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LHW090

Clinical Trial Protocol 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

Personal Data

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

Notification of serious adverse events

Refer to Section 9.2 of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and notify the Clinical Trial Leader.).

Contact information is listed in the Site Operations Manual.

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List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
ASL-MRI	arterial spin labeling magnetic resonance imaging
AST	aspartate aminotransferase
ANP	atrial natriuretic peptide
b.i.d.	twice a day
BMI	Body Mass Index
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CK	creatinine kinase
CKD	chronic kidney disease
CRF	Case Report/Record Form (paper or electronic)
CRI	chronic renal insufficiency
CRO	Contract Research Organization
CV	coefficient of variation
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FIH	first in human
GCP	Good Clinical Practice
hr	hour
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board

IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LLN	lower limit of normal
mg	milligram(s)
ml	milliliter(s)
o.d.	once a day
NEP	neprilysin
p.o.	oral
PA	posteroanterior
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
RBC	red blood cell(s)
RBF	renal blood flow
REB	Research Ethics Board
RHT	resistant hypertension
SAE	serious adverse event
SD	standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)

Pharmacokinetic definitions and symbols

AUC0-t	The area under the plasma concentration-time curve from time zero to time 't' where t is a defined time point after administration [ng x hr / mL]
AUClast	The area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration [ng x hr / mL]
AUCtau	The area under the plasma concentration-time curve from time zero to the end of the dosing interval tau [ng x hr / mL]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [ng / mL]
Tmax	The time to reach the maximum concentration after drug administration [hr]

Protocol synopsis

Protocol number	LHW090X2102
Title	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
Brief title	Study of the safety, tolerability, and pharmacokinetics of LHW090 in patients with moderately impaired renal function
Sponsor and Clinical Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	To determine whether LHW090 displays the clinical safety profile to support further development in patients with moderately impaired renal function.
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.
Secondary Objectives	**All Parts:** To evaluate the pharmacokinetics of LHW090 and its active metabolite, LHV527, in patients with moderate renal impairment. **All Parts:** To assess the safety and tolerability of LHW090 relative to placebo in patients with moderate renal impairment.
Study design	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.
Population	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.

Inclusion criteria	• Written informed consent must be obtained before any assessment is performed.
	• Male and female patients, age 40 to 85 years of age (inclusive) on a stable (at least 1 month) dose of an angiotensin receptor blocker (ARB) and stable moderately impaired renal function, defined here as an eGFR 30-59 mL/min/1.73m2 (inclusive) using the 4 variable MDRD Study equation for at least 3 months.
	• At screening, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the patient has rested for at least five minutes, and again after three minutes in the standing position. Sitting vital signs should be within the following ranges:
	  • oral body temperature between 35.0-37.5 °C
	  • systolic blood pressure, 100-170 mm Hg
	  • diastolic blood pressure, 50-100 mm Hg
	  • pulse rate, 50 - 95 bpm

	• Patients should be excluded if their standing vital signs (relative to sitting) show findings which, in the opinion of the Investigator, are associated with clinical manifestation of postural hypotension (i.e. absence of any other cause). The Investigator should carefully consider enrolling patients with either a > 20 mm Hg decrease in systolic or a >10 mm Hg decrease in diastolic blood pressure, accompanied by a > 20 bpm increase in heart-rate (comparing standing to sitting results). • Patients must weigh at least 50 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 40 kg/m2. BMI = Body weight (kg) / [Height (m)]2. • Able to communicate well with the investigator, to understand and comply with the requirements of the study.
Exclusion criteria	• History of angioedema, drug-related or otherwise, as reported by the patient. • Use of angiotensin converting enzyme inhibitors (ACE inhibitors), mineralocorticoid receptor antagonists (e.g. spironolactone or eplerenone), aliskiren, vasopressin receptor antagonists (e.g. tolvaptan), or oral alkalinizing agents (e.g. sodium and potassium citrate or Shohl's solution). Note: Patients who discontinue their ACE-inhibitor and substitute with an angiotensin receptor blocker (ARB) may be eligible to be re-screened provided their medication regimen has been stable for at least 1 month and their renal function has been stable for at least 3 months. Any substitutions or changes to a patient's medication regimen must be done under the guidance of the patient's treating physician. • History of a renal transplant. • Known current significant left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or significant severe valvular disease on prior or current echocardiogram. • A serum potassium ≤ 3.5 mmol/l or ≥ 5.5 mmol/l at screening. • A previous history or previously diagnosed kidney disorder which, in the opinion of the Investigator, may place the patient at higher risk from his/her participation in the study or is likely to confound the interpretation of the study results. Such kidney disorders may include renal cystic disease such as autosomal dominant polycystic kidney disease (history of an incidental asymptomatic acquired renal cyst(s) is excepted); obstructive uropathy; renal stone(s) in the past 2 years; chronic interstitial nephropathy; drug-induced nephropathy; residual renal insufficiency following an episode of acute kidney injury or acute tubular necrosis related to renal atheroembolic disease, septic shock or ischemic nephropathy; renal tubular acidosis requiring treatment; nephrotic syndrome or nephrotic range proteinuria; or renal artery stenosis. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant.
Investigational and reference therapy	• LHW090
Efficacy/PD assessments	• Not applicable

Safety assessments	• Vital signs • Hematology • Chemistry • Urinalysis Corporate Confidential Information • ECG evaluation • Physical exam • Columbia-Suicide Severity Rating Scale • AE/SAEs
Other assessments	• Pharmacokinetics Corporate Confidential Information
Data analysis	A sample size of 12 patients (2:1 active: placebo) will be considered for Part 1 to assess the safety and tolerability. A sample size of 72 patients (3:3:2 high dose:low dose:placebo) will be considered for Part 2 to assess the changes in serum creatinine. All data for vital signs, ECG evaluations, hematology, blood chemistry and urinalysis will be listed for each patient and summarized by descriptive statistics per part, treatment group, and for visit/ time interval where appropriate. Summary tables with the number, percentage, and severity of adverse events will be provided to assess safety and tolerability per part and treatment group. Proportion of patients change from baseline serum creatinine <0.3 mg/dL and ≥ 0.3 mg/dL will be evaluated and summarized. For Part 2, a Chi-square test will be performed to compare the proportion of patients who develop a renal event (a reproducible increase from baseline serum creatinine of ≥ 0.3 mg/dL confirmed on a repeat central laboratory measurement within 24-48 hours) in the LHW090 and placebo groups. For this endpoint, baseline is defined as the average of all available pre-dose measurements coming from central laboratory results. All PK data will be listed and summarized by part, treatment, and visit/timepoint.
Key words	Moderate renal impairment

1 Introduction

1.1 Background

The adequate and timely control of blood pressure in patients diagnosed with hypertension is an important public health goal. Hypertension is a major risk factor for heart disease, kidney disease and stroke. Despite the available medications that treat high blood pressure, hypertension remains uncontrolled in more than 50% of patients (Valderrama et al 2012). The phenomenon of resistant hypertension (RHT) was defined by JNC 7 in 2003 as blood pressure that was uncontrolled despite treatment with three or more anti-hypertensive agents, one of which is a diuretic (Chobanian et al 2003). More recently, the European Society for Cardiology (ESC) and the joint American Society of Hypertension and the International Society of Hypertension (ASH/ISH) have issued similar definitions (Mancia et al 2013; Weber et al 2014). Patients with RHT are more likely to display the sequelae of uncontrolled hypertension such as an enlarged heart or kidney damage. Depending on the population examined and the level of medical screening, it has been estimated that 5 to 30% of the hypertensive population may meet this definition (James et al 2014); however, the prevalence is likely to rise with aging of the population and the increasing incidence of diabetes, obesity, and chronic kidney disease.

The natriuretic peptide (NP) family mediates a wide-ranging number of potentially salutary effects on the heart, vasculature, kidney and other target tissues. The NP family is comprised of three structurally related peptide hormones-atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). ANP and BNP are primarily expressed in the heart and released by cardiomyocytes in response to mechanical stretch. Binding of natriuretic peptides to their receptors, NPR-A and NPR-B, activates a guanylate cyclase resulting in increased intracellular levels of cGMP. Physiologically, NPs have been shown to stimulate the excretion of sodium and water by the kidneys, induce relaxation of vascular smooth muscle cells, and have anti-fibrotic and anti-hypertrophic effects on the heart. ANP is largely degraded by a transmembrane endopeptidase called neprilysin (NEP) while a smaller fraction is removed from the circulation by binding to a clearance receptor, NPR-C. Studies suggest that circulating levels of ANP can be increased by inhibiting NEP. Thus, NEP inhibitors are a potential therapeutic target for the treatment of hypertension. Clinically, NEP inhibitors given in combination with an angiotensin receptor blocker (ARB) have been shown to reduce blood pressure in patients with essential hypertension (Bavishi et al 2015). NEP inhibition in combination with an ARB may represent an attractive therapeutic option for patients with RHT.

Chronic kidney disease is recognized as a risk factor for resistant hypertension and it is estimated that 20-25% of patients with RHT have some degree of renal impairment (Calhoun et al 2008). The purpose of the current study is to provide data on the clinical safety, tolerability and pharmacokinetics of 4 week dosing of LHW090 in patients with moderate renal impairment.

1.1.1 Relevant data summary

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigators Brochure.

1.2 Study purpose

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

2 Study objectives

2.1 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

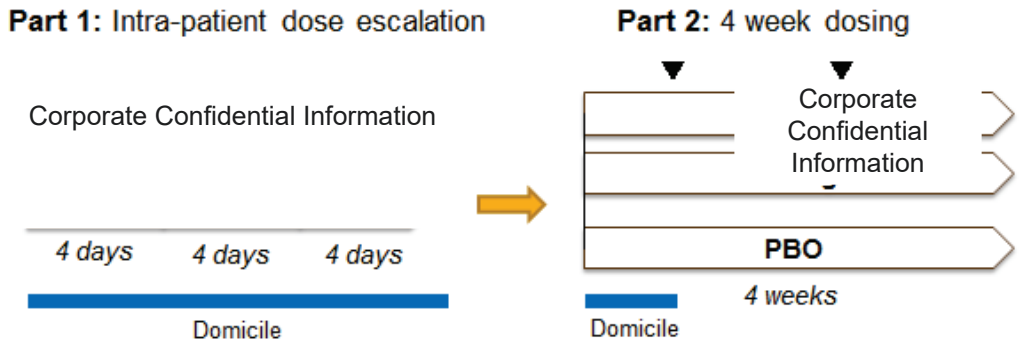
2.2 Secondary objective(s)

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	• Safety endpoints (including adverse

tolerability of LHW090 relative to placebo in patients with moderate renal impairment.	events and serious adverse events) up to and including the EOS

3 Investigational plan

3.1 Study design



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

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Part 2 First 16 patients will be domiciled for 1 week, from day -2 to Dav 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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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.

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 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.

Part 1 is comprised of a screening period, a baseline period, a treatment period and an end of study evaluation. Patients who meet the eligibility criteria at screening will be domiciled on Day -2 for diet stabilization. Laboratory assessments performed at screening will be used to determine patient eligibility for the trial. On Day -1, safety and baseline assessments of renal function Corporate Confidential Information will be performed Corporate Confidential Information Starting on Day 1, the patient will begin treatment with study drug or placebo, and dose will escalate two times for a total dosing period of 12 days. Pharmacokinetic assessments will be collected as shown in the assessment schedule. After completing dosing, patients will be monitored for an additional 48 hours after which they will be discharged at the discretion of the investigator. The patient will be asked to return to the site approximately one week later for end of study assessments.

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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, 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 Appendix 2) at the time of enrollment. Patients who meet the eligibility criteria at screening will have baseline assessments of renal function (serum creatinine, urinalysis) 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.

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 (see Table 8-3) On Day 7 at the investigator's discretion, the patients will be released to complete the remaining 3 weeks of the treatment phase.

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3.2 Rationale of study design

The primary objective(s) of this study is to collect information pertaining to the safety (including renal safety) and tolerability of LHW090 in patients with moderate renal impairment.

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Chronic kidney disease (CKD) is a risk factor for the development of drug-related nephrotoxicity (Loghman-Adham et al 2012)

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A two part sequential design was chosen to assess the safety and tolerability of doses lower than the expected therapeutic doses of LHW090 in renal patients before starting Part 2 which will test LHW090 daily for 4 weeks. For Part 1, an intra-patient dose escalation scheme was selected in order to reduce the number of patients and shorten the duration Two up-titrations after four days of once daily doses in Part 1 were chosen

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Patients in Part 1 will be domiciled beginning on Day -2 and for at least 48 hours after the last dose so that renal function and PK can be closely monitored as the dose is escalated to the target dose.

In Part 2, 4 weeks dosing was chosen Corporate Confidential Information to support future studies. Patients will be randomized in a 3:3:2 ratio to LHW090 or placebo, respectively, in order to have more patients exposed to repeat doses of LHW090 than to placebo and thus maximize the information collected with active treatment. The first 16 patients in Part 2 will be domiciled beginning on Day -1 and until Day 7 so that renal function and PK can be closely monitored. On Day 7 at the investigator's discretion, patients will be released to complete the remaining 3 weeks of the treatment phase.

An adaptive strategy will be used in Part 2 to efficiently identify whether the LHW090 Corporate Confidential Information administered for 4 weeks are safe and well-tolerated in this renally impaired population. A sponsor open, investigator-subject double-blind design was chosen to enable earlier detection of any potential safety issues in Part 2 and to allow opportunities for adaptive changes if safety or tolerability issues arise.

Since ARB therapy has been associated with increases in serum creatinine levels, which may be more pronounced in CKD patients; randomization for Part 2 will be stratified by ARB dose--"low" versus "usual" as described in Appendix 2 in order to balance the influence of ARB dose on serum creatinine. A cross-over design was not considered in order to minimize the potential for carry-over effects. A double-blind study was chosen to reduce bias.

3.3 Rationale of dose/regimen, duration of treatment

In Part 1, patients will receive escalating doses of LHW090 Corporate Confidential Information with each dose administered once daily for four days. Corporate Confidential Information

The pharmacokinetics of LHW090 and LHV527 is anticipated to be similar between Parts 1 and 2. Likewise, after the domiciling period for Part 2, LHW090 pharmacokinetics of LHW090 and LHV527 are also anticipated to be similar at the end of Part 2 (i.e., day 28).

In Part 2, importantly, although the proposed doses of LHW090 are once daily, pending evaluation of data from Part 1, a lower dose may be studied

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3.4 Rationale for choice of comparator

In this study, the comparator will be placebo in order to evaluate the effects of LHW090 in patients with moderate renal impairment on angiotensin receptor blocker therapy without interference by an active comparator.

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3.6 Risks and benefits

There is no benefit expected for subjects participating in this study.
In Part 1, patients will receive escalating doses of LHW090 over four days.

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Based on other compounds with a similar mode of action, low blood pressure may be a potential risk.

An allergic-type reaction called angioedema has been reported with a compound with a similar mode of action as LHW090. This risk may be increased when LHW090 is taken concomitantly with an ACE inhibitor. Subjects who are unable to substitute an ACE inhibitor with an angiotensin receptor blocker are excluded from this study. Due to the potential for pharmacokinetic drug-drug interactions, subjects taking statins should be monitored for statin-related myopathy during the duration of the study. For further details, refer to the Investigator Brochure and Section 5.2 "Prohibited treatment".

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, individual and study stopping criteria, and close clinical monitoring. Clinical monitoring includes regular monitoring of renal function in an in-patient setting in Part 1.

In Part 1, a maximum of 235 mL of blood is planned to be collected over a period of 7 weeks from each subject as part of the study. In Part 2, a maximum of 135 mL of blood is planned to be collected over a period of 9 weeks from each subject as part of the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

There may be unknown risks of LHW090 which may be serious and unforeseen.

4 Population

4.1 Population

The study population will be comprised of patients aged 40 to 85 (inclusive) on a stable dose of an ARB with stable (at least 3 months) moderately impaired renal function defined here as an eGFR of 30-59 mL/min/1.73m2 (inclusive).

For the purposes of this trial, eGFR will be calculated using the 4 variable MDRD Study equation as follows (Levey et al 2006): estimated GFR = $175 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times$ (0.742 if female) × (1.212 if African American) where Scr is serum creatinine in mg/dL.

For Part 1, a cohort of 12 patients will be enrolled and randomized. For Part 2, a total of approximately 72 patients will be enrolled and randomized.

Description for population **(Part 1, Part 2)**

4.2 Inclusion criteria

1. Written informed consent must be obtained before any assessment is performed.
   - *If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.*
2. Male patients and female patients without childbearing potential, age 40 to 85 years of age (inclusive) on a stable (at least 1 month) dose of an angiotensin receptor blocker (ARB) and stable moderately impaired renal function, defined here as an eGFR 30-59 mL/min/1.73m2 (inclusive) using the 4 variable MDRD Study equation for at least 3 months.
3. At screening, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the patient has rested for at least five minutes and again after three minutes in the standing position. Sitting vital signs should be within the following ranges:

   oral body temperature between 35.0-37.5 °C
   systolic blood pressure, 100-170 mm Hg
   diastolic blood pressure, 50-100 mm Hg
   pulse rate, 50 - 95 bpm

   Patients should be excluded if their standing vital signs (relative to sitting) show findings which, in the opinion of the Investigator, are associated with clinical manifestation of postural hypotension (i.e. absence of any other cause). The Investigator should carefully consider enrolling patients with either a > 20 mm Hg decrease in systolic or a >10 mm Hg decrease in diastolic blood pressure, accompanied by a > 20 bpm increase in heart-rate (comparing standing to sitting results).
4. Patients must weigh at least 50 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 40 kg/m^2. BMI = Body weight (kg) / $[Height (m)]^2$.
5. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.3 Exclusion criteria

1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
3. History of angioedema, drug-related or otherwise, as reported by the patient.
4. Use of angiotensin converting enzyme inhibitors (ACE inhibitors), mineralocorticoid receptor antagonists (e.g. spironolactone or eplerenone), aliskiren, vasopressin receptor antagonists (e.g. tolvaptan), or oral alkalinizing agents (e.g. sodium and potassium citrate or Shohl's solution).

   Note: Patients who discontinue their ACE-inhibitor and substitute with an angiotensin receptor blocker (ARB) may be eligible to be re-screened provided their medication regimen has been stable for at least 1 month and their renal function has been stable for at

least 3 months. Any substitutions or changes to a patient's medication regimen must be done under the guidance of the patient's treating physician.

5. History of a renal transplant.
6. Known current significant left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or significant severe valvular disease on prior or current echocardiogram.
7. A history of clinically significant ECG abnormalities, as determined by the Investigator, or any of the following ECG abnormalities at screening:
   - QTcF > 480 msec
8. Known history or current clinically significant arrhythmias.
9. History within the previous 6 months of myocardial infarction, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), stroke, transient ischemic attack (TIA) or acute kidney injury.
10. Hemoglobin levels below 9.0 g/dL at screening.
11. A serum potassium ≤ 3.5 mmol/l or ≥ 5.5 mmol/l at screening.
12. A previous history or previously diagnosed kidney disorder which, in the opinion of the Investigator, may place the patient at higher risk from his/her participation in the study or is likely to confound the interpretation of the study results. Such kidney disorders may include renal cystic disease such as autosomal dominant polycystic kidney disease (history of an incidental asymptomatic acquired renal cyst(s) is excepted); obstructive uropathy; renal stone(s) in the past 2 years; chronic interstitial nephropathy; drug-induced nephropathy; residual renal insufficiency following an episode of acute kidney injury or acute tubular necrosis related to renal atheroembolic disease, septic shock or ischemic nephropathy; renal tubular acidosis requiring treatment; nephrotic syndrome or nephrotic range proteinuria; or renal artery stenosis.
13. Donation or loss of 400 mL or more of blood within 8 weeks prior to initial dosing, or longer if required by local regulations.
14. Significant illness which has not resolved within two (2) weeks prior to initial dosing.
15. History of immunodeficiency diseases, including a positive HIV test result.
16. A positive Hepatitis B surface antigen or Hepatitis C test result.
17. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
18. Pregnant or nursing (lactating) women.
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), total hysterectomy or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

20. Sexually active males unwilling to use a condom during intercourse while taking drug and for 2 weeks after stopping study medication. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of the investigational drug via seminal fluid to their sexual partner. In addition, male participants should not donate sperm for the time period specified above.
21. On the Columbia-Suicide Severity Rating Scale, score "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal-Self Injurious Behavior" (question also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years.

    Any patient meeting this exclusion criterion should be excluded from the study and referred to a mental health care professional.
22. Any surgical or medical condition, which in the opinion of the Investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.

Subset of patients in MRI substudy **(Part 2),** inclusion/exclusion criteria:

1. Patients with contraindications to MRI, including:

- Brain aneurysm clip
- Implanted neural stimulator
- Implanted cardiac pacemaker or defibrillator, or presence of intracardiac wires
- Prosthetic heart valves
- Cochlear implant
- Ocular foreign bodies that might be ferromagnetic (e.g., metal shavings)
- Other implanted medical devices (e.g., insulin pumps)
- Metal shrapnel or bullets still in the body
- Severe claustrophobia
- Tattoos (as determined by the Investigator and Imager)
- Weight in excess of MRI machine capacity

Note: In the case where a safety laboratory assessment at screening is outside of the range specified above, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject is excluded from the study.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for study subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the following restrictions:

5.1 Contraception requirements

Not applicable. Only women of non-childbearing potential will be included in this study.

5.2 Prohibited treatment

Use of the following medications is not allowed during the course of the study from screening (Visit 1) to the end of the study. Patients who are receiving such medication(s) will be excluded, or if ethically and clinically justified, the medication(s) should be gradually withdrawn at least seven days before Visit 2:

- ACE inhibitors, mineralocorticoid receptor antagonists (e.g. spironolactone or eplerenone), aliskiren, vasopressin receptor antagonists (e.g. tolvaptan), or oral alkalinizing agents (e.g. sodium and potassium citrate or Shohl's solution)
    - Note: Patients who discontinue their ACE-inhibitor and substitute with an angiotensin receptor blocker (ARB) may be eligible to be re-screened provided their medication regimen has been stable for at least 1 month and their renal function has been stable for at least 3 months.
- Chronic administration (defined as >3 days per week) of NSAIDs or COX-2 inhibitors. The long-term chronic use of aspirin for cardiovascular prophylaxis is allowed provided the total daily dose does not exceed 325 mg. Intermittent doses of NSAIDs or COX-2 inhibitors are allowed but must not be within 48 hours prior to any scheduled visit or assessment or serum creatinine.
- Use of other investigational drugs at screening or within 30 days or 5 half-lives of the drug at screening, whichever is longer, unless local health authority guidelines mandate a longer period.
- Treatment with any medication that is contraindicated in renally impaired patients
- IV contrast dyes such as that used for a radiologic procedure
- Recombinant human erythropoietin

The following medications are prohibited due to potential for pharmacokinetic drug-drug interactions: bupropion, efavirenz, ifosfamide (sensitive CYP2B6 substrates); amodiaquine, paclitaxel, pioglitazone, repaglinide (sensitive CYP2C8 substrates); celecoxib, glimepiride, phenytoin, warfarin (sensitive or narrow index CYP2C9 substrates); glyburide (CYP2C9 and OATP1B1 substrate); irinotecan (OATP1B1 & BCRP substrate); topotecan (BCRP substrate); methotrexate (OAT1/3, BCRP substrate), bosentan (OATP1B1 substrate), atazanavir, cyclosporine, eltrombopag, gemfibrozil, lopinavir, rifampin, ritonavir, saquinavir, tipranavir (OATP1B1/1B3 inhibitors); cimetidine, diclofenac, probenecid (OAT1/3 inhibitor).

All other prior non-study medications (not specifically contraindicated in the exclusion criteria) will be allowed, provided the patient has been on a standard treatment regimen (at least 4 weeks of the same dose) and the treatment is not planned to be changed during the course of the study.

5.3 Dietary restrictions and smoking

- In Part 1, no alcohol is permitted from the domiciling period until after Study Completion evaluation. In Part 2, no alcohol will be permitted during the domiciling period and starting 24 hours prior to and during study visits.
- Intake of xanthine (e.g. caffeine) containing food or beverages (i.e., coffee, tea, soda, chocolate) will be restricted to no more than 2 cups/day.
- Subjects can drink water *ad libitum*. To ensure adequate hydration for urine collections in Part 1, subjects are recommended to have a fluid intake of at least 240 mL every 4 hours during waking hours in addition to fluid taken with meals and medication.
- Subjects should be counseled to avoid consuming large portions of cooked meat in the 24 hours prior to laboratory assessments. This restriction will reduce the variability in serum creatinine assessments which can be falsely elevated by dietary meat intake. During the domiciling period in Part 1 and Part 2, meals will be outlined by the study center's dietician in accordance with nutritional guidelines for patients with chronic kidney disease and nutritional counseling from the subject's physician.

Subjects will follow a standard weight maintaining diet while domiciled. No food other than that specified in the protocol will be consumed at any time during confinement. Subjects should be advised to consume the entire contents of the meal provided.

Meals should be provided only after all study procedures including blood and urine collections scheduled for that time have been completed.

A copy of the diet with content and nutritional information (amount of protein, carbohydrates, fat and calories for each meal) will be provided to the Sponsor prior to study start upon request.

5.4 General restrictions

- In Part 1, no strenuous physical exercise (e.g. weight training, aerobics, football) for 7 days prior to dosing until after Study Completion evaluation.
- In Part 2, no strenuous physical exercise (e.g. weight training, aerobics, football) for 7 days prior to dosing until after Study Completion evaluation, particularly for the 48 hours prior to study visits.

6 Treatment

6.1 Study treatment

Details on the storage and management of study medication, randomization and instructions for prescribing and taking study treatment are outlined in Section 3 of the Site Operations Manual.

6.1.1 Investigational treatment

The Investigational drug LHW090 Corporate Confidential Information matching placebos will be prepared by Novartis and supplied to the investigator site as open labelled bulk supply for Part 1.

For Part 2, LHW090 and its matching placebo will be supplied as double blind patient packs.

6.2 Treatment arms

Part 1: Subjects will be assigned to one of the following 2 treatment arms in a ratio of 2:1:

- A: LHW090 daily for 4 days, followed by 4 days followed by 4 days
- B: Matching placebo

Part 2: Subjects will be assigned to one of the following LHW090 treatment arms or placebo in a ratio of 3:3:2:

- A: LHW090 once daily
- B: LHW090 once daily
- C: Matching placebo

6.3 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments are not permitted. Subjects should be reminded of the importance of study drug compliance and compliance should be monitored and recorded.

In Part 2, patients should be instructed to bring their study medications with them on visit days for pill counts. If a short treatment interruption becomes necessary for an important reason, the subject may resume the study treatment. However, drug interruption should end, if possible, at least 3 days prior to the next study visit. A drug interruption occurring for ≥4 consecutive days or ≥5 total treatment days during the outpatient phase of the study will be considered a protocol deviation.

In the event that a subject will be transitioned to an ACE inhibitor at the end of the study or after premature discontinuation of study medication, a minimum of 72 hours must transpire between the last dose of LHW090 and the first dose of ACE inhibitor. Consideration should also be given to the existing ARB treatment of subjects in the study; concomitant treatment with an ACE inhibitor and an ARB should be avoided according to current guidelines and in compliance with the applicable local prescribing information of renin angiotensin aldosterone system (RAAS) agents.

6.4 Treatment assignment

Randomization numbers will be assigned in ascending, sequential order to eligible subjects (see Site Operations Manual for details). The investigator will enter the randomization number on the CRF.

In Part 1, randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management, using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for subjects will be reviewed and approved by a member of the Novartis Randomization Group.

In Part 2, at Visit 2, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the subject.

A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of treatment arms to randomization numbers. Once a patient is deemed eligible for enrollment into the study and ready for dosing, the next lowest available randomization number will be assigned. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply.

Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

6.5 Treatment blinding

This is a sponsor-open, investigator and subject double-blind study: subjects, investigator staff, and persons performing the assessments will remain blind to the identity of study treatments according to the specifications provided in Appendix 1.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Randomization data are kept strictly confidential, and are accessible only to authorized personnel (e.g. unblinded site staff (pharmacist or authorized designee at the site), unblinded sponsor staff (e.g. for drug resupply, unblinded monitor), and sample analysts), until unblinding of the trial as described in the table in the blinding table in Appendix 1.

The study statistician, the study programmer and other personnel involved in data analysis (e.g. biomarker expert) will have access to the randomization list for planned and unplanned interim analyses, and are allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in the blinding table in Appendix 1.

Unblinding will occur in the case of patient emergencies (see Section 6.6), at the time of the interim analysis and at the conclusion of the study.

6.6 Emergency breaking of assigned treatment code

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis for Part 1 of the study. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible in case of emergency. The investigator will receive a blinded code break card for each subject, with the details of drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. **The unblinded treatment code should not be recorded on the CRF.** The investigator must also immediately inform the Novartis local monitor that the code has been broken.

For Part 2, emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Head that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT/code break cards in case of emergency. If appropriate, the investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable.

An assessment will be done by the appropriate site personnel and the sponsor after an emergency unblinding to assess whether or not study drug should be discontinued for a given subject and, if applicable, whether the subject can continue into the next trial phase (e.g., an unblinded extension).

6.7 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with LHW090, as detailed in Section 8.5.

6.8 Recommended treatment of adverse events

Adverse events should be treated at the discretion of the Investigator based on his/her judgment and best medical practices. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.9 Rescue medication

Rescue medication to treat severe or serious conditions as per standard of care, at the discretion of the Investigator, is allowed. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF after start of study drug.

6.10 Concomitant treatment

All prescription medications, over-the-counter drugs, herbal medications and significant non-drug therapies (including physical therapy and blood transfusions) taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant Medications/Non-drug therapies page of the eCRF.

Certain prescription, over-the-counter or herbal medications will not be allowed during the course of the study unless the patient has been on a standard treatment regimen for at least 30 days prior to first dosing and will continue their regular regimen without changes throughout the study (unless required to treat adverse events). Some of these medications may have to be discontinued, as per discussion with the sponsor. Please refer to Section 5.2 for prohibited treatments.

Due to the potential for pharmacokinetic drug-drug interactions, subjects taking statins should be monitored for statin-related myositis (e.g. muscle pain or elevations in creatinine kinase) during the duration of the study. Under the guidance of their treating physician, subjects on rosuvastatin may consider halving their dose or switching to another statin for the duration of the study.

The investigator should instruct the patient to notify the study site about any new medications (prescription or over-the-counter) he/she takes after the start of the study drug. Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

7 Discontinuation and study completion

7.1 Discontinuation of study treatment

Study treatment must be discontinued and the patient withdrawn from the study if the patient withdraws consent. Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If a patient withdrawal occurs for any reason, the Investigator must make every effort to determine the primary reason for a patient's withdrawal from the study and record this information on the CRF.

The Investigator should discontinue study treatment for a given patient or withdraw the patient from study if on balance they believe that continuation would be detrimental to the patient's well-being. Under the following circumstances, individual study treatment must be discontinued and the patient monitored until resolution of the reason for discontinuation according to the Investigator's discretion:

- A reproducible and persistent (confirmed on repeat assessment within 24 – 48 hr) increase in serum creatinine ≥0.3 mg/dL from baseline. Any increases in serum creatinine ≥0.3 mg/dL based on local laboratory assessments should trigger repeat assessments of serum creatinine until event resolution (e.g. serum creatinine within 10% of baseline) or event stabilization. Baseline is defined as the average of all available pre-dose measurements.
- Systolic blood pressure <90 mm Hg (must be confirmed on repeat measurement after 30 minutes) or symptomatic hypotension
- Any protocol deviation (e.g. use of an ACE inhibitor) that results in a significant risk to the patient's safety

7.2 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last subject completes their End of Study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

At a minimum, subjects will be contacted for safety evaluations during the 30 days following the Study Completion visit, including a final post-study safety contact at the 30-day point after last visit. Documentation of attempts to contact the subject should be recorded in the source documentation.

7.2.1 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.3 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject does not want to participate in the study anymore **and** does not want any further visits or assessments **and** does not want any further study related contact **and** does not allow analysis of already obtained biologic material.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

7.4 Study Stopping rules

The study will be put on hold if any of the following criteria are met and no further dosing will occur pending a full safety review:

- 1 or more study-drug related SUSAR is reported
- 2 patients experience a systolic blood pressure <90 mm Hg that is persistent (>8 hours) and symptomatic and suspected to be related to the study drug
- 3 patients experience a doubling of their baseline serum creatinine (based on local laboratory assessments) that is suspected to be related to the study drug. Baseline is defined as the average of all available pre-dose measurements.
- 3 patients experience a similar AE which is assessed as moderate in intensity and is potentially related to the study drug

This study can continue if, after the review, the Investigator and Sponsor agree that it can safely continue.

The study may also be stopped at any time by the sponsor.

7.5 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, subjects should be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests.

The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

Table 8-1 Assessment Schedule, Part 1

Epoch	Screening						Treatment																			
Study Phase	Screening	Baseline					Treatment																			
Visit numbers (internal use only)	1	2	3				101	102	103	104							105	106	107	108						
Visit name (internal use only)	Screening	Day -2	Day -1				Day 1	Day 2	Day 3	Day 4							Day 5	Day 6	Day 7	Day 8						
Study Day(s)	-28 to -2	-2	-1				1	2	3	4							5	6	7	8						
Time (post-dose)	-	-	0h	4h	8h	12h	-	-	-	0h	1h	2h	3h	4h	8h	12h	-	-	-	0h	1h	2h	3h	4h	8h	12h
Informed consent	X																									
Inclusion / Exclusion criteria	X	X																								
Study drug administration							X	X	X	X							X	X	X	X						
Subjects domiciled		X												X												
Medical history/current medical conditions	X																									
Demography	X																									
Body height	X																									
Body weight	X																									
Vital Signs	X	X	X				X	X	X	X							X	X	X	X						
Physical examination	X	X																								
Hepatitis and HIV Screen	X																									
Alcohol Test, Drug Screen, and Cotinine Test	X																									
ECG evaluation	X	X																								
Hematology	X		X														X									

Epoch	Screening						Treatment																		
Study Phase	Screening	Baseline					Treatment																		
Visit numbers (internal use only)	1	2	3				101	102	103	104							105	106	107	108					
Visit name (internal use only)	Screening	Day -2	Day -1				Day 1	Day 2	Day 3	Day 4							Day 5	Day 6	Day 7	Day 8					
Study Day(s)	-28 to -2	-2	-1				1	2	3	4							5	6	7	8					
Time (post-dose)	-	-	0h	4h	8h	12h	-	-	-	0h	1h	2h	3h	4h	8h	12h	-	-	-	0h	1h	2h	3h	4h	8h	12h
Blood chemistry[2]	X		X				X	X	X	X							X	X	X	X						
Urinalysis	X		X				X										X									
Urine albumin:creatinine ratio[3]			X				X										X									
			X														X									
			X														X									
			X	X	X	X	X			X				X	X	X	X			X				X	X	X
				X	X	X	X							X	X	X	X							X	X	X
										X	X	X	X	X	X	X	X			X	X	X	X	X	X	X
							X																			
	X		X																X							
Columbia-Suicide Severity Rating Scale	X	X																								
Adverse events	X																									
Concomitant therapies	X																									
Phase/Study completion information			X																							

Epoch	**Treatment**													
Study Phase	**Treatment**												**Study Completion /Early termination**	**30 day Safety Follow up call**
Visit numbers (internal use only)	**109**	**110**	**111**	**112**							**113**	**114**	**199**	**n/a**
Visit name (internal use only)	**Day 9**	**Day 10**	**Day 11**	**Day 12**							**Day 13**	**Day 14**	**End of study**	
Study Day(s)	**9**	**10**	**11**	**12**							**13**	**14**	**21 -1 +2**	**51**
Time (post-dose)	**-**	**-**	**-**	**0h**	**1h**	**2h**	**3h**	**4h**	**8h**	**12h**	**-**	**-**	**-**	
Informed consent														
Inclusion / Exclusion criteria														
Study drug administration	X	X	X	X										
Subjects domiciled	X													
Medical history/current medical conditions														
Demography														
Body height														
Body weight														
Vital Signs	X	X	X	X							X	X	X	
Physical examination			X										X	
Hepatitis and HIV Screen														
Alcohol Test, Drug Screen, and Cotinine Test														
ECG evaluation													X	
Hematology	X										X		X	
Blood chemistry[2]	X	X	X	X							X	X	X	
Urinalysis	X										X		X	
Corporate Confidential Information	X										X		X	
	X										X			
	X										X		X	
	X			X				X	X	X	X			
	X							X	X	X	X			
PK blood collection[6]	X			X	X	X	X	X	X	X	X			

Epoch	Treatment													
Study Phase	Treatment												Study Completion /Early termination	30 day Safety Follow up call
Visit numbers (internal use only)	109	110	111	112							113	114	199	n/a
Visit name (internal use only)	Day 9	Day 10	Day 11	Day 12							Day 13	Day 14	End of study	
Study Day(s)	9	10	11	12							13	14	21 -1 +2	51
Time (post-dose)	-	-	-	0h	1h	2h	3h	4h	8h	12h	-	-	-	
Corporate Confidential Information														
													X	
Columbia-Suicide Severity Rating Scale											X		X	
Adverse events	X													X
Concomitant therapies	X													
Phase/Study completion information			X										X	

[1] Visit structure given for internal programming purpose only

[2] including Cystatin C

[3] First morning void

Corporate Confidential Information

[6] PK blood samples obtained at 0h will be pre-dose samples on Days 4, 8 and 12

[7] Pre-dose

Corporate Confidential Information

[9] Assessments on Study Days 1-3, 5-7, and 9-11 should be done pre-dose.

Table 8-2 Assessment schedule Part 2, Patients 1-16

Epoch	Screening		Treatment																							
Study Phase	Screening	Baseline	Treatment																						Study Completion	30 Day safety follow up call
Visit Numbers[1]	V1	V2[2]	V3	V3.1	V3.2	V3.3							V3.4	V3.5	V4[3]	V5	V6	V7							V777	n/a
Visit numbers (internal use only)	1	4	201	201.1	201.2	201.3							201.4	201.5	202	203	204	205							299	
Visit name (internal use only)	Screening	Day -1	Day 1	Day 2	Day 3	Day 4							Day 5	Day 6	Day 7	Day 14	Day 21	Day 28							End of study	
Study Day(s)	-28 to -4	-1	1	2	3	4							5	6	7 -1 +1	14 -1 +1	21 -1 +1	28 -1 +0							35 -1 +2	65
Time (post-dose)	-	0h	-			0h	1h	2h	3h	4h	8h	12h			-	-	-	0h	1h	2h	3h	4h	8h		-	
Informed consent	X																									
Inclusion / Exclusion criteria	X	X																								
Dose administration[4]			X																							
Domicile		X																								
Medical history/current medical conditions	X																									
Demography	X																									
Body height	X																									
Body weight	X																									
Hepatitis and HIV Screen	X																									
Vital Signs	X	X	X	X	X	X							X	X	X	X	X	X							X	
Physical	X	X																X							X	

Epoch	Screening		Treatment																						
Study Phase	Screening	Baseline	Treatment																					Study Completion	30 Day safety follow up call
Visit Numbers[1]	V1	V2[2]	V3	V3.1	V3.2	V3.3							V3.4	V3.5	V4[3]	V5	V6	V7						V777	n/a
Visit numbers (internal use only)	1	4	201	201.1	201.2	201.3							201.4	201.5	202	203	204	205						299	
Visit name (internal use only)	Screening	Day -1	Day 1	Day 2	Day 3	Day 4							Day 5	Day 6	Day 7	Day 14	Day 21	Day 28						End of study	
Study Day(s)	-28 to -4	-1	1	2	3	4							5	6	7 -1 +1	14 -1 +1	21 -1 +1	28 -1 +0						35 -1 +2	65
Time (post-dose)	-	0h	-			0h	1h	2h	3h	4h	8h	12h			-	-	-	0h	1h	2h	3h	4h	8h	-	
examination																									
Alcohol Test, Drug Screen, and Cotinine Test	X																								
ECG evaluation	X																							X	
Hematology	X	X														X		X						X	
Blood chemistry[5]	X	X	X	X	X	X							X	X	X	X	X	X						X	
Urinalysis	X	X	X	X	X	X							X	X	X	X	X	X						X	
Corporate Confidential Information	X	X	X	X	X	X							X	X	X	X	X	X						X	
		X													X			X							
	X	X	X												X	X		X						X	
	X	X													X			X							

Epoch	Screening		Treatment																							
Study Phase	Screening	Baseline	Treatment																						Study Completion	30 Day safety follow up call
Visit Numbers[1]	V1	V2[2]	V3	V3.1	V3.2	V3.3							V3.4	V3.5	V4[3]	V5	V6	V7							V777	n/a
Visit numbers (internal use only)	1	4	201	201.1	201.2	201.3							201.4	201.5	202	203	204	205							299	
Visit name (internal use only)	Screening	Day -1	Day 1	Day 2	Day 3	Day 4							Day 5	Day 6	Day 7	Day 14	Day 21	Day 28							End of study	
Study Day(s)	-28 to -4	-1	1	2	3	4							5	6	7 -1 +1	14 -1 +1	21 -1 +1	28 -1 +0							35 -1 +2	65
Time (post-dose)	-	0h	-			0h	1h	2h	3h	4h	8h	12h			-	-	-	0h	1h	2h	3h	4h	8h		-	
PK blood collection[9]						X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X			
Adverse events	X																									
Columbia-Suicide Severity Rating Scale	X	X														X		X							X	
Concomitant Medication	X																									
Arterial spin labeling MRI[10]		X													X											
Phase/Study completion information		X																							X	

[1] Visit structure given for internal programming purpose only

[2] MRI can be done within 2 days prior to the baseline visit

[3] MRI can be conducted within a day +/- of the Day 7 visit

[4] Patient is expected to take the drug every day for 4 weeks.

Table 8-3 Assessment Schedule, Part 2 Patients 17 to 72, approximately

Epoch	Screening		Treatment											
Study Phase	**Screening**	**Baseline**	**Treatment**										**Study Completion**	**30 Day safety follow up call**
Visit Numbers[1]	**V1**	**V2[2]**	**V3**	**V4[3]**	**V5**	**V6**	**V7**						**V777**	**n/a**
Visit numbers (internal use only)	**1**	**4**	**201**	**202**	**203**	**204**	**205**						**299**	
Visit name (internal use only)	**Screening**	**Day -1**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**						**End of study**	
Study Day(s)	**-28 to -4**	**-1**	**1**	**7 -1 +1**	**14 -1 +1**	**21 -1 +1**	**28 -1 +0**						**35 -1 +2**	**65**
Time (post-dose)	**-**	**0h**	**-**	**-**	**-**	**-**	**0h**	**1h**	**2h**	**3h**	**4h**	**8h**	**-**	
Informed consent	X													
Inclusion / Exclusion criteria	X	X												
Dose administration[4]			X											
Medical history/current medical conditions	X													
Demography	X													
Body height	X													
Body weight	X													
Hepatitis and HIV Screen	X													
Vital Signs	X	X	X	X	X	X	X						X	
Physical examination	X	X					X						X	
Alcohol Test, Drug Screen, and Cotinine Test	X													
ECG evaluation	X												X	
Hematology	X	X			X		X						X	
Blood chemistry[5]	X	X	X	X	X	X	X						X	
Urinalysis	X	X	X	X	X	X	X						X	
	X	X	X	X	X	X	X						X	
		X		X			X							
	X	X	X	X	X		X						X	
	X	X		X			X							
PK blood collection[9]				X	X	X	X	X	X	X	X	X		
Adverse events		X												X

Epoch	Screening		Treatment											
Study Phase	Screening	Baseline	Treatment										Study Completion	30 Day safety follow up call
Visit Numbers[1]	V1	V2[2]	V3	V4[3]	V5	V6	V7						V777	n/a
Visit numbers (internal use only)	1	4	201	202	203	204	205						299	
Visit name (internal use only)	Screening	Day -1	Day 1	Day 7	Day 14	Day 21	Day 28						End of study	
Study Day(s)	-28 to -4	-1	1	7 -1 +1	14 -1 +1	21 -1 +1	28 -1 +0						35 -1 +2	65
Time (post-dose)	-	0h	-	-	-	-	0h	1h	2h	3h	4h	8h	-	
Columbia-Suicide Severity Rating Scale	X	X			X		X						X	
Concomitant therapies	X													
Arterial spin labeling MRI[10]		X		X										
Phase/Study completion information		X											X	

[1] Visit structure given for internal programming purpose only
[2] MRI can be done within 2 days prior to the baseline visit
[3] MRI can be conducted within a day +/- of the Day 7 visit
[4] Patient is expected to take the drug every day for 4 weeks

8.1 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms will be recorded.

Investigators have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy / Pharmacodynamics

Efficacy is not measured in this clinical study.

8.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment Schedule detailing when each assessment is to be performed.

8.4.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

Information for all physical examinations should be included in the source documents and will not be transferred to the sponsor as part of the study analysis. Significant findings that are present prior to informed consent are included in the Relevant Medical History section of the source documents. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event eCRF section.

8.4.2 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse

8.4.3 Height and weight

- Height
- Body weight
- Body mass index (BMI) will be calculated (Body weight (kg) / [Height (m)]^2)

8.4.4 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

A central laboratory will be used for analysis of all specimens collected. For the purposes of monitoring, a separate sample will be obtained for serum creatinine and dipstick urine testing at a local laboratory and those results will be entered into the eCRF. Details on the collection, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the laboratory manual.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count will be measured.

Clinical chemistry

Blood samples for clinical chemistry should be collected early morning after an overnight fast of at least 8 hours.

Sodium, potassium, creatinine, estimated GFR using the 4 variable MDRD study equation, cystatin C, urea, uric acid, chloride, albumin, calcium, phosphate, alkaline phosphatase, total bilirubin, GGT, AST, ALT, aPTT (activated partial thromboplastin time), PT/INR, CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

In Part 1, LFTs (total bilirubin, AST, ALT, GGT, alkaline phosphatase) and coagulation tests (aPTT, PT/INR) will be included as part of the chemistry panel on screening, Days -1, 4, 8, 12, 14, and end of study visits.

Urinalysis

Urine samples for urinalysis, Corporate Confidential Information

will be requested while they are at the clinic.

Urine test by dipstick e.g. Combur9: leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/ hemoglobin

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts. If casts are noted, the type is to be specified on the relevant CRF page.

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8.4.5 Electrocardiogram (ECG)

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, be appropriately signed and dated to confirm review and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the sponsor.

Additional details of procedures relating to the ECG collection and reporting will be contained in the site operations manual.

For all studies:

PR interval, QRS duration, heart rate, RR, QT, QTc

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

8.4.6 Pregnancy and assessments of fertility

Not applicable. Only women of non-childbearing potential will be included in this study.

8.5 Pharmacokinetics

PK samples will be collected at the time-points defined in the Assessment schedule. Further details on sample collection, numbering, processing and shipment can be found in the Site Operations Manual. LHW090 and its active metabolite LHV527 will be determined in plasma using a validated LC-MS/MS method with the Lower Limit of Quantification (LLOQ) of 5.00 ng/mL. Untreated samples (placebo) will not be analyzed unless deemed necessary. Concentrations will be expressed in ng per mL units. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol. The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmax, Tmax, AUClast, AUC0-t, AUCtau from the plasma concentration-time data. Other pharmacokinetic parameters may be determined, if relevant.

8.6 Other assessments

9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver related events are included in Section 9.3.

Adverse events must be recorded on the Adverse Events CRF for subjects that pass screening and enter into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the severity grade
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities

- severe: prevents normal activities

2. its relationship to the study treatment (no/yes),
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE) See Section 9.2 for definition of SAE
5. action taken regarding [study/investigational] treatment(select as appropriate).

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e. further observation only)
- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged

6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or Core Data Sheet (for marketed drugs) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

The investigator should also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per Section 9.2.2.

9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 9-1 and Table 9-2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in in Table 9-2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug (refer to Section 7.1, if appropriate
- Hospitalization of the subject if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF, including the liver event overview CRF pages.

Table 9-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
Liver laboratory triggers	• 3 x ULN < ALT / AST £ 5 x ULN • 1.5 x ULN < TBL £ 2 x ULN
Liver events	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity *

Table 9-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for *more than 2 weeks*, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		

Criteria	Actions required	Follow-up monitoring
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study drug immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study drug interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

9.4 Renal safety monitoring

Renal events are defined as one of the following:

- confirmed (on repeat measurement within 24 – 48 hr timeframe) increase in serum creatinine of ≥ 0.3 mg/dL compared to baseline

The following two categories of abnormalities/adverse events have to be considered during the course of the study:

- Serum creatinine triggers that will require follow up and repeat assessments of the abnormal laboratory parameter
  - Urine dipstick triggers that will require follow up and repeat assessments of the abnormal laboratory parameter.

Please refer to Table 9-3 for specific renal alert criteria and actions.

Table 9-3 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Serum creatinine increase ≥0.3 mg/dL compared to baseline	Confirm ≥0.3 mg/dL increase in 24-48 hr timeframe Follow serum creatinine until event resolution or event stabilization
Serum creatinine increase ³ 50 % compared to baseline*	Follow up within 24-48h if possible Consider patient hospitalization /specialized treatment
Albumin- or Protein-creatinine ratio increase ≥ 2-fold Albumin-creatinine ratio (ACR) ≥ 30 mg/g; New dipstick proteinuria ≥ 1+ Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider drug interruption / discontinuation
New dipstick glucosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
Document contributing factors: co-medication, other co-morbid conditions, and additional diagnostic procedures performed in the CRF Monitor patient regularly (frequency at investigator's discretion) until one of the following: Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. *Baseline is defined as the average of all pre-dose measurements from central laboratory assessments.	

9.5 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence.

In addition, pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study.

Consent to report information regarding all pregnancy outcomes should be obtained from the mother. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

9.6 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior.

The C-SSRS, which uses a semi-structured interview to probe subject responses, will be administered by an individual who has received training and certification in its administration. At the first study visit, the "baseline/screening" version of the C-SSRS, will be administered. This version assesses Suicidal Ideation and Suicidal Behavior during the subject's lifetime and during a predefined period. At subsequent visits, the "since last visit" version will be administered.

If, at any time after screening and/or baseline, the score is "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS or "yes" on any item of the Suicidal Behavior section, the subject must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the subject is referred.

In addition, all life-threatening events should be reported as SAEs. For example, if a subject answers "yes" to one of the questions in the Suicidal Behavior section, an SAE must be reported if the event was life-threatening. All events of "Non-Suicidal Self-Injurious Behavior" (question also included in the Suicidal Behavior section) should be reported as AEs and assigned the appropriate severity grade.

All SAEs relating to suicidal behavior should be reviewed by the Safety Management Team or Early Project Teams.

9.7 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

10.3 Database management and quality control

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Novartis staff review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed locally and/or centrally as defined in the site operations manual and the results will be sent electronically to Novartis (or a designated CRO).

In Part 2 of the study, randomization codes and data in reference to dispensing of study drug(s) to the subject and all IRT recorded dosage changes will be tracked using Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis (Part 1 only).

Each occurrence of a code break via IRT (Part 2 only) will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

Not required.

11 Data analysis

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

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

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

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

11.2 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 Part, 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.

11.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

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

11.4 Analysis of the primary variable(s)

11.4.1 Variable(s)

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. This threshold in serum creatinine was selected based on the published definitions of acute kidney injury (Mehta et al 2007, Khwaja 2012). Change from baseline 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.

11.4.2 Statistical model, hypothesis, and method of analysis

Part 1:

The purpose of the dose escalation in Part 1 is to assess the renal safety and tolerability of multiple doses of LHW090 in patients with moderately impaired renal function starting with the highest single dose tested in renal patients in the first-in-human study before the start of Part 2. Descriptive summary statistics will be provided by treatment group and visit/sampling time point, for change from baseline serum creatinine including the frequency (n, %) of renal events <0.3 mg/dL and ≥ 0.3 mg/dL.

Concentration response modeling may be carried out in Part 1 to assess the correlation of change in serum creatinine with concentration. In the absence of a significant concentration effect on serum creatinine, Part 2 will be initiated Corporate Confidential Information If there is evidence of significant concentration effect, Part 2 of the study may not be initiated or a lower dose may be investigated.

Part 2:

For Part 2, a Chi-square test will be performed to compare the proportion of patients who develop a renal event in the LHW090 pooled active doses, LHW090 individual doses and placebo groups. This analysis will be stratified by ARB dose (see Appendix 2). A logistic model with the baseline ARB dose and the baseline creatinine level as covariates may also be used. P-value and 95% CI of the difference in proportions will be presented. Descriptive summary statistics will be provided by treatment and visit/sampling time point, for change from baseline serum creatinine including the frequency (n, %) of renal events <0.3 mg/dL and ≥ 0.3 mg/dL will be provided.

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.

Analyses stratified by degree of proteinuria (microalbuminuria or macroalbuminuria) and/or history of diabetes may also be conducted.

11.4.3 Handling of missing values/censoring/discontinuations

For the analysis of the proportion of patients with a renal events described in Section 11.4.3, patients who complete at least 2 weeks of treatment will be included in the denominator. For the analysis of change from baseline in serum creatinine described in Section 11.4.4, all available data will be included and missing data will not be imputed (it will be estimated from the likelihood of the repeated measures model). Patients discontinued by the investigator due to a doubling of serum creatinine from baseline (based on local measurements) will be counted as having a renal event in the primary analysis regardless of the availability of a central serum creatinine value. In case more than 10% of patients drop out before 2 weeks, a sensitivity analysis using multiple imputation techniques may be considered.

11.4.4 Supportive analyses

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.

11.5 Analysis of secondary and exploratory variables

11.5.1 Efficacy / Pharmacodynamics

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The peak and mean AUC (AUC0-24h) of plasma cGMP, Amount excreted (Ae) of Urine cGMP will be calculated and summarized by part and treatment. Change from baseline and percent change from baseline of these variables will also be calculated and summarized.

11.5.2 Safety

11.5.2.1 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.

11.5.2.2 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.

11.5.2.3 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. Summary statistics will be provided by Part, treatment group and visit/time.

Change from baseline data will also be listed and summarized.

11.5.2.4 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 Part and treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

11.5.2.5 Other safety evaluations

Urine albumin creatinine ratio and Fractional excretion of phosphate in urine data will be listed by Part, treatment group, subject and visit/time. Summary statistics will be provided by Part, treatment group and visit/time. Change from baseline data will also be listed and summarized.

11.5.3 Pharmacokinetics

All drug concentrations below the lower limit of quantification (LLOQ) will be reported as "zero" and will be treated as zero for calculation of PK parameters.

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. 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.

Pharmacokinetic parameters will be calculated as described in Section 8.5 and will be listed and summarized by part, treatment and subject.

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

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

11.5.5 Other assessments

11.6 Sample size calculation

For Part 1, the sample size is driven by feasibility considerations.

For Part 2, with 54 patients in the pooled LHW090 dose groups and 18 patients in the placebo group, we can detect a difference of 25% (increase from 3% on placebo to 28% on active) between the renal event rates on active (pooled doses) and placebo with 82% power and 10% type I error (1-sided test).

11.7 Power for analysis of key secondary variables

Not applicable.

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

13.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the CTL should be informed and (serious) adverse event reporting requirements (Section 9) followed as appropriate.

14 References

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15 Appendix 1: (Blinding table)

Role	Time or Event			
	Randomization list generated	**Trt allocation & dosing**	**Safety event (single subject unblinded)**	**IA & dose escalation**
Subjects	B	B	UI	B
Site staff e.g. investigator and study nurse	B	B	UI	B
Unblinded site staff e.g. pharmacy staff	B	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff e.g. for drug re-supply, unblinded monitor, sample analytics	B	UI	UI	UI
Statistician/statistical programmer/biomarker expert	B	B	UI	UI
Independent committees (e.g. DMC, internal stats analysis team) used for assessing interim results	NA	NA	NA	NA
All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions)	B	B	UI	UI

IA Interim analyses

UI Allowed to be unblinded on individual patient level

B Remains blinded

At Database lock all roles can be unblinded

Subjects and investigator will remain blinded to study treatment throughout the study (except in the case of a safety event necessitating unblinding). The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

With the exception of unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment during treatment allocation and at the point of subject dosing but may be unblinded to the treatment assignment of an individual subject in case of a safety event necessitating unblinding.

Unblinding a single subject for safety reasons (necessary for subject management) will occur via an emergency system in place at the site.

Unblinded site staff: Drug product will be supplied in bulk, so an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist will receive a randomization list or treatment allocation cards from Drug Supply Management with the appropriate treatment allocation numbers. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Unblinded sponsor staff: The following unblinded sponsor roles are required for this study:

- Unblinded monitor
- Unblinded sample analyst (PK blood and urine)
- Unblinded sample analyst (biomarker XXX)

The unblinded monitor is required to review drug accountability and allocation at site. The unblinded monitor is not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual subjects. The unblinded monitor will also be able to review the treatment allocation cards/randomization list provided to the unblinded pharmacist. The names of the unblinded monitor(s) are detailed in the Monitoring Plan.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office) to facilitate analysis of the samples. The sample analysts will provide the sample data to the team under blinded conditions. Both the pharmacist and bioanalyst will keep this information confidential until clinical database lock.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in the blinding table above. For example, unblinded summaries and unblinded individual data can be shared with the team for planned and unplanned interim analyses.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert) are allowed to access treatment assignment information for the purpose of conducting planned and unplanned interim analyses.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project while the study is ongoing.