CONFIDENTIAL

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
Investigational Product:	hLB-001 (recombinant AAV vector encoding human *MMUT* gene)
Sponsor Name and Address:	LogicBio Therapeutics 65 Hayden Ave, Floor 2 Lexington, MA 02421
Protocol Date:	Version 8.1, May 4, 2022

Protocol approved by [redacted] Date: 5/4/2022

CONFIDENTIALITY STATEMENT

The information in this document contains commercial information and trade secrets that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws and regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you, which is indicated as privileged or confidential.

INVESTIGATOR'S STATEMENT

Protocol Number: LB001-001

Protocol Version and Date: Version 8.1, May 4, 2022

I have read and understood the protocol and its attachment, I agree to conduct the study as described in the protocol and in accordance with the relevant laws/regulations and standards outlined in the Clinical Trial Agreement.

It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

Investigator's Signature: _____ _____

Date

Name (printed): _____

SUMMARY OF PROTOCOL AMENDMENTS

Version 1	• NA; no patients treated under this version
Version 2	• Schedule of events: updated to include additional timepoints for antibody response and ammonia, nutritional laboratory parameters, dietary optimization, and anti-albumin antibody testing have been added, and the screening period has been reduced • Section 4: survival added as secondary endpoint; multiple endpoints moved from secondary to exploratory • Section 5.1: cohort design updated to include 2 doses of hLB-001 and age de-scalation within each cohort; sentinel patient safety review increased to 6 weeks • Section 5.2: study suspension rules have been updated • Section 5.3.3. and 5.3.4: Retesting criteria for screening has been updated • Section 6.2: Inclusion criteria #5 has been updated • Section 6.3: Exclusion criteria #6 has been updated • Section 7.9: Details regarding dietary management have been added • Section 10.2: Additional information regarding the use and monitoring for adverse effects due to prophylactic steroids has been added • Throughout: Multiple clarifications and administrative corrections have been implemented
Version 3	• Schedule of events: added urine ketones to Day -1 to Day 3 and week 6 • Clarified 2-month corticosteroid administration (high-dose and taper) • Added a maximum daily dose of corticosteroids of 60 mg • Clarified DSMB review to focus on potential catabolic events • Section 10.2: updated monitoring language and added instructions for tapering, potential continuation of steroids, and cortisol testing • Updated DSMB reviews to reflect timing of safety review and steroid tapering • Updated study suspension rules
Version 3.1	• Schedule of events: added albumin-2A at week 6; removed exploratory DNA sample • Endpoints and section 7.15: removed exploratory DNA sample
Version 3.2	• Schedule of events and endpoints: methylcitrate added • Endpoints: Albumin 2A moved from exploratory to secondary • Schedule of events: removed neutralizing antibody titer at week 52

Version 4.0	• Added Saudi Arabia • Schedule of events: added collection of height/weight to baseline visit • Included language regarding pregnancy testing, female patients of child-bearing age
Version 5.0	• Schedule of events: removal of albumin locus DNA sample at screening • Schedule of events: changed timing of neutralizing antibody titer from 90 days to 30 days prior to dosing out of an abundance of caution in case of seroconversion • Removal of sick day diet measurement in inclusion criteria and in healthcare utilization, as this measure is not consistently defined across study sites • Clarified that methylmalonic acid testing is performed via serum • Added section 5.3.4 to allow for subject rescreening • Updated exclusion criteria # 11: Incorporating liver function testing in the exclusion criteria of AAV-based gene therapy trials is a standard practice aimed at minimizing risk of hepatic damage and inflammation, but the levels of these measures at which the risk becomes excessive have not been established. In the absence of sufficient evidence supporting a specific approach, we performed a review of the literature and www.clinicaltrials.gov to determine common practice, which showed that studies using liver-targeted AAV vectors typically include measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin, with exclusion criteria cut-offs set at >2 or >3x the upper limit of normal (NCT 0248092, 02395342, 03306277, 02651675, 04105166). AST is present in several tissues outside the liver, including muscle, brain, pancreas, lung, kidney, RBCs, and leukocytes, and therefore is a non-specific indicator of liver disease (Botros M 2013). On the other hand, ALT is specific to the liver, and the two tests are usually highly correlated (i.e. when ALT is high, AST is as well). Therefore, mild and isolated elevations in AST typically do not indicate liver disease but rather originate from non-hepatic sources, or are an artefact caused by hemolyzed RBCs (Xu Q 2015). No adverse events or altered liver function were reported in preclinical toxicology studies of cLB-001 in juvenile non-human primates. Isolated, spontaneous, reversible and low magnitude changes in ALT were described in some animals, which were mostly <2xULN, not dose dependent, and rarely accompanied by a mild AST elevation (<2xULN). Because of these factors, we have adjusted the cut-offs for ALT and bilirubin, and will require that an elevation in AST must be accompanied by an abnormality in

	another liver function test. Increased cut-off for amylase and lipase in order to detect acute pancreatitis but allow for the presence of mild chronic pancreatitis, which is often seen in methylmalonic acidemia (Hwang 2021). • Added instructions to stop continuous feeding for 1 hour prior to study blood draws
Version 6.0	• Creation of a single global protocol version; harmonization of the Saudi Arabia specific version of the protocol to include all Version 5 changes above as well as to specify that neurocognitive testing will be performed only in the US due to lack of availability of translations • Updated inclusion criteria #4 to reflect country specific vaccinations schedules • Updated inclusion criteria #6 to allow screening hematology to be used to meet criteria • Updated corticosteroid administration to reflect necessity of administering via g-tube as this patient population may not be able to ingest oral steroids • Updated sections 5.3.4 and 5.3.5 to clarify which lab tests need to be repeated for rescreening or extended screening windows • Schedule of events: updated baseline visit labs hematology/chemistry/coagulation/cystatin/eGFR/ammonia to be drawn only if screening labs are drawn > 14 days prior in order to reduce unnecessary duplicate labs; added MMUT antibody testing at several timepoints to allow additional monitoring • Added clarification/corrections to endpoint measurements for Propionate Oxidation, Albumin 2A and oral feeding • Section 7.15: Clarified analytes to be collected for local laboratory analysis
Administrative letter for Protocol V6.0; sent to sites to incorporate prior to Version 7.0 of protocol	Per the letter dated 03November2021 in regards to the SUSAR of 29Oct2021, the following changes impact LB001-001 Protocol Version 6.0 : • Patients will not be dosed within 2 weeks of a viral illness. • Regular home monitoring with urine dipsticks to enable rapid detection of hematuria or proteinuria between days 7 and 14. [Please note that this was removed in Version 7.0 as patients will be hospitalized during this time]
Version 7.0	• Please refer to the separate Summary of Changes document.
Version 8.0	• Please refer to the separate Summary of Changes document.
Version 8.1	• Please refer to the separate Summary of Changes document.

1 PROTOCOL SYNOPSIS

Sponsor: LogicBio Therapeutics
Study Treatment: hLB-001 is a liver-targeted, recombinant engineered adeno-associated viral (rAAV) vector utilizing the LK03 capsid (rAAV-LK03), designed to integrate the human methylmalonyl-CoA mutase gene (*MMUT* also referred to as *MUT*)
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
Number of Patients: Approximately 8, with the option to increase to 12
Study Sites: Approximately 8 in the United States and Saudi Arabia
Study Duration: 12- 13 months (screening run-in and 1-year follow-up postdosing) Note: At the end of the study, patients will be asked to rollover into a long-term follow up study
Objectives and Endpoints: **Primary Objective**: To assess the safety and tolerability of hLB-001 in pediatric patients with methylmalonic acidemia (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) **Secondary Objectives:** 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 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) 2. To assess clinical efficacy outcomes post hLB-001 dosing in pediatric patients with MMA Endpoints • Survival at 1-year post hLB-001 dosing **Exploratory Objectives** 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

- 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 predosing)
- 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 predosing to week 52-EOS visit as determined from standard growth curves)
- Vineland Adaptation Behavior Score (change in patient score from predosing to week 52-EOS visit)
- Parenting Stress Index (change in parenting total stress score (PSI-IV, 36-item short form) from predosing 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 predosing)
- Neurodevelopmental status (change in age-appropriate testing score from predosing to week 52-EOS visit, eg, Bayley, Wechsler) [note that these will be collected in the US only]

3. To assess change from predosing 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)

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 PI 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 (7.9 Dietary Management) 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

Patients will undergo an initial screening, which will include general health and disease complications, MMA diagnosis confirmation, dietary assessment, concomitant medications, 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.

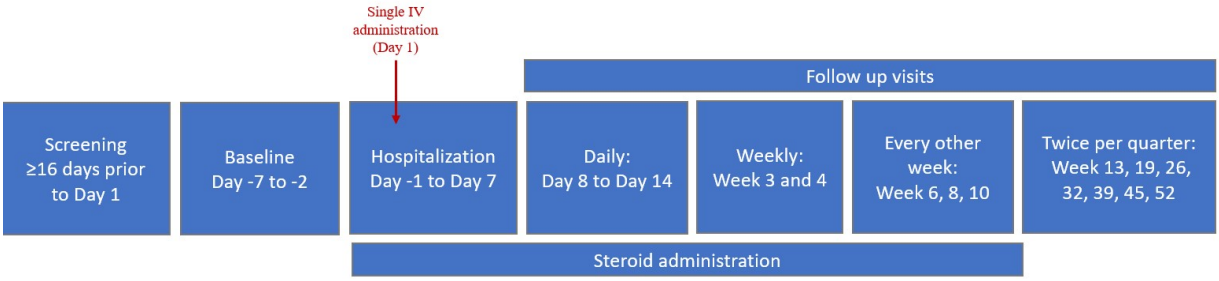
Patients meeting all initial screening criteria will undergo a run-in period of at least 16 days from start of screening to hLB-001 dosing. During this period, patients will establish a baseline for methylmalonic acid levels and demonstrate ongoing clinical stability. During the week prior to dosing, 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.

Once eligibility for the study has been assessed, a peripherally inserted central catheter (PICC line) will be placed for any patient who does not already have one, to allow for easier blood draws during the initial part of the study.

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. Administration may be oral or via g-tube if oral administration is not possible. 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 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 postdose. 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 day 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 three 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 one to two cohorts, cohort 1 (5 x 10^{13} vg/kg) and cohort 2 (1 x 10^{14} vg/kg).

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

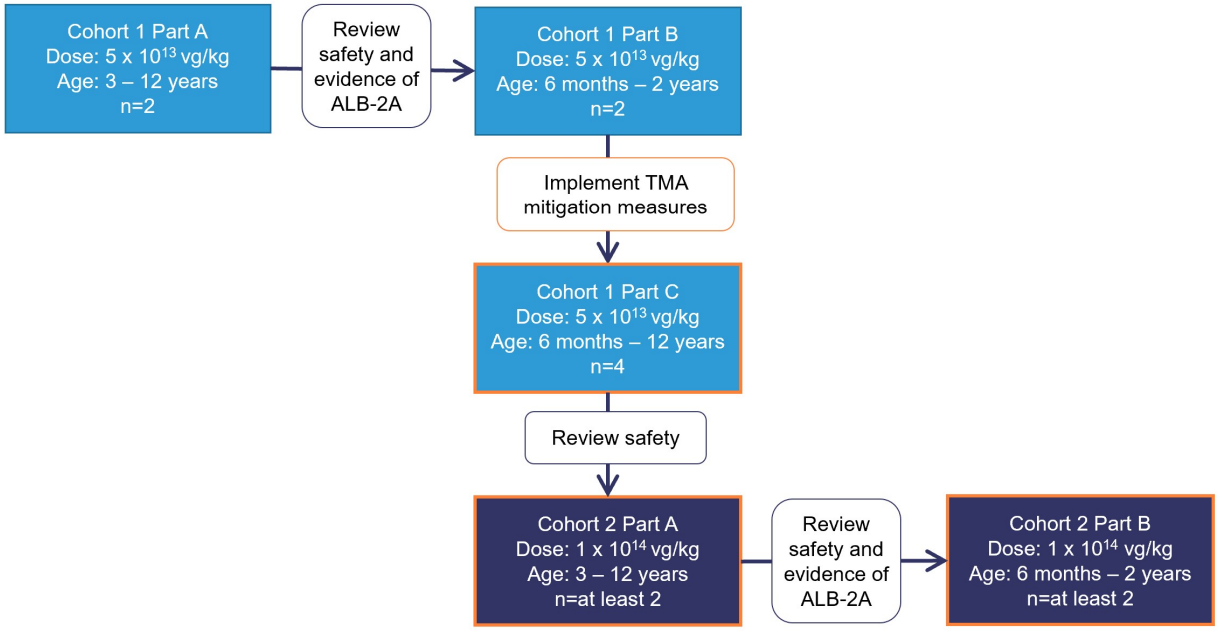
- Part A: 2 patients, aged 3-12 years will be enrolled. A minimum of 6 weeks of postdosing safety-related data will be evaluated by the DSMB chair and the Sponsor Medical Monitor between the dosing of each patient. The first patient must be at least midway through the corticosteroid tapering period for 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.
    - 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. A minimum of 6 weeks of postdosing safety-related data will be evaluated by the 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.
- Part C: Four additional patients, aged 6 months to 12 years of age, will be enrolled. A minimum of 4 weeks of postdosing safety-related data will be evaluated by the DSMB chair, the Sponsor Medical Monitor and TMA experts between the dosing of each patient. At a minimum of 4 weeks after the fourth patient is dosed, the independent DSMB will review all available safety data. If the safety review is sufficient, enrollment into Cohort 2 Part A may begin, however the Sponsor will assess all safety and efficacy data before dosing of this cohort will take place. If the risk/benefit is deemed unacceptable, cohort 2 will not be enrolled. The risk/benefit analysis will be shared with the FDA prior to commencing enrollment in cohort 2.

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

- Part A: At least 2 patients, aged 3-12 years will be enrolled. A minimum of 4 weeks of postdosing safety-related data will be evaluated by the DSMB chair, the Sponsor Medical Monitor, and TMA experts between the dosing of each patient. At a minimum of 4 weeks after the second patient is dosed, the independent DSMB will review all available safety data.
    - If the safety review from Cohort 2 Part A is sufficient and there is evidence of albumin-2A in Cohort 2 Part A, enrollment into Cohort 2 Part B may begin.
    - If the safety review is insufficient, or a patient needs to be replaced, an additional patient in Cohort 2 Part A may be enrolled.

- Part B: At least 2 patients, aged 6 months-2 years will be enrolled. A minimum of 4 weeks of postdosing safety-related data will be evaluated by the DSMB chair, the Sponsor Medical Monitor, and TMA experts between the dosing of each patient. At a minimum of 4 weeks after the second patient is dosed, the independent DSMB will review all available safety data.
    - If the safety review is insufficient, or a patient needs to be replaced, an additional patient in Cohort 2 Part B may be enrolled.

The cohort schematic is below:



Long-term Follow-up: Long-term follow-up will be completed under a separate study protocol. In brief, through 5 years postdosing, study patients will be followed by their health care providers (HCPs) in addition to annual visits to the clinical study site for safety and efficacy evaluations. From 6 to 15 years postdosing, they will be followed for potential delayed AEs to match the current regulatory recommendation of 15-year follow-up.

hLB-001 Administration

hLB-001 is prepared as a sterile, nonpyrogenic solution stored at -65°C or below until ready for use. It is thawed for administration as a one-time intravenous infusion over at least 30 minutes and at a flow rate of no more than 5 mL/kg per hour through a syringe pump.

Dose Cohorts, Study Suspension, and Study Stopping Rules

Dose Cohorts

Age de-escalation in Cohort 1 Part B and dose escalation in Cohort 2 Part A will not be opened for enrollment if either of the following is noted following hLB-001 treatment in Cohort 1 Part A or Part C. If either of the following is noted following hLB-001 treatment in Cohort 2 Part A, Cohort 2 Part B will not be opened for enrollment:

- Any Common Terminology Criteria for Adverse Events (CTCAE) grade 4 organ toxicity that does not improve to grade ≤ 2 within 4 weeks
- Any grade 3 or greater autoimmune toxicity

The Sponsor will assess all safety and efficacy data before dosing of cohort 2 will take place. The risk/benefit analysis will be shared with the FDA prior to commencing enrollment in cohort 2. If the risk/benefit is deemed unacceptable, cohort 2 will not be enrolled.

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 11.2.1 Adverse Events of Special Interest (AESI))
- The same or related grade 3 SAE in two subjects that is related to the study product or study procedures
- Despite corticosteroid use as described in 10.2 Prophylactic Administration of Corticosteroids and Monitoring/Risk Mitigation, alanine aminotransferase (ALT) values remain above the threshold of 2 X Upper Limit Normal (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 recommendation 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.

Inclusion/Exclusion Criteria

Inclusion Criteria

A patient must meet all the following inclusion criteria to be eligible for participation in this study:

1. At the time of dosing, patient must be 6 months to 12 years of age
2. Patient (and/or legally authorized representative) has voluntarily agreed to participate by giving written informed consent/assent in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations
3. Willingness and ability to comply with study procedures and scheduled visits
4. Current with local recommended vaccination schedule based on age (no vaccinations within 6 weeks pre- or post-hLB-001 dosing expectation of the need for live vaccinations while on corticosteroids and for 3 months following completion of corticosteroid dosing)
5. Males and females with diagnosis of severe MMA meeting all the following;
   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 PI 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 (7.9 Dietary Management) 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
6. Hematology laboratory results confirming:
   a. Hemoglobin ≥ 9 g/dL
   b. Absolute neutrophils count ≥ 1000/µL
   c. Platelet count ≥ 150,000/µL

Exclusion Criteria

A patient meeting any of the following exclusion criteria is not eligible for participation in the study:

1. Patients with organic acidemias other than isolated MMA, or with any other causes of hyperammonemia
2. Having received MMA-targeted gene therapy or nucleic acid therapy
3. Having received an investigational drug within 28 days or 5 half-lives of the drug, whichever is shorter, prior to initiation of screening
4. Patients on insulin or high dose hydroxocobalamin (> 1 mg/day OHB12 parenteral)
5. Kidney or liver transplant, including hepatocyte cell therapy
6. Estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 based on the creatinine-based "Bedside Schwartz" equations (2009), or ongoing dialysis for renal disease
7. Patient tests positive for anti-rAAV-LK03-neutralizing antibodies with titers above protocol-specified threshold of 1:10
8. Patient has received immune-modulating agents within 3 months prior to initiation of screening (use of inhaled corticosteroids to manage chronic respiratory conditions permissible)
9. Patient has a history of, or currently has, a clinically important condition not directly related to MMA, in the opinion of the investigator

10. History or presence of arrhythmia or other clinically significant abnormality on electrocardiogram (ECG)
11. Any of the following hepatic/gastrointestinal factors:
    a. Liver laboratory testing:
        - alanine aminotransferase (ALT) > 2.0 × upper limit of normal (ULN)
        - aspartate aminotransferase (AST) > 2.0 × ULN together with ALT, alkaline phosphatase or total bilirubin > ULN
        - total bilirubin > 2.0 × ULN
        - prothrombin time > 1.5 x ULN
    b. Pancreatic enzymes (amylase, lipase) > 3.0 × ULN
    c. Hyperammonemia characterized by ammonia ≥ 3 × ULN, or signs of active metabolic decompensation (eg, lethargy, irritability, and vomiting)
12. Any of the following oncologic factors:
    a. Liver abnormalities suspicious for malignancy on screening ultrasound
    b. History of any malignancy, test-positive for a cancer-predisposition syndrome, or family history for a cancer-predisposition syndrome and patient has not been tested
13. History of anaphylaxis or severe allergic reaction or allergy to antibiotics to be potentially administered
14. Patient has experienced a viral or bacterial illness and is still symptomatic within 6 weeks of dosing
15. Vaccinations administered within 6 weeks of dosing
16. History of deep vein thrombosis (DVT) or coagulopathy

Statistical Methods

The study will consist of at least 1 cohort with the option to add a second cohort at a higher dose level for a total sample size of approximately 8 patients and potentially up to 12 patients. The sample size is based on practical consideration considering the ultra-orphan patient population. The primary focus will be on determining the safety, tolerability, and biomarker/clinical efficacy profile of hLB-001. No specific statistical hypotheses are being evaluated with respect to the primary, secondary, or exploratory objectives and endpoints. Each patient will serve as his or her own control.

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

Graphical summaries of the data may be presented. Assessments will be displayed by cohort and time, as well as across cohorts for specific parameters.

Table 1. Schedule of Events

Throughout study	
Adverse events	Adverse event and concomitant medication collection begins with ICF and continues until end of study.
Concomitant medications	

Prior to Dosing			
Study Visit	**Screening/ Run-in**	**Baseline**	**Day -1 Admission** [c]
Window	Screening to start at least 16 days prior to Day 1	Day -7 to -2	
Informed consent/assent	X		
Demographics	X		
Inclusion/ exclusion criteria	X	X	X
Medical history	X		
Meningococcal vaccination	X		
	Administer at least 6 weeks prior to planned dosing day, if the subject has not already been vaccinated		
DNA for genetic analysis (*MMUT*)	X		
	Collect if no documentation from a CLIA certified lab of test result		
Neutralizing antibody titer (rAAV-LK03) [b]	X	X	
	Exclusion criterion to be evaluated from screening sample; to be repeated if sample taken more than 30 days prior to dosing		
Antibody response (rAAV-LK03, *MMUT*, ALB2A) [b]	X	LK03 only	
T cell response [b]	X	X	
	rAAV-LK03, *MMUT*, ALB2A. Collect at either screening or baseline visit (do not collect at both)		
Hematology and blood smear [b]	X Draw unless safety lab testing has occurred within the 2 weeks prior to consent/assent as part of routine care and dosing is within 30 days	X Draw only if screening sample taken >14 days prior	X
Chemistry [b]			BMP
Coagulation [b]			
TMA genetic panel	X		
CRP, ESR	X		X
Von Willebrand Disease profile	X		
LDH	X		
Haptoglobin			X
CH50	X	X	X

Prior to Dosing			
Study Visit	**Screening/ Run-in**	**Baseline**	**Day -1 Admission** [c]
Cb5-9, Bb		X	X
C3, C4		X	X
Ketones (urine dipstick)	X		
Urinalysis		X	Approximately 12 hours post start of steroids
Additional labs: eGFR calculation [b]	X	Draw only if screening sample taken >14 days prior	
Additional lab: Ammonia [b]	X	Draw only if screening sample taken >14 days prior	
Pancreatic enzymes (lipase, amylase) [b]	X		
Plasma amino acids, albumin, prealbumin and carnitine	X	Draw only if screening sample taken >14 days prior	
	Fasting for 3-4 hours (if possible); preferably morning draw		
Methylmalonic acid and methylcitrate [b]	X At least 14 days prior to baseline sample	X	
Albumin-2A level [b]		X	
FGF21 [b]	X	X	
Serum and plasma for exploratory biomarkers [b]	X		
Samples for viral shedding (saliva, stool, urine)			X
Physical examination	X		X
Vital signs	X		X
	BP, respiration rate, temp, heart rate		
ECG (single, 12-lead)	X	X	
Liver ultrasound and alpha-fetoprotein	X		
	If ultrasound was performed within 3 months prior to screening, it does not need to be repeated at screening.		
1-^{13}C propionate oxidation	X	X	
	Fasting for approximately 4 hours. Test will take approximately 2 hours to complete.		
Growth parameters	X Include 1-year prior data collection	Height/ length and weight	X
	weight, height/length, up to age 3: head circumference		
Patient diet diary	X Provide once informed consent signed	Provide the Day -1 diary in advance of Day -3 to allow for Day -1 completion	X
	Record for 3 days prior to each visit		
Diet optimization	X	X	

Prior to Dosing			
Study Visit	**Screening/ Run-in**	**Baseline**	**Day -1 Admission** [c]
	See 7.9 Dietary Management		
Vineland Adaptive Behavioral Scale			X
Motor and cognitive function assessments			X US only
Parenting stress index short form			X
Pregnancy risk assessment and testing	X		
	Female patients of child-bearing age with pregnancy risk		
Hospitalizations and healthcare utilization	X Include 1-year prior data collection	Record hospitalizations, including duration and primary reason Healthcare utilization includes ER visits and unscheduled visits to physician/hospital	
PICC line placement	At least 7 days prior to dosing date, for patients who do not already have a line		
Corticosteroid administration			Initiate 24 hours (± 4 hours) prior to hLB-001 infusion

Dosing to Hospital Discharge							
Patients to be hospitalized for 8 days, from day -1 to Day 7 post-dose							
Study Visit	**Day 1 Treatment**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7 / Week 1**
Antibody response [b]							LK03 only
Hematology and blood smear [b]	Pre-infusion	X	X	X	X	X	X
Chemistry [b]		BMP	X	BMP	BMP	BMP	X
Coagulation [b]			X				X
LDH	Pre-infusion		X		X		X
Haptoglobin		X		X		X	
CH50			X			X	
Cb5-9, Bb			X			X	
C3, C4		X	X	X	X	X	X
Ketones (urine dipstick)							
Urinalysis	Pre-infusion	X	X	X	X	X	X
Additional lab: Ammonia [b]							X
Serum and plasma for exploratory biomarkers [b]							Serum only
Samples for viral shedding (saliva, stool, urine)							X
Physical examination	targeted, predosing						targeted
Vital signs (BP, respiration rate, temp, and heart rate)	Take pre-dose (within 15 min of dosing); 30 min, 1, 2, 4, 6, and 8 hours (± 10 min) after start of infusion Pulse oximetry continuous monitoring starting prior to dosing then for 24 hours postdosing	X	X	X	X	X	X
ECG (single, 12-lead)		X					
hLB-001 administration	X						
	Screening weight to be used for dose calculation unless taken more than 30 days prior to dosing						
Corticosteroid administration	Daily dosing; potential corticosteroid steroid-associated adverse events will be monitored as described in 10.2 Prophylactic Administration of Corticosteroids and Monitoring/Risk Mitigation						

Dosing to Hospital Discharge							
Patients to be hospitalized for 8 days, from day -1 to Day 7 post-dose							
Study Visit	**Day 1 Treatment**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7 / Week 1**
Hospital discharge							X

Hospital Discharge to Week 6										
Study Visit	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14 / Week 2**	**Week 3**	**Week 4**	**Week 6**
Window								± 2 d	± 2 d	± 3 d
Antibody response [b]							rAAV-LK03 only	rAAV-LK03 only	rAAV-LK03, ALB2A, MMUT	
Hematology and blood smear [b]	X	X	X	X	X	X	X	X	X	X
Chemistry [b]	BMP	BMP	BMP	BMP	BMP	BMP	X	X	X	X
Coagulation [b]			X				X	X	X	X
LDH		X		X		X				
Haptoglobin	X		X		X		X			
CH50		X			X		X	Complement testing weekly until CH50 normalizes, if not normalized by Day 14		
Cb5-9, Bb		X			X		X			
C3, C4	X	X	X	X	X	X	X			
Ketones (urine dipstick)								X	X	X
Ketostick or equivalent (home administration)	As indicated – see 7.15 Laboratory Tests for additional information									
Urinalysis	X	X	X	X	X	X	X			
Additional lab: Ammonia [b]									X	
Methylmalonic acid and methylcitrate [b]									X	X
Albumin-2A level [b]									X	X
Serum and plasma for exploratory biomarkers [b]								serum only	serum only	
Samples for viral shedding (saliva, stool and urine)							X	X	X	X
Physical examination							targeted	targeted	targeted	targeted
Vital signs (BP, respiration rate, temp, and heart rate)	X	X	X	X	X	X	X	X	X	X

Hospital Discharge to Week 6										
Study Visit	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14 / Week 2**	**Week 3**	**Week 4**	**Week 6**
Window								± 2 d	± 2 d	± 3 d
Hospitalizations and healthcare utilization	Record hospitalizations, including duration and primary reason Healthcare utilization includes ER visits and unscheduled visits to physician/hospital									
Corticosteroid administration	Daily dosing followed by weaning schedule as described in section 10.2 Prophylactic Administration of Corticosteroids and Monitoring/Risk Mitigation									

Week 8 to Week 52									
Study Visit	**Week 8**	**Week 10**	**Week 13**	**Week 19**	**Week 26**	**Week 32**	**Week 39**	**Week 45**	**Week 52/EOS**
Window	± 3 d	± 3 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d
Antibody response [b]			rAAV-LK03, ALB2A, MMUT		rAAV-LK03 only		rAAV-LK03 only		rAAV-LK03, ALB2A, MMUT
	See 7.15 Laboratory Tests for potential for additional testing, including testing for anti-albumin antibodies								
T cell response [b]			X						
Hematology and blood smear [b]	X	X	X	X	X	X	X	X	X
Chemistry [b]	X	X	X	X	X	X	X	X	X
Coagulation [b]	X	X	X	X	X	X	X	X	X
CH50	Complement testing weekly until CH50 normalizes, if not normalized by Day 14								
Cb5-9, Bb									
C3, C4									
Ketones (urine dipstick)	X	X	X	X	X	X	X	X	
Ketostick or equivalent (home administration)	As indicated – see 7.15 Laboratory Tests for additional information								
Urinalysis									X
Additional labs: eGFR calculation [b]			X						X
Additional lab: Ammonia [b]	X		X		X		X		X
Plasma amino acids, albumin, prealbumin and carnitine			X		X		X		X
	Fasting for at 3-4 hours (if possible); preferably morning draw								
Methylmalonic acid and methylcitrate [b]	X	X	X	X	X	X	X	X	X
Albumin-2A level [b]	X	X	X	X	X	X	X	X	X
FGF21 [b]			X	X	X	X	X	X	X
Serum and plasma for exploratory biomarkers [b]			X		serum only		serum only		X
Samples for viral shedding	X		Stool, urine		Stool, urine		Stool, urine		Stool, urine

Week 8 to Week 52									
Study Visit	**Week 8**	**Week 10**	**Week 13**	**Week 19**	**Week 26**	**Week 32**	**Week 39**	**Week 45**	**Week 52/EOS**
Physical examination	targeted	targeted	X	targeted	targeted	targeted	targeted	targeted	X
Vital signs	X	X	X	X	X	X	X	X	X
ECG			X						X
Liver ultrasound and alpha-fetoprotein									X
1-^{13}C propionate oxidation			X	X	X	X	X	X	X
			Fasting for approximately 4 hours. Test will take approximately 2 hours to complete. This test will not be performed if the visit is completed via home healthcare.						
Growth parameters			X	Height/ length and weight	X	Height/ length and weight	X	Height/ length and weight	X
Patient diet diary			X		X		X		X
	Record for 3 days prior to each visit								
Diet optimization			X		X		X		X
Vineland Adaptive Behavioral Scale									X
Motor and cognitive function assessments									X US only
Parenting stress index short form									X
Hospitalizations and healthcare utilization	Record hospitalizations, including duration and primary reason Healthcare utilization includes ER visits and unscheduled visits to physician/hospital								
Corticosteroid administration	Daily dosing followed by weaning schedule as described in section 10.2 Prophylactic Administration of Corticosteroids and Monitoring/Risk Mitigation. Cortisol collection 2 weeks after discontinuation of steroids.								

ALB2A = albumin-2A; BP = blood pressure; CLIA = Clinical Laboratory Improvement Amendments; CRP = c-reactive protein; ECG = electrocardiogram; ESR – erythrocyte sedimentation rate; eGFR = estimated glomerular filtration rate; EOS = end-of-study; FGF21 = fibroblast growth factor 21; ICF = informed consent form; *MMUT* = human methylmalonyl-CoA mutase gene

a =	*Screening may occur over multiple days. Refer to sections 5.3.4 and 5.3.5 for rescreening and extended screening period requirements.*
b =	*Continuous feeds should be stopped 1 hour prior to collection*

c =	*If dosing (Day 1) is delayed after completing Day -1, it will not be necessary to repeat the scheduled assessments if dosing is rescheduled within 2 weeks. The following tests will not need to be repeated if dosing is rescheduled within 2 months: Viral shedding, Vineland Adaptive Behavioral Scale, Motor and cognitive function assessments [US only] and Parenting stress index.*

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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AAV	adeno-associated viral vector
ADA	Anti-drug antibodies
AE	adverse event
AESI	adverse events of special interest
Albumin-2A	alternative albumin isoform synthesized from loci with hLB-001 integration
BMP	basic metabolic panel
BP	blood pressure
CDC	Center for Disease Control
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
EOS	end-of-study
ER	emergency room
ESR	erythrocyte sedimentation rate
FGF21	fibroblast growth factor 21
FIH	first-in-human
GCP	Good Clinical Practice
HCC	hepatocellular carcinoma
HCP	health care provider
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ID	infectious disease
IRB	Institutional Review Board
LEC	Local Ethics Committee
MMA	methylmalonic acidemia
MMUT or MUT	the gene encoding methylmalonyl-CoA mutase; newer nomenclature may use *MMUT*
MUT or mut	methylmalonyl-CoA mutase enzyme; newer nomenclature may use mmut
NF	National Formulary
PCR	polymerase chain reaction
PD	pharmacodynamics

Ph Eur	European Pharmacopoeia
PICC	peripherally inserted central catheter
PK	pharmacokinetics
PSI-IV	parenting total stress score
rAAV	recombinant adeno-associated virus
SOP	Standard Operating Procedure
SRM	Study Reference Manual
TMA	thrombotic microangiopathy
ULN	upper limit of normal
vg/kg	vector genomes/kilogram
USP	United States Pharmacopeia

3 INTRODUCTION AND RATIONALE FOR DOSE SELECTION

3.1 Background Information

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 (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).

MMA has an autosomal recessive pattern of inheritance with an incidence in the United States and European Union of approximately 1 in 50,000 to 100,000 live births (Therell et al, 2014) (Almási et al, 2019). It is caused most commonly (60%) by mutations in the gene encoding the mitochondrial enzyme methylmalonyl-CoA mutase (MMUT), resulting in a failure of conversion of methylmalonyl-CoA to succinyl-CoA and a subsequent accumulation of methylmalonic acid in tissues and blood. Patients with MMA caused by *MMUT* gene mutations are typically non-B_{12} responsive, present at a younger age, and have a more severe phenotype (Manoli et al, 2016).

Severity of symptoms within the *MMUT* mutation patient population is correlated with the mutation type and the level of residual enzyme activity. Based on in vitro fibroblast assessments and/or gene allele correlations, MMA patients may have a complete loss of enzyme activity, designated as *mut0*, or a partial reduction, designated as *mut-*. The *mut0* subtype is more prevalent and associated with higher morbidity and mortality at an early age (Manoli et al, 2016).

While rapid MMA diagnosis via universal newborn screening can lead to early institution of medical and dietary management, the natural history of MMA remains characterized by periods of relative health alternating with intermittent and potentially life-threatening metabolic decompensations. Thus MMA continues to be associated with substantial morbidity despite improved survival (de Baulny et al, 2005) (Dionisi-Vici et al, 2006) (Kölker et al, 2015).

Currently, MMA has no curative therapies. Patients with mutase-deficient MMA are treated lifelong with a demanding dietary regimen of protein restriction in addition to ammonia scavenger therapy in an attempt to mitigate acute illnesses that contributes to metabolic brain injury and progression to renal failure. Liver transplantation is an emerging intervention in MMA patients, increasingly performed at an early age to suppress hyperammonemia episodes, stabilize neurocognitive function, and improve long-term survival (Niemi et al, 2015). However, donor

liver availability is limited; and transplantation has significant acute and long-term risks associated with the surgical procedure as well as prolonged immunosuppression.

3.2 Rationale for Study

In the first-in-human (FIH) hLB-001 clinical trial, LogicBio proposes to enroll pediatric patients with severe MMA who have not had liver transplantation. As a form of "molecular" liver 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. Additionally, hLB-001 is designed to be administered to the youngest of MMA patients before surgical liver transplantation is a viable option.

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.

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 MMA levels, and ameliorate the MMA disease state.

Restoration of normal and sustained levels of hepatic MMUT enzymatic activity through hLB-001 gene therapy could be transformative for patients and their caregivers, providing substantial clinical benefit by converting the disease to a more manageable if not asymptomatic state. This is supported by the clinical course of the majority of *mut-* MMA patients who retain some residual MMUT activity and have relatively delayed onset of symptoms with lower frequency of morbidity, mortality, and neurological complications (Hörster et al, 2007). Importantly, enrollment of patients with MMA in an hLB-001 trial would not preclude future intervention with liver transplantation.

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.

Further summary information on hLB-001 is provided in the Investigator's Brochure (IB).

Dose selection rationale, based on nonclinical data, may be found in the IB. To summarize, in an early proof of concept study, treatment of a mouse model of MMA with 1×10^{14} vg/kg mLB-001b, a mouse surrogate of hLB-001, demonstrated a significant improvement in animal survival whereas treatment with 2.5×10^{13} vg/kg mLB-001b did not. Later studies with intravenous administration of mLB-001b at 5×10^{13} vg/kg and 1×10^{14} vg/kg demonstrated evidence of efficacy that allowed a therapeutically active dose range to be identified. Specifically, these

studies demonstrated comparable bioactivity/efficacy for the 2 above-mentioned dose levels, based on clear improvement in clinically meaningful endpoints (animal survival, protection from body weight loss) and relevant biomarkers (maintenance of lower circulating methylmalonic acid levels) in the treated animals compared to the vehicle-treated control animals in response to protein challenge that is designed to mimic metabolic stress. These studies identified 5×10^{13} vg/kg as the minimum efficacious dose, and single IV administration of hLB-001 at this dose is expected to be biologically active and will be the first dose explored in this first clinical study.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective and Endpoints

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)

4.2 Secondary Objectives and Endpoints

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 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)

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

Endpoints

- Survival at 1-year post hLB-001 dosing

4.3 Exploratory Objectives and Endpoints

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

- Hospitalizations for MMA-related complications (number, reason for, and duration of MMA related hospitalizations from dosing through week 52-EOS visit with comparison to 1year period predosing)
- 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 predosing to week 52-EOS visit as determined from standard growth curves)
- Vineland Adaptation Behavior Score (change in patient score from predosing to week 52-EOS visit)
- Parenting Stress Index (change in parenting total stress score (PSI-IV, 36-item short form) from predosing 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 predosing)
- Neurodevelopmental status (change in age-appropriate testing score from predosing to week 52-EOS visit, eg, Bayley, Wechsler) [note that these will be collected in the US only]

3. To assess change from predosing 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)

5 STUDY DESCRIPTION

5.1 Study Design

Study LB001-001 is a 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 PI 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 (7.9 Dietary Management) 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 will 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.

Once eligibility for the study has been assessed, a peripherally inserted central catheter (PICC line) will be placed for any patient who does not already have one, to allow for easier blood draws during the initial part of the study.

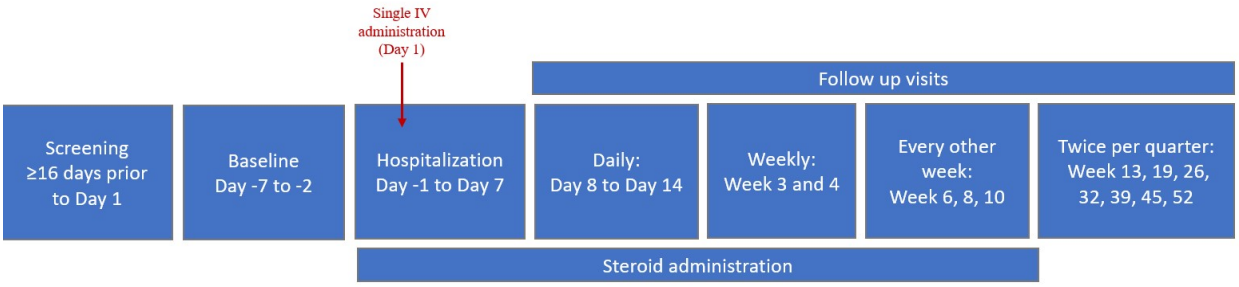
Administration of several AAV-based genetic therapies, including hLB-001, has been reported to be associated with the development of thrombotic microangiopathy (TMA), resulting in the use of a variety of mitigation approaches. Subjects with certain known risk factors such as

concurrent infection, recent vaccinations, and history of DVT or coagulopathy will be excluded. Additionally, subjects will be intensely monitored during the high-risk TMA period (i.e. two weeks post-dosing) in order to detect signs of TMA as early as possible, should they develop. The monitoring regimen will include frequent testing for laboratory signs of hemolysis, thrombocytopenia, kidney dysfunction, and complement activation. Results of this testing will be reviewed as they are available by the investigator, the TMA experts on the DSMB, and the Sponsor Medical Monitor.

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, followed by a taper (ZOLGENSMA prescribing information, 2019). In practice, the mean duration of steroids treatment is often longer, due to persistent elevations in transaminases, which has also been observed with hLB-001 (Chand 2021). 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. Administration may be oral or via g-tube if oral administration is not possible. 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. If the cortisol level is < 18 mcg/dL or within normal limits, patient will be referred to an endocrinologist for CRH or ACTH stimulation testing.

The anticipated period of study patient hospitalization is 8 days, from day -1 to Day 7 postdose. 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 day 14/week 2. Patients will return to the study site for weekly visits during month 1 (week 3 and 4), every other week until month 3 (weeks 6, 8 and 10), and twice every quarter thereafter until 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 three 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 one to two cohorts, cohort 1 (5 x 10^{13} vg/kg) and cohort 2 (1 x 10^{14} vg/kg).

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 two weeks in order to more fully assess the corticosteroid period.

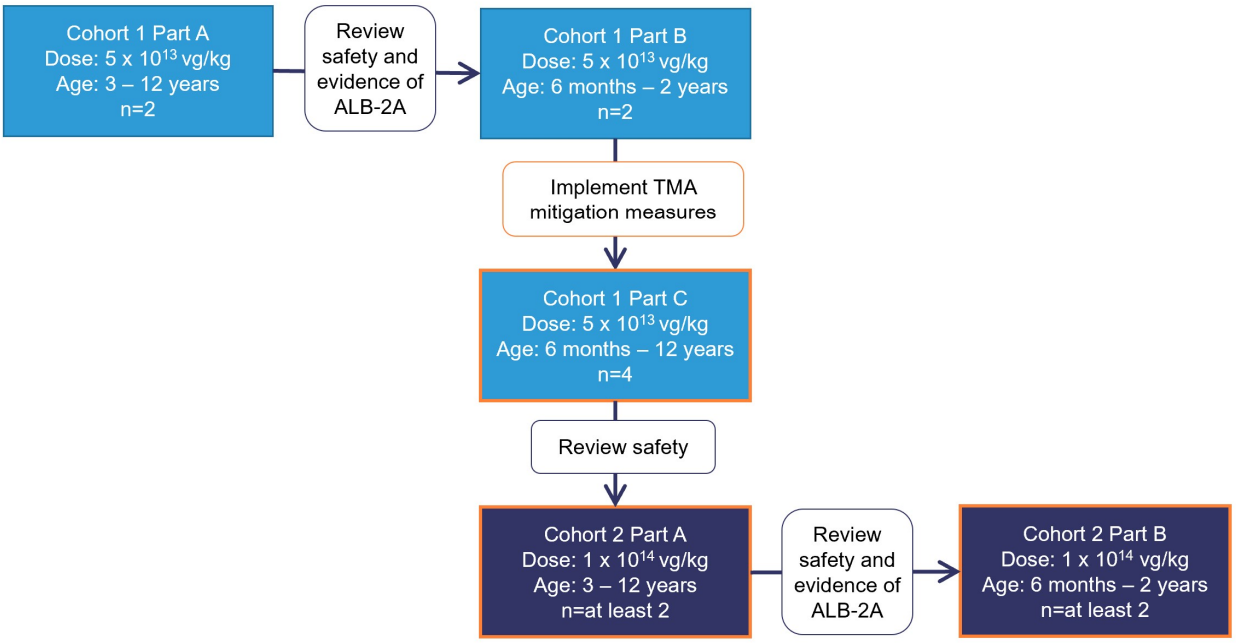
- Part A: 2 patients, aged 3-12 years will be enrolled. A minimum of 6 weeks of postdosing safety-related data will be evaluated by the DSMB chair and the Sponsor Medical Monitor between the dosing of each patient. The first patient must be at least midway through the corticosteroid tapering period for 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.
  - 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. A minimum of 6 weeks of postdosing safety-related data will be evaluated by the 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.
- Part C: Four additional patients, aged 6 months to 12 years of age, will be enrolled. A minimum of 4 weeks of postdosing safety-related data will be evaluated by the DSMB chair,

the Sponsor Medical Monitor and TMA experts between the dosing of each patient. At a minimum of 4 weeks after the fourth patient is dosed, the independent DSMB will review all available safety data. If the safety review is sufficient, enrollment into Cohort 2 Part A may begin, however the Sponsor will assess all safety and efficacy data before dosing of this cohort will take place. The risk/benefit analysis will be shared with the FDA prior to commencing enrollment in cohort 2. If the risk/benefit is deemed unacceptable, cohort 2 will not be enrolled.

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

- Part A: At least 2 patients, aged 3-12 years will be enrolled. A minimum of 4 weeks of postdosing safety-related data will be evaluated by the DSMB chair, the Sponsor Medical Monitor, and TMA experts between the dosing of each patient. At a minimum of 4 weeks after the second patient is dosed, the independent DSMB will review all available safety data.
  - If the safety review from Cohort 2 Part A is sufficient and there is evidence of albumin-2A in Cohort 2 Part A, enrollment into Cohort 2 Part B may begin.
  - If the safety review is insufficient, or a patient needs to be replaced, an additional patient in Cohort 2 Part A may be enrolled.
- Part B: At least 2 patients, aged 6 months-2 years will be enrolled. A minimum of 4 weeks of postdosing safety-related data will be evaluated by the DSMB chair, the Sponsor Medical Monitor, and TMA experts between the dosing of each patient. At a minimum of 4 weeks after the second patient is dosed, the independent DSMB will review all available safety data.
  - If the safety review is insufficient, or a patient needs to be replaced, an additional patient in Cohort 2 Part B may be enrolled.

The cohort schematic is below:



5.1.1 Long-term Follow-up

Long-term follow-up will be completed under a separate study protocol. In brief, through 5 years postdosing, study patients will be followed by their health care providers (HCPs) in addition to annual visits to the clinical study site for safety and efficacy evaluations. From 6 to 15 years postdosing, they will be followed for potential delayed AEs to match the current regulatory recommendation of 15-year follow-up.

5.1.2 Overall Safety Plan

Safety monitoring will begin once the informed consent form (ICF) has been signed.

All new or worsening AEs regardless of causality, including laboratory abnormalities that meet the definition of an AE, will be monitored and recorded in the designated electronic case report form (eCRF) through the last study visit. Emergence of any new clinical conditions (eg, transplantation, major decompensation event that triggers a change in status, basal ganglia stroke, death) that are reported or observed, and the action taken in response, will be reported to the sponsor. All study patients will be asked to participate in a long-term follow-up protocol for continued monitoring of gene therapy-related AEs.

5.2 Dose Cohorts, Study Suspension, and Study Stopping Rules

Dose Cohorts

Age de-escalation in Cohort 1 Part B and dose escalation in Cohort 2 Part A will not be opened for enrollment if either of the following is noted following hLB-001 treatment in Cohort 1 Part A or Part C. Also, if either of the following is noted following hLB-001 treatment in Cohort 2 Part A, Cohort 2 Part B will not be opened for enrollment.

- Any Common Terminology Criteria for Adverse Events (CTCAE) grade 4 organ toxicity that does not improve to grade ≤ 2 within 4 weeks
- Any grade 3 or greater autoimmune toxicity

The Sponsor will assess all safety and efficacy data before dosing of cohort 2 will take place. The risk/benefit analysis will be shared with the FDA prior to commencing enrollment in cohort 2. If the risk/benefit is deemed unacceptable, cohort 2 will not be enrolled.

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 11.2.1 Adverse Events of Special Interest (AESI))
- The same or related grade 3 SAE in two subjects that is related to the study product or study procedures
- Despite corticosteroid use as described in 10.2 Prophylactic Administration of Corticosteroids and Monitoring/Risk Mitigation, alanine aminotransferase (ALT) values remain above the threshold of 2 X Upper Limit Normal (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 recommendation 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.

5.3 Patient Staggering

The interval between doses for each subject is defined as follows:

- Cohort 1 Part A and B: A minimum of 6 weeks of postdosing safety-related data will be evaluated by the DSMB chair and the Sponsor Medical Monitor between the dosing of each patient. Each patient must be at least midway through the corticosteroid tapering period for the safety review to be completed.

- Cohort 1 Part C: A minimum of 4 weeks of postdosing safety-related data for the prior subject will be evaluated by the DSMB chair, the Sponsor Medical Monitor and TMA experts before dosing the next patient.

- Cohort 2 Part A and B: A minimum of 4 weeks of postdosing safety-related data for the prior subject will be evaluated by the DSMB chair, the Sponsor Medical Monitor and TMA experts before dosing the next patient.

Safety-related data is defined in the DSMB charter and will contain at a minimum: medical history, adverse events, chemistry, hematology and other local laboratory values, concomitant medications, and prednisolone administration. The DSMB will be presented with a listing that indicates if any study stopping or suspension criteria are met.

5.4 Study Schedule

The time and events schedule for this study can be found in Table 1. Schedule of Events.

5.4.1 Informed Consent/Assent

After the study has been fully explained, written informed consent and assent, as applicable, will be obtained from the patient and his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent/assent and the contents of the consent/assent must comply with the ICH-GCP and all applicable regulatory requirements as well as site standard operating procedures (SOPs).

5.4.2 Screening

After obtaining informed consent/assent, subjects will be evaluated for initial eligibility through the inclusion/exclusion criteria. The duration of screening is likely to be variable dependent upon testing turnaround times and is anticipated to be 16-30 days. Required screening procedures may take place over multiple days. If safety lab testing (hematology, chemistry, coagulation, renal markers, urinalysis) has occurred within the 2 weeks prior to consent/assent as part of routine care, and results are available, then those tests do not need to be repeated. Subjects will receive the meningococcal vaccine, if they have not already received it, at least 6-weeks prior to the planned dosing date.

5.4.3 Retesting

Subjects may have the following tests repeated once as part of inclusion/exclusion assessments:

Inclusion criterion #5- Screening serum methylmalonic acid level. Methylmalonic acid levels fluctuate and repeat testing once is allowed.

Inclusion criterion #6- Hematology. Transient decreases may occur in some patients and repeat testing once is allowed.

Exclusion criterion #7- Screening anti-recombinant adeno-associated virus **(**AAV) LK03-neutralizing antibodies. The screening assay for neutralizing antibody level may reflect waning maternal antibodies in young patients (Perocheau et al, 2019). Thus, it may be repeated once to assess whether the titer has now dropped to the 1:10 level or below.

Exclusion criterion #11- Laboratory testing results for hepatic/gastrointestinal function and pancreatic enzymes. Transient elevations may occur in some patients and repeat testing once is allowed.

5.4.4 Rescreening

Subjects not meeting one or more of the inclusion or the exclusion criteria will be considered screen failures. Subjects may rescreen once for the study. Screening assessments that were previously performed and are still within the specified window do not need to be repeated. See the following section if screening labs were taken more than 30 days prior to the expected dosing date.

5.4.5 Run-in Period to Dosing

The run-in period is defined as the time from initiation of screening to hLB-001 dosing and will be a minimum of 16 days to allow for at least 2 serum methylmalonic acid levels before dosing (at least 14 days apart) and confirmation of patient stability.

If this run-in period exceeds 3 months, repeat testing of the following will be required to assess eligibility for hLB-001 dosing: pancreatic enzymes (exclusion criterion 11).

The following should be repeated if screening labs were taken more than 30 days prior to the expected dosing date to assess eligibility: hematology/chemistry/coagulation, urine ketones, ammonia, methylmalonic acid, methylcitrate and neutralizing antibodies. Patient weight needs to be measured within 30 days of the dosing date.

A PICC line will be placed at least 7 days prior to dosing for any patient who does not already have one.

5.4.6 Baseline Assessment and Dosing

Study patients who have completed the run-in period will be eligible for hLB-001 dosing after the following have been confirmed in order to reduce procedure risk:

1. Continues to meet all screening inclusion/exclusion criteria (see Table 1 for baseline visit procedures, conducted at day -7 to day -2)
2. In the judgement of the site investigator the patient is medically stable

For dosing, the patient will be admitted to the hospital on day -1 and started on prophylactic steroids 24 hours (± 4 hours) prior to hLB-001 infusion. Treatment via a single administration of hLB-001 will occur on day 1. The patient will remain in the hospital for approximately 7 days after hLB-001 administration in order to evaluate safety. The patient will be required to remain within close proximity of the study site (within 1-hour access) for the first week of corticosteroid administration due to the risk of metabolic imbalance associated with corticosteroid administration.

5.4.7 Follow-up

Patients will return to the investigative site for regularly scheduled visits through 1-year postdosing as detailed in Table 1. Schedule of Events to evaluate the safety and efficacy of hLB-001. 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.

5.4.8 End of Study

Patients who complete the week 52 visit will have completed the study. If a patient withdraws early, an early EOS visit should be conducted at the time of study withdrawal. At study completion or early discontinuation, patients will be asked to participate in a long-term follow-up study to continue monitoring the long-term safety and efficacy of hLB-001.

5.4.9 Unscheduled Visits

Should there be need for an unscheduled visit, eg, to manage or follow-up on unresolved AEs, the investigator should use his/her judgment and perform adequate evaluation of the patient. All examination and testing results should be recorded in the unscheduled visit section of the eCRF. Healthcare utilization and hospitalization events will be collected as efficacy measures.

6 PATIENT ELIGIBILITY AND WITHDRAWAL CRITERIA

6.1 Number of Patients

The study is anticipated to enroll approximately 8, with the option to increase to 12, patients with severe MMA at approximately 8 sites in the United States and Saudi Arabia.

6.2 Inclusion Criteria

A patient must meet all the following inclusion criteria to be eligible for participation in this study:

1. At the time of dosing, patient must be 6 months to 12 years of age
2. Patient (and/or legally authorized representative) has voluntarily agreed to participate by giving written informed consent/assent in accordance with ICH GCP guidelines and applicable local regulations
3. Willingness and ability to comply with study procedures and scheduled visits
4. Current with the local recommended vaccination schedule based on age (no vaccinations within 6 weeks pre- or post-hLB-001 dosing; no expectation of the need for live vaccinations while on corticosteroids and for 3 months following completion of corticosteroid dosing)
5. Males and females with diagnosis of severe MMA meeting all the following;
    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 PI 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 (7.9 Dietary Management) 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
6. Hematology laboratory results confirming:
    a. Hemoglobin ≥ 9 g/dL
    b. Absolute neutrophils count ≥ 1000/µL
    c. Platelet count ≥ 150,000/µL

6.3 Exclusion Criteria

A patient meeting any of the following exclusion criteria is not eligible for participation in the study:

1. Patients with organic acidemias other than isolated MMA, or with any other causes of hyperammonemia
2. Having received MMA-targeted gene therapy or nucleic acid therapy
3. Having received an investigational drug within 28 days or 5 half-lives of the drug, whichever is shorter, prior to initiation of screening
4. Patients on insulin or high-dose hydroxocobalamin (> 1 mg/day OHB12 parenteral)
5. Kidney or liver transplant, including hepatocyte cell therapy
6. Estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 based on the creatinine-based "Bedside Schwartz" equation (2009), or ongoing dialysis for renal disease
7. Patient tests positive for anti-rAAV LK03-neutralizing antibodies with titers above protocol-specified threshold of 1:10
8. Patient has received immune-modulating agents within 3 months prior to initiation of screening (use of inhaled corticosteroids to manage chronic respiratory conditions permissible)
9. Patient has a history of, or currently has, a clinically important condition not directly related to MMA, in the opinion of the investigator
10. History or presence of arrhythmia or other clinically significant abnormality on electrocardiogram (ECG)
11. Any of the following hepatic/gastrointestinal factors:
    a. Liver laboratory testing values
        - alanine aminotransferase (ALT) > 2.0 × upper limit of normal (ULN)
        - aspartate aminotransferase (AST) > 2.0 × ULN together with ALT, alkaline phosphatase or total bilirubin > ULN
        - total bilirubin > 2.0 × ULN
        - prothrombin time > 1.5 x ULN
    b. Pancreatic enzymes (amylase, lipase) > 3.0 × ULN
    c. Hyperammonemia characterized by ammonia ≥ 3 × ULN, or signs of active metabolic decompensation (eg, lethargy, irritability, and vomiting)
12. Any of the following oncologic factors:
    a. Liver abnormalities suspicious for malignancy on screening ultrasound
    b. History of any malignancy, test-positive for a cancer-predisposition syndrome, or family history for a cancer-predisposition syndrome and patient has not been tested

13. History of anaphylaxis or severe allergic reaction or allergy to antibiotics to be potentially administered

14. Patient has experienced a viral or bacterial illness and is still symptomatic within 6 weeks of dosing

15. Vaccinations administered within 6 weeks of dosing

16. History of deep vein thrombosis (DVT) or coagulopathy

6.4 Patient Withdrawal

The patient has the right to withdraw from the study at any time. As hLB-001 is a one-time administration and safety follow-up is of high priority, every reasonable attempt should be made to have patients continue to be assessed at all scheduled visits.

The patient will be withdrawn from the study if:

1. Withdrawal of consent
2. Administrative decision by the sponsor or the investigator
3. Violation of the protocol inclusion and/or exclusion criteria prior to study drug administration, as deemed relevant by the investigator and discussed with the sponsor medical monitor
4. Patient noncompliance prior to dosing
5. In the investigator's judgment, it is in the best interest of the patient
6. Any transplant procedure
7. Lost to follow-up

Patients who withdraw from the study should be encouraged to enter the long-term follow-up study.

In cases where the patient is deemed 'lost to follow-up,' the investigator or designee must make every effort to regain contact with the patient; eg, 3 documented attempts, 1 of which must be a certified letter to the patient's last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical records. Should the patient continue to be unreachable, only then will he/she be considered to have withdrawn from the study with the primary reason as 'lost to follow-up.'

If hLB-001 infusion is stopped due to an AE, the patient will be considered discontinued from study treatment due to an AE, but the patient should be followed in the study as outlined in the schedule of events and all AEs followed until resolution or stabilization.

Withdrawal of full consent for the study means that the patient does not wish to undergo procedures and the patient does not wish to continue further study follow-up. Patient data collected up to withdrawal of consent will be retained and included in the analysis of the study;

and where permitted, publicly available data (death records) can be included after withdrawal of consent (FDA *Guidance for Industry: Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA–Regulated Clinical Trials* [October 2008]).

An early EOS visit should be conducted at the time of study withdrawal.

6.5 Patient Replacement

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.

7 STUDY PROCEDURES AND ASSESSMENTS

Study procedures are indicated in the Table 1. Schedule of Events. Additional details of procedures may be found in the Study Reference Manual (SRM).

7.1 Demographics and Medical History

Demographics and medical history, including disease history, will be collected.

7.2 Physical Examination

Complete and targeted physical examinations will be performed per Table 1. Schedule of Events. Please refer to the SRM for body systems to be covered in these examinations. Skin will be examined for rash or peeling as a possible indicator of protein over-restriction or nutrient deficiency.

Significant changes in the physical examination from screening will be recorded as AEs.

7.3 Vital Signs

Vital signs will include heart rate (HR), respiratory rate (RR), blood pressure systolic and diastolic (BP), and temperature. Age-specific techniques and devices should be used. Whenever possible, the measurements should be made by the same personnel using the same device at each evaluation. Pulse oximetry will be monitored starting prior to dosing then for 24 hours post dosing.

Note: vital signs the day of hLB-001 dosing should be taken:

1. Within 15 min of start of infusion
2. After start of infusion: at 30 minutes, 1 hour, 2, 3, 4, 6 and 8 hours (± 10 minutes)

   Example for 10:00 morning infusion:

   9:45-10:00, 10:30, 11:00, 12:00, 13:00, 14:00 16:00, 18:00

Additional vital signs may be taken as deemed necessary.

7.4 ECG

A 12-lead ECG will be obtained at the visits indicated.

7.5 Liver Ultrasound and Alpha-fetoprotein

Liver ultrasound and alpha-fetoprotein level will be followed as part of the recommended assessments for evaluation of patients at theoretical risk of hepatic malignancy. If a liver ultrasound was performed within 3 months prior to screening, it does not need to be repeated at screening.

7.6 1-13C-propionate Oxidation

Total body propionate oxidation can be quantified through breath collection of labelled $^{13}CO_2$ after oral dosing with ^{13}C-propionate (Gagné et al, 2016). When the oxidation assay is performed pre- and post-hLB-001 dosing, the difference represents a systemic, quantitative biomarker for mutase activity. These samples will be analyzed at a central laboratory.

7.7 Growth Parameters

Weight, height/length, and head circumference (up to age 3) will be assessed according to standard procedures.

7.8 Protein and Nutritional Intake/Patient Diary

Protein (intact and medical food), nutritional intake, and tube feeding details/days with oral feeds will be determined from the 3-day nutritional diary completed prior to specified visits.

7.9 Dietary Management

Dietary management in patients with MMA is critical to their health and safety. In addition, potential variability in dietary management may be a confounding factor in clinical trials for inborn errors of metabolism where diet is a mainstay of treatment, and the effect of diet can make interpretation of results difficult. To those ends, the following general guidelines will need to be met by all patients entering into and participating in the trial (Baumgartner et al, 2014) (Manoli et al, 2016) to ensure patients have optimized and stable diets prior to and throughout the study:

1. Study participants will follow dietary recommendations on adequate energy and protein intake to support normal growth, development and physical activity level (15 Appendix 1: FAO/WHO/UNU 2007 Safe Levels of Protein and Energy Intake for Different Age Groups)
2. Medical foods with free amino acid supplements are likely to be a part of the nutritional program. Their use and percent of total intake should be based on tolerance of protein load as assessed by plasma amino acid levels, MMA and ammonia levels
3. 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

Breastfeeding is allowed provided the intake is measured for diet diaries as required in Table 1. Schedule of Events

7.10 Cognitive and Motor Function Assessments

Cognitive and motor function assessments will be completed and scored based on patient age per Table 2. Due to the lack of available validated translations, these tests will be performed only in the US. Neurodevelopment will be assessed using age-appropriate testing as summarized below. The same test used at screening should be used again at week 52-EOS, for a given patient (Note:

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). Personal ability will be assessed using the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) tool, which includes a motor subscale for patients up to 9 years of age. Details on the assessments used in the study will be provided in the SRM.

These assessments must be completed prior to any other study assessments being performed.

Table 2. 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] = As noted above, 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.

7.11 Quality-of-Life Assessments

The endpoint for this assessment is the well-validated Parenting Stress Index, PSI-IV. The 36-question short form is recommended. Details on this assessment will be provided in the SRM.

7.12 Hospitalizations and Healthcare Utilization

The investigator will record the number, duration, and primary diagnosis for any hospitalizations or healthcare utilization.

Healthcare utilization includes ER visits and unscheduled visits to physician/hospital.

7.13 Change in Requirement for MMA-related Medications

All prescription and over-the-counter medications taken from initiation of screening through the EOS visit will be recorded in the eCRF, including any changes in dose or frequency per Section 10. Changes in medications related to MMA will be analyzed.

7.14 Adverse Events

The investigator (or designee) will determine during the course of all study periods whether any AEs have occurred. Patients will be questioned in a general way and no specific symptoms will be suggested. Section 11 contains additional information with regard to the definitions and reporting period for AEs.

7.15 Laboratory Tests

Clinical laboratory tests will be performed by a qualified laboratory, analyzed either at the investigative site or a central laboratory. Please refer to the SRM/Laboratory Manual for preparation and collection instructions of each sample. If a patient is on a continuous feed, the feed should be stopped for 1 hour prior to collecting blood samples.

Neutralizing antibody titer to rAAV-LK03: Samples for neutralizing antibodies to rAAV-LK03 will be collected to monitor for a humoral immune response to rAAV-LK03. The assay will be performed via a cell-based functional assay.

Albumin-2A: hLB-001 integration at the albumin locus in hepatocytes results in synthesis of both human MMUT enzyme and the modified protein albumin-2A (ALB2A). ALB2A is secreted into the bloodstream and thus represents a surrogate biomarker detectable in patient serum by an enzyme-linked immunosorbent assay (ELISA).

Antibody response: Samples for antibodies to rAAV-LK03, MMUT, and ALB2A will be collected and analyzed using an ELISA assay.

Anti-albumin antibodies:

Patients will be tested for the presence and titer of anti-ALB-2A antibodies as described in Table 1. Schedule of Events. The presence of sustained anti-ALB-2A antibodies (2 consecutive positive results above baseline) or an unexplained drop in serum albumin concentration will trigger investigations utilizing a specific assay that identifies the presence and titers of antibodies to native albumin. If the 3-month titer is above baseline, additional monitoring will occur every 6 weeks until titers return to baseline on 2 consecutive samples.

If anti-albumin antibodies are present in the setting of clinically-significant hypoalbuminemia or a worsening in clinical status, the option for immunosuppression should be discussed with an expert in autoimmune disorders.

T-cell response: The presence of T-cells specific for rAAV-LK03, MMUT, and ALB2A will be determined by an enzyme-linked immunospot (ELISPOT) assay.

Viral shedding: Saliva, urine, and stool will be collected to monitor for the presence of shed virus. Quantitative polymerase chain reaction will be used for analysis.

FGF21: Samples will be collected to assess systemic metabolism and analyzed using a multi-analyte, microsphere-based profiling system.

TMA genetic panel: Subjects will be tested for variants in genes associated with TMA to help determine a potential relationship between these genetic changes and the risk for TMA development.

Samples to be analyzed at local laboratory:

- Hematology and blood smear (hematocrit, hemoglobin, red blood count (RBC), white blood count (WBC), differentials (neutrophils, eosinophils, basophils, lymphocytes and monocytes), platelets and blood smear
- Chemistry (albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, chloride, CO2, creatinine, glucose, phosphorus, potassium, sodium and total bilirubin)

Note: eGFR to be calculated using the Serum creatinine (scr)-based "Bedside Schwartz" equation (2009):

  - $e\text{GFR}\ (\text{mL/min/1.73}\ m^2) = 0.413 \times height(cm) \div creatinine(mg/dL)$

- BMP: blood urea nitrogen, calcium, chloride, CO2, creatinine, glucose, potassium, sodium
- Coagulation (prothrombin time, aPTT or PTT)
- Alpha-fetoprotein
- Pancreatic enzymes (lipase, amylase)
- Ammonia
- Renal markers (eGFR calculation)
- Urinalysis and urine ketones (dipstick)
- Plasma amino acids, prealbumin, carnitine
- LDH/haptoglobin
- C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)
- von Willebrand profile

Samples to be sent to central laboratories:

- Serum methylmalonic acid and methylcitrate
- Serum albumin-2A
- Serum FGF21
- Immunogenicity and immune response parameters: Neutralizing antibody titer (rAAV-LK03), antibody response (rAAV-LK03, MMUT, ALB2A, albumin), T-cell response (rAAV-LK03, MMUT, ALB2A)
- Serum and plasma for exploratory biomarkers
- Viral shedding: saliva, stool, and urine
- TMA genetic panel
- Complement testing: CH50, Cb5-9, Bb

Samples to be sent to local or central laboratories:

- Complement testing: C3, C4

Home samples:

- Ketostix (or equivalent): sample to be collected and analyzed at patient's home, as instructed by the physician to detect the presence of ketone bodies in a home setting between site visits.

Sample testing may need to be prioritized based on blood volume required and age/weight of the patient. Institutional guidelines for allowable blood volumes will not be exceeded. Lab assessments may be collected over several days within the visit window.

As this is a pediatric trial, there will be cases where sufficient blood volume will not be available. Please see below for the priority order of blood draws in these cases.

For visits between screening and Day 14, please see below for priority order for blood draws, from top to bottom:

Table 3. Laboratory Priority

Screening	**Baseline**	**Day -1**	**Day 3**	**Day 6**	**Day 7**	**Day 9**	**Day 12**	**Day 14**
Methylmalonic acid / methylcitric acid	Methylmalonic acid / methylcitric acid	Hematology	Hematology	Hematology	Hematology	Hematology	Hematology	Hematology
Neutralizing antibodies	Hematology	BMP	Chemistry	BMP	Chemistry	BMP	BMP	Chemistry
Hematology	Chemistry	CH50	CH50	CH50	Coagulation	CH50	CH50	CH50
Chemistry	Coagulation	CRP	LDH	Haptoglobin	LDH	LDH	Haptoglobin	Coagulation
Coagulation	ALB2A	C5b-9	C5b-9	C5b-9	LK03 ADA	C5b-9	C5b-9	Haptoglobin
	FGF21	C3	C3	C3	C3	C3	C3	LK03 ADA
eGFR	LK03 ADA	C4	C4	C4	C4	C4	C4	C5b-9
ADAs	C5b-9	Haptoglobin	Coagulation	Bb	ammonia	Bb	Bb	C3
T-cell	Bb	ESR	Bb		biomarkers			C4
TMA genetic panel	C3	Bb						Bb
von Willebrand disease panel	C4							
Alpha-fetoprotein	Neutralizing antibodies							
CH50	T-cell							
Pancreatic enzymes								
CRP	Ammonia							
ESR	Amino acids							

LDH								
FGF21								
Ammonia								
Amino acids								
Biomarkers								

Days 2, 4, 5, 8, 10, 11, 13 (in order of priority): Hematology, BMP, C3, C4, LDH or haptoglobin
After Day 14 (in order of priority): Safety (hematology, chemistry, coagulation, renal markers), methylmalonic acid, albumin-2A, complement testing, antibody response (ADAs), FGF21, plasma amino acids, ammonia, T-cell response, serum and plasma for biomarkers

Local laboratory reports should be reviewed, signed, and dated by the investigator or delegated physician. Each abnormal result will be assessed as clinically or not clinically significant and a comment will be provided for all out-of-range analytes deemed clinically significant (ie, document probable cause for abnormal results). Laboratory data will be collected and entered into the eCRF, if collected at the site or by home health care, or transferred electronically if from a central laboratory.

7.16 Pregnancy Risk Assessment and Testing

At screening, female patients of child-bearing age will be questioned regarding potential pregnancy risk. If a risk is identified, a urine pregnancy test will be administered at screening.

7.17 PICC line

Once eligibility for the study has been assessed, a peripherally inserted central catheter (PICC line) will be placed for any patient who does not already have one, to allow for easier blood draws during the initial part of the study. The PICC line will be placed at least one week prior to the expected dosing date to allow for adequate healing. The PICC line will stay in place until at least week 3.

8 CONDUCT OF STUDY

8.1 Data Safety Monitoring Board

This study will utilize an independent DSMB, which will monitor patient safety and provide recommendations regarding dosing in each cohort. The composition of the DSMB and details of its function are described in the DSMB Charter. Section 5.1 provides an overview of DSMB activities. The DSMB may meet at additional timepoints as required for safety review. Following Cohort 1 Part B, TMA experts will be added to the DSMB. These experts will be convened to monitor safety and provide recommendations on prevention and management of TMA. In addition to the Principal Investigator and the Sponsor Medical Monitor, these experts will review the TMA-related laboratory results as they are available for each patient in Cohort 1 Part C, Cohort 2 Part A and Cohort 2 Part B during the high-risk period (first two weeks post-dosing). Additionally, these experts will meet in the event a patient receiving hLB-001 experiences signs of TMA to review the laboratory values and provide recommendations.

9 STUDY MEDICATION

9.1 Description of Study Medication

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. Details of this gene therapy product may be found in the IB.

The composition of the hLB-001 drug product is summarized in Table 4.

Table 4. Composition of hLB-001 Drug Product

Component	Reference to Quality Standards	Function
hLB-001 drug substance	In-house	Active
Sodium phosphate monobasic, monohydrate	USP	Buffering agent
Sodium phosphate dibasic, anhydrous	USP	Buffering agent
Sodium chloride	USP	Tonicity agent
Poloxamer 188	USP-NF, Ph Eur	Surfactant

NF = National Formulary; Ph Eur = European Pharmacopoeia; USP = United States Pharmacopeia.

9.2 Packaging and Labeling

hLB-001 is filled into a West 5-mL cyclic olefin polymer vial, sealed using a West chromobutyl, FluroTec B2 coated stopper, and a West overseal for single-use administration. It will be stored at -65°C or below and shipped to sites by LogicBio or designee.

The study drug labels will fulfill all requirements required by governing regulations.

9.3 Administration of Treatment

Study patients may be dosed with hLB-001 no earlier than 16 days following screening initiation. Prior to hLB-001 administration, study patients will have baseline hematology and chemistry laboratory studies as prescribed in Section 5.3.5. In addition, if the interval from screening laboratory studies to dosing exceeds 30 days, study patients should have repeat assessments as described in Section 5.3.5.

hLB-001 is thawed for administration as a one-time intravenous infusion on day 1 over at least 30 minutes and at a flow rate of no more than 5 mL/kg/hour through a syringe pump. Additional instructions may be found in the Pharmacy Manual. To alleviate potential immune response, a standard regimen of corticosteroids will be administered prophylactically starting approximately 24 ± 4 hours prior to hLB-001 (Day -1) per Section 10.2.

9.4 Dose Levels

Dose level 5×10^{13} vg/kg will be explored, with an option to increase explore a second dose level of 1×10^{14} vg/kg. Total dose will be calculated using the weight measured at screening/run-in; if the weight was measured more than 30 days prior to dosing, weight will be re-measured for the dosing calculation within the 30 days prior to dosing to allow shipping of study drug.

9.5 Storage, Handling, and Drug Accountability

On receipt at the investigative site, the study drug should remain in the box provided until use. The container should be stored frozen at -65°C or lower. All excursions should be reported to the sponsor or its designee for assessment and quarantined until authorized for use. The site will ensure that the drug is used before the expiry date provided by LogicBio.

Only trained staff should handle hLB-001. Please refer to the Pharmacy Manual for complete handling instructions.

A drug accountability record should be maintained by the person responsible for dispensing the study drug to the patient. This should record which supplies are issued to which patients. LogicBio or its designee should be notified immediately of details of any supplies which are inadvertently damaged. Details of any supplies which are inadvertently damaged or unusable for any reason should be noted on this drug accountability record, which will be collected by LogicBio or its designee at the end of the study.

All drugs will be inventoried by LogicBio or its designee during and at the conclusion of the study. Secure disposal at the site or return of unused supplies to the sponsor at the end of the study will be arranged.

10 CONCOMITANT MEDICATIONS AND VACCINATIONS

10.1 General Considerations

The investigator is to record the use of all concomitant medications, both prescribed and over-the-counter, in the eCRF, starting at informed consent until the end of study visit.

Concomitant medications for standard of care for patients with MMA will be permitted. Patients who are already receiving medications to treat hyperammonemia may continue. Additional medications should be discussed with the investigator and administered based on medical need.

10.2 Prophylactic Administration of Corticosteroids and Monitoring/Risk Mitigation

In patients with MMA, systemic corticosteroids should be used judiciously and with careful consideration of the associated benefit/risk to the patient. In the context of pediatric gene therapy trials, intravenous AAV administration of a different drug product at doses similar to those proposed in the LB001-001 study has been associated with acute serious liver injury and substantial elevations in aminotransferases (ZOLGENSMA prescribing information, 2019). More commonly, across studies of different AAV products at lower doses and a range of patients ages, systemic administration was associated with subacute, asymptomatic aminotransferase elevations and a significant loss of transgene expression (Scallan CD 2006) (Nathwani A 2014). While not expected for hLB-001 based on preclinical data, the risk of significant liver reaction to hLB-001 cannot be ruled out and hence the inclusion of corticosteroid administration in the LB001-001 study design.

Dosing Regimen

A standardized regimen of prednisolone 1 mg/kg/day or its equivalent will be initiated 24 ± 4 hours prior to beginning hLB-001 infusion and continuing for a total of 60 days. Administration may be oral or via g-tube if oral administration is not possible. The maximum dose to be administered is 60 mg per day. After 60 days of treatment, the dose of prednisolone can be tapered for patients in accordance with the following treatment guideline: 1 mg/kg/day until at least 60 days post-infusion, followed by a tapering protocol as follows: 0.5 mg/kg/day for 5 days, then 0.25 mg/kg/day for 5 days, then 0.25 mg/kg every other day for 16 days to complete a 26 day taper. Specific instructions on corticosteroid administration will be provided to patient caregivers by the treating physician. 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. Consult immunology expert(s) if patients do not respond adequately to the equivalent of 1 mg/kg/day prednisolone.

To date, four subjects have received corticosteroid prophylaxis in LB001-001. The first three subjects have completed their course, for a total of 55, 101, and 55 days. The fourth patient

treatment with steroids has received corticosteroids for 72 days and treatment is ongoing. One grade 1 AE of hyperglycemia was reported in one subject as related to steroid use on day 15 of the steroid course; the glucose value was found to be normal with the next test 6 hours later. No other steroid-related AEs or SAEs were reported, and no evidence for metabolic decompensation during full-dose steroids or the steroid taper was observed.

Monitoring and risk mitigation for corticosteroid-associated adverse effects including metabolic dysregulation:

- In addition to the regularly scheduled physical examinations, vital signs and behavioral assessments, key metabolic parameters will be monitored at the clinical site frequently in the first two months of the study and include acidosis, lactate, ammonia, serum methylmalonic acid and urinary ketones per Table 1. Schedule of Events.
- Because the time course in which steroid-related metabolic decompensation might occur is unknown, families will be provided with and instructed on the use of Ketostix Reagent Strips, in order to detect the presence of ketone bodies in a home setting between site visits. If urine ketones are present, the family will be instructed to contact their physician immediately for appropriate interventions.
- If metabolic decompensation occurs despite standard-of-care outpatient management, the recommendation will be for hospitalization with appropriate treatment measures to stabilize critically ill individuals under the care of a biochemical genetics expert (Manoli et al, 2016).
- Two weeks after discontinuing the glucocorticoid taper, adrenal suppression will be assessed based on the first morning cortisol (Ahmet et al, 2017). If the morning cortisol is 18 mcg/dL or higher or within normal limits, no further testing is needed. If the morning cortisol is less than 18 mcg/dL or not within normal limits, the patient should be referred to a pediatric endocrinologist for a CRH or ACTH stimulation test to further evaluate the HPA axis. If the HPA axis is determined to be recovered by stimulation testing, no further testing or stress doses of steroids is indicated. If not, patients should be referred to a pediatric endocrinologist for further management and should have access to stress doses of steroids in the event of an acute illness or metabolic stress, which will be discontinued after the acute illness has resolved.

10.3 Routine Vaccinations

Childhood vaccinations may be associated with AEs that could complicate assessment of potential hLB-001-associated safety signals. No vaccinations should be administered within a 6-week window either prior to or following hLB-001 administration.

In the special case of live vaccines, due to the potential for immunosuppression associated with corticosteroid administration, the CDC recommends that no live vaccines be administered during corticosteroid administration and for at least 3 months after stopping high-dose corticosteroids.

As mentioned in the next section, the meningococcal vaccine will be administered at least 6-weeks prior to the planned dosing date for any subjects who have not been previously vaccinated.

10.4 Administration of eculizumab and antibiotics

- Eculizumab is a complement inhibitor indicated for the treatment of patient with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA). In the event that a subject develops signs or symptoms suggestive of TMA or imminent TMA, eculizumab should be administered to block the complement pathway. TMA-related laboratory results will be reviewed as they are available by the investigator, the TMA experts on the DSMB and the Sponsor Medical Monitor, and advice on intervention will be provided based on these laboratory results. In general, treatment with eculizumab should be initiated for any of the following findings accompanied by evidence of activated complement: hemolysis (LDH above normal, presence of schistocytes on blood smear, and/or hemoglobin below normal), thrombocytopenia (platelets < 100K/µL), or proteinuria ≥30mg/dL.
- All subjects will receive the meningococcal vaccine at least 6-weeks prior to dosing in the event that eculizumab is administered. Subjects who receive eculizumab should be provided with antibacterial prophylaxis per the eculizumab label.

Table 5. Eculizumab Dosing Schedule

Body Weight	Eculizumab dosing
>40 kg	900 mg every 3 days until C5b-9 normalizes x 2, then weekly
10 – <40 kg	600 mg every 3 days until C5b-9 normalizes x 2, then weekly
5 – <10 kg	300 mg every 3 days until C5b-9 normalizes x 2, then weekly

In the case of incomplete complement inhibition (CH50 >10 U/mL), the subsequent eculizumab dose may be increased by 300 mg or an additional dose administered, after discussion with the Sponsor.

- Caregivers will be informed about the signs and symptoms of meningococcal infection and strongly advised to seek immediate medical attention if these signs or symptoms occur. Caregivers will be given a Patient Safety Information Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

- Beginning with the first dose of eculizumab, all subjects will be started on antimicrobial prophylaxis using an agent with activity against *Neisseria meningitides*.
    - Option 1: Age/weight based therapeutic dosing of oral amoxicillin. 45 mg/kg in divided doses every 12 hours.
    - Option 2: Age/weight based therapeutic dosing of ciprofloxacin. 15 mg/kg per dose every 12 hours.
    - If local strains of N. meningitis bacteria are resistant to either of these antibiotics or the patient is allergic or cannot otherwise tolerate the standard prophylactic treatment, the choice of antibiotic will be made upon local guidelines or the recommendation of the local Infectious Disease (ID) consultant.
- Antibiotic prophylaxis will be continued until CH50 recovery to normal or above normal levels is documented.

11 ADVERSE EVENTS

11.1 Pretreatment Adverse Event

A pretreatment event is any untoward medical occurrence in a patient who has signed informed consent/assent but prior to administration of hLB-001.

11.2 Adverse Event Definition

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with the pharmaceutical product treatment. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigative) product, whether or not related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of the study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline. Any abnormal test result that is determined to be an error does not require reporting as an AE.

If known, the diagnosis should be recorded, rather than listing individual signs and symptoms.

11.2.1 Adverse Events of Special Interest (AESI)

To date no experience exists regarding the administration of hLB-001 to humans, and therefore, no safety profile is available. However, it has been recognized in studies involving human AAV administration that asymptomatic transaminase elevation, even at levels between 1× and 2× ULN, may be a biologically significant finding consistent with patient immune response to and loss of transfected hepatocytes. The transaminitis is seen most commonly between 6 to 10 weeks post AAV infusion but may be detected earlier or later. This laboratory finding may be a harbinger of loss of AAV transgene expression and hence efficacy, and in some cases may rise to the level of a serious AE.

AESI #1 elevated transaminase: The LB001-001 study involves prophylactic corticosteroid dosing that may continue for as short a period as approximately 3 months following hLB-001 infusion (2-month full dose and 26 day taper). The presence of continuously rising transaminases while on corticosteroids, or transaminase elevation above the ULN when patient is no longer receiving corticosteroid, should be reported immediately to the sponsor for discussion of appropriate therapeutic response.

AESI #2 hepatocellular carcinoma/adenoma: While preclinical studies using murine and cynomolgus monkey surrogates of hLB-001 have not demonstrated an increased occurrence of hepatocellular carcinoma (HCC), the timing and occurrence risk to human subjects is unknown. Long-term monitoring during the 15-year follow-up (which will be conducted under a separate protocol) will include a-fetoprotein levels and liver imaging following guidance of the FDA, European Medicines Agency, and American Association for the Study of Liver Disease for

monitoring individuals at risk for HCC (Marrero et al, 2018). Any suspicion of hepatic adenoma or malignancy should be reported immediately to the sponsor.

AESI #3 Thrombotic microangiopathy (TMA) and TMA-like events: Two patients in Cohort 1 Part B experienced TMA with an onset within 2 weeks of LB-001 infusion. Both subjects were hospitalized, but each event has resolved. Features of TMA including microangiopathic hemolytic anemia, thrombocytopenia and/or acute kidney injury have been previously described in pediatric patients receiving AAV gene therapy at doses $\geq 5x10^{13}$ vg/kg (e.g., in SMA and DMD, using AAV9 vectors); in those reported cases, events have manifested within the first 2 weeks after dosing (typically day 6-10) and, although some cases have required hospitalization and interventional treatment, reported patients have recovered well within days or a few weeks. TMA or Atypical Hemolytic Uremic Syndrome (aHUS) after AAV administration have been linked to endothelial injury due to excessive activation of the classical or alternative complement pathways.

As a preventive measure and for early detection of any TMA-like signs, patients will be hospitalized for 7 days post dosing. Patients will be monitored daily until day 14. Additionally, in order to mitigate a known risk factor for TMA, patients will be excluded if a viral or bacterial infection has occurred within 6 weeks prior to dosing.

- In addition to the Principal Investigator and the Sponsor Medical Monitor, ongoing laboratory results collected during the high-risk period will be reviewed as they are available by TMA experts serving on the DSMB, who will provide recommendations on management and monitoring of each subject.
- Should signs of TMA develop (see section 10.4), consultation with hematology and nephrology will be obtained immediately, and eculizumab should be instituted, and additional treatment should be initiated as per local guidelines, which may include red blood cell and/or platelet transfusions, dialysis, intravenous hydration, nutrition support, and other supportive management. Signs of TMA may include a decrease in platelets or hemoglobin, presence of schistocytes on blood smear, an increase in creatinine, an increase in LDH or haptoglobin, an increase in C5b-9, decreased C3 and/or C4, elevated blood pressure, or presence of blood or protein in urine.
- Eculizumab may be administered per Section 10.4 Administration of eculizumab and antibiotics
- Hematology and nephrology consultants should be made aware of the potential need for their involvement prior to dosing of LB-001.

11.3 Serious Adverse Event Definition

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- Requires inpatient hospitalization or prolongation of existing hospitalization (This is defined as the patient being hospitalized overnight, or the patient's hospital stay being prolonged for at least an additional overnight stay. Preplanned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization. "Twenty-three hour hospitalizations" for observation should be discussed with the medical monitor to determine whether they are appropriate for SAE reporting.)
- Results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered to be SAEs.

11.4 Reporting of Adverse Events and Serious Adverse Events

All AEs spontaneously reported and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF.

The severity of the AE will be graded using CTCAE Version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

The investigator will make a judgment regarding whether or not the AE was related to study drug, as outlined below.

None:	The AE is caused by the patient's clinical state, or the study procedure/conditions (ie, it has no association with the study drug).
Unlikely:	The temporal association between the AE and the study drug is such that the study drug is not likely to have any reasonable association with the AE.
Possible:	The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the patient's clinical state or the study procedures/conditions.
Definite:	The AE follows a reasonable temporal sequence from the time of study drug administration, abates upon discontinuation of the study drug, and reappears when the study drug infusion is continued, or the study drug is the most likely cause of the AE.

The investigator will record the action taken and outcome for each AE.

LogicBio or its designee has procedures that will be followed for the recording and expedited reporting of SAEs that are consistent with global regulations and the associated detailed guidances.

11.5 Adverse Event Reporting Period

Adverse events, whether serious or nonserious, will be monitored from the date of ICF/assent until the EOS visit.

Any SAE, whether or not related to the study treatment, must be reported within 24 hours to the sponsor's medical monitor or designee as instructed in the SRM.

LogicBio or its designee will provide details to the investigator of all serious, unexpected, and related AEs (or other events depending on the specific requirements) from any other ongoing clinical trials that should be reported to the IRB/LEC, as appropriate. Confirmation that these serious, unexpected, and related AEs have been submitted to the IRB/LEC per local site regulations must be kept in the investigator files.

If any AEs are present when a patient completes the study or is withdrawn from the study, the patient should be re-evaluated within 2 weeks. At the investigator's discretion, minor AEs can be re-evaluated via telephone and documented. If the AE has still not resolved, additional follow-up should be performed as appropriate. Every effort is to be made by the investigator or delegate to contact the patient until the AE has resolved or stabilized or the medical monitor and investigator agree that further follow-up is not necessary. This should be documented in the patient's medical records.

12 STATISTICAL METHODS AND DATA ANALYSIS

12.1 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.

12.2 Study Populations

Given that the study evaluates a single-dose of hLB-001, the safety population will consist of all patients receiving study drug and will be used for all safety analyses. For efficacy, each patient will serve as his or her own control. Therefore, the intent-to-treat population will include patients receiving study drug who have baseline data and at least 1 postdose measurement. Further analyses will be specified in the statistical analysis plan.

12.3 Demographic/Baseline Information

Given the small sample size and open-label nature of the study, demographic/baseline information will not be compared between dose groups but will be summarized by treatment group using descriptive statistics. For continuous variables, mean, standard deviation, median, minimum, and maximum will be presented. For categorical variables, frequency count and percentage will be presented.

12.4 Analysis of Safety Data

The safety endpoint data will be summarized for the safety population.

The AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities. The incidence of treatment-emergent AEs (TEAEs) will be summarized by body system and preferred term. A general summary of TEAEs and SAEs will be prepared, with overall numbers of AEs, and their intensity and relationship to study drug, per treatment group. All AEs will be presented in a listing. The numbers of AEs leading to withdrawal or SAEs leading to death will also be summarized. The World Health Organization Drug Dictionary Enhanced will be used to classify concomitant medications by therapeutic class and drug name.

The safety laboratory data and vital signs will be summarized by visit and treatment group, along with the change from baseline.

The ECG data will be summarized by standard parameter by time point/visit and treatment group, along with the change from baseline.

12.5 Analysis of Efficacy Data

This FIH dose-finding study is not powered for statistical analysis of efficacy or biomarker endpoints.

Results of secondary and exploratory results will be descriptive with presentation of the following endpoints:

- Number of days of hospitalizations due to MMA in the year following hLB-001 administration compared to the year prior to administration
- Change in weight, length/height or head circumference z-scores at 1 year following hLB-001 administration
- Changes in the Adaptive Behavioral Score at 1 year following hLB-001 administration
- Changes in standard scores on the cognitive and motor function scales at 1-year following hLB-001 administration
- Changes in the Parenting Stress Index at 1 year following hLB-001 administration
- Changes in serum methylmalonic acid level from pre-dosing (average of all pre-dose levels) at 1 year following hLB-001 administration
- FGF21 levels ≤ 1500 pg/mL at 1 year following hLB-001 administration (Molema et al, 2018)
- Change in 13C-propionate oxidation at 1 year following hLB-001 administration
- Number of patients requiring a liver and/or kidney transplant

12.6 Interim Analysis

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.

13 STUDY MANAGEMENT AND DATA COLLECTION

13.1 Ethical Conduct of the Study

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s).

13.2 Institutional Review Board/Local Ethics Committee

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/LEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. Other regulatory or institutional specific committee reviews may also need to be conducted per site guidelines.

The study will be conducted only at sites where IRB/LEC and other required approval has been obtained. The protocol, ICF, advertisements (if applicable), written information given to the patients, and any revisions to these documents will be provided to the IRB/LEC by the investigator or the sponsor, as allowed by local regulations.

13.3 Patient Informed Consent/Assent

After the study has been explained, written informed consent and assent, as applicable, will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent/assent and the contents of the consent/assent must comply with the ICH-GCP and all applicable regulatory requirements as well as site SOPs.

13.4 Compliance with the Protocol

The investigator will conduct the study in compliance with the protocol provided by LogicBio and given approval by the IRB/LEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and LogicBio. Changes to the protocol will require written IRB/LEC approval before implementation. LogicBio, or its designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

Any failure to follow the protocol for any reason must be documented by the investigator or designee and provided to LogicBio.

13.5 Study Monitoring

Monitoring procedures developed or approved by LogicBio or its designee will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, review pharmacy

records and study drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

13.6 Case Report Form

LogicBio or its designee will provide the study sites with secure access to and training on the Electronic Data Capture (EDC) application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

An eCRF will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for whom he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

LogicBio, or its designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the investigator's study file.

13.7 Audits

Regulatory authorities, the IRB/LEC, and/or LogicBio or its designee may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

13.8 Retention of Records

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of hLB-001 or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and LogicBio must be notified.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICF, copies of all CRF, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities and LogicBio or its designees.

13.9 Insurance and Indemnity

In the event that a patient suffers injury or death as a direct result of participation in this study, LogicBio will reimburse the reasonable cost of appropriate treatment and/or reasonable compensation will be paid to the patient by LogicBio in accordance with applicable federal and international laws and/or guidelines. Payments will not be offered for other expenses (such as time off work, lost wages, childcare, etc.).

13.10 Termination of the Study

The sponsor may terminate the study at any time. Furthermore, if it becomes apparent that patient recruitment into the study is unsatisfactory with respect to quality or quantity, or that data recording is inaccurate or incomplete on a chronic basis, the sponsor has the right to terminate the study and remove all study materials from the investigational site. A written statement will be provided to the investigator, the IRB/LEC, and regulatory authorities, if required.

14 USE OF INFORMATION

14.1 General Aspects

All information concerning LogicBio that may be provided, such as patent applications, formula, manufacturing processes, basic scientific data, or formulation information supplied by LogicBio and not previously published, are considered LogicBio's confidential information and shall remain the sole property of LogicBio and shall be treated in accordance with the Clinical Trial Agreement between the contract research organization or sponsor and investigator's site or institution. The investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent of LogicBio, except for official representatives, such as regulatory authorities.

It is understood by the investigator that the information derived from this study, in or related to connection with this study or the development of hLB-001, will be used by LogicBio and, therefore, may be disclosed by LogicBio as required to other clinical investigators, other pharmaceutical companies, and to other government agencies. In order to allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide to LogicBio complete test results and all data compiled in this study.

14.2 Patient Confidentiality and Data Protection

LogicBio and its designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, all data will be linked to the CRF via a unique identification number and the patient's initials, as allowed. The data will be blinded correspondingly in all data analyses.

However, in compliance with the guidelines of the US FDA concerning the acceptance of clinical studies in support of an NDA and the ICH Guidelines (whether performed in the United States or elsewhere), and in fulfillment of its obligations to LogicBio to verify compliance with this protocol, the LogicBio designee requires that the investigator permit its study monitor, representatives from the FDA, LogicBio-designated auditors, IRB/LEC, and other governmental regulatory authorities to review the patient's primary medical records (source data or documents), including but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports of deaths occurring during the study.

Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the investigator will obtain such permission in writing from the patient before the patient is entered into the study.

14.3 Final Report and Publication Policy

Upon completion of the clinical study and evaluation of results by LogicBio, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement. At the conclusion of the study, after the data are analyzed, LogicBio or its designee will prepare a final clinical study report.

15 APPENDIX 1: FAO/WHO/UNU 2007 SAFE LEVELS OF PROTEIN AND ENERGY INTAKE FOR DIFFERENT AGE GROUPS

Table 11 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.

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