NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LHW090X

CLHW090X2102

A two part randomized, double-blind, parallel-group, placebo-controlled study to evaluate the renal safety, tolerability and pharmacokinetics of LHW090 in patients with moderately impaired renal function on angiotensin receptor blockers

Statistical Analysis Plan (SAP)

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Amendment 3

Personal Data

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1 Introduction

1.1 Scope of document

The SAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CLHW090X2102".***

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

1.2 Study reference documentation

Protocol Version v04 is referred for the current SAP.

1.3 Study objectives

Primary objective(s)

Primary objective(s)	*Endpoints related to primary objective(s)*
• **Part 1:** To assess the safety and tolerability of doses of LHW090 in patients with moderate renal impairment to inform design of Part 2. • **Part 2:** To assess the renal safety of LHW090 in patients with moderate renal impairment.	• **Part 1:** Safety endpoints (including adverse events and serious adverse events) up to and including the EOS; plasma pharmacokinetic parameters, and serum creatinine • **Part 2:** Proportion of patients who develop a renal event as defined by a ≥0.3 mg/dL increase in serum creatinine from baseline

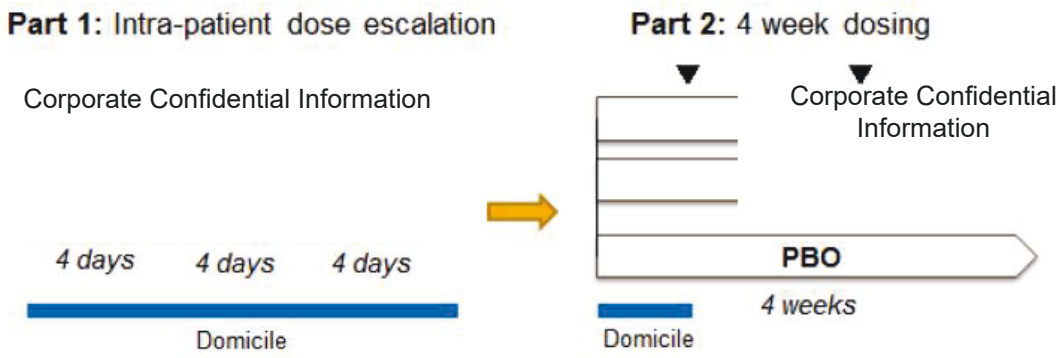
Secondary objective(s)

Secondary objective(s)	*Endpoints related to secondary objective(s)*
• **All Parts:** To evaluate the pharmacokinetics of LHW090 and its active metabolite, LHV527, in patients with moderate renal impairment.	• Plasma pharmacokinetic parameters (Cmax, Tmax, AUC)
• **All Parts:** To assess the safety and tolerability of LHW090 relative to placebo in patients with moderate renal impairment.	• Safety endpoints (including adverse events and serious adverse events) up to and including the EOS

1.4 Study design and treatment

The study purpose is to determine whether LHW090 displays the clinical safety profile to support further development in patients with moderately impaired renal function.

This is a randomized, double-blind, parallel group, placebo-controlled study, in two sequential parts to evaluate the renal safety, tolerability and pharmacokinetics of LHW090 in patients with moderately impaired renal function. Patients aged 40 to 85 (inclusive) with an estimated glomerular filtration rate (eGFR) between 30 and 59 mL/min/1.73m^2 at screening (inclusive) on a stable dose of an angiotensin receptor blocker (ARB) will be considered for this study.



Part 1 will be enrolled as a cohort of 12 subjects (2:1 LHW090 and placebo). Patients will be domiciled from Day -2 to Day 14.

Corporate Confidential Information

Part 2 First 16 patients will be domiciled for 1 week, from day -2 to Day 7. Rest of the dosing will be done off site. Part 2 will enroll n=72 patients randomized 3:3:2 to LHW090 and placebo.

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The study will be conducted in two parts. Part 1 will enroll a single cohort of 12 patients who will be randomized in a 2:1 ratio of LHW090 to placebo. An intra-patient dose escalation scheme will be employed starting at a once daily dose for the first four day cycle, and then the dose will be escalated once daily for the next four days and then once daily for four days. If a renal event occurs during the treatment periods of the study or any of the individual stopping criteria are met, then dosing will be stopped for that individual patient. For the purposes of this study, a renal event will be defined as a reproducible increase from baseline serum creatinine of ≥ 0.3 mg/dL confirmed on a repeat measurement within 24-48 hours (Mehta et al 2007, Khwaja 2012). Throughout the study, any serum creatinine assessment that is increased ≥0.3 mg/dL compared to baseline will trigger a repeat assessment of serum creatinine after 24 hours to confirm whether criterion for a renal event is met.

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Part 2 will be double-blind and placebo-controlled to assess the safety and tolerability of 2 dose levels of LHW090, once daily for 4 weeks. Approximately 72 patients will be enrolled in Part 2 and randomized in a 3:3:2 ratio to LHW090 and placebo. Therefore, in Part 2, approximately 27 patients are expected to be randomized to each of the active doses, and 18 patients are expected to be randomized to placebo. Randomization will be stratified by ARB dose (see Protocol) at the time of enrollment. Patients who meet the eligibility criteria at screening will have baseline assessments of renal function collected on Day -1 prior to beginning the treatment phase on Day 1. Centrally-analyzed laboratory assessments performed at screening will be used to determine patient eligibility for the trial.

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The first 16 patients in Part 2 will be domiciled for the first 7 days of dosing to ensure careful monitoring of renal function and pharmacokinetic parameters. On Day 7 at the investigator's discretion, the patients will be released to complete the remaining 3 weeks of the treatment phase

2 First interpretable results (FIR)

FIR contains the key outputs

4 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 received study drug and with no protocol deviations with relevant impact on safety 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 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 all *(safety, PK, PD)* analysis in case of these PDs:		
INC01	Written informed consent was not obtained prior to performing study assessment.	Excluded from safety, PK, PD analysis set
TRT03	Subject did not receive any dose of study treatment.	Excluded from Safety, PK and 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

5.1 Variables

PK parameters Cmax, Tmax, AUClast, AUC0-t, AUCtau and other relevant PK parameters will be considered.

5.2 Descriptive analyses

LHW090/LHV527 plasma concentration data will be listed by Part, treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. 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. The day 28, 24 h concentrations will not be included in these analyses since they were not actually collected in this study.

Pharmacokinetic parameters will be listed and summarized by part, treatment and subject. In order to calculate AUCtau, day 28, 24 h concentrations are to be set equal to the day 28, 0 h (predose) concentrations based on the assumption that steady-state had been achieved. Day 28, 24 h PK samples were not actually collected in this study.

Unbound PK concentration and PK parameter data will be listed and summarized for Part 1 as feasible.

5.3 Statistical model, assumptions and hypotheses

No formal statistical analyses will be performed for PK data.

5.3.1 Model checking procedures

Not applicable.

5.4 Graphical presentation of results

Individual PK profiles and Arithmetic (SD) profile will be provided by part and treatment.

7 Statistical methods for safety and tolerability data

7.1 Variables

The primary safety variable will be the proportion of patients who develop a renal event.
The two parts of the study will be analyzed separately. A renal event is defined as a reproducible increase in serum creatinine of ≥0.3 mg/dL from baseline confirmed on a repeat measurement within 24 to 48 hours.

Change from baseline for serum creatinine will be evaluated and categorized as <0.3 mg/dL and ≥0.3 mg/dL. The analysis will be based on central laboratory results. Baseline will be defined as the average of all available pre-dose measurements (excluding screening values).

7.2 Statistical model, assumptions and hypotheses

For Part 2, no inferential analysis of renal events will be conducted due to only having 1 subject that fulfilled the criteria. A frequency table will be produced instead.

Historical data from internal Novartis studies in a similar patient population may be used to supplement the information from patients on placebo in the current study.

For each part, change from baseline for serum creatinine data will be analyzed using a linear mixed effects model for repeated measurements. The model will include treatment as a fixed effect, visit as a repeated effect, treatment by visit interaction and baseline as a continuous covariate. An unstructured covariance model will be used. Point estimates and the associated 95% confidence intervals for the difference between treatment and placebo at each visit will be provided.

7.2.1 Model checking procedures

For the frequency table of the proportion of patients with a renal events, patients who complete at least 2 weeks of treatment will be included in the denominator.

7.3 Pharmacokinetic / Safety interactions

The relationship between PK and safety may be explored using a graphical approach. Scatter plot between PK concentration and safety at respective time points along with regression may be provided.

7.4 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by part, treatment group and subject. Summary statistics 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 part, treatment group and subject.

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by part, treatment group and subject.

Vital signs

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

ECG evaluations

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

Clinical laboratory evaluations

All laboratory data will be listed by part, treatment group, 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 part, treatment group, and visit/time. Change from baseline data will also be listed and summarized.

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.

7.5 Graphical presentation

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

Mean (SD) for Serum creatinine and change from baseline profiles will be provided.

9 Reference list

ARB dose (refer protocol).