CLINICAL STUDY PROTOCOL

A MULTIPLE-DOSE, STEADY-STATE, DOUBLE-BLIND, ASCENDING DOSE SAFETY, TOLERABILITY, PHARMACOKINETIC STUDY OF AL001 IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE AND HEALTHY ADULT SUBJECTS ("MAD STUDY")

Version 8, Amendment 6

Date: **Nov. 28, 2022**

Clinical Trials.gov Identifier: **NCT05363293**

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Title of Study:

A Multiple-Dose, Steady-State, Double-Blind, Ascending Dose Safety, Tolerability, Pharmacokinetic Study of AL001 in Patients with Mild to Moderate Alzheimer's Disease and Healthy Adult Subjects ("MAD Study")

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Publication (reference):

None at the time of this report

Study Period:		**Phase of Development:**
Study Initiation Date:	2022/05/04	Phase 1 (Healthy Subjects [Canada])
Study Completion Date:	2023/05/15	Phase 2a (Alzheimer's Subjects [USA])

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Objectives:

Primary

- To evaluate the safety and tolerability of AL001 under multiple-dose, steady-state conditions in Alzheimer's disease (AD) subjects and healthy adult subjects.

Secondary

- To characterize the maximum tolerated dose (MTD) of AL001 in subjects with mild-to-moderate AD and healthy adult subjects.

Exploratory

- To explore the difference in pharmacokinetic (PK) profile between the non-elderly vs elderly subjects (healthy subjects only).
- For AD subject cohorts (Cohorts 1, 2b, 3b, 4b, and 5b), determination of qualitative and quantitative evaluations of AD subject desirable characteristics for future Phase 2 and 3 clinical studies in order to:
  - facilitate recruitment into subsequent AL001 clinical trials.
  - facilitate trial-adherence to completion of study requirements including treatment adherence.

Study Design and Conduct:

This was a Phase 1/2a, multi-center, double-blind, placebo-controlled, randomized, multiple ascending dose (MAD) clinical study to determine the safety and maximum tolerated dose (MTD) of AL001 in subjects with mild-to-moderate AD (Food and Drug Administration Classification of Stage 2 to 4 AD) and healthy adult subjects. Cohorts 1, 2b, 3b, 4b, and 5b were planned to include AD subjects (between the ages of 50 and 80 years, inclusive) and Cohorts 2a, 3a, 4a, and 5a were planned to include healthy subjects (non-elderly adults between the ages of 18 to 64 years, inclusive, and healthy elderly adults between the ages of 65 to 80 years, inclusive).

Each cohort was enrolled sequentially and randomized separately using a standard computerized method. The data from the previous cohort was deemed safe before the next sequential cohort was enrolled and dosing initiated.

Cohort 1 was planned to include 8 AD subjects (6 active and 2 placebo). Each of the Cohorts 2 to 5 was sub-divided into 2 cohorts: Cohorts 2a, 3a, 4a, and 5a (healthy subjects) and Cohorts 2b, 3b, 4b, and 5b (AD subjects).

At each dose level in Cohorts 2 to 5, the healthy subject cohort "a" (up to 8 subjects) was first completed up to Day 15 and the blinded safety (laboratory reports, AEs, tolerability) and PK data collected up to that point were reviewed by the Safety Review Committee. The initiation of the next dose cohort could be delayed up to approximately 4 weeks following the last dose of the last subject in the preceding cohort to allow for this process. If the dose level was endorsed as safe, the committee permitted progression to the AD subject cohort "b" at the same dose level, as well as progression to the next dose level of healthy subject cohort. The healthy subject cohorts proceeded to the next higher dose level

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without having to wait for the corresponding AD subject cohort to be completed and reviewed by the Safety Review Committee.

Cohort 5b was planned but was not conducted due to PK-based stopping rules designed to assure that the assigned MTD is unlikely to result in plasma trough lithium concentrations above 1.0 mEq/L (healthy elderly and Alzheimer's subjects) and 1.2 mEq/L (healthy non-elderly subjects). For salicylate, the maximum threshold value was 30 mg/dL for all subjects. These values pertain to subjects/patients with adequate renal function (estimated glomerular filtration rate [eGFR] ≥60 mL/minute/1.73 m^2).

For each cohort in which the subjects were dosed, subjects were randomized to 1 of 2 treatment groups in a 6:2 ratio of AL001 (active study medication) to placebo. Subjects in each of these cohorts were dosed 3 times daily (TID) for 14 days at the planned dose level indicated in the table below or placebo:

Cohort	Lithium Carbonate Equivalent Daily Dosing Level	No. of AL001 210 mg Capsules	AL001 Daily Dose
Cohort 1	60% of 450 mg lithium carbonate	3 capsules TID	1890 mg × 14 days
Cohort 2a/ Cohort 2b	100% of 450 mg lithium carbonate	5 capsules TID	3150 mg × 14 days
Cohort 3a/ Cohort 3b	140% of 450 mg lithium carbonate	7 capsules TID	4410 mg × 14 days
Cohort 4a/ Cohort 4b	160% of 450 mg lithium carbonate	8 capsules TID	5040 mg × 14 days
Cohort 5a/ Cohort 5b	200% of 450 mg lithium carbonate	10 capsules TID	6300 mg × 14 days[a]

Abbreviation: TID = 3 times daily.

Note: 7 mg of AL001 has the lithium content of 1 mg lithium carbonate

a. Lithium dose equivalent to that routinely used for bipolar disorder type 1 treatment.

Subject population:

Cohorts 1, 2b, 3b, 4b, and 5b:

Male and female adult subjects with mild-to-moderate AD, between the ages of 50 and 80 years, inclusive

Cohorts 2a, 3a, 4a, and 5a:

Healthy adult male and female subjects, between the ages of 18 to 64 years, inclusive (non-elderly) and between the ages 65 to 80 years, inclusive (elderly).

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Number of subjects (planned and analyzed):

Planned for inclusion:

- 40 AD subjects (5 cohorts of 8 subjects each)
- 32 healthy subjects (4 cohorts of 8 subjects each)

Included:

- 33 subjects in AD cohorts
- 32 subjects in healthy cohorts

Participation discontinued:

- 1 subject in AD cohorts
- 2 subjects in healthy cohorts

Included in the Safety Analysis Set:

- 33 subjects in AD cohorts
- 32 subjects in healthy cohorts

Included in the PK Analysis Set:

- 25 subjects in AD cohorts
- 24 subjects in healthy cohorts

Investigational product:

Name: AL001 210 mg Immediate Release Capsules

Dosage form/Route of administration: Capsule/Oral

Regimen: TID dose administrations (8 AM, 2 PM, and 8 PM) for 14 days

Batch number: B210312

Placebo:

Description: Placebo for AL001 210 mg Immediate Release Capsules

Dosage form/Route of administration: Capsule/Oral

Regimen: TID dose administrations (8 AM, 2 PM, and 8 PM) for 14 days

Batch number: B220065

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Study Duration and Subject Confinement:

The study consisted of 3 phases:

1. Screening Phase – up to 28 days (from Days -28 to -1)
2. Treatment Phase – 16 days (from Day -1 to Day 15):
    - Subjects were admitted to the study site on Day -1. Subjects received 14 days of TID dosing with assigned study medication from Days 1 to 14 and remained confined until Day 15.
3. Follow-up Phase - 1 month
    - Subjects were followed up after discharge from the study site on Day 15, with a post-treatment clinic visit on Day 23 and a post-treatment telephone call on Day 42.

Each subject participated in the study for up to approximately 2.5 months.

Criteria for Evaluation/Endpoints:

Pharmacokinetics:

- Prevalence of peak salicylate plasma concentrations above 30 mg/dL
- Prevalence of trough plasma lithium concentrations above 1.2 mEq/L for healthy adult subjects or 1.0 mEq/L for healthy elderly and AD subjects.

Descriptive statistics for PK were represented by treatment group and compared between non-elderly and elderly subjects.

Safety:

Safety assessments included vital signs (blood pressure, heart rate, and oral body temperature), 12-lead electrocardiogram (ECG), physical examination, safety laboratory tests (hematology, chemistry [including thyroid stimulating hormone, vitamin B12, and magnesium], hemoglobin A1c (HbA1c), and urinalysis, and reported and observed AEs/serious AEs (SAEs)/tolerability observations including signs and/or symptoms of lithium and/or salicylate toxicity.

Demographic characteristics of all screened and successfully enrolled AD subjects were documented.

Statistical methods:

Pharmacokinetics:

In order to characterize the MTD of AL001 in subjects with AD and healthy subjects, descriptive statistics are presented by treatment group for each cohort and overall for the following:

- Proportion of healthy non-elderly subjects with trough lithium concentrations >1.2 mEq/L
- Proportion of subjects with peak (C_{max}) salicylate concentrations >30 mg/dL
- Proportion of healthy elderly and, separately, AD subjects with plasma trough measurements of lithium >1.0 mEq/L

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Summary statistics of the plasma concentration data were calculated for the PK population, unless otherwise indicated. Summary statistics were calculated for concentration at each individual time point.

Concentration data were summarized by treatment group and compared between non-elderly and elderly subjects only for healthy cohorts using the following statistics: number of observations (N), arithmetic mean (mean), SD, geometric mean, minimum (min), median, maximum (max), and coefficient of variation (CV).

For healthy subject cohorts, to explore differences in PK between non-elderly and elderly subjects, descriptive statistics were presented by treatment group.

Safety Statistical Methodology:

Descriptive statistics were used to summarize AEs, safety results and demographic variables (age, height, weight, and body mass index).

Summary - Conclusions

Pharmacokinetic Results:

The observed AL001 MTD (the Cohort 4a/4b dosing level, 1680 mg given TID at 8 AM, 2 PM, and 8 PM, total daily dose 5040 mg) provided lithium at a lithium carbonate equivalent dose of 240 mg TID (720 mg daily) or a lithium citrate oral solution or syrup (8 mEq/5 mL) equivalent dose of 4 mL TID (19.2 mEq daily), all under fasted conditions. With respect to salicylate, these levels of exposure can be justified as safe *a posteriori* since they are less than the maximum for prescriptive aspirin/salicylate indications and are to be used for a serious medical condition. There were no undue safety concerns identified in the AL001-ALZ02 Study and so none were considered to be related to PK exposures. The MTD was selected to mitigate or obviate the need for AL001 therapeutic drug monitoring (TDM) in targeted neurodegenerative, neurological, and neuropsychiatric conditions, at least for subjects without undue renal compromise.

Under the conditions of this study, no clinically obvious or relevant lithium or salicylate PK differences were observed between non-elderly and elderly healthy subjects.

There were no obvious demographic characteristics observed under the conditions of this study that can be used to improve future enrollments when screening subjects.

Safety Results:

AD Subject Cohorts

- No deaths or SAEs occurred during the study. No subject prematurely discontinued the study due to a treatment-emergent AE (TEAE).
- AL001 was well tolerated in AD subjects regardless of their comorbidities and concomitant medications.
- A total of 24 TEAEs were experienced by 12 of 25 subjects who received AL001 and 6 TEAEs were experienced by 4 of 8 subjects in the pooled placebo group. The proportion of AD subjects with TEAEs increased with increasing dose levels of AL001, with the lowest proportions of subjects in Cohorts 1 (14.3%; AL001 1890 mg) and 2b (16.7%; AL001 3150 mg), and the highest proportion observed (83.3%) in Cohorts 3b (AL001 4410 mg) and 4b (AL001 5040 mg). The proportion of subjects with TEAEs in the pooled placebo group (50.0%) was between that observed in AL001 Cohorts 2b and 3b.
- All TEAEs were experienced by only 1 subject who received either AL001 or placebo, except headache (1 of 6 subjects [16.7%] each in Cohorts 3b and 4b) and pollakiuria (2 of 6 subjects [33.3%] in Cohort 4b).
- No AEs of special interest were reported for AD subjects.
- The majority of TEAEs were mild. (14 TEAEs across AL001 cohorts and 5 TEAEs with placebo). No TEAE was considered severe, life-threatening, or resulted in death.
- Most TEAEs were considered unrelated to study treatment by the Investigator (13 TEAEs across AL001 cohorts and 6 TEAEs with placebo).
- All TEAEs were resolved by the end of the study, except for 1 case each of new left bundle branch block (Cohort 3b/placebo) and hypopigmentation (Cohort 4b/AL001 5040 mg).
- Two laboratory-associated TEAEs were reported, both of which occurred in subjects who received AL001. Hepatic enzyme increased was of mild intensity, considered possibly related to AL001 by the Investigator, and was resolved at the end of the study. Blood thyroid stimulating hormone increased was of moderate intensity and considered unrelated to AL001 by the Investigator. This subject had an ongoing medical history of hypothyroidism and the TEAE resolved after adjusting the dose of levothyroxine.
- One ECG-associated TEAE, bundle branch block left, was reported for 1 subject in Cohort 3b (placebo). The TEAE was mild, considered not related to study drug administration by the Investigator, and was ongoing at last contact.
- No clinically significant abnormal findings in vital signs, ECGs, or physical examinations were noted during the study.

Healthy Subject Cohorts

- No deaths or SAEs occurred during the study. No subject prematurely discontinued the study due to a TEAE.
- AL001 was well tolerated in healthy elderly and non-elderly subjects.
- A total of 76 TEAEs were experienced by 16 of 24 subjects who received AL001 and 21 TEAEs were experienced by 5 of 8 subjects in the pooled placebo group. The proportion of healthy subjects with TEAEs was comparable across cohorts and pooled placebo treatment groups, with

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the highest proportion (83.3%) observed in AL001 Cohorts 3a (AL001 4410 mg) and 5a (AL001 6300 mg), compared to a proportion of 62.5% for the pooled placebo group.

- The most commonly reported TEAE across all treatments was constipation, experienced by 1 of the 6 subjects (16.7%) in Cohort 2a, 4 of the 6 subjects (66.7%) in Cohort 3a, and 2 of the 6 subjects (33.3%) each in Cohorts 4a and 5a, and 3 of the 8 subjects (37.5%) in the pooled placebo group.
- The overall proportion of subjects with TEAEs appeared higher for non-elderly subjects (75%) compared to elderly subjects (56.3%).
- For combined healthy subjects, AEs of special interest were reported with the highest proportion of subjects at the highest dose level in Cohort 5a (50.0%).
- The majority of TEAEs were mild (72 TEAEs across AL001 treatments and 20 TEAEs with placebo). Three moderate TEAEs (2 TEAEs with AL001 and 1 TEAE with placebo) and 2 severe TEAEs (with AL001) were also reported. The severe TEAEs were alanine aminotransferase increased (Cohort 3a/AL001 4410 mg) and hepatic enzyme increased (Cohort 5a/AL001 6300 mg). Both severe TEAEs were considered by the Investigator to be possibly related to AL001 and were resolved at the end of the study. No TEAEs were considered life-threatening or resulted in death.
- The majority of TEAEs were considered to be related to study treatment (65 TEAEs across AL001 and 16 TEAEs with placebo) by the Investigator.
- All TEAEs were resolved at the end of the study, except for acne (Cohort 5a/placebo), rash and pruritus (Cohort 5a/AL001 6300 mg), and tinnitus (Cohort 5a/AL001 6300 mg), each in 1 subject.
- Four laboratory-associated TEAEs were reported, all of which were resolved at the end of the study. Alanine aminotransferase increased and hepatic enzyme increased were both of severe intensity and considered possibly related to AL001 by the Investigator. Another TEAE of hepatic enzyme increased was of moderate intensity and was considered possibly related to AL001 by the Investigator. A TEAE of mild hypothyroidism was considered possibly related to placebo by the Investigator. One additional TEAE of urinary tract infection was reported in the setting of clinically significant elevated urine protein; this TEAE was of mild intensity and was considered unrelated to AL001 by the Investigator.
- No clinically significant abnormal findings in vital signs, ECGs, or physical examinations were noted during the study.

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Conclusion:

- Under the conditions of this study, multiple dose administrations of AL001 was well tolerated in healthy elderly and non-elderly subjects, and in subjects with AD, regardless of their comorbidities and concomitant medications.
- The observed AL001 MTD (1680 mg given TID at 8 AM, 2 PM, and 8 PM, total daily dose 5040 mg) provided lithium at a lithium carbonate equivalent dose of 240 mg TID (720 mg daily) or a lithium citrate oral solution or syrup (8 mEq/5 mL) equivalent dose of 4 mL TID (19.2 mEq daily), all under fasted conditions. The MTD was selected to mitigate or obviate the need for TDM in targeted neurodegenerative, neurological, and neuropsychiatric conditions, at least for subjects without undue renal compromise.
- With respect to salicylate, these levels of exposure can be justified as safe *a posteriori* since they are less than the maximum for prescriptive aspirin/salicylate indications and are to be used for a serious medical condition.
- No clinically obvious or relevant lithium or salicylate PK differences were observed between non-elderly and elderly healthy subjects, under the conditions of this study.
- No obvious demographic characteristics were observed under the conditions of this study that can be used to improve successful future enrollments when screening subjects.

Date of Report: 2024/10/30