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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LML134

CLML134X2201

A randomized, subject and investigator-blinded, placebo controlled, cross-over, multi-center Proof of Concept (PoC) study to assess the wakefulness promoting effect, safety, tolerability, and pharmacokinetics of LML134 in shift work disorder (SWD) patients

Statistical Analysis Plan (SAP) Amendment V02

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CLML134X2201".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

A study protocol (v04) is available at the time of finalization of Statistical Analysis Plan.

1.3 Study objectives

1.3.1. Primary objective(s)

Primary objective(s)	*Endpoints related to primary objectives*
• To demonstrate that wakefulness in SWD patients is significantly increased after treatment with LML134 compared to placebo	• Average sleep latency over two consecutive test nights as measured by the MSLT

1.3.2. Secondary objective(s)

Secondary objective(s)	*Endpoints related to secondary objective(s)*
• To assess the safety and tolerability of LML134 compared to placebo in SWD patients	• Standard safety assessments such as vital signs, ECG, hematology, blood chemistry, urinalysis, AE reporting, and daytime PSG to assess drug effect on sleep
• To assess the plasma pharmacokinetics of LML134 in SWD patients	• Due to sparse sampling, only plasma concentrations will be listed and no PK parameter will be evaluated by noncompartmental analysis. The data will be part of the overall Population PK model
• To evaluate the time course of LML134 effect on wakefulness compared to placebo	• MSLT at each time point averaged over two consecutive test nights

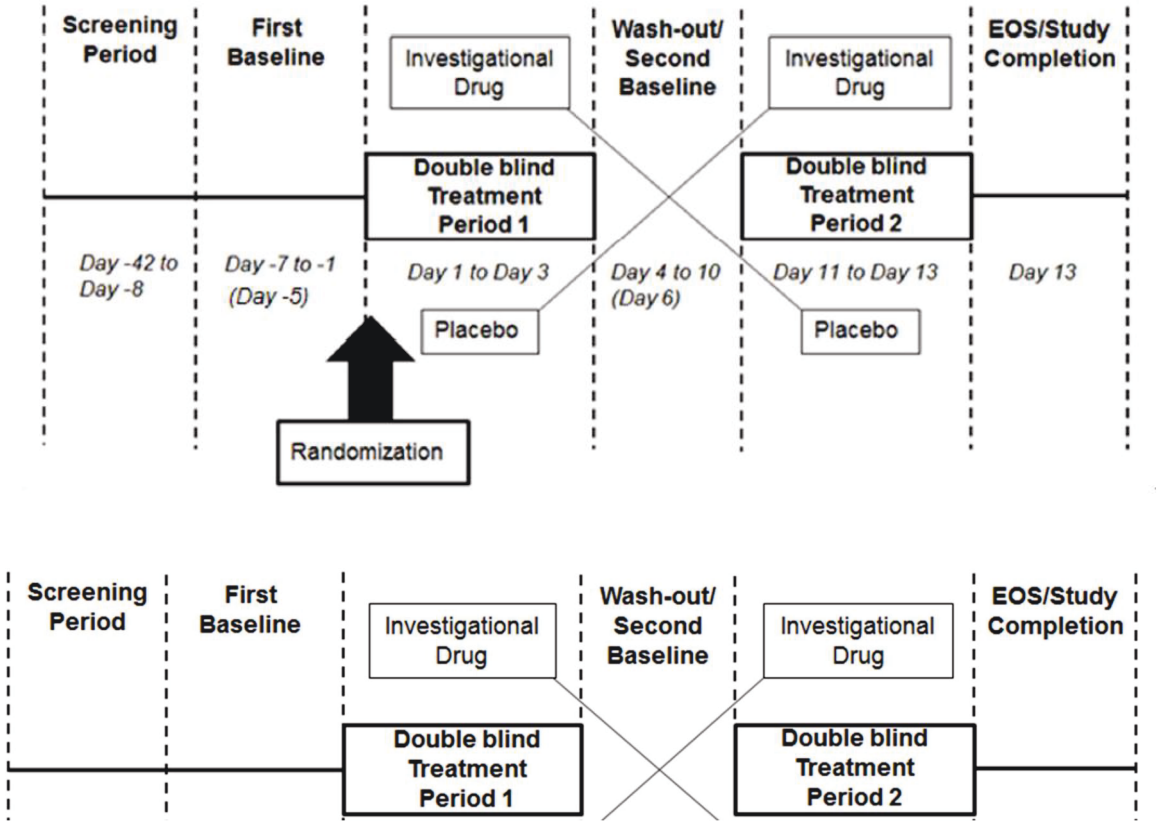
1.4 Study design and treatment

This is a randomized, subject and investigator-blinded, placebo controlled, crossover, multi-center Proof of Concept (PoC) study with in-house simulated laboratory night shifts in patients with SWD.

This non-confirmatory study will include two treatment arms: LML134 and placebo. The study will utilize a 2x2 crossover design, with two treatment periods and two sequences as shown in Figure 1-1 whereas assessment details are shown in Figure 1-2.

Approximately 46 subjects were planned to be randomized in this study (to achieve 36 completers). All subjects will receive both treatments (LML134 and placebo), one in each treatment period, with the order of treatment being randomized. The study is prematurely terminated based on business decision after 18 completers.

Figure 1-1 Study Design



2 First interpretable results (FIR)

No first interpretable result (FIR) is planned for this study. All the results will be represented in clinical study report (CSR).

4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analysed according to the actual study treatment(s) received. This is due to fact that it is known that a few subjects has been mis-randomized to a different treatment group as compared to the planned list of randomization. In order to make use of full data , all analysis will be performed on actual treatment group received by subject instead of a planned one.

The full analysis set will include all subjects that received any study drug and had any post-baseline assessment.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

For subjects for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

For subjects for which the actual sequence of treatments received does not match the randomized sequence of treatments, the actual sequence will be used for analysis involving a sequence component (e.g. ANOVAs with a sequence effect) if the actual sequence is one of the sequences planned in the study design. If the actual sequence is not one of the sequences planned in the study design, the randomized sequence will be used for analysis involving a sequence component but data points from periods in which the subject has not received the randomized treatment will be excluded from the analysis.

Types of analysis/endpoints	**Analysis set to be used**
Demographics and baseline characteristics	Full analysis set
Analysis of safety data	Safety set
Analysis of PK data	PK set

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

All subjects within the PK analysis set will be included in the PK data analysis.

5.1 Variables

LML134 plasma concentration will be the PK variable of interest for this study. Conventional PK parameters will not be calculated by noncompartmental analysis due to the limited sampling schedule. The data will be part of the overall Population PK model.

5.2 Descriptive analyses

LML134 plasma concentration data will be listed by treatment, subject, and sampling time point. Descriptive summary statistics will be provided by treatment and sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum, and the frequency (n, %) of concentrations below the LLOQ. Concentrations below LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

Graphical methods will be employed to show mean and individual concentration-time profiles. For the plots, time will be defined as the hours post first-dose within each period.

6 Statistical methods for Pharmacodynamic (PD) parameters

All subjects within the full analysis set will be included in the PD data analysis.

6.1 Primary objective

The primary objective of this study is to demonstrate that wakefulness in shift work disorder (SWD) patients is significantly increased after treatment with LML134 compared to placebo.

6.1.1 Variables

The mean of multiple sleep latency test (MSLT) scores is the primary variable of this study.

Each subject will undergo a sleep latency test assessment at each period, at approximately 1:30, 3:30, 5:30 and 7:30 in Day 2 (Night 1) and Day 3 (Night 2) during Treatment Period 1 and same time points in Days 12 and 13 in Treatment Period 2. In total, a subject will have 8 sleep latency test assessments in each treatment period. The mean value of all the sleep latencies from a subject within a period will be defined as mean sleep latency score for that subject for that period.

No change from baseline comparison will be used as no baseline is collected due to the short duration of the study.

6.1.2 Descriptive analyses

The primary variable will be listed by treatment sequence, patient and period, and descriptive statistics will be provided by treatment. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum.

Boxplots will be employed to present the MSLT results by treatment.

6.1.3 Statistical model, assumptions and hypotheses

MSLT from both periods will be included in the analysis.

Due to high variability and time difference between screening MSLT and post treatment records, screening MSLT will not be used as a covariate for modelling . Total sleep time from sleep diary data during baseline will be used as baseline covariate. Therefore both smoking status (nicotine intake) and total sleep time at baseline will be considered as covariates in the model.
The primary variable, mean MSLT of a subject within a period, will be analyzed using a mixed effect analysis of variance model. This model will have the mean MSLT as the dependent variable; treatment, actual treatment sequence, smoking status at screening, total sleep time at baseline, treatment interaction with total sleep time at baseline and smoking status and period as fixed effects and a subject level random intercept. Primary analysis will be assessed over full analysis set.

Least square estimates for each treatment (LML134 and placebo) and treatment difference (LML134 vs placebo) along with 95% confidence interval will be reported.

The following assessments will be performed to judge efficacy of LML134:

1. Statistical significance: One sided (superiority) p-value of LML134 vs placebo from above fitted ANOVA model will be reported.

A p-value <0.1 will be considered as a positive sign for statistical significance.

2. Estimate of treatment difference (LML134 vs Placebo) will be reported.
   An estimate of treatment difference > 1 minute would be considered as significant.

6.1.3.1 Handling of missing values/censoring/discontinuations

If a subject has missing data at any time-point at night 1(/2), then the missing observation will be imputed as average of observed values from nearest neighbourhood of that day.

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If all observations at a night are missing the values from other night will be used for MSLT evaluation.

6.1.3.2 Sensitivity analyses

Mean of multiple sleep latency test (MSLT) score is essentially a positive outcome. Thus, a supportive analysis will be performed using log transformed mean sleep latency scores. Log transformed mean sleep latency score data will be analysed using a mixed effect ANOVA model with treatment, actual treatment sequence, smoking status at screening, total sleep time at baseline treatment interaction with total sleep time at baseline and smoking status and period as fixed effects and subject as a random effect. Geometric means of each treatment and their ratio (LML134 vs placebo) along with 95% confidence intervals will be estimated using least square means by back transforming to the original scale.

A supportive analysis with may be performed with additional covariates (total sleep time on actigraphy during baseline, key PSG parameters at screening/baseline) that may potentially affect individual mean MSLT data.

6.1.3.3 Supportive Analysis

Primary analysis as mentioned in section 6.1.3 may be performed in a bayesian platform with non-informative priors for both LML and placebo. Corporate Confidential Information

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6.2 Secondary objectives

6.2.1 Variables

The secondary variable is MSLT at each time point (1:30, 3:30, 5:30 and 7:30) separately, averaged over two consecutive test nights.

6.2.2 Descriptive analyses

MSLT

The secondary variable will be listed by treatment sequence, patient, period and time, and descriptive statistics will be provided, by treatment and time. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum.

An arithmetic mean +/- SD time profile (time-points: 1:30 AM, 3:30 AM, 5:30 AM, and 7:30 AM) plot will be provided for each treatment.

6.2.3 Statistical model, assumptions and hypotheses

MSLT

A mixed model repeated measure (MMRM) analysis of variance model, will be performed over mean sleep latency test (MSLT) scores with treatment, actual treatment sequence, period, time-point, and treatment*time-point as fixed effects. A saturated covariance structure will be used for observations coming from same subject. If an unstructured covariance cannot be fitted simpler covariance structures will be examined.

The overall treatment effect for LML134 vs placebo will be reported along with a 95% CI.

A line graph of means of MSLT with 95% CI over time may be provided .

A supportive analysis with may be performed with additional covariates (total sleep time on actigraphy during baseline, key PSG parameters at baseline/screening) that may potentially affect individual mean MSLT data.

6.2.3.1 Handling of missing values/censoring/discontinuations

Please refer section 6.1.3.1 .

7 Statistical methods for safety and tolerability data

All analysis will be performed under safety analysis set.

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, AE and polysomnography (PSG) as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment and subject. Summary statistics will be provided for all subjects, as well as for each treatment.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment and subject.

Treatment

Data for study drug administration and concomitant therapies will be listed by treatment and subject.

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and time.

Summary statistics of height, weight, temperature, blood pressure, and pulse rate will be provided by treatment and time using statistics like N, mean, median, standard deviation, and range.

ECG evaluations

All ECG data will be listed by treatment, subject and time, abnormalities will be flagged. Summary statistics will be provided by treatment and time.

Each ECG parameter will be summarized by treatment, time using statistics like N, mean, median, standard deviation, and range.
The same data will be plotted using arithmetic mean-SD graphs over time for each parameter separately. Separate lines will be drawn for each treatment in order to see any potential differences. Reference lines will be drawn for normal ranges (if available).

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment.

Separate tables will be presented indicating event severity and study drug relationship.

An adverse event starting in one period and continuing into the next period is counted only in the onset period. A subject with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

Polysomnography

Polysomnography data will be listed by treatment, subject and time. Summary statistics will be provided by treatment and time.

Other safety evaluations

Columbia suicide severity rating, alcohol test, drug test, cotinine test, pregnancy and assessment of fertility data will be listed by treatment and time.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter, PSG) will be created.

ECG and vital signs data will also be plotted using arithmetic mean-SD graphs over time for each parameter separately. Separate lines will be drawn for each treatment in order to see any potential differences