SYNOPSIS

Study Title:

A Phase 1/2 Open-label Clinical Study of hLB-001 Gene Therapy in Pediatric Patients with Methylmalonic Acidemia Characterized by *MMUT* Mutations

Study Number: LB001-001

Pediatric Investigational Plan Number: Not applicable

Study Phase: Phase 1/2

Name of Study Intervention: hLB-001 (recombinant AAV vector encoding human *MMUT* gene)

Name of Sponsor:

Alexion Pharmaceuticals, Inc. (formerly LogicBio Therapeutics)
121 Seaport Blvd
Boston, MA 02210

Number of Study Center(s) and Countries:

This study was conducted at 4 centers in the United States.

Publications: Not applicable

Study Period: 02 Feb 2021 to 10 Jan 2023

Rationale:

Methylmalonic acidemia (MMA) is a metabolic disorder caused by mutations in the gene encoding methylmalonyl-coenzyme A (CoA) mutase *(MMUT*) gene or by defects in the transport and metabolism of its cofactor, 5'-deoxyadenosylcobalamin, that result in the cobalamin subtypes. These mutations result in the disruption of metabolic pathways and the inability to process certain amino acids and fats properly. The MMUT protein is not secreted, therefore pharmacodynamic biomarkers such as methylmalonic acid, methylcitrate, fibroblast growth factor 21 (FGF21), and propionate oxidation have been studied in this disease.

hLB-001 is a novel genome editing therapy intended to provide durable hepatocyte expression of the gene encoding MMUT without the use of exogenous promoters or nucleases. hLB-001 is delivered to hepatocytes intravenously via a liver-targeted, engineered recombinant adeno-associated virus (rAAV) vector (rAAV-LK03). hLB-001 uses the natural cellular process of homologous recombination to integrate a copy of the human mutase gene into the albumin locus.

As a form of "molecular" hepatocyte transplantation, the outcome goals following hLB-001 administration are to provide similar clinical and biochemical benefits of surgical transplantation without the morbidity and mortality associated with the procedure and its immunosuppressive therapies. Patients who are likely to benefit from this intervention are primarily mutase-null (*mut0*) but may include those with partial mutase deficiency (*mut-*) if they present with a severe

phenotype. As patients with severe MMA are more likely to suffer debilitating, life-threatening events, these patients would most benefit by early and efficacious treatment.

Patients with mutase-deficient MMA with an early and severe clinical presentation have a well-documented unmet medical need. hLB-001, through its sustained restoration of hepatic mutase activity, offers an opportunity to intervene at an early age before patients succumb to the disease or suffer irreversible neurologic injury.

Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints
Primary	
To assess the safety and tolerability of hLB-001 in pediatric participants with methylmalonic acidemia (MMA).	• Incidence of treatment-emergent adverse events (TEAEs) • Incidence of infusional toxicities (hLB-001-related AEs that limit, delay, or require medical intervention during administration)
Secondary	
To assess change from baseline in pharmacodynamic (PD) biomarkers post hLB-001 dosing in pediatric participants with MMA. To assess clinical efficacy outcomes post hLB-001 dosing in pediatric participants with MMA (not analyzed).	• Serum methylmalonic acid and methylcitrate (Week 52-end-of-study [EOS] visit absolute value and percent change from average predosing level). • Serum fibroblast growth factor 21 (FGF21) level (Week 52-EOS visit absolute value and percent change from predosing level). • Propionate oxidation rate (Week 52-EOS visit change from predosing level). • Serum albumin-2A level (alternative albumin isoform synthesized from loci with hLB-001 integration, change from predosing baseline to Week 52-EOS visit). • Survival at 1-year post hLB-001 dosing (not analyzed because survival was 100%)

Statistical Analyses:

The planned sample size was approximately 8 to 12 participants. The sample size was based on practical considerations for an ultra-orphan patient population. No statistical hypotheses were evaluated with respect to the study endpoints. Each participant served as their own control.

All analyses were descriptive. Descriptive statistics on continuous data included means, medians, standard deviations, and ranges. Categorical data were summarized using frequency counts and percentages.

Methodology:

Study LB001-001 was a first-in-human, Phase 1/2 open-label interventional study designed to evaluate the safety, tolerability, biologic activity, and clinical efficacy of hLB-001 in pediatric participants with MMA. Participants enrolled had a severe form of MMA associated with

deficiency of *MMUT*. Participants underwent a Screening Period, followed by a Run-in Period, Dosing/Hospitalization Period, and a Follow-up Period.

Two dose levels of hLB-001 were planned to be administered as single IV doses across 2 cohorts: Cohort 1 (5×10^{13} vg/kg) and Cohort 2 (1×10^{14} vg/kg). Cohort 1 consisted of 2 parts: Part A enrolled participants aged 3 to 12 years, and Part B enrolled participants aged 6 months to 2 years. After 2 patients developed thrombotic microangiopathy (TMA), Cohort 1 Part C was added to the protocol to enroll participants aged 6 months to 12 years for further safety evaluation prior to enrolling participants at the higher dose level (Cohort 2). No participants were enrolled in Part C and thus Cohort 2 was not initiated.

For Cohort 1 Part A and B, a minimum of 6 weeks of postdosing safety-related data were evaluated by an independent Data Safety Monitoring Board (DSMB) chair and the Sponsor medical monitor after the dosing of each participant. The first participant had to be at least midway through the planned corticosteroid tapering period for the safety review to be completed. At a minimum of 6 weeks after the second participant in each study part was dosed, the independent DSMB reviewed all available safety data. The second participant had to be at least midway through the planned corticosteroid tapering period for the safety review to be completed.

Number of Participants (Planned and Analyzed):

Planned: 8 to 12 participants

Analyzed: 4 participants

All 4 participants who received hLB-001 were included in the Safety Population and the Intent-to-treat (ITT) Population.

Diagnosis and Main Criteria for Inclusion and Exclusion:

This study enrolled male and female pediatric participants aged 6 months to 12 years of age with a severe form of MMA associated with deficiency of *MMUT* with the following main criteria:

a) Isolated MMA with genetically confirmed pathogenic mutations in the *MMUT* gene.

b) Screening serum methylmalonic acid level of ≥100 µmol/L.

c) One or more of the following considered by the Principal Investigator to be MMA-related:

    a. An unscheduled emergency room visit or hospitalization in the year prior to Screening Visit.

    b. Developmental delay, movement disorder, optic neuropathy or feeding disorder with tube feeding requirement.

d) Medically stable for the 2 months prior to the start of Screening Period, defined as following a dietary management plan meeting the standard practice guidelines for patients with MMA in addition to having no changes in chronic treatment other than adjustments to medications and diet for weight gain and nutritional laboratory evaluations as required for optimal care.

Potential participants with organic acidemias other than isolated MMA or with any other causes of hyperammonemia were excluded.

Full inclusion and exclusion criteria are provided in the study protocol.

Study Intervention(s), Dose, and Mode of Administration:

hLB-001 is a genetically engineered, liver-targeted, rAAV chimera (rAAV-LK03) containing 5' and 3' DNA homology arms corresponding to the human albumin locus, and a codon optimized form of the human *MMUT* sequence preceded by a 2A peptide encoding sequence. hLB-001 was prepared as a sterile, nonpyrogenic solution stored at -65°C or below until ready to be thawed for use. hLB-001 was infused via filled syringes using an infusion pump. Participants received a single intravenous (IV) infusion over 1 hour on study Day 1.

Duration of Study Intervention:

The study consisted of a Screening Period (multiple days), a ≥16-day Run-in Period from start of the Screening Period to hLB-001 dosing (Day 1), a Hospitalization Period, and a Follow-up Period of 52 weeks. The planned Hospitalization Period was 4 days (Day -1 to 48 hours postdose) until Protocol Version 6 was enacted and the planned Hospitalization Period was changed to 8 days (Day -1 to Day 7 postdose). No participants were enrolled under Protocol Version 6 or later versions.

Summary of Results and Conclusions:

Demographic and Other Baseline Characteristics:

Four participants were enrolled in the study, including 2 participants in Part A (75 and 113 months old at study entry; 78 and 114 months old at dosing) and 2 participants in Part B (20 and 22 months at study entry; 20 and 25 months at dosing).

In Part A, both participants were male. One participant was white and 1 participant's race was reported as "other". At baseline, 1 participant weighed 19.2 kg and 1 participant weighed 29.3 kg.

In Part B, 1 male and 1 female participant. One participant was white and 1 participant's race was reported as "other". At baseline, 1 participant weighed 11.2 kg and 1 participant weighed 13.8 kg.

All participants had the mut0 phenotype and 3 of 4 participants were diagnosed via newborn screening. All participants received a portion of their food via a gastrostomy tube.

At study entry and baseline, all participants were negative for neutralizing antibodies to the LK-03 capsid.

Exposure

All 4 participants received 100% of the single planned dose of hLB-001 at a dose level of 5×10^{13} vg/kg. In Part A, the total doses infused (vg) were 1.4×10^{15} and 9.8×10^{14} and, in Part B, the total doses were 7.3×10^{14} and 5.0×10^{14}.

Pharmacodynamic Results:

Serum albumin-2A will only be seen in participants where integration has occurred. Detectable levels of serum albumin-2A were observed in all participants. Sustained increases were observed in 2 participants, showing selective advantage of the corrected hepatocytes. At Week 52, analyses of change from baseline in serum methylmalonic acid, methylcitrate, FGF21, and propionate oxidation showed no clinically meaningful improvements.

Safety Results:

All 4 participants in the study experienced at least 1 treatment emergent adverse event (TEAE), including events in 3 participants (1 in Part A and 2 in Part B) that were treatment-emergent serious adverse events (TESAEs).

The TESAEs included the following:

- 2 events of hyperkalemia in 1 participant in Part A; not related to hLB-001
- 1 event of TMA in each of the 2 participants in Part B; related to hLB-001
- 1 event of cytokine release syndrome in 1 participant in Part B; related to hLB-001.

All TESAEs were resolved during the study.

Two participants, both in Part B, experienced adverse events of special interest (AESI). Both of these participants experienced hLB-001-related events of TMA that were considered serious at onset before resolving as non-serious events.

Transaminases increased was the only other AESI observed. Hepatotoxicity has been observed in many AAV-based gene therapies, typically at 1-3 months post administration. All participants experienced increases in transaminases with hLB-001 administration. Elevated alanine transaminase (ALT) remained below 2 × ULN in 2 participants and did not necessitate increasing the planned length of steroid administration. In 2 participants, increases in ALT resulted in the need to lengthen the steroid course, including the time on full dose steroids. One participant had ALT that peaked at 2.25 × ULN. The second participant had ALT that exceeded 8 × ULN.

No participant experienced a TEAE that led to dose interruption or withdrew from the study due to a TEAE. No participant died during the study.

Conclusions:

This study was the first to demonstrate homologous recombination genome editing without the use of nucleases in a pediatric population. All participants showed evidence of integration via measurable serum albumin-2A. Sustained increases were observed in 2 participants, which were continuing at the end of the study and may continue to increase over time as selective advantage continues. At the end of this study, however, they had not increased to the level that a therapeutic benefit would be expected.

Of the 2 participants without sustained increases in albumin-2A, 1 participant's loss of expression of serum albumin-2A was presumed to be associated with elevated transaminases. While the reason the other participant did not have sustained increases in albumin-2A is unclear,

it is possible this participant's disease was well controlled and therefore there was not enough selective pressure to cause an increase.

As may be expected with the currently achieved serum albumin-2A levels, analyses of change from baseline in serum methylmalonic acid, methylcitrate, FGF21, and propionate oxidation showed no clinically meaningful improvements at the end of this study.

Participants in this study are being followed in a long-term follow up study in which albumin-2A and other pharmacodynamic measures are continuing to be measured.

As in other gene therapy trials, TMA and elevated transaminases were observed in this study. The steroid course had to be prolonged in 2 of the 4 participants, however participants did not experience toxicity due to steroid administration.

Analysis of TEAEs, safety laboratory tests, vital signs measurements, and electrocardiograms did not suggest any other significant safety concerns related to hLB-001 administration.