Protocol Addendum H8H-MC-LAHX(1.1)

A Phase 1, Open-Label, Single-Dose Pharmacokinetic Study of Lasmiditan in Pediatric Patients with Migraine

NCT03988088

Approval Date: 11-Jun-2019

1. Protocol Addendum H8H-MC-LAHX(1.1) An Open-Label Study of Lasmiditan in Pediatric Patients with Migraine

Confidential Information

Lasmiditan (LY573144)

This addendum is to be performed in addition to all procedures required by protocol H8H-MC-LAHX or any subsequent amendments to that protocol.

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Protocol Addendum (1) Electronically Signed and Approved by Lilly: 29 March 2019
Revised Protocol Addendum (1.1) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 11-Jun-2019 GMT

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3. Rationale for Addendum

Country and Sites

This addendum applies only to participants in Study H8H-MC-LAHX (LAHX) at clinical sites in the United States (US).

Rationale

This addendum provides participants the opportunity to treat up to 4 migraine attacks per month with lasmiditan for a period of 3 months after completing pharmacokinetic (PK) assessments in the single-dose PK study LAHX.

4. Protocol Additions or Changes

This protocol addendum provides the requirements applicable to the open-label extension of Study LAHX.

4.1. Objectives and Endpoints

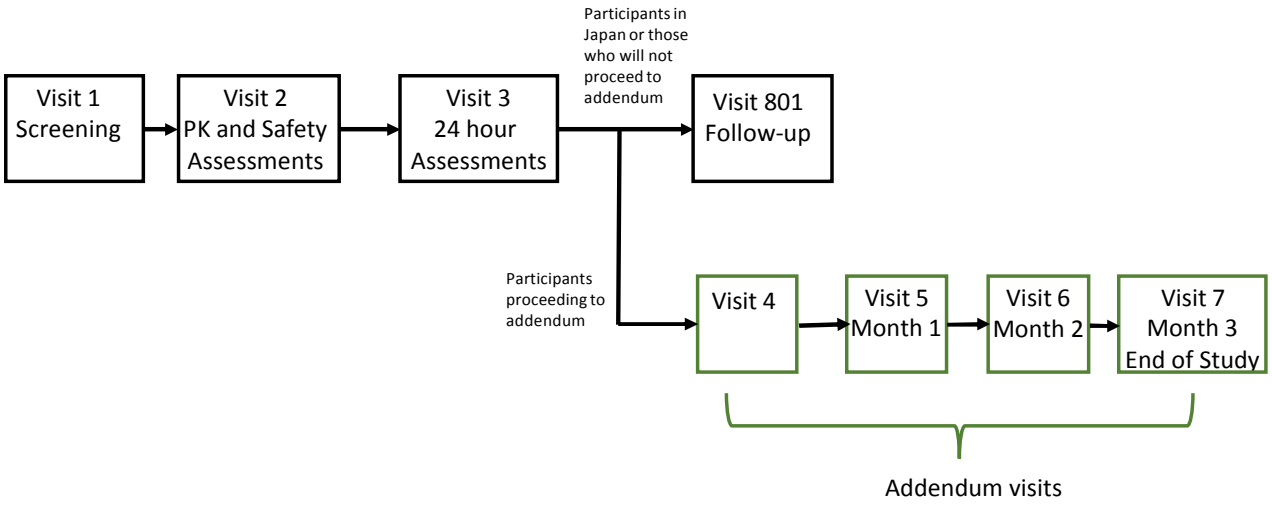
Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the safety and tolerability of 3-month intermittent use of lasmiditan in the acute treatment of migraine in pediatric patients	• TEAEs • SAEs • AEs of interest • Change from baseline in laboratory, ECG, and vital sign parameters
Secondary To characterize the reasons for discontinuation	• Discontinuation rates
Exploratory To describe patient-reported global impression of change after treatment with lasmiditan	The proportion of migraine attacks with PGI-C scores of better or a lot better

Abbreviations: AE = adverse event; ECG = electrocardiogram; PGI-C = Patient Global Impression of Change; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4.2. Study Design

This is an open-label, 3-month extension of Study LAHX in pediatric patients with migraine (Figure LAHX(1)1).



Abbreviations: PK = pharmacokinetic.

Figure LAHX(1)1. Study design visit schedule.

Visit 4

All potential study participants will complete assessments noted in the Schedule of Activities in Attachment 1 to determine if they are eligible to participate in this addendum.

Enrolled study participants and their parent or guardian will receive instructions regarding study procedures. The participant's parent or guardian is responsible for assisting children, if necessary, with completion of the diary assessments and other study procedures.

Lasmiditan will be dispensed to enrolled participants. The amount of lasmiditan dispensed will be determined by weight measured at Visit 4, and will be sufficient to treat up to 4 migraine attacks per month with 1 dose of lasmiditan per 24 hours.

Visits 5 and 6

Study participant assessments will be completed as noted in the Schedule of Activities.

Participant diaries will be reviewed and recorded in the appropriate electronic case report form (eCRF).

Lasmiditan will be dispensed at each visit. The amount of lasmiditan dispensed will be sufficient to treat up to 4 migraine attacks per month with 1 dose of lasmiditan per 24 hours.

Visit 7

This is the end of study visit. Study participant assessments will be completed as noted in the Schedule of Activities.

4.3. Justification for Dose

This addendum will include doses corresponding to the 100-mg adult equivalent exposure. Because the main PK study will still be ongoing at the start of this open-label addendum, a conservative approach was taken to target a lower exposure than that used in the main protocol. This will provide additional safety information for treatment of multiple migraine attacks in the pediatric population.

4.4. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for Study LAHX apply to this addendum with the exception of the following changes.

Inclusion Criterion [3] and Exclusion Criterion [24] are not applicable for this addendum.

[3] Are migraine free on day of lasmiditan administration at the time of predose assessments.

[24] Are on a central nervous system active drug, which is known to affect levels of attention or sedation, such as a benzodiazepine for sleep or anxiety, or stimulants for Attention Deficit Hyperactivity Disorder.

Exclusion criterion 23 is changed to

[23] Have a positive urine drug screen for any substances of abuse.
One retest is allowed if the urine drug screen is positive, at the investigators discretion. Positive results are acceptable if due to regular and medically acceptable use of a prescribed medication, such as a benzodiazepine for sleep or anxiety, or stimulants for Attention Deficit Hyperactivity Disorder.

4.5. Lifestyle and Dietary Considerations

Diary

Participants will record information about the migraine attacks, use of medication, global impression of change, and any adverse events (AEs) in a paper diary between study visits.

Both study participants and their parent or guardian will receive instructions for completion of the diary in case participants need help completing the assessments.

Activity Restrictions

During the treatment of a migraine attack, patients may have some transient restrictions on their usual activities due to the experience of pain and symptoms of a migraine attack, study procedures, and effects of study treatment.

4.6. Method of Treatment Assignment

Patients who meet all criteria for enrollment will receive blisters that contain doses of lasmiditan 50 mg or lasmiditan 100 mg, according to their body weight determined at Visit 4.

The lasmiditan dose will be determined by the participant's weight, with the target to achieve an adult exposure equivalent of 100 mg (Table LAHX(1).1).

Participants can take a single dose of lasmiditan to treat up to 4 migraine attacks per month.

Only 1 lasmiditan dose is allowed per 24 hours.

Lasmiditan will be supplied to the clinical sites in blisters.

Table LAHX(1).1. Planned Treatment Regimen

Participant Body Weight	15 kg to ≤40 kg	>40 kg to ≤55 kg
Treatment Name	Lasmiditan	Lasmiditan
Dosage Formulation	Tablet	Tablet
Unit Dose Strength(s)/Dosage Level(s)	50 mg x1	100 mg x1
Route of Administration	Oral	Oral
Dosing Instructions	With approximately 240 mL of room temperature water in a sitting position	

The investigator or his or her designee is responsible for

- explaining the correct use of lasmiditan to the patient and parent or guardian and site personnel
- ensuring that patients are able to swallow whole tablets
- verifying that instructions are followed properly
- maintaining accurate records of lasmiditan dispensing and collection at each visit, and
- returning all unused medication to Eli Lilly and Company (Lilly), or its designee, unless the sponsor and sites have agreed that all unused medication is to be destroyed by the site, as allowed by local law.

The participant's parent or guardian is responsible for

- maintaining control and inventory of lasmiditan, and
- ensuring that lasmiditan is taken properly.

4.7. Dose Modification

No dose modification is allowed in this study.

4.8. Preparation/Handling/Storage/Accountability

Lasmiditan will be labeled in accordance with regulatory requirements.

All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator or his or her designee is responsible for

- confirming that appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment
- ensuring that only participants enrolled in the study receive study treatment and only authorized site staff supply study treatment, and
- study treatment accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy manual.

4.9. Study Treatment Compliance

Participant compliance with study treatment will be assessed at each visit by counting returned tablets. Deviation(s) from the prescribed dosage regimen will be recorded in the eCRF.

4.10. Concomitant Therapy

What Is Allowed

Patients may use their usual treatment for migraine attacks when they do not choose to treat with lasmiditan.

For patients taking medication for a chronic condition, including preventive medications for migraine, treatment regimen must be stable for at least 3 months prior to Visit 4.

What Is Not Allowed

Any investigational treatment other than lasmiditan is prohibited for the duration of a patient's participation in the study from Visit 4 through end of study.

If a patient requires the initiation of concomitant medication to reduce the frequency of migraine episodes, or a change in ongoing migraine medication after Visit 4, they should be withdrawn from the study.

Patient Diary

Patients will be asked to record all medication use, including changes in dosing of previous medications, in a paper diary. Information needed includes

- name of medication
- reason for use

- start and end dates of medication, and
- dosage strength and frequency.

Parents or guardians can assist the patient in completing the diary. This information will be reviewed with the clinic site staff during each clinic visit.

4.10.1. Rescue

Rescue medication is permitted as needed 2 hours after taking lasmiditan.

The patient may use their usual headache therapy.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the paper diary.

Exceptions

Ergots, opioids, and barbiturates may not be used until 24 hours after lasmiditan administration.

4.11. Discontinuation of Study Treatment

Possible reasons leading to discontinuation of lasmiditan:

- Pregnancy
- The participant or the participant's parents or legal guardian requests to discontinue lasmiditan
- A hepatic event or liver test abnormality
  Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a patient meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:
    - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8x upper limit of normal (ULN)
    - ALT or AST >5x ULN sustained for more than 2 weeks
    - ALT or AST >3x ULN and total bilirubin level (TBL) >2x ULN or international normalized ratio >1.5
    - ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
    - alkaline phosphatase (ALP) >3x ULN
    - ALP >2.5x ULN and TBL >2x ULN
    - ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

  Participants who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF.
- Participants experiencing signs of suicidal ideation or behavior
  Discontinuation of investigational product should be considered, following a risk assessment, for participants who
    - answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale (C-SSRS), **or**

- answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

Participants discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up procedures per Attachment 1 (Schedule of Activities) of the addendum, and Section 8.2 (Safety Assessments) and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

4.12. Discontinuation from the Study Addendum

The investigator will confirm eligibility of the patient for this addendum during Visit 4 as defined in the Schedule of Activities. Patients who do not meet eligibility will be discontinued from the study addendum.

4.13. Study Assessments and Procedures

Attachment 1 lists the Schedule of Activities, detailing the study procedures and their timing.

Attachment 2 lists the Clinical Laboratory Tests.

4.13.1. Efficacy Assessment

A Patient Global Impression of Change (PGI-C) is a patient-rated global measure of change (Guy 1976) and represents a global assessment of effects of the study medication on multiple outcomes, including migraine pain, associated symptoms, side effects, and function (Geisser et al. 2010; Scott and McCracken 2015).

Patients will be asked to record their PGI-C at approximately 2 hours after dosing with lasmiditan in the patient diary. Results will be reviewed at each patient visit and entered in the eCRF.

4.13.2. Safety

4.13.2.1. Safety Assessments

Unscheduled or repeat safety assessments may be performed at the discretion of the investigator as needed.

4.13.2.2. Clinical Safety Laboratory Assessments

For each patient, laboratory tests detailed in Attachment 2 should be conducted according to the Schedule of Activities (Attachment 1).

4.13.2.3. Puberty and Menstrual Status

During the open-label extension addendum, only menstrual status will be collected at each visit.

4.13.3. Adverse Events and Serious Adverse Events

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

If a participant's lasmiditan is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible the circumstances leading to discontinuations of treatment.

4.13.3.1. Method of Detecting AEs and SAEs

Patients will record AEs that occur during the treatment period in a paper diary. Information will include start and end dates of AEs and severity.

At every postscreening visit, site personnel will review the patient paper diary with the patient/guardian and record any change in the preexisting condition(s) and any new conditions as AEs.

Investigators should record the following via eCRF for each AE: date of onset, date of termination, severity, and their assessment of the potential relatedness of each AE to investigational product.

4.14. Treatment of Overdose

There is limited clinical trial experience with lasmiditan overdose. There were no instances of overdose in the clinical pharmacology program. In the Phase 2 and Phase 3 clinical studies, the maximum dose received by any adult patient in a 24-hour period was 600 mg. No treatment-emergent AEs (TEAEs) were reported following any instance of dosing >400 mg (in a 24-hour period). Doses exceeding the maximum therapeutic dose may be associated with increased incidence and/or severity of AEs. Therefore, the patient should be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

4.15. Pharmacokinetics

Pharmacokinetics is not applicable for this addendum.

4.16. Statistical Considerations and Data Analysis

4.16.1. Sample Size Determination

Only previously enrolled participants of Study LAHX at clinics in the US are eligible for this addendum. Therefore, the sample size is determined by the number of these participants who decide to continue in this addendum.

4.16.2. Statistical Analyses

Statistical analysis of this addendum will be the responsibility of Lilly or its designee.

Efficacy and safety analyses will be conducted for all enrolled patients who receive a dose of lasmiditan in this addendum.

Data analyses will be presented by body weight category.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

4.16.2.1. Efficacy Analyses

The proportion and exact 95% confidence interval of patients reporting a PGI-C score better or a lot better for each migraine attack after baseline will be reported.

Additional analyses of the PGI-C will be included in the statistical analysis plan.

4.16.2.2. Clinical Evaluation of Safety

All investigational product and protocol procedure-related AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

Adverse events will be classified by the most suitable term from the most current Medical Dictionary for Regulatory Activities (MedDRA) version.

The incidence of TEAEs will be presented by severity and by association with investigational product as perceived by the investigator. Adverse events reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study.

All serious adverse events (SAEs) will be reported and classified by the most suitable term from the most current MedDRA version.

4.16.2.3. Statistical Evaluation of Safety

Safety parameters for analysis will be

- AEs (including clinically significant ECGs [electrocardiograms])
- clinical laboratory parameters
- vital signs
- C-SSRS assessments

The parameters will be listed, and summarized using standard descriptive statistics.

Additional analysis will be performed if warranted upon review of the data.

4.16.3. Pharmacokinetic Analyses

Pharmacokinetic analyses are not applicable for this addendum.

4.16.4. Data Review during the Study

Safety data will be reviewed on an ongoing basis. Additional reviews may be performed, as deemed appropriate.

4.16.5. Interim Analyses

There will be no interim analyses in this addendum.

5. References

Geisser ME, Clauw DJ, Strand V, Gendreau RM, Palmer R, Williams DA. Contributions of change in clinical status parameters to Patient Global Impression of Change (PGIC) scores among persons with fibromyalgia treated with milnacipran. *Pain.* 2010;149(2):373-378.

Guy W. Clinical Global Impressions (028-CGI), ECDEU Assessment Manual for Psychopharmacology, US Department of Health, Education, and Welfare, ADAMHA, NIMH Psychopharmacology Research Branch. Rockville (MD); 1976; p 217-222.

Scott W, McCracken LM. Patients' impression of change following treatment for chronic pain: global, specific, a single dimension, or many? *J Pain*. 2015;16(6):518-526.

Attachment 1. Schedule of Activities

Schedule of Activities for Patients Participating in H8H-MC-LAHX(1) Addendum

Visit		Month 1	Month 2	Month 3 EOS	ED	Notes
	4[a]	5	6	7		
(Target) interval (days) since previous visit		30±3	30±3	30±3		
Procedure/Assessments						
Informed consent/assent	X					Consent and assent form signed by patient and parent or guardian.
Physical examination	X	X	X	X	X	
Vital signs	X	X	X	X	X	Blood pressure, pulse, and temperature. Triplicate measurements at all visits, in the sitting position. Measure blood pressure by an automated calibrated machine, if calibration is required
Weight	X					
Menstrual status	X	X	X	X		
12-lead ECG (single)	X			X	X	Patients must be supine for at least 5 minutes before collection and remain supine, but awake during the procedure
Concomitant medications	X	X	X	X	X	
Adverse events	X	X	X	X	X	
Study drug dispensed	X	X	X			Provide detailed instructions to participant for study drug
Review study diary	X	X	X	X	X	
Study drug accountability		X	X	X	X	Collect empty dosing card(s) and unused study drug. Review dosing compliance
Clinical Laboratory Tests						
Hematology	X			X	X	
Clinical chemistry	X			X	X	
Urinalysis	X			X	X	
Urine drug screen	X	X	X	X	X	For patients aged ≥ 10 years
Pregnancy test for females of childbearing potential	X	X	X	X	X	A positive urine pregnancy test must be followed by a serum pregnancy test for confirmation
Scales and Questionnaires						
C-SSRS/SHSF/SHFU	X	X	X	X	X	Suicidal ideation and behavior subscales are adapted for the assessment of 11 preferred ideation and behavior categories. The C-SSRS will be collected only in patients ≥7 years old. The SHFU Form is required only if triggered by the SHSF
PGI-C		X	X	X	X	The PGI-C is contained within the patient diary

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; EOS = end of study visit; PGI-C = Patient Global Impression of Change; SHFU = Self-Harm Follow-Up form; SHSF = Self-Harm Supplement Form.

[a] The confirmation of eligibility visit for the addendum will occur at the same time as Study LAHX Day 14, Follow-up visit.

Attachment 2. Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a,]
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Magnesium
Platelets	
Absolute counts of:	Total bilirubin
Neutrophils	
Lymphocytes	Direct bilirubin
Monocytes	Alkaline phosphatase (ALP)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Alanine aminotransferase (ALT)
	Blood urea nitrogen (BUN)
	Creatinine
Urinalysis[a,]	Uric acid
Specific gravity	
pH	Glucose (random)
Protein	Albumin
Glucose	Total protein
Ketones	
Bilirubin	
Urobilinogen	**Other Tests**
Leukocyte esterase[b]	Serum pregnancy test[a]
Blood	Urine pregnancy test (local)
Nitrite	
Urine culture[b]	Urine drug screen[a]
Microsopic analysis[b]	

Abbreviations: RBC = red blood cell; WBC = white blood cell.

[a] Assayed by sponsor-designated laboratory.

[b] A positive leukocyte esterase result will require a follow-up sample with microscopic analysis and possibly a urine culture.

Note: Additional tests may be performed at the discretion of the investigator as needed.

Protocol H8H-MC-LAHX Addendum Sampling Summary

Purpose	Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Total Volume (mL)
Hematology[a]	2	2	4
Chemistry[a]	2.5	2	5
Serum pregnancy test[a,b]	0	1	0
Total			9
Total for clinical purposes rounded up to the nearest 10 mL			10
Hepatic monitoring[c]			3-30

Abbreviations: CRP = Clinical Research Physician; CRS = Clinical Research Scientist.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Sample volume included with chemistry test volume.

[c] Unscheduled hepatic monitoring testing may be performed as part of patient follow-up, based on laboratory safety values and in consultation with Lilly CRP/CRS.

Attachment 3. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some institutional review boards [IRBs]/ethical review boards [ERBs]).
AST	aspartate aminotransferase
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	electronic case report form
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
MedDRA	Medical Dictionary for Regulatory Activities
open label	A study in which there are no restrictions on knowledge of treatment allocation; therefore the investigator and the study participant are aware of the drug therapy received during the study.
PGI-C	Patient Global Impression of Change
PK	pharmacokinetic

SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
TBL	total bilirubin
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
US	the United States

Attachment 4. Protocol Addendum LAHX(1.1) Revisions

Overview

Protocol Addendum I6T-MC-LAHX(1) has been revised. The revised protocol addendum is indicated by revision (1.1) and will be used to conduct the study in place of any preceding version of the protocol addendum.

This table describes the changes to this addendum.

Section	Additions	Deletions	Rationale
Attachment 2 Clinical Laboratory Tests	Urinalysis: • Blood • Nitrite Clinical Chemistry: • Bicarbonate • Chloride • Calcium • Phosphorus • Magnesium Alkaline phosphatase	• Triglycerides • Total cholesterol • Bone specific alkaline phosphatase	Tests were added/deleted to harmonize with what is collected in the main protocol.

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