical analysis plan (SAP), a companion document to this protocol, will provide how these results are displayed in tables, listings, and figures (TLFs). The lithium brain and brain structure neuroimaging pharmacokinetic results are expected to provide a novel scientific contribution to lithium pharmacology, and will be similarly communicated.

Continuous variables will be summarized using the number of observations, mean, standard deviation, minimum, median, and maximum. Pharmacokinetic variables will also be summarized using the geometric mean (i.e., the mean calculated on the $\log_e$ scale transformed back to the original scale). Categorical variables will be summarized using frequencies and the corresponding percentage.

Baseline for each safety parameter is defined as the last value collected prior to the first dose of study drug.

8.4. Disposition of Subjects

The number of subjects in each analysis set will be summarized by treatment group for each sequence cohort/neuroimaging group and overall (aggregate). In addition, the number of subjects in the Randomized and Safety Analysis Sets who complete the clinical trial and who prematurely discontinue, including the reason for premature discontinuation, will be summarized by treatment group sequence cohort/neuroimaging group and overall (aggregate).

8.5. Demographic & Baseline Characteristics

Descriptive statistics for demographic (e.g., age, race, and sex) and baseline characteristics (e.g., body height, body weight, body mass index) will be presented by treatment group for each sequence cohort and overall.

Demographic and baseline characteristics (including age, sex, weight, etc.) will be summarized descriptively using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Continuous variables will be summarized using the number of observations, mean, standard deviation, minimum, median, and maximum.

Variables that will be included in demographic and baseline summaries will be provided in detail in the SAP.

8.6. Primary Analyses

8.6.1. Efficacy Analysis

Not Applicable.

8.6.2. Safety Analyses

Demographic and baseline characteristics (including age, sex, weight, etc.) will be summarized descriptively using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate for each treatment group. Summaries will be presented by sequence, if deemd necessary.

Safety endpoints are as follows:

- Adverse events (AEs)/serious adverse events (SAEs).
- Vital signs (blood pressure, pulse rate, temporal artery body temperature).
- 12-lead ECG.
- Physical examination.
- Safety laboratory tests (standard hematology, blood chemistry panel, and urinalysis).
- Prevalence of plasma lithium concentrations above 1.2 mEq/L.
- Prevalence of plasma salicylic acid concentrations above 30 mg/dL.

In order to evaluate the safety and tolerability of AL001 capsule and lithium carbonate capsule under the conditions of this study, descriptive statistics will be presented by treatment group. If deemed necessary and appropriate, descriptive statistics will also be presented for each sequence cohort and/or overall for the following:

- Proportion of subjects with TEAEs.
- Proportion of subjects with SAEs.
- Proportion of subjects with TEAEs that lead to premature discontinuation.
- Change from baseline for each safety laboratory test.
- Proportion of subjects with abnormal values for each safety laboratory test.
- Change from baseline for each ECG parameter.
- Proportion of subjects with abnormal values for each ECG parameter.

Planned summaries of safety endpoints will be provided in detail in the SAP.

8.6.3. Pharmacokinetics 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 capsule and lithium carbonate capsule will use pharmacokinetic and statistical conventions consistent with FDA guidance for bioequivalence testing:

- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-approaches-establishing-bioequivalence
- https://www.fda.gov/files/drugs/published/Bioavailability-and-Bioequivalence-Studies-Submitted-in-NDAs-or-INDs-%E2%80%94-General-Considerations.pdf
- https://www.fda.gov/media/121311/download

8.6.3.1. Analysis of PK Concentrations and derived PK measures/parameters

Plasma concentrations of lithium and salicylic acid, lithium brain/brain structure PK values, with derived PK measures are to be listed by subject identifier, nominal and actual times of sampling (where appropriate), and summarized by nominal time point and by treatment including number of observations (N), arithmetic mean (mean), standard deviation (SD), geometric mean, minimum (min), median, maximum (max), and coefficient of variation (CV%) for AL001 capsule and lithium carbonate capsule treatments.

In order to assess whether PK steady state has been approximately achieved, descriptive statistics for 3 trough measurements of lithium and salicylic acid will be presented for Day 13 (8 AM), Day 14 (8 AM) and Day 15 (8 AM, 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. Alternative approaches to estimate achievement of steady-state conditions may be used, as appropriate. This will be discussed in the SAP.

Plasma concentration data from individual subjects will be used to derive the following pharmacokinetic parameters for AL001 capsule and lithium carbonate capsule:

- Plasma $AUC_{tau\ ss}$ = Area under the plasma concentration versus time curve from time zero to the end of the 24-hour 3-dose interval at steady-state
- Brain $AUC_{tau\ ss}$ = Area under the brain concentration versus time curve from time zero to the end of the 24-hour 3-dose interval at steady-state
- Plasma $C_{max\ ss}$ = Maximum plasma concentration at steady-state
- Brain $C_{max\ ss}$ = Maximum brain concentration at steady-state
- Plasma $t_{max\ ss}$ = Time to reach the maximum plasma concentration at steady-state
- Brain $t_{max\ ss}$ = Time to reach the maximum brain concentration at steady-state
- Plasma $C_{min\ ss}$ = Minimum plasma concentration at steady-state (if at end-of-24 hour dosing interval: C_{trough})
- Brain $C_{min\ ss}$ = Minimum brain concentration at steady-state (if at end-of-24 hour dosing interval: C_{trough})
- Plasma $t_{min\ ss}$ = Time to reach the minimum plasma concentration at steady-state over 24 hours
- Brain $t_{min\ ss}$ = Time to reach the minimum brain 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 ($C_{max\ ss}$ - $C_{min\ ss}$) 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 swing 24 h = [($C_{max\ ss}$ - $C_{min\ ss}$)/ $C_{min\ ss}$]
- 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)*
- 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 documented as accurate and precise.
- Individual brain structure (e.g., hypothalamus, frontal cortex) $AUC_{tau\ ss}$ to total brain $AUC_{tau\ ss\ brain}$ ratios will be calculated when documented as accurate and precise. Statistical analysis will be conducted as for $AUC_{brain\ ss}$ to $AUC_{plasma\ ss}$.
- Steady-state conditions will be assessed by applying linear regression of 3 trough analyte plasma concentrations presenting on Days 13, 14 and 15 or by other appropriate method(s).

*Mean Residence Time following oral doses at steady-state from time zero to 24 hours {MRT oral doses ($_{0\text{-}24h\ ss}$)} is a pharmacokinetic parameter that represents the average time a drug molecule remains in a biological matrix at steady-state under the dosing conditions of this study, unadjusted for the mean input times (MIT) for AL001 and Li_2CO_3.

See: https://www.certara.com/knowledge-base/mean-residence-time-mrt-understanding-how-long-drug-molecules-stay-in-the-body

The calculation of MRT is often adjusted to the IV bolus case when the route of administration is other than IV bolus to account for the time required for the drug to enter the biological matrix, otherwise there is artifact (the value is dosing-condition dependent) due to the MIT. However, in the current study MRT values will only be used for the purpose of calculating and statistically assessing comparative persistence of lithium in biological matrices following when these test articles, AL001 and Li_2CO_3, are administered. Both AL001 and Li_2CO_3 are given PO with identical lithium doses TID for 14 days (8 AM, 2 PM, 8 PM). No adjustments for MIT are appropriate due to known rapid and complete systemic absorption of both treatments, documented single-dose bioequivalence in plasma, and established linear systemic lithium pharmacokinetic behavior at the lithium doses administered. The method of Denney et al. for steady-state conditions adjusted for the conditions of this study will be deployed for MRT calculations (See: https://humanpred.github.io/pknca/reference/pk.calc.mrt.html).

8.6.3.2. Analysis of PK Parameters

PK parameters listed above will be summarized separately for AL001 capsule and lithium carbonate capsule. Summaries will include number of subjects, mean, median, geometric mean (as appropriate), minimum, maximum, and coefficient of variation (as appropriate).

Analysis of variance will be performed on log(AUC_{tau}) and log(C_{max}). Point estimates and 90% confidence intervals 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. No adjustment will be made of multiplicity.

The SAP will provide in detail a list of PK parameters to be summarized and the associated summary statistics to be presented for each parameter. Statistical analyses that are planned for key PK parameters will also be provided in detail in the SAP.

8.6.3.3. Aggregate Analysis of PK Parameters

PK parameter data from this healthy subject study (AL001-ALZ03) will be combined, as appropriate, with results from planned studies on subjects with bipolar I disorder (AL001-BD01), subjects with major dipressive disorder (AL001-MDD01), subjects with post-traumatic stress disorder (AL001-PTSD01), and subjects with Alzheimer's disease (AL001-ALZ04). These 5 studies, all conducted using a similar two-treatment, two-period, cross-over design, are expected to provide data from 30 subjects total. This combined dataset will be statistically analyzed as appropriate to evaluate similarities and differences of AL001 capsule to lithium carbonate capsule across 5 study populations.

Details of planned aggregate analyses will be provided in the SAP.

8.7. Exploratory Analyses

Analysis of endpoints for plasma salicylic acid PK will be the same as for the primary endpoints for plasma lithium PK.

Magnetic resonance spectroscopy (MRS) techniques will be also applied to explore brain metabolism, including possible metabolic similarities/differences between treatments. The healthy subject data collected during this study are expected to be combined/compared with analogous results from BD1 subjects, MDD subjects, PTSD subjects, and AD subjects to complete an aggregate total of 30 subjects under multiple INDs. The potential disease-modifying effects of lithium on these and other neurodegenerative, neurological and neuropsychiatric conditions may be explored.

Details of other exploratory analyses planned will be provided in the SAP.

8.8. Interim Analysis

No interim analysis is planned.

8.9. Study Randomization and Blinding

Enrolled subjects will be equally randomized to one of two treatment sequences (see Table 9).

Table 9: Study Treatment Sequence

Treatment Sequence	Treatment Order
A	AL001 – Lithium Carbonate
B	Lithium Carbonate – AL001

This is an open label study and neither subjects nor investigative staff will be blinded.

8.10. Subject Recruitment/Deployment

All potential subjects will be made aware of the opportunity to take part in this study. Informative IRB-approved brochures and/or flyers will be made available to interested candidates. Subjects

will be informed about the study and allowed to discuss and ask questions about the requirements and procedures related with the study before providing informed consent. Subjects will be encouraged to discuss the study with their healthcare provider. Subjects will be admitted to the clinical research unit at least 16 hours prior to the initial study drug administration in each treatment period, and undergo 2 x 16-day confinement periods. Subjects will be asked to return to the clinic on Day 23 (P2) ±2 days, 9 days after last dose of the second study period, for a safety Follow-up visit and will have a telephone call on Day 42 (P2) ±2 days. Subjects will then be discharged from the study provided no follow-up until resolution of an AE is necessary.

9. ETHICS

9.1. Independent Ethics Committee or Institutional Review Board (IRB)

This protocol, the ICF, any materials used for subject recruitment, and any handouts to the subjects as well as any subsequent modifications to these documents will be reviewed and approved by the relevant IRB/Independent Ethics Committee (IEC) responsible for oversight of the study. A letter from the IRB/IEC indicating approval of the study and these documents will be provided to the Sponsor prior to initiation of any subject Screening activity at the study site. All reviews and approvals by the IRB/IEC will be in accordance with 21 CFR Part 56 and ICH Good Clinical Practice (GCP).

9.2. Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor, its authorized US representative and Investigator(s) abide by GCP as described in ICH Guideline E6, and in US regulations described in 21 CFR Parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles that have their origins in the Declaration of Helsinki.

9.3. Subject Information and Consent

The ICF document must be signed and dated by the subject prior to the initiation of any study-related procedures. The original signed ICF for each subject shall be filed with records kept by the Investigator. A copy of the fully executed ICF must be provided to the subject.

9.4. Confidentiality

Personal study subject data collected and processed for the purposes of this study should be managed by the Investigator and study staff with adequate precautions to ensure the confidentiality of those data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors and other authorized agents of the Sponsor, the IRB approving this research, and any applicable regulatory authorities will be granted direct access to the study subjects' medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentation of the results of this study at meetings or in publications, the subjects' identity will remain confidential.

9.5. Insurance Policy

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all local indemnification requirements. The civil liability of the Investigator, the persons instructed by the Investigator, the hospital, practice, or institute in which they are employed, and the liability of the Sponsor in respect to financial loss due to personal injury and other damage, which may

arise as a result of conducting this study, are governed by the applicable law. As a precautionary measure, the Investigator, the persons instructed by him/her and the hospital, practice or institute are included in such cover in regards to work done by them in carrying out this study to the extent that the claims are not covered by their own professional indemnity insurance. The Sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical product being tested or by medical steps taken in the course of the study. Such insurance is taken out by the Sponsor in accordance with regulations in the country concerned. To the extent that payments are made under such insurance, the right to claim damages from the Sponsor extinguishes.

9.6. Subjects' Compensation

Subjects will be compensated for participating in this research study in an amount that is equitable and not considered coercive by the IRB. The compensation amount will be determined by the study site for this type of study as per the site's practices and market.

10. SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

10.1. Source Documents

The Investigator and/or study staff will complete and maintain source documents for each subject enrolled in the study. The source documents should contain all demographic and medical information, including laboratory data. However, safety laboratory reports can be treated as source documents. The subject's source documents file should also indicate that they are participating in the clinical study, referencing the study number and the study medication.

All information required by the protocol should be documented in the source records initially. An explanation must be given for any omissions. Each evaluation recorded will be performed at the time specified in the protocol. Alternative approaches regarding source records will be considered by the Sponsor to facilitate study site policies, procedures and productivity tools/approaches.

10.2. Electronic Data Capture Forms

The study will use an EDC system which is 21 CFR Part 11 compliant. Whenever possible, data should always be collected in source documents initially and transcribed to the corresponding eCRF. An exception may be safety laboratory data. This data collection process will be described in detail in the Data Management Plan (DMP). All information recorded via EDC will be tracked by an internal audit built into the EDC system. The specific data recorded directly to EDC without supporting source documents will be designated in the DMP.

After each subject visit prior to treatment initiation and during confinement, all information collected from the subject must be transcribed from the source document into the EDC system in real time whenever possible (or within the timeframe specified in the DMP if transcription in real time is not possible) and be made available for review by the CRA and/or Medical Monitors, in order to verify the validity and completeness of the data and to permit prompt transmission of the data. The Investigator should review all data recorded via EDC for completeness, accuracy, and legibility.

10.3. Monitoring

A study site initiation meeting will be conducted by the CRA. At this meeting, the protocol, the procedure for recording data in the EDC system, and pertinent aspects of the EDC will be reviewed with the Investigator and study staff.

Monitoring will be conducted routinely during the study. The Investigator will make a reasonable amount of time available to the CRA to assist in answering questions and discuss the progress of the study. At each visit, the CRA will review the source documents against the eCRF in order to ensure that all items have been completed and that the data entered in the EDC system are accurate and obtained in the manner specified in the Clinical Monitoring Plan (CMP) and the DMP. The CRA will also review the Investigational Site File (ISF) and the Trial Master File (TMF) to ensure all regulatory documents and study documentation is complete and up-to-date, as well as source documents related to the study drugs (drug accountability, storage and temperature logs, and shipment) and PK samples (collection, processing, storage, and shipment), and neuroimaging procedures.

11. DATA QUALITY ASSURANCE

11.1. Auditing

In addition to study monitoring visits, a study site may undergo a quality assurance (QA) audit. The Sponsor, or their authorized representatives may conduct a QA audit. Also, a regulatory agency, such as the FDA or the IRB, may conduct an audit. If the FDA requests an audit of the study site, the Investigator is required to inform the CRA and/or the Sponsor immediately.

11.2. Record Retention

The Investigator will maintain adequate records so that the conduct of the study can be fully documented and monitored. Copies of protocols, printed EDC forms, the EDC audit trail, test result source documents, all drug accountability records, correspondence, subject ICFs, and any other documents relevant to the conduct of the study will be kept on file by the Investigator. Study documents will not be destroyed. For regulatory inspections, it will be necessary to have access to the complete study subject records, provided that subject confidentiality is maintained.

Per the Clinical Trial Agreement (CTA) between the Investigational Study Site and the Sponsor, and/or their authorized representatives, the Investigator must retain subjects' study records for 7 years after the study closeout or for a period of 2 years after FDA approval of the study drug (whichever is longer), or until written approval to destroy the documentation is provided by the Sponsor. The documentation must be retained longer if so required by local law. The Investigator must notify the Sponsor and its representative, in writing, if any of the following situations arise in order to make arrangements for the maintenance of study files: 1) intention to destroy documents (request for approval), 2) changes in address, or 3) sale of practice or closure of study site. In addition, the Investigator should provide documentation of the facility where study records will be stored long term.

12. USE OF INFORMATION AND PUBLICATION

12.1. Use of Information

Regardless of the outcome of a clinical study, the Sponsor is dedicated to openly provide information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results.

12.2. Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of this clinical study will be considered as a joint publication by the Investigator and the Sponsor. The Investigator will provide the Sponsor with copies of any proposed written publications (including abstracts and posters) in advance of submission. This review by the Sponsor is to confirm accuracy of the submission (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential information is not inadvertently divulged (including patent protection), to allow adequate input or supplementary information that may not have been available to the Investigator, and to allow establishment of co-authorship. Any such intent by the Investigator, presentation or publication of data will require prior written approval by the Sponsor.

13. COMPLETION OF THE STUDY

13.1. Protocol Amendment and Administrative Change

All changes to the protocol must be documented by amendments or administrative changes where applicable. The amended protocol must be signed by the Sponsor and the Investigator. The amended protocol and a revised ICF will be submitted to the IRB for approval when safety of subjects can be affected. If the protocol modifications affect the EDC database, then database will be revised accordingly, provided to the study site, and submitted with the amended protocol for IRB submission if required by regulations.

13.2. Pre-Mature Termination or Suspension of the Study

The Sponsor and the Investigator reserve the right to voluntarily terminate the study at any time for scientific or corporate reasons. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of each subject's interests and safety.

If the trial is prematurely terminated or suspended for any reason, the study site or the Investigator (or delegate) should promptly inform the trial subjects and follow-up with the subjects as appropriate, and should inform the regulatory authority(ies) when required. As applicable, subjects shall be scheduled for an early termination (ET) visit or other appropriate follow-up visit(s).

14. REFERENCES

References listed below are on file and can be furnished upon request.

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