A Phase 2 Safety and Tolerability Study of an Anti CD40L Antibody, AT-1501 in Adults with ALS

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Background

Amyotrophic Lateral Sclerosis (ALS) is a fatal, degenerative disorder of motor neurons that results in progressive wasting and paralysis of voluntary muscles. There is mounting evidence that the disease progression is mediated in part by immune activation. Preclinical testing in a murine model of ALS has demonstrated statistically significant slowing of the disease course in animals treated with a hamster antibody against murine CD40L. [Lincecum 2010].

CD40L is a costimulatory type II transmembrane receptor for CD40. Binding of CD40L on T helper cells to CD40 on antigen-presenting cells induces multiple downstream immune and inflammatory responses. These include B and T cell clonal expansion; antibody production, class-switching, and maturation; and pro-inflammatory cytokine and chemokine production. AT-1501 is a humanized IgG1, kappa monoclonal antibody that blocks CD40L (CD154, gp39) binding to CD40.

A Phase I single ascending dose study of AT-1501 with doses ranging from 0.5 mg/kg to 8 mg/kg in healthy adults and adults with ALS (1mg/kg) demonstrated a safety profile that was comparable to placebo.

This is a Phase 2a, open label, multiple dose ascending safety and tolerability study of AT-1501 in adults with ALS. Approximately 54 adults with ALS will be enrolled in up to 13 clinical sites in North America.

The pharmacokinetics (pK) and exposure levels of AT-1501, biomarkers of target engagement, pro-inflammatory cytokines, neurofilament light chain levels, and clinical endpoints will also be explored.

Figure 1: AT-1501 Mechanism of Action

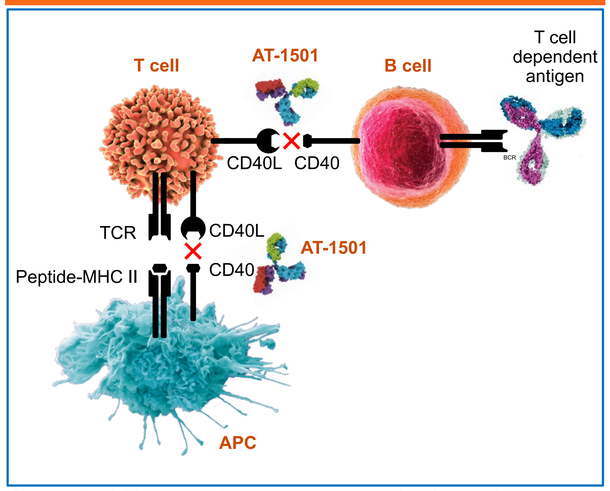


Figure 1: The initiation of an immune response to antigen is a multi step process with the presentation of peptide on MCH cell surface receptors on antigen presenting cells to the T cell receptor (TCR) on lymphocytes. The second critical step in pro-inflammatory signaling is the binding of CD40L on lymphocytes to the CD40 receptor on the antigen presenting cell.

Study Design

Objectives

Primary Objective

- To determine the safety and tolerability of IV administration of multiple doses of AT-1501 (planned 1.0, 2.0, 4.0 and 8.0 mg/kg).

Exploratory Objectives

- To quantify the effect of treatment on biomarkers of inflammation (e.g., TNF-a, MCP-1, IL-6, IL1β, Enraged), neurodegeneration (e.g., NFL & NFH) and other proteins in peripheral blood.
- To correlate biomarkers with AT-1501 levels simulated from study AT-1501 PK profiles and plasma concentrations from the current study.
- To determine the effect on the ALS Functional Rating System-Revised (ALSFRS-R) and spirometry as a result of administration of multiple doses of AT-1501.
- To understand the immunogenicity profile of AT-1501.

Inclusion/Exclusion Criteria

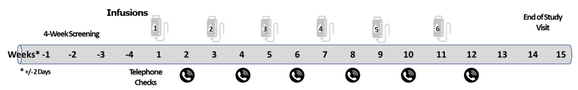
Inclusion Criteria

- ALS diagnosed as possible, laboratory supported probable, probable, or definite as defined by revised El Escorial criteria.
- ALSFRS-R Aggregate score of 35 or greater, and an aggregate score of 9 or greater at Screening for domains 10 Dyspnea, 11 Orthopnea and 12 Respiratory Insufficiency.
- No more than 24 months from diagnosis.

Exclusion Criteria

- Any other central or peripheral nervous system disease that may interfere with the evaluation of ALS or its progression.
- Presence of a tracheostomy, or use of permanent assistive ventilation (ventilatory support for 23 hours per day or more).
- Previous exposure to AT-1501.
- Abnormal function of the immune system resulting from infection or immunosuppressive medications.
- History of deep venous thrombosis or pulmonary embolism.

Study Design



Four ascending doses of AT-1501 (1.0 mg/kg; 2.0 mg/kg; 4.0 mg/kg and 8.0 mg/kg) will be administered as 6 bi-weekly IV infusions to sequentially enrolling cohorts.

The 1.0 mg/kg and 2.0 mg/kg cohorts will consist of 9 participants each and the 4.0 mg/kg and 8.0 mg/kg cohorts will consist of 18 participants each.

A Data Monitoring Committee (DMC) comprised of 2 independent physicians (with ALS experience) and a statistician will review all of the available safety and laboratory data in each cohort, including but not limited to platelet levels and coagulation data, and make recommendations regarding escalation to the next higher dose. AT-1501 plasma concentration data may be reviewed depending on data availability.

DMC members have no other involvement in the trial.

The Committee will meet following the administration of 6 doses to a minimum of 33% of participants:

- cohorts 1 and 2 - after 3 participants have received 6 doses
- cohorts 3 and 4 - after 6 participants have received 6 doses

The committee may recommend a revision of the dose escalation scheme based on review of the emerging data.

Biomarker Endpoints

Target Engagement

- Inhibition of CD40L signaling inhibits germinal cell formation, B cell maturation, antibody production, and antibody class switching.
- CXCL13 is a marker of follicular T cell B cell interactions in germinal centers and ectopic secondary lymphoid structures.
- CXCL13 will be measured by Quanterix assay.
- Percent of subjects with a change in CXCL13 from baseline.

Pro-Inflammatory Markers

- Multiple published reports have characterized increased levels of TNF-α, MCP-1, IL-6, IL1β, and Enraged and other pro-inflammatory chemokines and cytokines in circulation in ALS patients.
- These markers are represented on the HumanMap Luminex Panel developed by Rules Based Medicine.
- Percent of subjects with a change from baseline.

Neurofilament Light Chain (NFL)

- NFL is a cytoskeletal protein expressed in neuronal cells that has been shown to be increased in the cerebral spinal fluid (CSF) and in circulation (plasma or serum) in patients with ALS.
- NFL will be measured by Quanterix assay.
- Percent of subjects with a change in NFL from baseline.

Current Accrual

- There are 13 open sites: 12 sites in the United States and 1 site in Canada.
- The nine subjects in Cohort 1 (1.0 mg/kg) have completed the study.
- The nine subjects in Cohort 2 (2.0 mg/kg) have completed the study.
- Cohort 3 (4.0 mg/kg) is fully enrolled as of July 2021.
- We anticipate completing enrollment of Cohort 4 (8.0 mg/kg) in Q4 2021.