STATISTICAL ANALYSIS PLAN

STUDY SPONSOR:	LogicBio Therapeutics 65 Hayden Ave, Floor 2 Lexington, MA 02421
SPONSOR REPRESENTATIVE:	[redacted]
PROTOCOL TITLE:	A Phase 1/2 Open-label Clinical Study of hLB-001 Gene Therapy in Pediatric Patients with Methylmalonic Acidemia Characterized by MMUT Mutations
PROTOCOL NUMBER:	LB001-001
PROTOCOL VERSION AND DATE:	Version 8.1, May 04, 2022
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METHODOLOGY:	Open label
ANALYSIS PLAN DATE:	May 02, 2023
ANALYSIS PLAN VERSION:	Version 1.0
AUTHOR:	[redacted]

APPROVAL SIGNATURE PAGE

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Veristat, Inc. Author:	134 Turnpike Road, Ste. 200Southborough, MA 01772

Approval Signature	Job Title
[redacted]	

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

Approval Signature	Job Title
[redacted]	[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AAV	adeno-associated viral vector
AE	adverse event
AESI	adverse events of special interest
Albumin-2A	alternative albumin isoform synthesized from loci with hLB-001 integration
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
ER	emergency room
FGF21	fibroblast growth factor 21
ICF	Informed consent form
ICH	International Council for Harmonisation
ITT	Intent-to-Treat
MMA	methylmalonic acidemia
MMUT or MUT	the gene encoding methylmalonyl-CoA mutase; newer nomenclature may use MMUT
NF	National Formulary
PCR	polymerase chain reaction
PD	pharmacodynamics
PSI-IV	parenting total stress score
rAAV	recombinant adeno-associated virus
SAP	Statistical analysis plan
ULN	upper limit of normal
vg/kg	vector genomes/kilogram

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.1.2. Study Background

LogicBio is developing hLB-001 for the treatment of patients with isolated methylmalonic acidemia (MMA) associated with mutations in the gene encoding methylmalonyl-CoA mutase *(*MMUT*)* gene (Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT): 42393006|Methylmalonic acidemia [disorder]).

MMA is a metabolic disorder in which the body is unable to process certain amino acids and fats properly. Infants considered to have severe MMA are diagnosed in the first days to weeks of life either based on newborn screening results or following presentation with clinical signs including vomiting, lethargy, respiratory distress, hypotonia, hypothermia, hepatomegaly, and progressive encephalopathy. Key laboratory findings to support diagnosis include hyperammonemia, elevated serum lactate, abnormally high methylmalonic acid in the blood and urine (Hörster et al, 2007), pancytopenia, and elevated urine ketone bodies (Baumgartner et al, 2014). Infants with the severe form of MMA are at risk for neurologic injury including basal ganglia stroke, failure to thrive, and poor feeding. Subsequently, they may progress to impaired cognition, severe infections, and renal failure with devastating impact on patient quality of life and survival (Manoli et al, 2016).

hLB-001 is a novel gene therapy intended to provide durable hepatocyte expression of the MMUT gene without the use of exogenous promoters or nucleases. hLB-001 uses the natural cellular process of homologous recombination to integrate a copy of the human mutase gene into the albumin locus. The albumin target site was selected to permit high level expression of MMUT protein in transduced hepatocytes, which is anticipated to restore mitochondrial function, reduce serum methylmalonic acid levels, and ameliorate the MMA disease state.

In summary, mutase-deficient MMA patients 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.

1.1.3. Study Objectives and Endpoints

The primary objective is to assess the safety and tolerability of hLB-001 in pediatric patients with MMA.

Endpoints

- Incidence of treatment-emergent adverse events (AEs)
- Incidence of infusional toxicities (hLB-001-related AEs that limit, delay, or require medical intervention during administration)

The secondary objectives are:

1. To assess change from baseline in pharmacodynamic biomarkers post hLB-001 dosing in pediatric patients with MMA

   Endpoints

   - Serum methylmalonic acid and methylcitrate (week 52-end-of-study [EOS] visit absolute value and percent change from average pre-dosing level)
   - Serum fibroblast growth factor 21 (FGF21) level (week 52-EOS visit absolute value and percent change from pre-dosing level)
   - Propionate oxidation rate (week 52-EOS visit change from pre-dosing level)
   - Serum albumin-2A level (alternative albumin isoform synthesized from loci with hLB-001 integration, change from pre-dosing baseline to week 52-EOS visit)

2. To assess clinical efficacy outcomes post hLB-001 dosing in pediatric patients with MMA

   Endpoints

   - Survival at 1-year post hLB-001 dosing

The exploratory objectives are:

1. To assess hLB-001 viral shedding

   Endpoints

   - Viral shedding (presence and copy number of viral genomes determined by polymerase chain reaction [PCR] on urine, saliva and stool samples)

2. To assess clinical efficacy outcomes post hLB-001 dosing in pediatric patients with MMA

Endpoints

- Hospitalizations for MMA-related complications (number, reason for, and duration of MMA-related hospitalizations from dosing through week 52-EOS visit with comparison to 1-year period pre-dosing)
- Surgical liver and/or kidney transplant (number of patients with liver, kidney, or combined liver-kidney transplants)
- Growth parameters (change in age-specific z-scores for weight, height/length, and head circumference from pre-dosing to week 52-EOS visit as determined from standard growth curves)
- Vineland Adaptation Behavior Score (change in patient score from pre-dosing to week 52-EOS visit)
- Parenting Stress Index (change in parenting total stress score [PSI-IV, 36-item short form] from pre-dosing to week 52-EOS visit)
- Healthcare utilization (number of Emergency Room [ER] visits and unscheduled physician visits from dosing through week 52-EOS visit with comparison to 1-year period pre-dosing)
- Neurodevelopmental status (change in age-appropriate testing score from pre-dosing to week 52-EOS visit, e.g., Bayley, Wechsler [note that these will be collected in the US only])

3. To assess change from pre-dosing baseline in diet, oral intake, and medications

   Endpoints

   - Protein intake (determined from 3-day nutrition diary at week 52-EOS visit)
   - Oral feeding (determined from 3-day nutrition diary at week 52-EOS visit)
   - MMA-related medication use (prescription medications started/discontinued or change in dose other than weight-related adjustments)

4. To investigate exploratory pharmacodynamic (PD) biomarkers

   Endpoints

   - Exploratory serum/plasma biomarkers associated with MMA

5. To assess immunological changes

   Endpoints

   - Incidence of immunological changes (defined as antibody or cellular immune response to hLB-001 itself or the proteins expressed following integration)

1.2. Study Design

1.2.1. Synopsis of Study Design

Study LB001-001 is a first-in-human (FIH) phase 1/2 open-label interventional study to evaluate the safety, tolerability, biologic activity, and clinical efficacy of hLB-001 in pediatric patients with MMA. Patients to be enrolled will have a severe form of MMA associated with deficiency of methylmalonyl-CoA mutase (commonly referred to as MMUT) with the following 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:
    i. An unscheduled ER visit or hospitalization in the year prior to screening visit
    ii. 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, 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

Approximately 8, with the option to increase to 12, patients were planned to be enrolled at approximately 8 centers in the United States and Saudi Arabia.

Patients will undergo an initial screening, which will include general health and disease complications, MMA diagnosis confirmation, dietary assessment, concomitant medications, adeno-associated viral vector (AAV) neutralizing antibody titers, and liver and renal function testing. The screening assessments may take place over multiple days. Patients who are receiving MMA-related medications should continue these medications as per the standard-of-care at the clinical site.

Patients meeting all initial screening criteria will undergo a run-in period of at least 16 days from start of screening to hLB-001 dosing. During this period, patients will establish a baseline for methylmalonic acid levels and other disease biomarkers and demonstrate ongoing clinical stability. During the week prior to dosing, it will be confirmed that the patient continues to meet all inclusion/exclusion criteria and the patient will be admitted to the study site for study drug administration.

AAV administration to pediatric patients has been associated with clinically significant liver enzyme elevations, resulting in a recommendation of prophylactic steroid administration for a minimum duration of 1 month (ZOLGENSMA prescribing information, 2019). A standardized regimen of prednisolone 1 mg/kg/day or its equivalent (not to exceed 60 mg per day) will be initiated 24 ± 4 hours prior to starting the hLB-001 infusion. Daily corticosteroid dosing will

continue for a planned 60-day course followed by a 26-day taper. The taper will be delayed if the patient has alanine aminotransferase (ALT) values > 2 X Upper Limit Normal (ULN), or aspartate aminotransferase (AST) > 2.0 × ULN together with ALT, alkaline phosphatase or total bilirubin > ULN. If liver function abnormalities persist at 60 days, systemic corticosteroids (equivalent to prednisolone at 1 mg/kg/day) may be continued for up to 2 weeks until findings return to baseline levels or in discussion with the Medical Monitor, and the corticosteroid dose will be tapered over the next 26 days. Two weeks after steroid discontinuation, normalized adrenal function will be confirmed by AM cortisol level, and CRH or ACTH stimulation testing will be performed if cortisol < 18 mcg/dL or within normal limits.

The anticipated period of study patient hospitalization is 8 days, from day -1 to Day 7 post-dose. For a period of 1 week following hospital discharge, patients will be asked to remain within a 1-hour access of the study site due to the possible risk for metabolic imbalance associated with corticosteroid administration and to allow for daily study visits until 14/week 2. Patients will then return to the study site for weekly visits during month 1 (week 3 and 4), every other week until month 3 (week 6, 8 and 10), and twice every quarter thereafter until the completion of the study (weeks 13, 19, 26, 32, 39, 45 and 52). Home healthcare visits may be conducted at weeks 3, 6, 10, 19, 32 and 45; additional home visits may be discussed with the study physician and Sponsor for consideration. Dietary assessments including laboratory evaluations will take place at study entry and every 3 months throughout the study. Study participants will follow dietary recommendations on adequate energy and protein intake to support normal growth, development, and physical activity level. Nutritional goals to be met by all study participants will be assessed at study entry and on a regular basis during study participation by a nutritional specialist familiar with dietary management in MMA. Following completion of their EOS visit, study patients will be asked to participate in a separate long-term follow-up study to continue monitoring the long-term safety and efficacy of hLB-001.

A schematic of the study design is as follows:

Two dose levels of hLB-001 are planned to be administered in 8, up to 12, patients, across 1 to 2 cohorts, Cohort 1 (5×10^{13} vector genomes/kilogram [vg/kg])) and Cohort 2 (1×10^{14} vg/kg).

For Cohort 1, part A and B, a minimum of 6 weeks of postdosing safety-related data will be evaluated by the Data Safety Monitoring Board (DSMB) chair and the Sponsor Medical Monitor between the dosing of each patient. The first patient must be at least midway through the corticosteroid tapering period for the safety review to be completed. At a minimum of 6 weeks after the second patient is dosed, the independent DSMB will review all available safety data. The second patient must be at least midway through the corticosteroid tapering period for the safety review to be completed.

Cohort 1: Dose level 5 x 10^{13} vg/kg IV

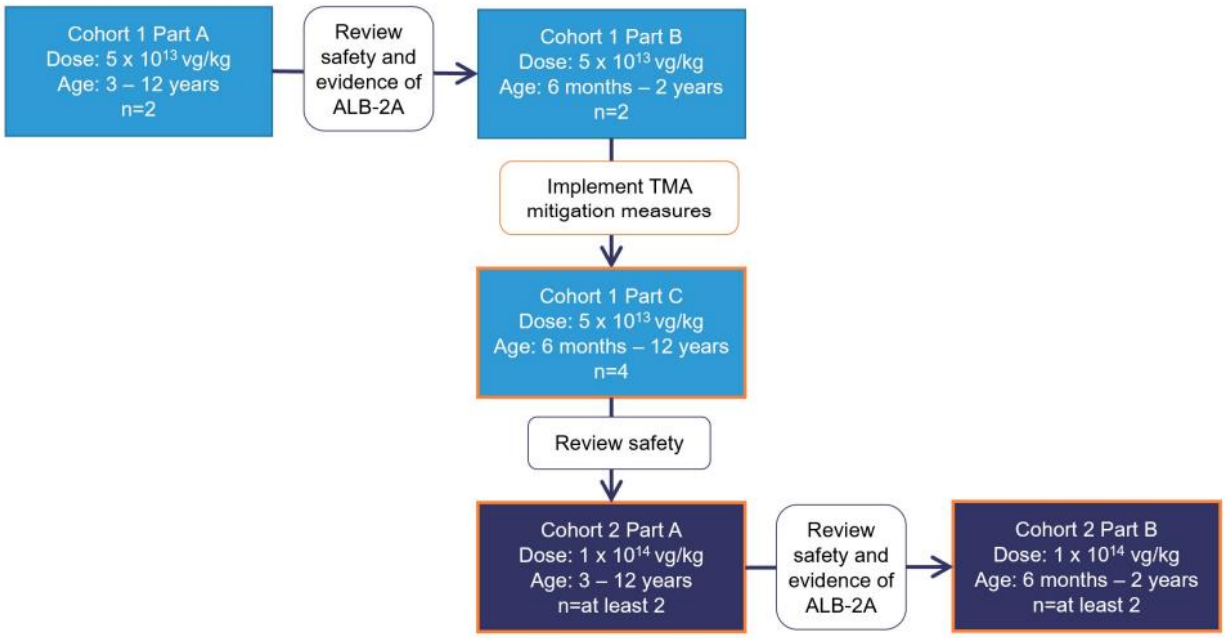
The DSMB will review safety data as described below. The safety review will include a focus on any potential signs of steroid-induced catabolic stress. The DSMB may recommend optimizing the steroid regimen or delaying enrollment into the next group by 2 weeks in order to more fully assess the corticosteroid period.

- Part A: 2 patients, aged 3-12 years will be enrolled.
    -
    - If the safety review is sufficient and there is evidence of albumin-2A, enrollment into Cohort 1 Part B may begin.
- Part B: 2 patients, aged 6 months-2 years will be enrolled.
- Part C: Four additional patients, aged 6 months to 12 years of age, were planned to be enrolled.
    -

Cohort 2: Dose level 1 x 10^{14} vg/kg IV

- Part A: At least 2 patients, aged 3-12 years were planned to be enrolled.
- Part B: At least 2 patients, aged 6 months-2 years were planned to be enrolled.

The cohort schematic was planned as below:



1.2.2. Randomization Methodology

There will be no randomization in this study as it is a single group/arm study.

1.2.3. Suspension Rules and Stopping Rules

Study Suspension Rules

Study hLB-001 dosing will be suspended if any of the following occurs:

- Any event of TMA
- A patient experiences a Grade 4 or higher AE
- A patient develops a malignancy
- A patient dies
- Any grade 4 SAE that could be related to study procedures (e.g., complications from prophylactic steroids)
- Any grade 3 SAE of Special Interest (as defined in protocol section 11.2.1 – Adverse Events of Special Interest (AESI))
- The same or related grade 3 SAE in 2 subjects that is related to the study product or study procedures
- Despite corticosteroid use as described in protocol section 10.2 - Prophylactic Administration of Corticosteroids and Monitoring/Risk Mitigation, alanine aminotransferase (ALT) values, remain above the threshold of 2 X ULN.

- The DSMB chair and/or sponsor determine that an event or current data warrant further evaluation by the full DSMB

Upon study suspension, the DSMB will evaluate all clinical safety data and provide recommendations on whether dosing should continue, whether changes should be made in the study, or in consultation with the sponsor, whether the study should be stopped.

During any period of study suspension, enrollment and treatment will be paused while the DSMB investigates whether a grade 3 or grade 4 SAE could be related to the study product or study procedures. Patients who have been dosed with hLB-001 will continue to be followed for safety and PD/clinical efficacy through their scheduled EOS visit.

Study Stopping Rules

Study enrollment and dosing will be discontinued permanently if any of the following occurs:

- Sponsor or a regulatory agency decides for any reason that an event or current data warrant study termination
- A patient develops a malignancy assessed as related to hLB-001 by the investigator and/or sponsor
- A patient death is assessed as related to hLB-001 by the investigator and/or sponsor
- Any medically unacceptable risk of hLB-001 is identified by the DSMB and/or sponsor

If study dosing is stopped, patients who have already been dosed with hLB-001 will continue to be followed for safety and PD/clinical efficacy through their scheduled EOS visit.

1.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol.

2. STUDY POPULATION

2.1. Population Definitions

The following study populations will be evaluated and used for presentation and analysis of the data:

- Safety Population: All subjects who received at least 1 dose of study drug.
- Intent-to-Treat (ITT) Population: All subjects receiving study drug who have baseline data and at least 1 post-dose measurement.

The Safety population is the primary population for the analysis of safety endpoints. The ITT population is the primary population for the analysis of efficacy endpoints.

2.2. Protocol Violations

At the discretion of the Sponsor, major protocol violations, as determined by a review of the data and the conduct of statistical analyses. The Sponsor or designee will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with Veristat and the Sponsor Medical Monitor as applicable. This file will be finalized prior to hard database lock.

Major protocol deviations will be tabulated including the frequency and percentage of subjects with each type of deviation by treatment group for the ITT population. All protocol violations will be presented in a data listing.

2.3. Impacts from COVID-19

This study was conducted during the global SARS-Cov-2 pandemic. The impact of COVID-19 was mitigated based on the evolving EMA and FDA COVID-19 guidelines [European Medicines Agency 2020; US Food and Drug Administration 2020]. National guidelines were also reviewed and acted upon, and when needed authorities and/or Independent Ethics Committees/Institutional Review Boards were contacted for advice/approval. Implementation of critical components and initiatives were discussed and endorsed at internal meetings with the Sponsor's clinical operation, clinical development, regulatory, biostatistics and pharmacovigilance teams.

A listing of all patients affected and how their participation in the study was altered, including missed visits, missed assessments and other deviations from protocol procedures may be provided, if COVID-19 effect on study is judged major.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

No formal power calculations were performed to estimate appropriate group sizes since this is the first clinical evaluation of hLB-001. Cohort size was selected to achieve an appropriate balance between unnecessarily exposing a large number of patients to a novel therapeutic regimen, and having sufficient patients administered study drug to make a reasonable assessment of the dose-related safety of hLB-001. Each patient will serve as his or her own control.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of study medication infusion which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. Relative days for post baseline assessments will be calculated as Date of Assessment – Date of Infusion + 1. For pre-baseline assessments, relative days will be calculated as Date of Assessment – Date of Infusion.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonization (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

This study is primarily descriptive in nature; therefore, there are no formal statistical hypothesis tests planned. Data will be presented by subject and summarized by treatment group and overall.

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24 or higher. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version March 2021 B3 or newer, if applicable.

3.4. Baseline Definitions

For Methylmalonic Acid and Methylcitrate levels, multiple levels will be averaged for each subject to define the baseline. At least 2 specimens will be collected at least 14 days apart prior to LB-001 administration to subjects who are metabolically stable throughout this screening period.

For all other analyses, baseline will be defined as the average of measurements prior to administration of the first dose of study drug.

3.5. Methods of Pooling Data

Pooling data is not applicable to this study.

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

3.7. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study.

3.8. Subpopulations

No analyses of subject subgroups are planned.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Withdrawn patients who have received hLB-001 will be replaced if there is insufficient safety data for DSMB evaluation. Patients who have signed the ICF but have not received hLB-001 will be replaced.

3.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the electronic case report form (eCRF) will be included in data listings that will accompany the CSR.

When tabulating adverse event data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment. An end date completely missing will be imputed as “ongoing.”

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. If the evaluation visit is missing in the database but there is data from an unscheduled or additional visit that is inside the visit window, the data from the unscheduled or additional visit will be used in data summaries. Note, if the circumstance arises where an

unscheduled or additional visit falls within 2 separate nominal visit windows, the unscheduled or additional visit will be considered for the earlier of the 2 nominal visits. In data listings, the relative day of all dates will be presented.

3.12. Interim Analyses

No formal interim analysis is planned for this study. Given the open-label nature of the study design and the first administration of hLB-001, the data will be reviewed in an ongoing manner.

4. STUDY ANALYSES

4.1. Subject Disposition

Subject disposition will be tabulated and include the number screened, the number screen failed, the number in each subject population for analysis, the number of completion and the number who withdrew prior to completing the study and reason(s) for withdrawal.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and presented by treatment group and overall. Age, height/length, weight, Estimated Gestational Age and head circumference will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). The number and percentage of subjects in premature birth, gender, each ethnicity and race category will also be presented. Medical history will also be tabulated.

Demographic and baseline data for each subject will be provided in data listings. MMA Genetic Testing, MMA Diagnosis and History and Medical History will also be presented in data listings.

4.3. Safety Analyses

Safety analyses will be conducted using the Safety population.

4.3.1. Study Drug Exposure

The number and percentage of subjects who completed infusion with no interruption and experienced infusion interruptions will be tabulated by treatment group, as well as permanent discontinuations and the reason for the interruption (e.g., adverse event, other reason).

Study drug exposure and corticosteroid administration will be presented for each subject in data listings.

4.3.2. Adverse Events

All reported AEs will be coded using the MedDRA coding system and displayed in tables and data listings using system organ class (SOC) and preferred term (PT). The severity of AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Grade 1 - Mild to 5 - Death).

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any AE with onset after the administration of study medication, or any event that was present at baseline but worsened in either severity or frequency following study drug administration.

The number of events, along with number and percentage of subjects with any treatment-emergent adverse event (TEAE), with any TEAE assessed by the Investigator as related to treatment (definite, probable, or possible relationship), with any TEAE by severity, with any serious TEAE, with any TEAE leading to study withdrawal, with any TEAE leading to infusion interruption, with any adverse events of special interest (AESI), and with any TEAE leading to death will be summarized by treatment group and overall.

In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs occurring on-study will be listed in by-subject listings. By-subject listings also will be provided for the following: subject deaths, SAEs, AESIs, and AEs leading to withdrawal.

4.3.3. Laboratory Data

Clinical laboratory values will be expressed in reported units or SI units.

The actual value and change from baseline to each on-study evaluation will be summarized for each clinical laboratory parameter, including hematology, clinical chemistry, and coagulation. In the event of repeat values, the last non-missing value per study day/time will be used.

Laboratory abnormalities will be graded according to the CTCAE. Shift tables of change in CTCAE grade of laboratory parameters from baseline to worst value and from baseline to last value on study will be presented.

Clinical laboratory parameters include:

- Hematology (hematocrit, hemoglobin, red blood count, white blood count, differentials [neutrophils, eosinophils, basophils, lymphocytes, monocytes], and platelets).
- Chemistry (albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, chloride, CO2, creatinine, glucose, phosphorus, potassium, sodium and total bilirubin)
- Coagulation (prothrombin time, aPTT or PTT)

All laboratory data will be provided in data listings. Also, blood smear, alpha-fetoprotein, pancreatic enzymes (lipase, amylase), ammonia, renal markers (estimated glomerular filtration rate [eGFR] calculation), urinalysis and urine ketones (dipstick), LDH/haptoglobin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), von Willebrand profile, TMA genetic panel, complement testing: (CH50, Cb5-9, Bb, C3, C4), and urine ketones as measured by Ketostix will be presented in data listings.

4.3.4. Vital Signs and Physical Examination

Observed and change from baseline in vital signs (BP, respiration rate, temperature, and heart rate) will be summarized by visit, treatment group, and overall.

Vital sign measurements will be presented for each subject in a data listing and all physical examination findings will be presented in a data listing.

4.3.5. Electrocardiogram

Observed and change from baseline in electrocardiogram (ECG) results for standard parameter will be summarized by visit, treatment group, and overall.

Electrocardiogram data for each subject will be provided in a data listing.

4.3.6. Prior and Concomitant Medications

Prior and concomitant medications including corticosteroid will be coded using the WHO Drug Dictionary. Results will be tabulated by Anatomic Therapeutic Chemical Class level 3 (ATC3) and preferred term by treatment group and overall. In these tabulations, each participant will contribute only once to each ATC and PT regardless of the number of uses.

A prior medication is defined as any medication that has a stop date prior to administration of the first dose of study drug.

A concomitant medication is defined as any medication that has a stop date that is on or after the date of first dose of study drug. If an end date is missing or the medication is ongoing, the medication will be included.

The use of prior and concomitant medications will be included in a by-subject data listing.

Corticosteroid administration will be presented separately.

4.4. Efficacy Analyses

Efficacy analyses will be conducted using the ITT populations.

4.4.1. Serum Methylmalonic Acid and Methylcitrate Levels

Observed, changes from baseline and percent changes from baseline values in serum methylmalonic acid (MMA) and methylcitrate levels will be summarized by visit and presented by treatment group and overall. The methylmalonic acid and methylcitrate levels, as absolute values and change from baseline when applicable, will be displayed in listings by subject.

4.4.2. Serum Fibroblast Growth Factor 21

Observed, changes from baseline and percent changes from baseline values in FGF21 will be summarized by visit and presented by treatment group and overall. FGF21 levels, as absolute values and change from baseline when applicable, will be displayed in listings by subject.

4.4.3. Propionate Oxidation Rate

Observed, and changes from baseline in 1-13C-propionate Oxidation rates (% Dose Oxidized at 90 minutes) will be summarized by visit, timepoint and presented by treatment group and overall. 1-13C-propionate Oxidation rates, as absolute values and change from baseline when applicable, will be displayed in listings by subject.

4.4.4. Albumin 2A Levels

Observed and changes from baseline values in Albumin 2A levels at week 52-end-of-study (EOS) will be summarized by visit and presented by treatment group and overall. Albumin 2A levels, as absolute values and change from baseline when applicable, will be displayed in listings by subject.

4.5. Exploratory Analyses

Exploratory analyses will be conducted using the ITT populations.

4.5.1. Viral Shedding

Viral shedding will be assessed. Saliva, urine, and stool will be collected and monitored monitor for the presence of shed virus. Quantitative PCR will be used for analysis.

All vector shedding findings will be presented in a data listing.

4.5.2. Hospitalization and Healthcare Utilization

Pre-dosing or post-dosing hospitalizations, Emergency Room (ER) visits and unscheduled physician visits will be presented for each subject in a data listing. Hospitalization and healthcare utilization related to MMA complications will also be indicated in the listing.

Healthcare utilization will be provided in a data listing.

4.5.3. Surgical liver and/or kidney transplant

Concomitant procedures (including surgical liver and kidney transplant) will be presented for each subject in a data listing.

4.5.4. Growth Parameters

Absolute values and change from baseline in weight, length/height and head circumference age-specific z-scores will be summarized by visit and presented by treatment group and overall. Weight, length/height, head circumference actual values and age specific z-scores for each subject and visit will be provided in data listings.

4.5.5. Adaptive Behavioral Score.

Vineland Adaptive Behavioral Score (VABS-3) will be presented for each subject in a data listing.

4.5.6. Parenting Stress Index

Parenting Stress Index (PSI-IV) will be presented for each subject in a data listing.

4.5.7. Neurodevelopmental Status

The changes in age-appropriate testing score from pre-dosing to week 52-EOS visit will be presented for each subject in data listings. The table below presented the Cognitive and Motor Function Scales by age group.

Age Group	**Scale**[a]
6 months to 36 months	Bayley Scales of Infant and Toddler Development, 4th Edition (includes norms for 1-42 months)
37 months to 6 years	Wechsler Preschool and Primary Scale of Intelligence, 4th Edition (includes norms for 2 years 6 months to 7 years 7 months)
6 years 1 month to 12 years	Wechsler Intelligence Scale for Children, 5th Edition (includes norms for 6 years 0 months to 16 years 11 months)
[a] if a child will have exceeded the upper age limit for a test's norms at the 52-EOS, then the test appropriate for the older age should be given on both occasions.	

4.5.8. Protein Intake and Oral Feeding

The summary statistics in normalized total calories, total protein, intact protein (percent of the total protein), medical protein (percent of the total protein) and total calories via g-tube (percent of the total calories) will be summarized by visit and presented by treatment group and overall. Those parameters for each subject and visit will be provided in data listings as well. Total calories will be normalized using the subject weight and age (see Appendix 6.1).

4.5.9. Immunological Changes

Immunological changes on immune response parameters [Neutralizing antibody titer (rAAV-LK03), antibody response (rAAV-LK03, MMUT, ALB2A, albumin), T-cell response (rAAV-LK03, MMUT, ALB2A)] will be provided in a data listing.

5. CHANGES TO PLANNED ANALYSES

Survival at 1-year post hLB-001 dosing will not be analyzed.

Hospitalizations for MMA-related complications (number, reason for, and duration of MMA-related hospitalizations from dosing through week 52-EOS visit with comparison to 1-year period pre-dosing) will not be analyzed. Instead, pre-dosing or post-dosing hospitalization and healthcare utilization will be presented in a data listing. Hospitalization and healthcare utilization related to MMA complications will also be indicated in the listing.

Exploratory serum/plasma biomarkers associated with MMA will not be analyzed.

6. APPENDIX

6.1. FAO/WHO/UNU 2007 Safe Levels of Protein and Energy Intake for Different Age Groups

Energy requirements					Protein requirements*	
Age	kJ/kg/day		kcal/kg/day		Age	g/kg/day
	FAO/WHO/UNU 2007		Converted from FAO/WHO/UNU 2007			
Infants (y)	Males	Females	Males	Females	Infants (y)	
0.5	335	340	80.0	81.2	0.1	1.77
					0.2	1.5
					0.25	1.36
					0.5-1	1.31
Children (y)					Children (y)	
2.5	348	334	83.1	79.8	1-10	0.84-0.90
5.0	315	305	75.2	72.8		
10	275	248	65.7	59.2		
15	230	193	54.9	46.1	11-16	0.92-1.14
Adults (y)					Adults (y)	
(Moderate activity, 70 kg)						
18-29	183	159	43.7	38.0	>16	0.84-0.87
30-59	175	148	41.8	35.3		
Adults (y)						
(Moderate activity, 50 kg)						
18-29	212	180	50.6	43.0		
30-59	212	183	50.6	43.7		

*The FAO/WHO/UNU (2007) have set safe levels of protein intake titrated as an age adjusted mean + 2 SD. Values for safe levels of protein intake apply to males and females.

7. REFERENCES

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