NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LHW090

Study CLHW090X2202

A randomized, sponsor open, site and subject double blind, parallel group, placebo-controlled study to evaluate the safety and efficacy of LHW090 after 4 weeks treatment in patients with resistant hypertension

Statistical Analysis Plan (SAP)

Author(s): Personal Data

Document type: Statistical Analysis Plan: Detailed Statistical Methodology

Document status: Final Amendment 3

Corporate Confidential Information

Table of contents

List of tables

1 Introduction to RAP documentation

1.1 Scope

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CLHW090X2202".***

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

2 Study objectives and design

2.1 Study objectives

2.1.1 Primary objectives

- To assess the safety and tolerability of LHW090 for 4 weeks on a background of conventional anti-hypertensive medications in patients with resistant hypertension.
- To evaluate the effect of LHW090 on placebo-adjusted mean daytime systolic blood pressure (SBP) after 4 weeks in patients with resistant hypertension.

2.1.2 Secondary objective

- To evaluate the pharmacokinetics (PK) of LHW090 and its active metabolite LHV527 in patients with resistant hypertension.

2.1.3 Exploratory objectives

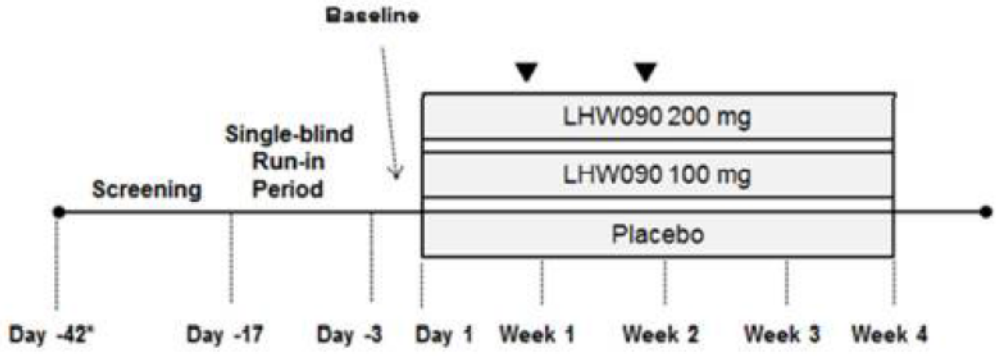
2.2 Study design and treatment

This is a non-confirmatory, randomized, sponsor open, site and subject blind, parallel group, placebo-controlled study to evaluate the safety and efficacy of 4 weeks once daily treatment with LHW090 in patients with resistant hypertension. Patients with uncontrolled hypertension as defined as a mean daytime systolic blood pressure ≥ 135 mmHg by ambulatory blood pressure monitoring (ABPM) on a stable (at least 2 months) regimen of an angiotensin receptor blocker (ARB) plus a thiazide diuretic plus at least one of the following commonly used classes of anti-hypertensive medications—beta-blockers or calcium channel blockers—will be considered for this trial. Patients with resistant hypertension will be randomized to

either placebo or 1 of 2 dose regimens of LHW090, i.e. LHW090 100 mg once daily or LHW090 200 mg once daily, as an add-on to their anti-hypertensive regimen at baseline.

Each patient will participate in an up to 3 week screening period, a 2-week single blind placebo run-in period, baseline assessments, a 4 week treatment period, and an end of study assessment as demonstrated in Figure 2-1. During the 2 week placebo run-in period, patients will receive regular reminders by the site to be compliant with their anti-hypertensive medications. At the end of this run-in period, patients who demonstrate ≥ 80% compliance with placebo will be randomized. Compliance will be established by pill count and review of medication diary. Patients will be advised that study entry cannot be fully determined until the completion of the run-in period.

Figure 2-1 Study design



Approximately a total of 80 patients to be randomized in the study: Placebo (n~40), LHW090 100 mg (n~20), LHW090 200 mg (n~20)

*Up to 25 days allowed for screening, but patient may proceed to run-in phase at any time once all screening requirements have been met

▼Interim analysis

3 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 the TFL shells document and marked as "Key" in the Tracking sheet output list.

4 Interim analyses

5 Statistical methods: Analysis sets

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

All subjects that were randomized will be included in the safety analysis set.

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 experienced no protocol deviations with relevant impact on PK data.

The primary PD analysis set will include all subjects that received any study drug, with any available post-dose PD data.

The secondary PD analysis set will include all subjects that received any study drug, with any available post-dose PD data and experienced no protocol deviations with relevant impact on PD data.

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

Table 5-1 Protocol deviation severity codes and analysis sets

Protocol deviation severity code		Safety analysis set	PK analysis set	PD analysis set	Secondary PD analysis set
Code	Text				
5	Exclude subject from all safety analysis	-	-	-	-
8	*Exclude from all analyses*	-	-	-	-
20	Exclude subject from PK analysis set	+	-	+	+
22	Exclude subject from PD analysis set	+	+	-	-
23	Exclude subject from PK and PD analysis set	+	-	-	-
49	Report relevant protocol deviation – include subject in all analysis sets	+	+	+	+

+ = include in analysis set, - = exclude from analysis set, NA = not applicable

6 Statistical methods for Pharmacokinetic (PK) parameters

6.1 Variables

Corporate Confidential Information

6.2 Descriptive analyses

Corporate Confidential Information

6.3 Graphical presentation of results

6.4 Pharmacokinetic / pharmacodynamics interactions

The relationship between PK and key PD parameters may be explored using a graphical approach. Descriptive statistics may be provided.

7 Statistical methods for Pharmacodynamic (PD) parameters

7.1 Analysis of the primary variables

The first primary variables are adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals and laboratory measurements.

The second primary variable will be the change in the 12 hour average of SBP measured by ABPM 28 days following the start of treatment.

7.1.1 Variable

The primary safety variables are defined in Section 8, below.

The primary efficacy variable is defined as the 12 hour daytime average SBP on day 28 minus the 12 hour daytime average SBP on day -1.

7.1.2 Descriptive analyses

The descriptive analyses of the safety variables are shown in the safety analyses in Section 8.

Summary statistics of the ABPM data and change from baseline data will be provided by treatment and visit/time.

7.1.3 Statistical model, assumptions and hypotheses

Analyses of the safety data will be descriptive, as shown in Section 8.

Corporate Confidential Information

7.1.4 Handling of missing values/censoring/discontinuations

Missing data will not be imputed. The longitudinal repeated measures mixed model analysis method allows missing values.

7.1.5 Supportive analyses

Corporate Confidential Information

7.1.6 Graphical presentation of results

Arithmetic mean (SD) ABPM data will be plotted across time.

7.2 Analysis of the exploratory efficacy variables

Corporate Confidential Information

8 Statistical methods for safety and tolerability data

8.1.1 Variables

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

8.1.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics (mean, standard deviation, minimum, median and maximum) will be provided by treatment group

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

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject. The number and percentage of subjects completing treatment for each treatment group and cohort will be tabulated. For those not completing treatment, the reason for discontinuation will be listed by treatment group 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 visit/time.

ECG evaluations

All ECG data will be listed by treatment, subject 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, subject, and visit/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 visit/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. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment. The number and percentage of subjects with adverse events by maximum severity of adverse event will be tabulated by body system and preferred term with a breakdown by treatment.

Columbia-Suicide Severity Rating Scale (C-SSRS)

All C-SSRS results will be listed by subject and visit/time.

8.1.3 Graphical presentation of results

Corporate Confidential Information

9 Statistical methods for Biomarker data

Corporate Confidential Information

Corporate Confidential Information