Sponsor

Novartis Pharmaceuticals

Generic Drug Name

LHW090

Trial Indication(s)

Patients with hypertension and moderately impaired renal function

Protocol Number

CLHW090X2102

Protocol 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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 2

Study Start/End Dates

Study Start Date: March 2017 (Actual)

Primary Completion Date: October 2018 (Actual)
Study Completion Date: October 2018 (Actual)

Reason for Termination (If applicable)

N/A

Study Design/Methodology

This was a randomized, double-blind, parallel group, placebo-controlled, two sequential parts study to evaluate the safety (including renal safety), tolerability, and pharmacokinetics (PK) of LHW090 in patients with moderately impaired renal function.

Centers

12 centers in 2 countries: United States (7), Germany(5)

Objectives:

Primary objective
Part 1: To assess the safety and tolerability of ascending 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

Test Product (s), Dose(s), and Mode(s) of Administration

In Part 1, LHW090 capsules were supplied to the investigators as hard gelatin capsules at dose

strengths of 12.5 mg and 100 mg. Placebo was supplied as tablets of 12.5 mg and 100 mg dose strength.
Part 1. In Part 2, LHW090 100 mg and its matching placebo were supplied as double blind patient packs.
Part 1: Subjects were assigned to one of the following 2 treatment arms in a ratio of 2:1:
A: LHW090 25 mg daily for 4 days, followed by 50 mg daily for 4 days followed by 100 mg daily for 4 days
B: Matching placebo
Part 2: Subjects were assigned to one of the following LHW090 treatment arms or placebo in a ratio of 3:3:2:
A: LHW090 100 mg once daily
B: LHW090 200 mg once daily
C: Matching placebo

Statistical Methods

The two parts of the study were analyzed separately. In Part 1, the primary variable was the assessment of the safety and tolerability of escalating doses of LHW090 in subjects with moderate renal impairment.
In Part 2, the primary safety variable was the proportion of patients who developed a renal event.
Descriptive summary statistics were 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 (<26.52 µmol/l)
and ≥ 0.3 mg/dL (≥26.52 µmol/l) were provided.
The secondary variables were evaluation of PK parameters (Cmax, Tmax, AUClast, AUC0-24h, DN AUClast, DN Cmax, Clast and Tlast) and assessment of safety and tolerability of LHW090.
LHW090/LHV527 plasma concentration data was listed by part, treatment, subject, and visit/sampling time point.
Descriptive summary statistics were provided by treatment and visit/sampling time point.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria (all Parts):
- 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/1.73m^2 (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:
o oral body temperature between 35.0-37.5 °C

o systolic blood pressure, 100-170 mm Hg
o diastolic blood pressure, 50-100 mm Hg
o 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 - 38 kg/m^2. 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 rescreened 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 ≥ 5.2 mmol/l at screening.
- A previous history or previously diagnosed 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.

Participant Flow Table

PART 1

	LHW090 (PART 1)	Placebo (PART 1)	LHW090 100mg (PART 2)	LHW090 200mg (PART 2)	Placebo (PART 2)	Total
Arm/Group Description	For Part 1, patients will receive 3 doses of LHW090 once daily with escalating doses every 4 days for a total 12 days of treatment.	For Part 1, patients will receive matching placebo once daily for 12 days.	For PART 2, patients will receive LWH090 100 mg for 4 weeks	For PART 2, patients will receive LWH090 200 mg for 4 weeks	For Part 2, patients will receive matching placebo once daily for 4 weeks.	
Started	7	4	0	0	0	11
Completed	7	4	0	0	0	11
Not Completed	0	0	0	0	0	0

PART 2

	LHW090	Placebo	LHW090 100mg	LHW090 200mg	Placebo	Total

	(PART 1)	(PART 1)	(PART 2)	(PART 2)	(PART 2)	
Arm/Group Description	For Part 1, patients will receive 3 doses of LHW090 once daily with escalating doses every 4 days for a total 12 days of treatment.	For Part 1, patients will receive matching placebo once daily for 12 days.	For PART 2, patients will receive LWH090 100 mg for 4 weeks	For PART 2, patients will receive LWH090 200 mg for 4 weeks	For Part 2, patients will receive matching placebo once daily for 4 weeks.	
Started	0	0	28	27	18	73
Completed	0	0	25	26	18	69
Not Completed	0	0	3	1	0	4
Adverse Event	0	0	2	1	0	3
Withdrawal by Subject	0	0	1	0	0	1

Baseline Characteristics

	LHW090 (PART 1)	Placebo (PART 1)	LHW090 100mg (PART 2)	LHW090 200mg (PART 2)	Placebo (PART 2)	Total
Arm/Group Description	For Part 1, patients will receive 3 doses of LHW090 once daily with escalating doses every 4 days for a total 12 days of treatment.	For Part 1, patients will receive matching placebo once daily for 12 days.	For PART 2, patients will receive LWH090 100 mg for 4 weeks	For PART 2, patients will receive LWH090 200 mg for 4 weeks	For Part 2, patients will receive matching placebo once daily for 4 weeks.	
Number of Participants [units: participants]	7	4	28	27	18	84
Age Continuous (units: years) Mean ± Standard Deviation						
	68.3±3.64	67.5±16.01	71.0±9.18	69.0±8.82	65.3±11.58	68.8±9.69
Sex: Female, Male (units:)						

Count of Participants (Not Applicable)						
Female	1	3	8	10	9	31
Male	6	1	20	17	9	53

Race (NIH/OMB) (units: Participants) Count of Participants (Not Applicable)						
American Indian or Alaska Native	0	0	0	0	0	0
Asian	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
Black or African American	1	1	1	3	0	6
White	6	3	27	24	18	78
More than one race	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0

Summary of Efficacy

Primary Outcome Result(s)

Number of patients with reported adverse events receiving escalating doses of LHW090 (Part 1)
(Time Frame: Adverse events were collected from first dose of study treatment until end of study treatment, (12 days

dosing period + 9 days follow up (PART 1) plus 30 days post treatment, up to maximum duration of approximately 20 months)

	LHW090 25 mg (PART 1)	LHW090 50 mg (PART 1)	LHW090 100 mg (PART 1)	Placebo (PART 1)
Arm/Group Description	For Part 1, patients will receive 3 doses of LHW090 25 mg once daily with escalating doses every 4 days for a total 12 days of treatment.	For Part 1, patients will receive 3 doses of LHW090 50 mg once daily with escalating doses every 4 days for a total 12 days of treatment.	For Part 1, patients will receive 3 doses of LHW090 100 mg once daily with escalating doses every 4 days for a total 12 days of treatment.	For Part 1, patients will receive matching placebo once daily for 12 days.
Number of Participants Analyzed [units: participants]	7	7	7	4

Number of patients with reported adverse events receiving escalating doses of LHW090 (Part 1)
(units: Count of Participants)

Number of patients with at least one AE	1	0	1	2
Gastrointestinal disorders	1	0	1	2
Skin and subcutaneous tissue disorders	0	0	1	2
General disorders & administration site conditions	0	0	0	1
Musculoskeletal and connective tissue disorders	0	0	0	1
Nervous system disorders	0	0	0	1
Psychiatric disorders	0	0	0	1

Pharmacokinetics of LHW090/LHV527 (active metabolite) in plasma: area under the plasma concentration-time curve from time zero time 't' where t is a defined time point after administration (AUC0-t) (PART 1)
(Time Frame: Within 60 minutes prior to dosing, post dose +/- 10 min from greater or equal to 1 hr to 24 hrs.)

	LHW090 25 mg (PART 1)	LHW090 50 mg (PART 1)	LHW090 100 mg (PART 1)	LHW090/LHV527 25 mg (PART 1)	LHW090/LHV527 50 mg (PART 1)	LHW090/LHV527 100 mg (PART 1)
Arm/Group Description	For Part 1, patients will	For Part 1, patients will	For Part 1, patients will	For Part 1, patients will receive 3 doses	For Part 1, patients will receive 3 doses	For Part 1, patients will receive 3 doses

	receive 3 doses of LHW090 25 mg once daily with escalating doses every 4 days for a total 12 days of treatment.	receive 3 doses of LHW090 50 mg once daily with escalating doses every 4 days for a total 12 days of treatment.	receive 3 doses of LHW090 100 mg once daily with escalating doses every 4 days for a total 12 days of treatment.	of LHW090 25 mg once daily with escalating doses every 4 days for a total 12 days of treatment. (PK draw with active metabolite, LHV527)	of LHW090 50 mg once daily with escalating doses every 4 days for a total 12 days of treatment. (PK draw with active metabolite, LHV527)	of LHW090 100 mg once daily with escalating doses every 4 days for a total 12 days of treatment. (PK draw with active metabolite, LHV527)
Number of Participants Analyzed [units: participants]	7	7	7	7	7	7
Pharmacokinetics of LHW090/LHV527 (active metabolite) in plasma: area under the plasma concentration-time curve from time zero time 't' where t is a defined time point after administration (AUC0-t) (PART 1) (units: h*ng/mL)						

Mean ± Standard Deviation						
	3750 ± 815	7150 ± 1480	13900 ± 2180	19200 ± 3990	36500 ± 5720	68800 ± 11800

Number of patients who developed a renal event (PART 2)
(Time Frame: Baseline, within 24 to 48 hours of post-dose weekly for up to 8 weeks)

	LHW090 100mg (PART 2)	**LHW090 200mg (PART 2)**	**Placebo (PART 2)**
Arm/Group Description	For PART 2, patients will receive LWH090 100 mg once daily for 4 weeks	For PART 2, patients will receive LWH090 200 mg once daily for 4 weeks	For Part 2, patients will receive matching placebo once daily for 4 weeks.
Number of Participants Analyzed [units: participants]	28	27	18
Number of patients who developed a renal event (PART 2) (units: Participants) Count of			

Participants (Not Applicable)			
	0	1	0

Secondary Outcome Result(s)

Cmax : Pharmacokinetics of LHW090/LHV527 (active metabolite) in plasma: observed maximum plasma concentration following administration of LHW090 (PART 1/PART 2)
(Time Frame: PART 1: within 60 minutes prior to dosing, post dose +/- 10 min from greater or equal to 1 hr to 24 hrs. PART 2: within 60 min +/- 10 min from greater or equal to 1 hr to 8 hours after 4 weeks dosing.)

	LHW090 25 mg (PART 1)	LHW090 50 mg (PART 1)	LHW090 100 mg (PART 1)	LHW090 100mg (PART 2)	LHW090 200mg (PART 2)
Arm/Group Description	For Part 1, patients will receive 3 doses of LHW090 25 mg once daily with escalating doses every 4 days for a total 12 days of	For Part 1, patients will receive 3 doses of LHW090 50 mg once daily with escalating doses every 4 days for a total 12 days of	For Part 1, patients will receive 3 doses of LHW090 100 mg once daily with escalating doses every 4 days for a total 12 days of	For PART 2, patients will receive LWH090 100 mg once daily for 4 weeks	For PART 2, patients will receive LWH090 200 mg once daily for 4 weeks

	treatment.	treatment.	treatment		
Number of Participants Analyzed [units: participants]	7	7	7	28	27
Cmax : Pharmacokinetics of LHW090/LHV527 (active metabolite) in plasma: observed maximum plasma concentration following administration of LHW090 (PART 1/PART 2) (units: ng / mL) Mean ± Standard Deviation					
PK Value for LHW090	1160 ± 589	2000 ± 1020	4230 ± 1400	4470 ± 1690	7530 ± 3750
PK Value for LHW090/LHV527(active metabolite)	1690 ± 338	3070 ± 682	5100 ± 734	6200 ± 1560	10300 ± 1440

AUC0-t: Pharmacokinetics of LHW090/LHV527 (active metabolite)in plasma: area under the plasma concentration-time curve from time zero time 't' where t is a defined time point after administration (PART 2)
(Time Frame: PART 2: within60 min +/- 10 min from greater or equal to 1 hr to 8 hours after 4 weeks dosing.)

	LHW090 100 mg (PART 2)	**LHW090 200mg (PART 2)**	**LHW090/LHV527 100 mg (PART 2)**	**LHW090/LHV527 200 mg (PART 2)**
Arm/Group Description	For PART 2, patients will receive LWH090 100 mg once daily	For PART 2, patients will receive LWH090 200 mg once daily	For PART 2, patients will receive LWH090 100 mg once daily for 4 weeks. (PK draw with active metabolite,	For PART 2, patients will receive LWH090 200 mg once daily for 4 weeks. (PK draw with active metabolite,

	for 4 weeks	for 4 weeks	LHV527)	LHV527)
Number of Participants Analyzed [units: participants]	28	27	28	27
AUC0-t: Pharmacokinetics of LHW090/LHV527 (active metabolite)in plasma: area under the plasma concentration-time curve from time zero time 't' where t is a defined time point after administration (PART 2) (units: h* ng/mL) Mean ± Standard Deviation				
	21500 ± 6810	42900 ± 20700	96700 ± 32800	181000 ± 51100

Tmax: Pharmacokinetics of LHW090/LHV527 in plasma: time to reach the maximum concentration after administration of LHW090 (PART 1/PART 2)

(Time Frame: Part 1: within 60 minutes prior to dosing, post dose +/- 10 min from greater or equal to 1 hr to 24 hrs. Part2: within60 min +/- 10 min from greater or equal to 1 hr to 8 hours after 4 weeks dosing.)

	LHW090 25 mg (PART 1)	LHW090 50 mg (PART 1)	LHW090 100 mg (PART 1)	LHW090 100mg (PART 2)	LHW090 200mg (PART 2)
Arm/Group Description	For Part 1, patients will receive 3 doses of LHW090 25 mg once daily with escalating doses every 4 days for a total 12 days of treatment.	For Part 1, patients will receive 3 doses of LHW090 50 mg once daily with escalating doses every 4 days for a total 12 days of treatment.	For Part 1, patients will receive 3 doses of LHW090 100 mg once daily with escalating doses every 4 days for a total 12 days of treatment	For PART 2, patients will receive LWH090 100 mg once daily for 4 weeks	For PART 2, patients will receive LWH090 200 mg once daily for 4 weeks
Number of Participants Analyzed [units: participants]	7	7	7	28	27
Tmax: Pharmacokinetics of LHW090/LHV527 in plasma: time to reach the maximum concentration after administration of LHW090 (PART 1/PART 2) (units: hour (hr)) Median (Full Range)					
PK Value for LHW090	2.00 (1.00 to	1.02 (1.00 to	1.00 (1.00 to	2.00 (1.00 to	2.50 (1.00 to

	3.00)	3.00)	4.00)	4.00)	12.0)
PK Value for LHW090/LHV527(active metabolite)	3.58 (2.00 to 12.0)	4.00 (2.00 to 12.0)	4.00 (2.00 to 8.00)	3.00 (2.00 to 8.00)	4.00 (3.00 to 12.0)

Summary of Safety

Safety Results

All-Cause Mortality

	LHW090 25 mg (PART 1) N = 7	LHW090 50 mg (PART 1) N = 7	LHW090 100 mg (PART 1) N = 7	PART 1 Placebo N = 4	LHW090 100mg (PART 2) N = 28	LHW090 200 mg (PART 2) N = 27	Placebo (PART 2 N = 18
Arm/Group Description	For Part 1, patients will receive 3 doses of LHW090 25 mg once daily with escalating doses every 4	For Part 1, patients will receive 3 doses of LHW090 50 mg once daily with escalating doses every 4	For Part 1, patients will receive 3 doses of LHW090 100 mg once daily with escalating doses every 4	For Part 1, patients will receive matching placebo once daily for 12 days.	For PART 2, patients will receive LWH090 100 mg once daily for 4 weeks	For PART 2, patients will receive LWH090 200 mg once daily for 4 weeks	For Part 2, patients will receive matching placebo once daily for 4 weeks.

	days for a total 12 days of treatment.	days for a total 12 days of treatment.	days for a total 12 days of treatment.				
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment, plus 30 days post treatment, up to maximum duration of approximately 20 months
Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment

	LHW090 25 mg (PART 1) N = 7	**LHW090 50 mg (PART 1) N = 7**	**LHW090 100 mg (PART 1) N = 7**	**PART 1 Placebo N = 4**	**LHW090 100mg (PART 2) N = 28**	**LHW090 200 mg (PART 2) N = 27**	**Placebo (PART 2 N = 18**
Arm/Group Description	For Part 1, patients will	For Part 1, patients will	For Part 1, patients will	For Part 1, patients will	For PART 2, patients will receive	For PART 2, patients will	For Part 2, patients will

	receive 3 doses of LHW090 25 mg once daily with escalating doses every 4 days for a total 12 days of treatment.	receive 3 doses of LHW090 50 mg once daily with escalating doses every 4 days for a total 12 days of treatment.	receive 3 doses of LHW090 100 mg once daily with escalating doses every 4 days for a total 12 days of treatment.	receive matching placebo once daily for 12 days.	LWH090 100 mg once daily for 4 weeks	receive LWH090 200 mg once daily for 4 weeks	receive matching placebo once daily for 4 weeks.
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (10.71%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications							
Radius fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)
Skin laceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders							
Angioedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment, plus 30 days post treatment, up to maximum duration of approximately 20 months
Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	LHW090 25 mg (PART 1) N = 7	**LHW090 50 mg (PART 1) N = 7**	**LHW090 100 mg (PART 1) N = 7**	**PART 1 Placebo N = 4**	**LHW090 100mg (PART 2) N = 28**	**LHW090 200 mg (PART 2) N = 27**	**Placebo (PART 2 N = 18**
Arm/Group Description	For Part 1, patients will receive 3 doses of LHW090 25 mg once daily with escalating doses every 4 days for a total 12 days of	For Part 1, patients will receive 3 doses of LHW090 50 mg once daily with escalating doses every 4 days for a total 12	For Part 1, patients will receive 3 doses of LHW090 100 mg once daily with escalating doses every 4 days for a total 12 days of	For Part 1, patients will receive matching placebo once daily for 12 days.	For PART 2, patients will receive LWH090 100 mg once daily for 4 weeks	For PART 2, patients will receive LWH090 200 mg once daily for 4 weeks	For Part 2, patients will receive matching placebo once daily for 4 weeks.

	treatment.	days of treatment.	treatment.				
Total participants affected	1 (14.29%)	0 (0.00%)	1 (14.29%)	2 (50.00%)	13 (46.43%)	16 (59.26%)	9 (50.00%)
Ear and labyrinth disorders							
Vertigo	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)
Eye disorders							
Eye pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (3.70%)	0 (0.00%)
Lacrimation increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders							
Abdominal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)
Diarrhoea	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	4 (14.81%)	1 (5.56%)
Dry mouth	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dyspepsia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (5.56%)
Faeces discoloured	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Frequent bowel movements	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Nausea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)
General disorders							

and administration site conditions							
Chest discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Fatigue	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	1 (3.70%)	0 (0.00%)
Infusion site haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oedema peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	2 (11.11%)
Pyrexia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)
Xerosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)
Immune system disorders							
Hypersensitivity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)
Infections and infestations							
Gastrointestinal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (5.56%)
Rhinitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Viral upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)

Investigations							
Blood creatinine increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (5.56%)
Blood pressure decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	0 (0.00%)
Metabolism and nutrition disorders							
Gout	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Hyperkalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (3.70%)	0 (0.00%)
Lactose intolerance	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)
Musculoskeletal and connective tissue disorders							
Arthralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)
Back pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Muscle spasms	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Lipoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Nervous system disorders							

Dizziness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (3.70%)	0 (0.00%)
Headache	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders							
Abnormal dreams	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Apathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)
Insomnia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Sleep disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	0 (0.00%)
Renal and urinary disorders							
Dysuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)
Haematuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)
Pollakiuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (3.70%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders							
Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Epistaxis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)
Nasal dryness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Nasal pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (14.81%)	0 (0.00%)
Oropharyngeal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)

Rhinorrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (5.56%)
Skin and subcutaneous tissue disorders							
Acne	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	0 (0.00%)
Alopecia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Drug eruption	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Ecchymosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (5.56%)
Pruritus	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	6 (21.43%)	1 (3.70%)	1 (5.56%)
Pruritus generalised	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	0 (0.00%)
Rash macular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)
Vascular disorders							
Haematoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)	0 (0.00%)	1 (5.56%)
Hypotension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.14%)	2 (7.41%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

In this study, dosing with LHW090 100 mg and 200 mg once daily for up to four weeks was safe and generally well-tolerated in subjects with moderately impaired renal function on stable angiotensin receptor blocker background therapy.

One subject from LHW090 200 mg treatment group had a renal event, however, serum creatinine returned to levels similar to baseline, despite ongoing treatment with LHW090. Markers of renal function seemed in general similar between the LHW090 and the placebo
groups. There was a higher frequency of pruritus AEs in the LHW090 groups, however, most of these AEs were mild in severity and none of these AEs resulted in discontinuation from the study. Given the renal clearance of the active metabolite, LHV527, there was a ~2.7-fold increase in dose-normalized exposure compared to healthy volunteers from the previously conducted first in human study.

Date of Clinical Trial Report

21-Mar-2019 (content final)