Quantitate Differences in Lithium Brain-to-Plasma Exposure in PTSD Subjects Between AL001 and Lithium Carbonate

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Background

- Alzamend Neuro, Inc. is developing a proprietary technology: a lithium salicylate/L-proline cocrystal (referred to as AL001) for treatment of mild, moderate, and severe Alzheimer's disease (AD) and for other neurodegenerative, neurological and neuropsychiatric conditions including post-traumatic stress disorder (PTSD). AL001 is a novel formulation that, based on preclinical mouse data, may favorably alter lithium brain pharmacokinetics (PK-penetration through the blood-brain barrier and persistence) in humans. This may serve to reduce systemic exposure and the potential for adverse events (AEs). Lithium salts and solution/syrup products are marketed for treatment of patients suffering from bipolar disorder type 1 (BD1).
- The current study is designed to quantitate differences in lithium brain-to-plasma exposure in PTSD subjects between AL001 and lithium carbonate for the purpose of contributing to a composite 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 Alzheimer's disease, bipolar disorder type 1, major depressive disorder and post- traumatic stress disorder. It's 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 and lithium carbonate and, by equivalence inference, lithium citrate solution and syrup. This is to guide reduction in AL001 lithium oral dose amounts and, therefore, reduction in systemic lithium exposure for a comparable efficacy outcome.

Learning Objectives

1. To understand the potential safety and tolerability of AL001 under multiple-dose, steady-state conditions in PTSD subjects and discuss the implications for veterans and active military personnel.
2. To comprehend potential differences in brain and/or brain structure lithium PK relative to plasma PK for AL001 compared to lithium carbonate.
3. To comprehend AL001 salicylate PK systemic exposure at the anticipated dose for treatment of PTSD.

Introduction

- Lithium salts are first line drugs for treatment of bipolar disorder type 1 and have been used off-label for many conditions including PTSD, but because it is a narrow therapeutic index drug and requires monitoring of drug levels for safety, it has limited use. Its effective dose and blood levels are close to the toxic dose and close to toxic blood levels. There's an important need for a next generation lithium product that delivers lithium preferentially to the brain while having an enhanced safety and efficacy profile. That is, a lithium product that is dose-sparing, so it can be toxicity sparing to the kidney and thyroid gland.
- Chemists at the University of South Florida (USF) designed, synthesized and characterized a novel ionic co-crystal of lithium. A co-crystal in drug delivery refers to a crystalline solid formed by the combination of at least one salt and a neutral molecule, also called a conformer, held together by non-covalent interactions to enhance the physicochemical properties of a drug.

Product Development Methodologies

Favorable AL001 Brain Penetration/Persistence in Mice When Compared to Lithium Carbonate

Original University of South Florida publication: "LISPRO mitigates β-amyloid and associated pathologies in Alzheimer's mice" (Habib, 2017)

- **AL001 showed higher brain exposure at 2 weeks**
- **AL001 showed higher lithium brain exposure at 8 weeks (~50% effect size)**
- **AL001 showed a higher brain to plasma lithium ratio compared to lithium carbonate and lithium salicylate**
- **Translation to humans with neurodegenerative, neurological and neuropsychiatric disorders can result in a "dose-sparing" lithium delivery system to the target organ for efficacy (brain) thereby improving the safety profile**

Figure 2: Plasma and Brain Lithium Pharmacokinetics following Chronic Oral Treatment with AL001 (LISPRO), Li_2CO_3 and Lithium Salicylate in B6129SF2/J, Tg2576, and 3XTg-AD Mice

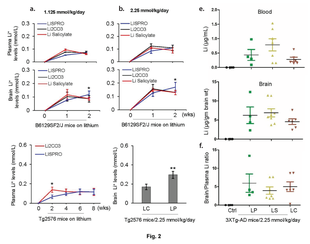


Fig. 2

- **(a, b)** B6129SF2/J mice (n=2–4 mice/group, male) at 2 months of age were treated for 1 or 2 weeks (wks) with 3 diets containing AL001 (LISPRO or LP), Li_2CO_3 (LC), Lithium Salicylate (LS) yielding lithium at 1.125 or 2.25 mM/kg/day.
- **(c, d)** Tg2576 mice (n=8, 4 female/4 male) at 6 months of age were treated for 8 weeks with 2 diets containing AL001 (LISPRO or LP) or LC yielding 2.25 mM/kg/day.
- **(e, f)** Further, 3XTg-AD female mice (n=4–8 mice/group) at 5 months of age were treated for 28 weeks with 3 diets containing AL001 (LISPRO or LP), LS or LC yielding lithium at 2.25 mM/kg/day, or normal mouse chow (Habib, 2017).

The allometric (that is, human to mouse) scaled dose from this study is the dose to be used in ongoing and future human studies. It has the equivalent lithium content of the lowest lithium carbonate dose (150 mg thrice daily) in FDA labelling for treatment of bipolar disorder type 1 in humans so there is a sizable margin of safety.

Clinical Studies Completed and Ongoing

First-in-human Study: A Single-dose Crossover Study AL001-ALZ01 in Humans Demonstrated Systemic Bioequivalence of AL001 (test) to Marketed Lithium Carbonate (reference)

Subsequent Study: A Multiple Ascending dose (MAD) Study AL001-ALZ02 Confirmed Safety and Tolerability of AL001

Study AL001-ALZ02 was 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 elderly and non-elderly subjects ("MAD Study"). This study characterized an MTD based on safety, tolerability, and pharmacokinetic (PK) data. Salicylate exposure at the MTD was within the established plasma concentration therapeutic range for treatment of pain and inflammation (≤ 30 mg/dL), thereby presenting a benign safety profile.

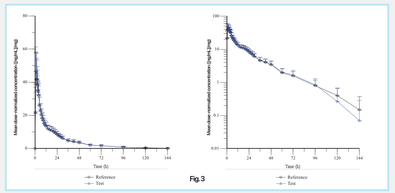


Fig. 3

Fig. 3: Mean (+SD) Lithium Dose-Normalized Concentration-Time Profiles After Single-Dose Administration --PK Population (Linear and Semi-Logarithmic Scale)

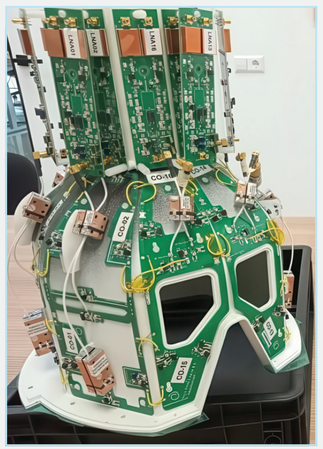
Alzamend's full data set confirmed the successful determination of a maximum tolerated dose ("MTD") for AL001. Identified by an independent safety review committee, this MTD represents a pivotal step forward; it delivers lithium at a lithium carbonate equivalent dose of 240 mg, which represents a daily decrease of 20% of lithium given to a patients.

In each cohort, consisting of six active and two placebo subjects (as per randomization), multiple ascending doses were administered three times a day ("**TID**") for 14 days, up to tolerability/safety limits. The results were:

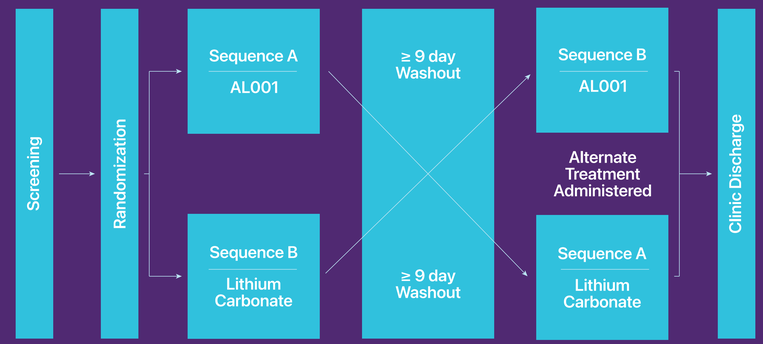
- The safety profile was demonstrated to be benign at all dose levels, and so the selected dose level chosen for further development was based on avoidance of plasma drug concentrations associated in the medical literature with exceeding the upper limit of the therapeutic range of drug concentrations, thereby serving to mitigate potential toxicity;
- Under the conditions of this study, multiple dose administrations of AL001 were well tolerated in healthy elderly and non-elderly subjects, and in subjects with Alzheimer's, regardless of their comorbidities; and
- No clinically obvious or relevant lithium or salicylate pharmacokinetic differences were observed between non-elderly and elderly healthy subjects, or Alzheimer's subjects under the conditions of this study.

Post-Traumatic Stress Disorder (PTSD) Study at Massachusetts General Hospital

- A randomized, balanced, phase 1/2a, 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 formulation compared to a marketed immediate-release lithium carbonate capsule formulation in post-traumatic stress disorder subjects
- Five studies were initiated at the Massachusetts General Hospital (MGH) to compare AL001 to lithium carbonate blood, brain and brain structures lithium pharmacokinetics and pharmacodynamics (metabolic changes) using MRI scans in healthy subjects, and subsequently for those with (PTSD-the current study of interest), major depressive disorder (MDD), bipolar disorder type 1 (BD1), and Alzheimer's disease (AD). These are now being used to explore translation to humans of the AL001 lithium dose sparing properties observed in mouse studies
- Alzamend Neuro developed a novel MRI head coil in collaboration with Tesla Dynamic Coils BV for this study. Key aspects of this technology:
- Enables high-resolution visualization of lithium distribution in the brain. It will be utilized to compare AL001, a novel lithium delivery system, with traditional lithium carbonate.The coil allows for whole-brain lithium imaging and precise quantification within brain structures. It will be used to help identify the disease-specific target doses of AL001 that improve the balance of safety and efficacy compared to lithium carbonate for PTSD and other disorders. By analyzing brain lithium content, Alzamend aims to determine the minimum effective and safe dose of AL001 compared to existing lithium salts. AL001 is anticipated to demonstrate a more favorable safety profile and eliminate the need for therapeutic drug monitoring that is often associated with traditional lithium salts.
- **To the Right** is an image of the specialized Tesla head coil for non-invasive assessment of lithium brain and brain structure concentrations and pharmacodynamic effects (metabolic biomarkers)



Study Schema



For each period, 14 days of dosing with intensive lithium pharmacokenitic sampling and brain-litium neuroimaging on dosing Day 14.

Discussion with Relevance to Veterans' Health

- Post-traumatic stress disorder (PTSD) is a significant mental health concern for both active-duty military personnel and veterans. The prevalence of PTSD is higher in veterans compared to the general population, and it can significantly impact their lives, affecting their mental and physical health, relationships, and ability to function in daily life. While approximately 6% of the general adult population experiences PTSD, the rate is higher among veterans, with studies showing rates ranging from 10% to over 20%. Combat-related trauma is a major risk factor for PTSD, but other traumatic events, such as military sexual trauma, accidents, or witnessing serious injuries, can also lead to PTSD. The prevalence of PTSD can vary based on factors like the specific conflict (e.g., higher rates among veterans of recent operations in Iraq and Afghanistan), the type and intensity of trauma experienced, and individual vulnerabilities. PTSD can affect relationships, work performance, social interactions, and overall quality of life.

Links:
https://www.hillandponton.com/resources/veterans-statistics-ptsd/
https://pmc.ncbi.nlm.nih.gov/articles/PMC9040390/
https://www.ptsd.va.gov/understand/common/common_veterans.asp

- Food and Drug Administration (FDA)-approved drugs for the treatment of PTSD are the SSRIs sertraline (Zoloft®) and paroxetine HCl (Paxil®), and the SNRI venlafaxine (Effexor®). Hoskins et al. completed reviews of pharmacological monotherapy in 2015 and 2021 which found that paroxetine, fluoxetine, sertraline, and venlafaxine could be effective for PTSD, but the magnitude of the effect was small and the clinical relevance was unclear (Hoskins 2015; Hoskins 2021). Medications, other than some SSRIs or SNRIs, do not have enough evidence to support their use and, in the case of benzodiazepines, may worsen outcomes (Guina 2015; Hoskins 2015; Huang 2020).
- Case reports suggest that lithium treatment may be useful for treating PTSD patients (Forster 1995). Kitchner and Greenstein provided case histories of 4 males who suffered from PTSD as a consequence of their experiences in the Vietnam War (Kitchner 1985). Results from treatment with low doses (300–600 mg/day) of lithium carbonate were reported to provide effective treatment in reduction of inappropriate anger, irritability, anxiety, and insomnia. The clinical observation of mood swings beyond the normal range but milder than those associated with BD1 reportedly suggested the presence of a subthreshold mood disorder in these PTSD patients. It has also been proposed that treatment of trauma with lithium to forestall the development of PTSD may be provided by pharmacological induction of a mild transient amnesia (Wallace 2013).
- In addition to being a first-line treatment option for BD type 1, lithium is also prescribed off-label for MDD (often as an adjunct therapy), BD1 (including without a history of mania), and PTSD, among other neurodegenerative, neurological, and neuropsychiatric disorders. The toxicity of lithium when delivered via currently approved salt forms limits utility of the drug. The current effort is intended to deliver lithium via a safer new chemical entity, thereby enhancing the potential for routine, safe, effective and practical pharmacologic management of veterans suffering from PTSD.