Statistical Analysis Plan: H8H-MC-LAHX(V2)

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

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1. Statistical Analysis Plan: H8H-MC-LAHX: A Phase 1, Open-Label, Single-dose Pharmacokinetic Study of Lasmiditan in Pediatric Patients with Migraine

Confidential Information

Lasmiditan (LY573144)

Indication: Acute treatment of migraine in pediatric patients

Study H8H-MC-LAHX is a Phase 1, open-label, single-dose, pharmacokinetic (PK) and tolerability study of lasmiditan in pediatric patients with a diagnosis of migraine.

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Protocol H8H-MC-LAHX
Phase 1
Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 15-Jul-2019 GMT

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3. Revision History

SAP Version 1 was approved prior to the first visit when a patient receives study drug.

SAP Version 2 was approved prior to the first visit when a patient receives study drug.

Changes in Version 2 include:

- Removal of analyses for orthostatic pulse (Section 6.7.5).
- Addition of normative population standard deviation and test-reliability values for Cogstate reliable change index, and corresponding references (Section 6.7.7, Appendix 1, References).
- Addition of potential hypersensitivity reactions as a safety topic of interest (Section 6.7.8.7).

4. Study Objectives

Table LAHX.4.1 shows the objectives and endpoints of the study.

Table LAHX.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary To assess the single-dose pharmacokinetics of lasmiditan in pediatric migraine patients	Pharmacokinetic parameters including: • Maximum observed drug concentration (C_{max}) • Time to reach C_{max} (t_{max}) • Area under the concentration-versus-time curve (AUC) from time zero to infinity ($AUC_{[0-\infty]}$) • AUC from time zero to the time t, where t is the last time point with measurable concentration ($AUC_{[0-tlast]}$)
Secondary To assess the safety and tolerability of a single dose of lasmiditan in pediatric migraine patients	Summary of: • SAEs • AEs • ECG • Vital signs
Exploratory To assess the safety, tolerability, and pharmacokinetics of lasmiditan in Japanese pediatric migraine patients	Pharmacokinetic parameters including: • C_{max} • t_{max} • $AUC_{[0-\infty]}$ • $AUC_{[0-tlast]}$ Summary of adverse events, SAEs, ECG, and vital signs.

Abbreviations: AE = adverse event; ECG = electrocardiogram; SAE = serious adverse event.

5. Study Design

5.1. Summary of Study Design

This is a Phase 1, multi-center, open-label, single dose study to determine the pharmacokinetic (PK), safety, and tolerability of lasmiditan in pediatric patients with a diagnosis of migraine.

Two cohorts will be evaluated:

- Primary **Cohort 1**: 15 kg to ≤40 kg
- Secondary **Cohort 2**: >40 kg to ≤55 kg

The planned doses for Cohorts 1 and 2 are 100 mg and 200 mg, respectively.

Study Period I (Screening)

All patients are screened to determine if they are eligible to participate in the study.

Screening will occur 28 days to 3 days prior to lasmiditan dosing.

Study Period II (PK Assessment/Safety)

Enrolled patients and the patient's parent or guardian will receive instructions regarding study procedures prior to dosing, including fasting requirements.

Day 1:

- Patients arrive at the Clinical Research Unit (CRU) for assessments prior to dosing.
- Patients receive the single lasmiditan dose.
- Patients can go home after the 12-hour assessments. Patients may be offered the opportunity to spend the night depending on CRU capabilities.

Day 2:

- Patient assessments are done at the CRU approximately 24 hours after dosing.

Study Period III (Follow-Up Period)

Patients return to the CRU for a follow-up visit approximately 14 days after dosing.

5.2. Determination of Sample Size

For the primary cohort (body weight between 15 and ≤40 kg, inclusive), approximately 13 patients may be enrolled to obtain at least 11 patients with evaluable PK data. Patients who do not have evaluable PK data may be replaced.

From the population PK analysis in adults, the inter-patient coefficient of variation was estimated to be 43% for C_{max} and 39% for AUC. Assuming the coefficient of variation of total variability is not larger than 45%, 11 pediatric patients will provide at least 80% coverage probability that the 95% confidence interval (CI) for the geometric mean of these key PK parameters will be within 70% and 140%. The coefficient of variation for apparent total body clearance and

apparent central volume of distribution are similar and, therefore, the precision of estimates for these parameters are expected to be sufficient.

Moreover, approximately 8 patients (body weight >40 kg and ≤55 kg) in the secondary cohort may be enrolled to obtain at least 6 patients with evaluable PK data. This sample size is customary for Phase 1 studies evaluating PK, safety, and tolerability, and is not powered on the basis of statistical hypothesis testing.

Efforts will be made to enroll female and male patients of varying body weights across the weight range defined for the primary and secondary cohorts.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment at Visit 2 will receive an open label dose of lasmiditan 200 mg or lasmiditan 100 mg, according to their body weight, as shown in Table LAHX.5.1 below.

Table LAHX.5.1. Planned Treatment Regimen

Cohort	1	2
Participant Body Weight	15 kg to ≤40 kg	>40 kg to ≤55kg
Treatment Name	Lasmiditan	lasmiditan
Dosage Formulation	Tablet	Tablet
Unit dose strength(s)/Dosage Level(s)	50 mg x2 or 100 mg x1	50 mg x4 or 100 mg x2
Route of Administration	Oral	Oral
Dosing instructions	With approximately 240 mL of room temperature water in a sitting position	

6. A Priori Statistical Methods

6.1. General Considerations

Data listings will be provided for all data that is databased, and will be presented by cohort. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum and number of patients that provided data (N). For log-normal data (eg, the PK parameters: AUCs and C_{max}), the geometric mean and the corresponding 95% CI, and geometric CV% will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all patients up to their last collected measurement, and will highlight patients who discontinue from the study before follow-up. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Change from baseline values will be calculated for laboratory data, vital signs data, and Cogstate Pediatric Brief Battery data. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the timepoint. Mean change from baseline is the mean of all individual patients' change from baseline values. The individual patients' change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Individual derived parameters (eg, PK parameters) and appropriate summary statistics will be reported to 3 significant figures. Observed concentration data, eg, C_{max}, should be reported as received. Observed time data, eg, t_{max}, should be reported as received. Observed safety data should be reported as received. Counts should be reported as whole numbers and percentage values should be reported to 1 decimal place. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

Pharmacokinetic analyses will be conducted on data from all patients who receive a dose of the investigational product and have evaluable PK data. Patients may be excluded from the PK summary statistics and statistical analysis if a patient has an adverse event (AE) of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (t_{max}).

Safety analyses will be conducted for all enrolled patients who receive a dose of the investigational product, whether or not they completed all protocol requirements.

Pharmacokinetic data analyses will be presented by:

- body weight category (15 kg to ≤40 kg, >40 kg to ≤55 kg)
- age category (6 to <12 years of age, 12 to <18 years of age)
- body surface area (0.65 m^2 to ≤1.3 m^2, >1.3 m^2 to ≤1.6 m^2)
- glomerular filtration rate (<75 mL/min/1.73 m^2, ≥75 mL/min/1.73 m^2)
- region (Japan, US), if appropriate

Safety data analyses will be presented by body weight category or age category, as appropriate.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when PK and safety analyses are conducted.

Data analysis will be performed using SAS® Version 9.4 or greater.

6.2. Handling of Dropouts or Missing Data

Missing data will not be displayed in listings.

Some of the tables, figures, and listings (TFLs) may not have sufficient numbers of patients or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occurred for this study".

6.3. Extent of Exposure

Dosing details for each patient will be displayed in a listing.

6.4. Patient Disposition

Patient disposition will be displayed in a listing.

6.5. Patient Characteristics

6.5.1. Demographics

The following patient characteristics at screening will be summarized for all enrolled patients who receive a dose of the investigational product, and presented by body weight category and age category:

- Age (continuous variable)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Caucasian, Multiple, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Height (cm) (continuous variable)
- Weight (kg) (continuous variable)
- Average number of attacks per month in the last 2 months (continuous variable)
- Body mass index (BMI) (weight (kg) / [height (m)]^2) (continuous variable)
- Body surface area (0.65 m^2 to ≤1.2 m^2, >1.2 m^2 to ≤1.6 m^2) (Sharkey et al. 2001)
- Glomerular filtration rate (<75 mL/min/1.73 m^2, ≥75 mL/min/1.73 m^2) (Pottel et al. 2015)
- Menstrual status for female patients (Pre-menarchal, Menarchal)
- Pubertal status (Prepubertal, Pubertal)

Age will be calculated using the difference in days between the date of birth and the date of informed consent.

Body surface area (m^2) will be calculated as: $0.03330 * W^{(0.6157-0.0188log_{10}(W))} * H^{0.3}$, where W is weight (kg) and H is height (cm) (Boyd 1935).

Height will be measured in triplicate and the mean value will be recorded.

Glomerular filtration rate will be calculated using the Bedside Schwartz formula: 0.413 x (height [cm] /serum creatinine [mg/dL]) (Schwartz et al. 2009).

All demographic data will be presented in a listing. For Japanese patients, glomerular filtration rates in this listing will be calculated using both the Bedside Schwartz formula and the Japanese Society for Pediatric Nephrology formula: 110.2*(reference serum creatinine [mg/dL]/patient serum creatinine [mg/dL]) + 2.93 (Uemura 2015).

6.6. Pharmacokinetic Assessment

6.6.1. Pharmacokinetic Analysis

Pharmacokinetic parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 6.4 or later). Pharmacokinetic analysis using a compartmental modeling approach will be described in a separate PK/pharmacodynamic analysis plan document.

Plasma concentrations of lasmiditan will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	ng.h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
$t_{½}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the clinical study report. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures, and abbreviations will follow the Eli Lilly and Company (Lilly) Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero. For non-bolus, multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.
- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than 1 time point, t_{max} will be assigned to the first occurrence of C_{max}.
- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification, with at least 1 of these concentrations following C_{max}. AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{½}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each patient will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.
- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.
- The parameters based on predicted concentration at last quantifiable timepoint will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:
    - The compound is non-endogenous.
    - The samples are from the initial dose period for a patient or from a subsequent dose period following a suitable wash-out period.
    - The time points occur before the first quantifiable concentration.
- All other BQL concentrations that do not meet the above criteria will be set to missing.
- In addition, where 2 or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.
- The average concentration profiles will be graphed using arithmetic average concentrations.
- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the final study report.
- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.
- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.
2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
    a. Transform all values in the calculation to the logarithmic domain.
    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.
    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.
    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.
    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many

times as necessary, excluding only 1 suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

6.6.2. Pharmacokinetic Statistical Methodology

Pharmacokinetic parameter estimates will be listed and summarized using descriptive statistics, which will be presented separately by body weight category, age category, body surface area, glomerular filtration rate, and region (if applicable).

For log-normal data (eg, the PK parameters: AUCs and C_{max}), the geometric mean and the corresponding 95% CI, and geometric CV% will also be presented.

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

6.7. Safety and Tolerability Assessments

6.7.1. Adverse Events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the patient has provided written informed consent and is ongoing at consent. A treatment-emergent AE (TEAE) is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose. A non-treatment emergent AE (non-TEAE) is defined as an AE which starts after informed consent but prior to dosing.

All AEs occurring on or after the date of informed consent form signing, discontinuations due to AEs, pre-existing conditions and medical history, serious AEs, and serious TEAEs will be listed.

The number and percentage of patients who report TEAEs will be summarized using preferred terms (PTs) from the most current version of Medical Dictionary for Regulatory Activities (MedDRA), where PTs will be nested within system organ class (SOC). System organ classes will be listed alphabetically and PTs within each SOC will be listed by decreasing frequency in the total population. The number and percentage of patients who report TEAEs will also be summarized using MedDRA PTs listed by decreasing frequency in the total population.

The number and percentage of patients with TEAEs by maximum severity will be summarized using MedDRA PTs listed by decreasing frequency in the total population. For each patient and TEAE, the maximum severity for the MedDRA PT is the maximum post-baseline severity observed from all associated lower level terms mapping to the MedDRA PT. The maximum severity will be determined based on the non-missing severities. If all severities are missing for the defined postbaseline period of interest, it will show as missing in the table.

The number and percentage of patients with TEAEs that are related to study drug will be summarized using MedDRA PTs listed by decreasing frequency in the total population. Related TEAEs are those that are recorded on the AE CRF page as related to study treatment or those with a missing relationship.

For events that are gender-specific, the denominator and computation of the percentage will include only patients from the specific gender.

Descriptive statistics will be presented separately by body weight category and age category.

6.7.2. Concomitant Therapy

Concomitant medications taken during the study will be coded using the most current version of the World Health Organization drug dictionary. All concomitant medications will be listed.

6.7.3. Prior Migraine Therapy

All migraine therapies that patients have stopped taking prior to the date of informed consent signing will be provided in a listing.

6.7.4. Clinical Laboratory Evaluation

6.7.4.1. Clinical Laboratory Parameters

All clinical chemistry, hematology, and urinalysis data will be summarized by parameter, and listed. Values for any clinical chemistry, hematology, and urinalysis that are outside the reference ranges will be flagged as high or low on the individual patient data listings.

Change from baseline will be summarized for all lab parameters measured at 24 hours postdose, where baseline is defined as the predose measurement for all laboratory parameters.

6.7.4.2. Hepatic Monitoring

Patients with the following elevations in hepatic laboratory tests at 24 hours postdose will be listed:

- Patients with an alanine aminotransferase (ALT) measurement greater than or equal to 3X, 5X, and 10X the performing laboratory upper limit of normal (ULN) at 24 hours postdose will be listed by the following subsets based on various levels of baseline value.
    - The analysis of 3X ULN will contain 4 subsets:
        - patients whose non-missing baseline ALT value is less than or equal to 1X ULN
        - patients whose baseline ALT value is greater than 1X ULN but less than 3X ULN
        - patients whose baseline ALT value is greater than or equal 3X ULN
        - patients whose baseline ALT values are missing

  - The analysis of 5X ULN will contain 5 subsets:
    - patients whose non-missing baseline ALT value is less than or equal to 1X ULN
    - patients whose baseline ALT value is greater than 1X ULN but less than 3X ULN
    - patients whose baseline ALT value is greater than or equal to 3X ULN but less than 5X ULN
    - patients whose baseline ALT value is greater than or equal to 5X ULN
    - patients whose baseline ALT values are missing
  - The analysis of 10X ULN will contain 6 subsets:
    - patients whose non-missing baseline ALT value is less than or equal to 1X ULN
    - patients whose baseline ALT value is greater than 1X ULN but less than 3X ULN
    - patients whose baseline ALT value is greater than or equal to 3X ULN but less than 5X ULN
    - patients whose baseline ALT value is greater than or equal to 5X ULN but less than 10X ULN
    - patients whose baseline ALT value is greater than or equal to 10X ULN
    - patients whose baseline ALT values are missing

- Patients with an aspartate aminotransferase (AST) measurement greater than or equal to 3X, 5X, and 10X the performing lab ULN at 24 hours post-dose will be listed by subsets based on various levels of baseline value, as described above for ALT.
- Patients with an alkaline phosphatase (ALP) measurement greater than or equal to 2X the performing lab ULN at 24 hours post-dose will be listed by the following subsets based on various levels of baseline.
  - The analysis of 2X ULN will contain 4 subsets:
    - patients whose non-missing baseline ALP value is less than or equal to 1X ULN
    - patients whose baseline ALP value is greater than 1X ULN but less than 1.5X ULN
    - patients whose baseline ALP value is greater than or equal to 1.5X ULN

    - patients whose baseline ALP values are missing

- Patients with a total bilirubin (TBIL) measurement greater than or equal to 2X the performing lab ULN at 24 hours postdose will be listed by the following subsets based on various levels of baseline:
    - patients whose non-missing baseline TBIL value is less than or equal to 1X ULN
    - patients whose baseline TBIL value is greater than 1X ULN but less than 2X ULN
    - patients whose baseline TBIL value is greater than or equal to 2X ULN
    - patients whose baseline TBIL values are missing

Baseline is defined as the predose measurement for all hepatic laboratory parameters.

6.7.5. Vital Signs

Where supine blood pressure is measured in triplicate, the mean value will be calculated and used in all subsequent calculations. When triplicate blood pressure measurements precede a standing measurement, the last supine blood pressure measurement will be used for orthostatic calculations. Orthostatic values will be calculated as the standing value minus the last supine value taken prior to the standing value.

Vital signs data for individual patients will be listed by time point. Vital signs data will also be summarized at each time point by body weight category and age category, together with changes from baseline for supine vital signs. For supine vital signs, baseline is defined as the mean of the triplicate measurement taken at predose. Figures of mean vital signs and mean changes from baseline profiles will be presented by cohort and region over time.

Counts and percentages of patients displaying categorical shifts (as given by the criteria in Table LAHX.6.1) will be summarized by body weight category. Table LAHX.6.1. displays the Lilly-defined criteria for categorical shifts for supine blood pressure, pulse, and orthostatic blood pressure. The last column of the table displays the patient populations defined by baseline categories.

Table LAHX.6.1. Criteria for Categorical Shifts in Vital Signs

Parameter	Age Group	Direction	Criteria	Patient Population defined by Baseline Categories
Systolic BP (mm Hg) (supine)	6-9	Low	≤80 and decrease ≥15	>80
		High	≥122 and increase ≥15	<122
	10-11	Low	≤85 and decrease ≥20	>85
		High	≥126 and increase ≥20	<126
	12-14	Low	≤90 and decrease ≥20	>90
		High	≥136 and increase ≥20	<136
	15-17	Low	≤90 and decrease ≥20	>90
		High	≥140 and increase ≥20	<140
Diastolic BP (mm Hg) (supine)	6-9	Low	≤45 and decrease ≥10	>45
		High	≥78 and increase ≥10	<78
	10-11	Low	≤50 and decrease ≥10	>50
		High	≥82 and increase ≥10	<82
	12-14	Low	≤50 and decrease ≥10	>50
		High	≥86 and increase ≥10	<86
	15-17	Low	≤50 and decrease ≥10	>50
		High	≥90 and increase ≥10	<90
Pulse (bpm) (supine)	6-9	Low	<60 and decrease ≥25	≥60
		High	>150 and increase ≥25	≤150
	10-11	Low	<60 and decrease ≥25	≥60
		High	>140 and increase ≥25	≤140
	12-14	Low	<50 and decrease ≥15	≥50
		High	>120 and increase ≥15	≤120
	15-17	Low	<50 and decrease ≥15	≥50
		High	>100 and increase ≥15	≤100
Systolic BP (mm Hg) (orthostatic)	All	Decrease	Decrease ≥ 20	All patients
Diastolic BP (mm Hg) (orthostatic)	All	Decrease	Decrease ≥ 10	All patients

Abbreviations: BP = blood pressure; bpm = beats per minute; mm Hg = millimeters of mercury.
Note: "all patients" include all safety analysis patients with both a non-missing baseline (predose) measure and at least 1 non-missing postbaseline measure.
Beasley and Moscarelli 2015.

The criteria consist of 2 parts, an absolute threshold and a change from baseline (predose) amount.

- The absolute threshold in the criteria is based on: 1) minimum postbaseline when the direction is low; 2) maximum postbaseline when the direction is high.
- The change from baseline amount in the criteria is: 1) decrease from non-missing baseline to minimum postbaseline when the direction is low; 2) increase from non-missing baseline to maximum post baseline when the direction is high.

6.7.6. Electrocardiograms

Any clinically significant electrocardiogram (ECG) finding that results in a diagnosis and that occurs after the patient receives lasmiditan will be reported as an AE.

Counts and percentages displaying shifts from normal, abnormal (not clinically significant), or abnormal (clinically significant) at baseline (predose) to normal, abnormal (not clinically significant), or abnormal (clinically significant) at 24 hours postdose will be summarized. Baseline is defined as ECG findings taken at predose.

Descriptive statistics will be presented separately by body weight category and age category.

6.7.7. Cognition

Data for the following Cogstate Pediatric Brief Battery parameters will be listed by time point:

- Detection Test score: mean of the $\log_{10}$ transformed reaction times for correct responses
- Identification Test score: mean of the $\log_{10}$ transformed reaction times for correct responses
- One Back Test score: mean of the $\log_{10}$ transformed reaction times for correct responses
- One Card Learning Test score: arcsine transformation of the square root of the proportion of correct responses

For each test score, listings will also include change from baseline (predose) and the reliable change index (RCI) score at each post-dose time point, which will be computed as follows:

$$RCI = \frac{score_{post} - score_{baseline}}{s_{norm}\sqrt{2(1-r)}} \times Multiplicand$$

where:

- $score_{post}$ = patient's score at the given post-dose time point
- $score_{post}$ = patient's score at baseline
- s_{norm} = population standard deviation from age-matched normative data
- r = normative test-retest reliability
- $Multiplicand$ = -1 for the Detection, Identification, and One Back tests
  = +1 for the One Card Learning test

The number and percent of patients with at least 2 RCI scores less than or equal to -1.65 will be reported and summarized by age category at each postdose time point (Ingraham and Aiken 1996; Louey et al. 2014). Age-specific normative s_{norm} and r values for each test are provided in Appendix 1 (Cromer et al. 2015; Hammers et al. 2012; Mollica et al. 2005; Rosenfeld et al. 2018; Yoshida et al. 2011).

Descriptive statistics for the Detection, Identification, One Back, and One Card Learning test scores, together with changes from baseline, will be presented by age category at each time point. For each test score, the Cohen's d effect size measure (Cohen 1988) will also be computed at each postdose time point as follows:

$$d = \frac{mean_{change,cat,1} - mean_{change,cat,2}}{s_{change}}$$

where:

- $mean_{change,cat,i}$ = mean change from baseline for the i^{th} age category (i = 1 → 6 to <12 years of age; i = 2 → 12 to <18 years of age)
- s_{change} = standard deviation of change from baseline values, pooled across the 2 age categories

6.7.8. Safety Topics of Interest

This section includes areas of interest whether due to observed safety findings, potential findings based on drug class, or requested by a regulatory agency for any reason.

Standardized MedDRA Queries (SMQs) are groupings of terms from 1 or more MedDRA SOCs that relate to a defined medical condition or area of interest. When an SMQ is specified, the resulting tabular display will include counts and percentages by treatment group at the SMQ level and at the PT level within the SMQ. When an SMQ involves both narrow and broad terms, the summaries will occur at the SMQ level, then the narrow/broad level, and subsequently the PT level within the SMQ.

6.7.8.1. Evaluation of Cardiovascular Safety

Definitions of Lilly Search Categories (LSCs) for cardiovascular (CV) events:

1. Potential CV AEs: all PTs (for TEAEs and AEs) in the SMQs listed below plus PTs of abdominal pain, abdominal pain upper, and abdominal pain lower.
2. Likely CV AEs: a subset of the potential CV AEs. All clinical information from patients who reported the PT events identified from the search described above for potential CV AEs will undergo medical review and medical judgment will be applied to determine if the AE (for each patient) was likely CV in nature. If so, it will be defined as a likely CV AE.

SMQs:

- broad and narrow terms in cardiac arrhythmias (includes sub SMQs) (SMQ 20000049)
- broad and narrow terms in cardiac failure (SMQ 20000004)
- broad and narrow terms in cardiomyopathy (SMQ 20000150)
- broad and narrow terms in central nervous system vascular disorders (includes sub SMQs) (SMQ 20000060)
- broad and narrow terms in embolic and thrombotic events (includes sub SMQs) (SMQ 20000081)
- broad and narrow terms in hypertension (SMQ 20000147)

- broad and narrow terms in ischemic heart disease (includes sub SMQs) (SMQ 20000043)
- broad and narrow terms in pulmonary hypertension (SMQ 20000130)
- broad and narrow terms in Torsade de pointes/QT prolongation (SMQ 20000001)

Patient narratives will be provided for patients with potential and likely CVs, likely CV SAEs, and likely CV AEs leading to discontinuations.

6.7.8.2. Evaluation of Hepatic Safety

Refer to Section 6.7.4.2 for a description of hepatic analyses.

6.7.8.3. Evaluation of Injuries and Accidents Secondary to Neurologic Adverse Events

The number and percentage of patients with at least 1 TEAE in the 'Nervous System Disorders' SOC and/or at least 1 AE in the 'Injury, Poisoning, and Procedural Complications' SOC will be summarized.

Among patients with at least 1 AE in the 'Injury, Poisoning, and Procedural Complications' SOC, the number and percentage of patients who reported AEs in this SOC will be summarized, using MedDRA PTs listed by decreasing frequency in the total population. For each AE in this summary, the number and percentage of patients who reported at least 1 TEAE in the 'Nervous System Disorders' SOC will also be summarized. Descriptive statistics will be presented separately by body weight category and age category.

Outcomes will be evaluated by medical review of any other AEs (for example, falls, fractures, sprains, head injury) reported when the patients experienced neurologic-related events. Patient narratives for patients with adverse functional outcomes associated with neurologic-related events will be provided based on medical review that includes the neurologic-related events and any other AEs indicative of an adverse outcome that could be potentially related to the neurological TEAE.

6.7.8.4. Road Traffic Accidents

Patient narratives for patients who reported AEs with PTs of road traffic accident, impaired ability to use machinery, or accident, will be provided.

6.7.8.5. Drug Abuse Liability Evaluation

With 2 exceptions described below (SMQ of Drug abuse and dependence, listing of patients with reported overdose AEs), all analyses to evaluate abuse potential will only be performed in patients 12 to <18 years of age.

The following event clusters will be used to evaluate potential abuse liability:

- The SMQ of Drug abuse and dependence [20000101], including individual PTs, all narrow terms, and all (narrow and broad) terms. This will also be done separately in patients 6 to <12 years of age.

- The LSC of "Additional potential abuse liability" terms. This LSC contains additional terms based on Food and Drug Administration guidance (FDA 2017 [WWW]) that are not included in the Drug abuse and dependence SMQ, including terms for Dissociation/psychotic, Euphoria, Impaired attention, Cognition and mood, and Other abuse-related terms. Summaries will be provided at the PT level and the overall level.

The term list is based on the most current MedDRA version and is provided in Appendix 2.

The analyses in this section will include a total count of patients experiencing TEAEs from the above search and will be listed by SMQ or LSC Additional potential abuse liability terms, and then sorted by decreasing frequency in the total population within each SMQ or LSC Additional Terms group. For the SMQ, a summary will also be provided at the narrow and broad level. For both the SMQ and LSC Additional potential abuse liability terms list, each PT will be summarized. Additionally, the overall number (the number and percent of patients who experienced any TEAE from the above search) will be analyzed.

Patient narratives of possible abuse related events (time of onset and duration of event, dose of drug, severity and outcome) will be provided.

The following additional analyses will be performed:

- Times to onset and durations of TEAEs which may represent a sign of abuse liability (AL) will be summarized for individual abuse potential terms and any AL term.
- Onset times relative to first dose and durations of AEs for patients with at least 2 AL TEAEs will be plotted for any abuse potential AEs for these patients.
- Onset/duration plots (see Appendix 3) by cohort for each AL TEAE. In the event that 1 or more AL TEAEs occur in a disproportionate percentage of the population, this analysis will exclude those terms.

All the time to onset analysis will exclude events that are missing event start times/dates or missing dosing times/dates, and all duration analysis will exclude events that are missing event start or stop times/dates or missing dosing times/dates.

Descriptive statistics will be presented separately by body weight category and age category.

6.7.8.6. Suicide-Related Thoughts and Behaviors

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent, based on the Columbia-Suicide Severity Rating Scale (C-SSRS)-Children's Version (Posner et al. 2011), will be listed for individual patients by time point. Only patients that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be displayed (ie, if a patient answers are all 'no' for the C-SSRS, then that patient will not be displayed). However, if a patient reported any suicidal ideation/behavior or self-injurious behavior without suicidal intent at any time point then all their ideation and behavior will be displayed, even if not positive.

6.7.8.7. Potential Hypersensitivity Reactions

Potential hypersensitivity reactions are AEs whose MedDRA PTs are contained in the following SMQs:

- broad and narrow terms in anaphylactic reaction (SMQ 20000021)
- broad and narrow terms in hypersensitivity (SMQ 20000214)
- broad and narrow terms in angioedema (SMQ 20000024)

Patient narratives will be provided for patients with potential immediate hypersensitivity reactions (TEAEs that are potential hypersensitivity reactions) and for those with potential non-immediate hypersensitivity reactions (non-TEAEs that are potential hypersensitivity reactions).

6.7.9. Other Assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

6.7.10. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

6.8. Interim Analyses and Data Monitoring

No interim statistical analyses are planned.

6.9. Changes from the Protocol Specified Statistical Analyses

There were no changes from the protocol specified statistical analyses.

6.10. Reports to be Generated

All reports will be generated at final database lock.

6.11. Clinical Trial Registry Analyses

Additional analyses will be performed for fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset, which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized by treatment group and MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each 'Serious' AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term

  - the number of events experienced
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/patients in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the clinical study report, manuscripts, and so forth.

7. References

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8. Appendices

Appendix 1. Cogstate Normative Population Standard Deviation and Test-Retest Reliability Values

For each Cogstate test, normative population standard deviation (s_{norm}) and test-retest reliability (r) values are listed below for each age.

Detection Test (Reaction Time)

Age	s_{norm}	r
6	0.09264	0.79
7	0.09901	0.79
8	0.13746	0.79
9	0.13506	0.79
10	0.08007	0.79
11	0.07896	0.79
12	0.07682	0.79
13	0.07535	0.79
14	0.08101	0.79
15	0.07674	0.79
16	0.07644	0.79
17	0.07528	0.79

Identification Test (Reaction Time)

Age	s_{norm}	r
6	0.06801	0.80
7	0.07695	0.80
8	0.11548	0.80
9	0.09222	0.80
10	0.07096	0.80
11	0.07068	0.80
12	0.06719	0.80
13	0.06782	0.80
14	0.06954	0.80
15	0.06687	0.80
16	0.06561	0.80
17	0.06456	0.80

One Back Test (Reaction Time)

Age	s_{norm}	r
6	0.06515	0.78
7	0.11496	0.78
8	0.11140	0.78
9	0.11960	0.78
10	0.09147	0.78
11	0.08742	0.78
12	0.08970	0.78
13	0.08832	0.78
14	0.08875	0.78
15	0.08837	0.78
16	0.08920	0.78
17	0.09017	0.78

One Card Learning Test (Accuracy)

Age	s_{norm}	r
6	0.16830	0.70
7	0.17329	0.70
8	0.14007	0.70
9	0.16395	0.70
10	0.08819	0.70
11	0.08805	0.70
12	0.08754	0.70
13	0.08762	0.70
14	0.08567	0.70
15	0.08539	0.70
16	0.08588	0.70
17	0.08719	0.70

Appendix 2. Lilly Search Category of Additional Potential Abuse Liability Terms

Lilly Search Category of Additional Potential Abuse Liability Terms

The following are the MedDRA v21.1 terms and categories to comprise the Lilly Search Category that will be used for analysis of drug abuse potential.

Cluster	Preferred Term (PT)	PT code
Dissociation/psychotic	ACUTE PSYCHOSIS	10001022
Dissociation/psychotic	AGGRESSION	10001488
Dissociation/psychotic	AGITATION	10001497
Dissociation/psychotic	ALICE IN WONDERLAND SYNDROME	10001666
Dissociation/psychotic	ANGER	10002368
Dissociation/psychotic	ANTISOCIAL BEHAVIOUR	10002820
Dissociation/psychotic	BELLIGERENCE	10004224
Dissociation/psychotic	CONFABULATION	10010297
Dissociation/psychotic	CONFUSIONAL STATE	10010305
Dissociation/psychotic	DEJA VU	10012177
Dissociation/psychotic	DELIRIUM	10012218
Dissociation/psychotic	DELUSION	10012239
Dissociation/psychotic	DELUSION OF GRANDEUR	10012241
Dissociation/psychotic	DELUSION OF REFERENCE	10012244
Dissociation/psychotic	DELUSION OF REPLACEMENT	10012245
Dissociation/psychotic	DELUSIONAL DISORDER, EROTOMANIC TYPE	10012249
Dissociation/psychotic	DELUSIONAL DISORDER, GRANDIOSE TYPE	10012250
Dissociation/psychotic	DELUSIONAL DISORDER, JEALOUS TYPE	10012251
Dissociation/psychotic	DELUSIONAL DISORDER, MIXED TYPE	10012252
Dissociation/psychotic	DELUSIONAL DISORDER, SOMATIC TYPE	10012254
Dissociation/psychotic	DELUSIONAL DISORDER, UNSPECIFIED TYPE	10012255
Dissociation/psychotic	DELUSIONAL PERCEPTION	10012258
Dissociation/psychotic	DERAILMENT	10012411
Dissociation/psychotic	DIENCEPHALIC SYNDROME OF INFANCY	10012774
Dissociation/psychotic	DISORIENTATION	10013395
Dissociation/psychotic	DISSOCIATION	10013457
Dissociation/psychotic	DISSOCIATIVE AMNESIA	10013461

Dissociation/psychotic	DISSOCIATIVE IDENTITY DISORDER	10013468
Dissociation/psychotic	EROTOMANIC DELUSION	10015134
Dissociation/psychotic	FEAR	10016275
Dissociation/psychotic	FLASHBACK	10016754
Dissociation/psychotic	FORMICATION	10017062
Dissociation/psychotic	HALLUCINATION	10019063
Dissociation/psychotic	HALLUCINATION, AUDITORY	10019070
Dissociation/psychotic	HALLUCINATION, GUSTATORY	10019071
Dissociation/psychotic	HALLUCINATION, OLFACTORY	10019072
Dissociation/psychotic	HALLUCINATION, TACTILE	10019074
Dissociation/psychotic	HALLUCINATION, VISUAL	10019075
Dissociation/psychotic	HALLUCINATIONS, MIXED	10019079
Dissociation/psychotic	HOMICIDE	10020364
Dissociation/psychotic	HOSTILITY	10020400
Dissociation/psychotic	HYPNAGOGIC HALLUCINATION	10020927
Dissociation/psychotic	HYPNOPOMPIC HALLUCINATION	10020928
Dissociation/psychotic	IDEAS OF REFERENCE	10021212
Dissociation/psychotic	ILLOGICAL THINKING	10021402
Dissociation/psychotic	ILLUSION	10021403
Dissociation/psychotic	IRRITABILITY	10022998
Dissociation/psychotic	JAMAIS VU	10023118
Dissociation/psychotic	JEALOUS DELUSION	10023164
Dissociation/psychotic	MAGICAL THINKING	10025429
Dissociation/psychotic	PANIC ATTACK	10033664
Dissociation/psychotic	PANIC REACTION	10033670
Dissociation/psychotic	PARAMNESIA	10033848
Dissociation/psychotic	PARANOIA	10033864
Dissociation/psychotic	PERSECUTORY DELUSION	10034702
Dissociation/psychotic	PERSONALITY CHANGE	10034719
Dissociation/psychotic	PERSONALITY DISORDER	10034721
Dissociation/psychotic	PHYSICAL ASSAULT	10034983
Dissociation/psychotic	PSYCHOTIC BEHAVIOUR	10037249
Dissociation/psychotic	SENSORY DISTURBANCE	10040026
Dissociation/psychotic	SLEEP TERROR	10041010
Dissociation/psychotic	SOMATIC DELUSION	10041317
Dissociation/psychotic	STARING	10041953
Dissociation/psychotic	SUSPICIOUSNESS	10042635
Dissociation/psychotic	THOUGHT BLOCKING	10043495
Dissociation/psychotic	THOUGHT INSERTION	10043496
Dissociation/psychotic	THOUGHT WITHDRAWAL	10043497
Dissociation/psychotic	VIOLENCE-RELATED SYMPTOM	10047426
Dissociation/psychotic	HYPERVIGILANCE	10048533
Dissociation/psychotic	HOMICIDAL IDEATION	10049666
Dissociation/psychotic	IMPATIENCE	10049976
Dissociation/psychotic	THOUGHT BROADCASTING	10052214

Dissociation/psychotic	DELUSIONAL DISORDER, PERSECUTORY TYPE	10053195
Dissociation/psychotic	REACTIVE PSYCHOSIS	10053632
Dissociation/psychotic	TRANSIENT PSYCHOSIS	10056326
Dissociation/psychotic	SENSORY LEVEL ABNORMAL	10061567
Dissociation/psychotic	PARASOMNIA	10061910
Dissociation/psychotic	PSYCHOTIC DISORDER	10061920
Dissociation/psychotic	HYSTERICAL PSYCHOSIS	10062645
Dissociation/psychotic	SOMATIC HALLUCINATION	10062684
Dissociation/psychotic	HALLUCINATION, SYNAESTHETIC	10062824
Dissociation/psychotic	DEPRESSIVE DELUSION	10063033
Dissociation/psychotic	PAROXYSMAL PERCEPTUAL ALTERATION	10063117
Dissociation/psychotic	SLEEP SEX	10067492
Dissociation/psychotic	CONFUSIONAL AROUSAL	10067494
Dissociation/psychotic	REBOUND PSYCHOSIS	10074833
Dissociation/psychotic	MIXED DELUSION	10076429
Dissociation/psychotic	FRUSTRATION TOLERANCE DECREASED	10077753
Dissociation/psychotic	DEPERSONALISATION/DEREALISATION DISORDER	10077805
Euphoria	ATTENTION-SEEKING BEHAVIOUR	10003739
Euphoria	DISINHIBITION	10013142
Euphoria	DIZZINESS	10013573
Euphoria	EUPHORIC MOOD	10015535
Euphoria	FEELING ABNORMAL	10016322
Euphoria	FEELING DRUNK	10016330
Euphoria	FEELING JITTERY	10016338
Euphoria	FEELING OF RELAXATION	10016352
Euphoria	FLIGHT OF IDEAS	10016777
Euphoria	IMPULSIVE BEHAVIOUR	10021567
Euphoria	INAPPROPRIATE AFFECT	10021588
Euphoria	INCOHERENT	10021630
Euphoria	JUDGEMENT IMPAIRED	10023236
Euphoria	LOGORRHOEA	10024796
Euphoria	LOOSE ASSOCIATIONS	10024825
Euphoria	MANIA	10026749
Euphoria	MOOD SWINGS	10027951
Euphoria	PSYCHOMOTOR HYPERACTIVITY	10037211
Euphoria	RESTLESSNESS	10038743
Euphoria	TANGENTIALITY	10043114
Euphoria	THINKING ABNORMAL	10043431
Euphoria	ENERGY INCREASED	10048779
Euphoria	HOT FLUSH	10060800
Euphoria	ABNORMAL BEHAVIOUR	10061422

Euphoria	CENTRAL NERVOUS SYSTEM STIMULATION	10061444
Euphoria	GAMBLING DISORDER	10078070
Impaired attention, cognition and mood	ABNORMAL DREAMS	10000125
Impaired attention, cognition and mood	AFFECTIVE DISORDER	10001443
Impaired attention, cognition and mood	ALTERED STATE OF CONSCIOUSNESS	10001854
Impaired attention, cognition and mood	AMNESIA	10001949
Impaired attention, cognition and mood	ANHEDONIA	10002511
Impaired attention, cognition and mood	ANTEROGRADE AMNESIA	10002711
Impaired attention, cognition and mood	ANXIETY	10002855
Impaired attention, cognition and mood	APATHY	10002942
Impaired attention, cognition and mood	ASOCIAL BEHAVIOUR	10003472
Impaired attention, cognition and mood	ASTHENIA	10003549
Impaired attention, cognition and mood	BLUNTED AFFECT	10005885
Impaired attention, cognition and mood	COMPULSIONS	10010219
Impaired attention, cognition and mood	COORDINATION ABNORMAL	10010947
Impaired attention, cognition and mood	CRYING	10011469
Impaired attention, cognition and mood	DEPRESSED LEVEL OF CONSCIOUSNESS	10012373
Impaired attention, cognition and mood	DISTURBANCE IN ATTENTION	10013496
Impaired attention, cognition and mood	DYSARTHRIA	10013887
Impaired attention, cognition and mood	DYSPHORIA	10013954
Impaired attention, cognition and mood	EMOTIONAL DISORDER	10014551
Impaired attention, cognition and mood	EMOTIONAL POVERTY	10014557
Impaired attention, cognition and mood	FATIGUE	10016256
Impaired attention, cognition and mood	FEELING OF DESPAIR	10016344
Impaired attention, cognition and mood	FLAT AFFECT	10016759
Impaired attention, cognition and mood	MEMORY IMPAIRMENT	10027175
Impaired attention, cognition and mood	MENTAL DISABILITY	10027353
Impaired attention, cognition and mood	MENTAL IMPAIRMENT	10027374
Impaired attention, cognition and mood	MOANING	10027783
Impaired attention, cognition and mood	MOOD ALTERED	10027940
Impaired attention, cognition and mood	PREMENSTRUAL SYNDROME	10036618
Impaired attention, cognition and mood	PSYCHOMOTOR RETARDATION	10037213
Impaired attention, cognition and mood	RETROGRADE AMNESIA	10038965
Impaired attention, cognition and mood	SEDATION	10039897
Impaired attention, cognition and mood	SOMNOLENCE	10041349
Impaired attention, cognition and mood	STUPOR	10042264
Impaired attention, cognition and mood	TRANSIENT GLOBAL AMNESIA	10044380
Impaired attention, cognition and mood	MENTAL STATUS CHANGES	10048294
Impaired attention, cognition and mood	EMOTIONAL DISTRESS	10049119
Impaired attention, cognition and mood	PSYCHOMOTOR SKILLS IMPAIRED	10049215
Impaired attention, cognition and mood	IMPAIRED DRIVING ABILITY	10049564
Impaired attention, cognition and mood	BALANCE DISORDER	10049848
Impaired attention, cognition and mood	BRADYPHRENIA	10050012

Impaired attention, cognition and mood	CONSCIOUSNESS FLUCTUATING	10050093
Impaired attention, cognition and mood	PREMENSTRUAL DYSPHORIC DISORDER	10051537
Impaired attention, cognition and mood	ALTERED VISUAL DEPTH PERCEPTION	10053549
Impaired attention, cognition and mood	AFFECT LABILITY	10054196
Impaired attention, cognition and mood	DYSLOGIA	10054940
Impaired attention, cognition and mood	COGNITIVE DISORDER	10057668
Impaired attention, cognition and mood	MENTAL DISORDER	10061284
Impaired attention, cognition and mood	AMNESTIC DISORDER	10061423
Impaired attention, cognition and mood	ABNORMAL SLEEP-RELATED EVENT	10061613
Impaired attention, cognition and mood	EXECUTIVE DYSFUNCTION	10070246
Impaired attention, cognition and mood	IMPAIRED REASONING	10071176
Impaired attention, cognition and mood	SLOW SPEECH	10071299
Impaired attention, cognition and mood	NEUROLEPTIC-INDUCED DEFICIT SYNDROME	10075295
Impaired attention, cognition and mood	ALEXITHYMIA	10077719
Other abuse-related terms	ACCIDENTAL POISONING	10000383
Other abuse-related terms	ALCOHOL ABUSE	10001584
Other abuse-related terms	ALCOHOL PROBLEM	10001606
Other abuse-related terms	ALCOHOLIC HANGOVER	10001623
Other abuse-related terms	ALCOHOLISM	10001639
Other abuse-related terms	ATAXIA	10003591
Other abuse-related terms	COMPLETED SUICIDE	10010144
Other abuse-related terms	HANGOVER	10019133
Other abuse-related terms	HEADACHE	10019211
Other abuse-related terms	INCREASED APPETITE	10021654
Other abuse-related terms	INTENTIONAL SELF-INJURY	10022524
Other abuse-related terms	MIOSIS	10027646
Other abuse-related terms	MUSCLE RIGIDITY	10028330
Other abuse-related terms	MYDRIASIS	10028521
Other abuse-related terms	NASAL NECROSIS	10028747
Other abuse-related terms	NASAL SEPTUM PERFORATION	10028765
Other abuse-related terms	NASAL SEPTUM ULCERATION	10028766
Other abuse-related terms	PARAESTHESIA	10033775
Other abuse-related terms	SUICIDAL IDEATION	10042458
Other abuse-related terms	SUICIDE ATTEMPT	10042464
Other abuse-related terms	TOBACCO ABUSE	10043903
Other abuse-related terms	TREATMENT NONCOMPLIANCE	10049414
Other abuse-related terms	PRESCRIBED OVERDOSE	10051076
Other abuse-related terms	SELF-INJURIOUS IDEATION	10051154
Other abuse-related terms	URINE AMPHETAMINE POSITIVE	10051400
Other abuse-related terms	ALCOHOL WITHDRAWAL SYNDROME	10053164
Other abuse-related terms	ANALGESIC THERAPY	10053469
Other abuse-related terms	ANTITUSSIVE THERAPY	10055120

Other abuse-related terms	NICOTINE DEPENDENCE	10057852
Other abuse-related terms	MUSCLE RELAXANT THERAPY	10058909
Other abuse-related terms	TOBACCO WITHDRAWAL SYMPTOMS	10059612
Other abuse-related terms	URINE AMPHETAMINE	10059955
Other abuse-related terms	POISONING	10061355
Other abuse-related terms	DECREASED APPETITE	10061428
Other abuse-related terms	AMPHETAMINES	10063227
Other abuse-related terms	AMPHETAMINES POSITIVE	10063228
Other abuse-related terms	ACCIDENTAL DEATH	10063746
Other abuse-related terms	SUICIDAL BEHAVIOUR	10065604
Other abuse-related terms	ANXIOLYTIC THERAPY	10066478
Other abuse-related terms	PRODUCT TAMPERING	10069330
Other abuse-related terms	PRODUCT USED FOR UNKNOWN INDICATION	10070592
Other abuse-related terms	BINGE DRINKING	10071238
Other abuse-related terms	BENZODIAZEPINE DRUG LEVEL	10072337
Other abuse-related terms	DOPAMINERGIC DRUG THERAPY	10072385

Appendix 3. Onset/Duration of Plots (Mock Plots)

Onset/Duration of Plots (Mock Plots)