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Biostatistics & Statistical Programming /
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LJN452

CLJN452X2202

A double blind, randomized placebo controlled crossover multiple dose study of LJN452 to assess safety, tolerability and efficacy in patients with primary bile acid diarrhea (pBAD)

Statistical Analysis Plan (SAP)

Personal Data

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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 CLJN452X2202.

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

1.2 Study reference documentation

This SAP has been developed using Clinical Trial Protocol version v02 (incorporating Amendment 2) approved by the SRC on 09 August 2016.

1.3 Study objectives

1.3.1 Primary objectives

- To determine the safety and tolerability of LJN452 in patients with primary bile acid diarrhea (pBAD)
- To assess the effect of LJN452 on clinical symptoms experienced by patients with pBAD

1.3.2 Secondary objectives

- To assess the pharmacokinetics of LJN452 in pBAD patients
- To assess the effect of LJN452 on use of rescue medications during the study period

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1.4 Study design and treatment

This is a multi-center, double blind (patient and investigator blind, sponsor open label), randomized placebo controlled, crossover study to assess safety, tolerability and efficacy of LJN452 in patients with pBAD. In this study approximately 30 patients will be enrolled to have 24 completers.

This is a non-confirmatory trial.

Figure 1-1 Study design
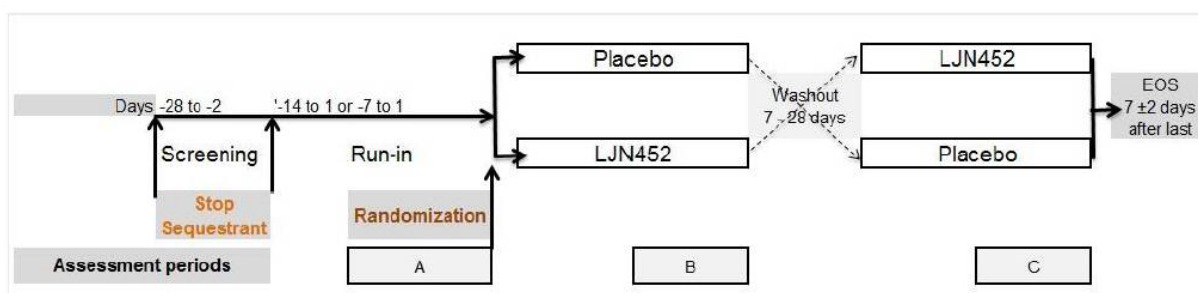
In treatment period 1 on Day 1 patients will receive either 60 μg LJN452 or placebo orally once daily for 14 days in a 1:1 ratio. Pharmacokinetic (PK), pharmacodynamic (PD) and safety samples will be collected on Day 1 for up to 8 hours post dose and on Day 2 pre-dose, which corresponds to 24 h after Day 1 dosing.

Patients will be handed over trial medication, to be administered at home enough to cover dosing for 14 days in each period. Throughout the 14 days of the treatment period, patients will be directed to take study drug at home with water in the morning in a fasting state, 2 hours prior to the first meal of the day, preferably at the same time of the day.

After 2 weeks of treatment with LJN452 or placebo, patients will undergo a washout of at least 7 days, up to a maximum of 28 days. At the end of the washout period, patients will return to the study site for period 2 of the study. Period 2 will be identical to period 1 except that the treatments will be crossed over.

The randomization will be maintained at a 1:1 ratio over the entire study in order to avoid any sequence bias.

2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

The study FIR template (mock slides) can be found in CREDI in the study RAP folder.

The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be highlighted in TFL shells document and marked as "Key" in the Programming Deliverables Tracker (PDT) output list.

3   Interim analyses

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4   Statistical methods: Analysis sets

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

For patients 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 patient has not received the randomized treatment will be excluded from the analysis.

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

The PK analysis set will include all patients with available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set will include all patients with available PD data and no protocol deviations with relevant impact on PD data.

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
Patients are excluded from all *(safety)* analysis in case of these PDs:		Exclude patient completely from all analysis sets
I01	ICF not obtained	Yes
S01	Subject did not receive any study drug	Yes

Category Deviation code	Text description of deviation	Data exclusion
Patients are excluded from PK analysis in case of these PDs:		Exclude patient from PK analysis set
S01	Subject did not receive any study drug	Yes
I01	ICF not obtained	Yes
Patients are excluded from PD analysis in case of these PDs:		Exclude patient from PD analysis set
S01	Subject did not receive any study drug	Yes
I01	ICF not obtained	Yes
Patients are excluded from PK and PD analysis in case of these PDs:		Exclude patient from PK and PD analysis sets
S01	Subject did not receive any study drug	Yes
I01	ICF not obtained	Yes

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

5.1 Variables

The following and other appropriate pharmacokinetic parameters may be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.3 or higher): AUClast, AUCtau, Cmax, Cmin, Cav,ss, Tmax, CL/F, Racc (accumulation ratio = AUCtau,ss/AUCtau,day 1).

5.2 Descriptive analyses

LJN452 concentration data will be listed by patient and visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point.

Pharmacokinetic parameters will be calculated as described in Section 5.1 of the protocol and will be listed by patient and visit. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

5.2.1 Graphical presentation of results

Arithmetic mean (SD) and geometric mean (95% CI) plasma concentration data will be plotted across time.

Overlaying individual plasma concentration-time profiles will be generated.

Individual plasma concentration-time profiles will be generated.

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6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

To assess the effect of LJN452 on clinical symptoms experienced by patients with pBAD.

6.1.1 Variables

The primary analysis variables are: a) stool frequency, b) and stool form assessed by the Bristol stool chart.

6.1.2 Descriptive analyses

Summary statistics (including median and IQR) of the stool frequency and average stool form (weekly and biweekly) for each treatment as well as the difference and % change between the 2 treatments will be provided by visit. Baseline data will be summarized by treatment and visit. The number and percentage of patients with each stool form will be provided by treatment and visit. The stool frequency and stool form data will be listed by treatment sequence, patient and visit.

6.1.3 Statistical model, assumptions and hypotheses

A repeated measures analysis will be done for the two-dimensional endpoint: weekly stool frequency and the corresponding average stool form. The analysis will include fixed effects for sequence (Drug/Placebo or Placebo/Drug), Treatment (Week 1 drug, Week 2 drug, Week 1 placebo or Week 2 Placebo), and period (1 or 2). The model will assume an arbitrary 2 by 2 covariance matrix for the two-dimensional endpoint (frequency, form) and a compound symmetry covariance matrix for each individual end point. Point estimates of the weekly & biweekly treatment effect on stool frequency and the corresponding average stool form will be reported together with 95% simultaneous confidence intervals (confidence ellipsoids).

6.1.3.1 Handling of missing values/censoring/discontinuations

Missing values will be assumed missing at random. No imputation of missing values will be done for any analyses.

6.1.3.2 Graphical presentation of results

Boxplots to visualize treatment differences in stool frequency and stool form will be created.

6.1.3.3 Supportive analysis

Baseline weekly stool frequency and the corresponding average stool form will be analyzed using the same method as described in Section 6.1.3 to assess unequal carryover effects.

The number and percentage of subjects using loperamide will be tabulated by treatment. Total weekly loperamide use (in mg) will be summarized by treatment and visit (including baseline). The stool index, calculated as [weekly stool frequency*mean stool form]+loperamide use [weekly mg*3], will also be summarized and analyzed using a linear mixed effects model including sequence, period and treatment as fixed effects and subject nested within sequence as a random effect.

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7 Statistical methods for safety and tolerability data

7.1 Primary objective
To determine the safety and tolerability of LJN452 in patients with pBAD.

7.1.1 Variables

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

7.1.2   Descriptive analyses

Patient demographics and other baseline characteristics

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

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

Treatment

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

Vital signs

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

ECG evaluations

All ECG data will be listed by treatment sequence, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment sequence, patient, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a patient with any abnormal values. Summary statistics will be provided by treatment and visit/time. Baselines will be the last available measurement in each treatment period post washout and prior to dosing.

Log-transformed lipid (total Cholesterol, LDL, HDL, triglycerides) and LFT (GGT, ALP, AST, ALT) data will be analyzed using a mixed effects model including sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect.

Adverse events

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

The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A patient with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

7.1.3   Graphical presentation

Boxplots to visualize trends in longitudinal safety data (lab parameters) will be created.