

Sponsor

Novartis

Generic Drug Name

Not applicable

Trial Indication(s)

Resistant hypertension

Protocol Number

CLHW090X2101

Protocol Title

A partially-blinded, randomized, placebo-controlled, adaptive single and multiple ascending dose study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of LHW090 in healthy volunteers and in subjects with renal dysfunction

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

01-Mar-2013 to 28-Jun-2014

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This study was an exploratory (non-confirmatory), five stage, multi-center study as follows:

- Stage 1 – an open-label, single dose (1 mg), single administration cohort in healthy volunteers to determine the preliminary pharmacokinetics of LHW090.
- Stage 2 – double-blind, randomized, placebo-controlled, single ascending dose (SAD) cohorts in healthy volunteers to determine safety, tolerability and PK/PD profile of LHW090.
- Stage 3 – double-blind, randomized, placebo-controlled multiple ascending dose (MAD) cohorts in healthy volunteers to determine safety, tolerability and PK/PD profile of LHW090.
- Stage 4 – adaptive, open-label, single dose administration cohorts in subjects with CRI. Two or more doses of LHW090, selected from Stage 2, were tested in Stage 4 to determine the safety, tolerability and PK/PD profile of LHW090 in this subject population.

- Stage 5 –double-blind, randomized, placebo-controlled, MAD cohorts in subjects with CRI. A dose of LHW090 from Stage 4 was tested in Stage 5 to determine the safety, tolerability and PK/PD profile of LHW090 in this subject population. Each subject received 4 doses of LHW090.

Centers

3 centers in 1 country: United States (3)

Objectives:**Primary objective(s)**

- To evaluate the safety and tolerability of single oral doses of LHW090 in healthy volunteers.
- To evaluate the safety and tolerability of multiple oral doses of LHW090 in healthy volunteers.
- To evaluate the safety and tolerability of single oral doses of LHW090 in patients with chronic renal insufficiency.
- To evaluate the safety and tolerability of multiple oral doses of LHW090 in patients with chronic renal insufficiency.

Secondary objective(s)

- To evaluate and compare the pharmacokinetic and pharmacodynamic profiles (i.e., plasma atrial natriuretic peptide (ANP) and cyclic guanosine monophosphate (cGMP) levels) of single doses of LHW090 and its metabolites in healthy volunteers and in subjects with chronic renal insufficiency (CRI).
- To evaluate the pharmacokinetics of LHW090 and its metabolites after single and multiple doses to healthy volunteers.
- To evaluate the pharmacokinetics of LHW090 and its metabolites after single and multiple doses in subjects with CRI.

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

The investigational drug, LHW090, (0.1 mg, 0.5 mg, 1 mg, 12.5 mg, 100 mg and matching placebo capsules)

Statistical Methods

- For primary objective of safety, within each of Stage 2, 3, and 5, placebo subjects from across the cohorts were pooled together for assessment. Summary statistics were provided by treatment and visit/time.
- The secondary PD variables analyzed were plasma cGMP and ANP. Plasma cGMP and ANP were listed by treatment, subject, and visit/time. Summary statistics were provided by treatment and visit/time for each stage.
- Pharmacokinetic (PK) parameters were summarized using descriptive statistics and dose proportionality was assessed using the power model.
- The relationship between PK and key PD parameters (plasma ANP and cGMP) were explored using a graphical approach. Scatter plots along with regression line between plasma PD parameters levels with plasma PK concentration of LHW090 and LHV527 were provided.

Study Population: Key Inclusion/Exclusion Criteria**Inclusion Criteria:**

For Stage 1, 2 and 3 subjects only:

- Subjects eligible for inclusion in these stages of the study have to fulfill all of the following criteria at screening:
- Healthy male and female subjects age 18 to 45 years of age included, and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
- At screening, and first baseline, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the subject has rested for at least three minutes, and again (when required) 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, 90-140 mm Hg diastolic blood pressure, 50-90 mm Hg pulse rate, 40 - 90 bpm

For Stage 4 subjects only:

- Male and female subjects, age 18 to 75 years of age included, with previously identified chronic renal insufficiency (estimated or measured GFR $\leq$ 45ml/min/1.73m², or diabetic with estimated or measured GFR $\leq$ 60ml/min/1.73m².) Diabetes can be established by the prescription and current use of anti-glycemic drugs, a random fasting glucose level of $\geq$ 144mg/dl or a hemoglobin A1c of $\geq$ 6.5%

At screening, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the subject has rested for at least three minutes, and again (when required) 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, 90-179 mm Hg
- diastolic blood pressure, 50-100 mm Hg
- pulse rate, 40 - 95 bpm

Exclusion Criteria:

For Stages 1, 2 and 3, subjects fulfilling any of the following additional criteria are not eligible for inclusion in this study:

- An active history of clinically significant ECG abnormalities as determined by the Investigator, or any of the following ECG abnormalities at Screening or Baseline:
 - Long QT syndrome
 - QTcF > 450 msec (males; at screening)
 - QTcF > 460 msec (females; at screening)
- Known history of current clinically significant arrhythmias.
- Use of phosphodiesterase-5 inhibitors, UNLESS subjects agree to discontinue use of the drug for the duration of the study.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant
- Smokers (use of tobacco products in the previous 3 months). Urine cotinine levels will be measured during screening and at each baseline for all subjects. Smokers will be defined as any subject who reports tobacco use and/or who has a urine cotinine $\geq$ 500 ng/ml.
- Hemoglobin levels below 11.0 g/dl at screening.

Subjects in Stage 3 only of the study will be excluded if they have any of the following:

- A history of allergy to topical anesthetic drops
- A history of corneal disease
- A history of eye surgery within three months prior to screening
- A history of corneal surgery (including refractive surgery and corneal transplantation)

For Stage 4, subjects fulfilling any of the following additional criteria are not eligible for inclusion in this study:

- An active history of clinically significant ECG abnormalities as determined by the Investigator, or any of the following ECG abnormalities at Screening or Baseline:
- Long QT syndrome
- QTcF > 480 msec at screening
- Use of phosphodiesterase-5 inhibitors, UNLESS subjects agree to discontinue use of the drug for the duration of the study.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant
- Significant smokers. Significant smokers who are unable to tolerate using no more than 4 cigarettes a day should be excluded
- History of right ventricular dysfunction within the last 12 months
- Hemoglobin levels below 9.0 g/dl at screening.
- Use of angiotensin converting enzyme inhibitors (ACEi), UNLESS subjects agree to either a withholding of their ACEi, or a switch to an angiotensin receptor blocker, starting 5 days (or 5 half-lives whichever is longer) prior to initiation of study and extending to the end-of-study visit. Patient who withhold their ACEi for the specified duration must first consult with their primary physician to determine their suitability and safety for this temporary withholding of ACEi.
- Diuretic-dependence, i.e. unable to produce urine without diuretics, or at high risk of flash pulmonary edema without diuretics. Use of diuretics will exclude subjects UNLESS subjects agree to withhold diuretics starting the day prior to check-in and extending to discharge. Consultation of the subject with their primary physician must be used to determine their suitability and safety for temporary withholding of their diuretics.

Participant Flow Table

Subject disposition – n (percent) of subjects - Stage 1 (safety analysis set)

	LHW090 1mg N=3
Subjects	
Completed	3 (100)

Subject disposition – n (percent) of subjects - Stage 2 (safety analysis set)

	1mg SAD N=8	5mg SAD N=8	25mg SAD N=8	50mg SAD N=8	100mg SAD N=8	0.1mg SAD N=8	200mg SAD N=8	400mg SAD N=8	800mg SAD N=8	400mg SAD (Japanese ethnicity) N=8	Pooled placebo N=20	Total N=100
Subjects												
Completed	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	20 (100)	100 (100)

Subject disposition - n (percent) of subjects - Stage 3 (Safety analysis set)

	LHW090 5mg MAD N=6	LHW090 25mg MAD N=6	LHW090 50mg MAD N=6	LHW090 100mg MAD N=6	LHW090 200mg MAD N=6	LHW090 400mg MAD N=6	Pooled placebo N=12	Total N=48
Subjects								
Completed	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	12 (100)	48 (100)

Subject disposition – n (percent) of subjects - Stage 4 (Safety analysis set)

	LHW090 5mg SAD N=6	LHW090 12.5mg SAD N=9	LHW090 25mg SAD N=9	LHW090 2mg SAD N=9	LHW090 5mg SAD N=9	Total N=42
Subjects						
Completed	5 (83.3)	9 (100)	9 (100)	9 (100)	9 (100)	41 (97.6)
Discontinued	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Main cause of discontinuation						
Subject withdrew consent	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)

Subject disposition – n (percent) of subjects - Stage 5 (Safety analysis set)

	LHW090 5mg MAD N=9	Pooled placebo N=3	Total N=12
Subjects			
Completed	9 (100)	3 (100)	12 (100)

Baseline Characteristics
Demographic summary by treatment group - Stage 1 (safety analysis set)

		LHW090 1mg N=3
Age (years)	Mean (SD)	25.0 (2.65)
	Median	26.0
	Range	22-27
Height (cm)	Mean (SD)	181.00 (11.358)

		LHW090 1mg N=3
Weight (kg)	Median	176.00
	Range	173.0-194.0
	Mean (SD)	80.97 (16.745)
Body mass index (kg/m ²)	Median	74.40
	Range	68.5-100.0
	Mean (SD)	24.51 (2.250)
Sex – n (%)	Median	24.86
	Range	22.11-26.57
	Male	3 (100)
Predominant race – n (%)	Caucasian	2 (66.7)
	Black	1 (33.3)
	Other	3 (100)

Demographic summary by treatment group - Stage 2 (safety analysis set)

		LHW090 1mg SAD N=8	LHW090 5mg SAD N=8	LHW090 25mg SAD N=8	LHW090 50mg SAD N=8	LHW090 100mg SAD N=8	LHW090 0.1mg SAD N=8	LHW090 200mg SAD N=8	LHW090 400mg SAD N=8	LHW090 800mg SAD N=8	LHW090 400mg SAD (Japanese ethnicity) N=8	Pooled placebo N=20	Total N=100
Age (years)	Mean (SD)	28.0 (6.23)	28.9 (6.77)	26.8 (7.98)	25.4 (4.93)	31.3 (7.44)	30.3 (5.95)	26.4 (7.61)	29.0 (6.93)	33.5 (7.87)	32.5 (8.14)	29.0 (8.20)	29.1 (7.30)
	Median	26.0	25.0	23.0	24.5	29.0	29.0	25.5	28.5	32.0	33.0	29.0	27.5
	Range	21-37	23-40	20-43	20-34	24-45	24-42	20-44	21-41	24-45	19-41	19-43	19-45
Height (cm)	Mean(SD)	179.66 (7.179)	180.18 (8.100)	179.91 (5.731)	183.40 (7.473)	175.94 (5.615)	178.80 (6.158)	179.36 (6.034)	172.70 (4.370)	176.94 (6.361)	170.26 (3.905)	176.71 (6.768)	177.52 (6.872)
	Median	177.65	181.50	179.40	183.00	175.60	179.90	180.85	171.50	175.60	170.55	177.80	177.65
	Range	172.0- 191.4	166.0- 189.0	172.0- 188.5	172.6- 193.0	167.3- 184.0	168.0- 187.0	167.2- 186.1	168.4- 179.5	171.1- 191.0	163.5- 176.1	162.6- 190.0	162.6- 193.0
Weight (kg)	Mean(SD)	86.56 (16.825)	90.06 (12.296)	82.54 (7.799)	85.41 (16.680)	87.56 (12.853)	78.69 (17.487)	91.29 (14.746)	80.14 (6.531)	85.12 (11.945)	70.59 (8.253)	81.66 (13.054)	83.37 (13.489)
	Median	88.55	86.00	85.35	84.05	86.50	77.95	91.35	81.15	89.70	71.25	80.65	82.75
	Range	62.4- 106.0	77.1- 108.6	69.4- 91.5	67.2- 106.7	65.6- 105.6	58.3- 113.7	69.1- 112.3	72.7- 88.3	64.8- 99.1	58.2- 82.0	61.2- 108.8	58.2- 113.7
Body mass index (kg/m2)	Mean(SD)	26.72 (4.411)	27.74 (3.280)	25.47 (1.792)	25.20 (3.255)	28.16 (2.883)	24.49 (4.737)	28.42 (4.708)	26.93 (2.695)	27.18 (3.567)	24.31 (2.309)	26.19 (4.218)	26.41 (3.703)
	Median	27.35	27.05	25.81	25.86	28.53	23.25	29.47	26.85	27.71	24.44	25.23	25.98
	Range	20.56- 32.00	24.06- 33.15	22.15- 27.44	20.89- 29.25	23.44- 32.30	20.66-35.33	22.43- 33.83	23.01- 30.54	21.35- 32.11	20.76- 27.56	19.71- 33.39	19.71- 35.33
Sex - n (%)	Male	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	20 (100)	100 (100)

		LHW090 1mg SAD N=8	LHW090 5mg SAD N=8	LHW090 25mg SAD N=8	LHW090 50mg SAD N=8	LHW090 100mg SAD N=8	LHW090 0.1mg SAD N=8	LHW090 200mg SAD N=8	LHW090 400mg SAD N=8	LHW090 800mg SAD N=8	LHW090 400mg SAD (Japanese ethnicity) N=8	Pooled placebo N=20	Total N=100
Predom inant race - n (%)	Caucasian	6 (75.0)	4 (50.0)	3 (37.5)	7 (87.5)	5 (62.5)	4 (50.0)	8 (100)	2 (25.0)	4 (50.0)	0 (0.0)	16 (80.0)	59 (59.0)
	Black	2 (25.0)	4 (50.0)	5 (62.5)	1 (12.5)	3 (37.5)	4 (50.0)	0 (0.0)	6 (75.0)	4 (50.0)	0 (0.0)	2 (10.0)	31 (31.0)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (100)	2 (10.0)	10 (10.0)
Ethnicit y - n (%)	Hispanic/L atino	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	3 (15.0)	5 (5.0)
	Japanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (100)	2 (10.0)	10 (10.0)
	Mixed ethnicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (5.0)	2 (2.0)
	Other	8 (100)	8 (100)	8 (100)	8 (100)	7 (87.5)	8 (100)	8 (100)	8 (100)	6 (75.0)	0 (0.0)	14 (70.0)	83 (83.0)

Demographic summary by treatment group - Stage 3 (safety analysis set)

		LHW090 5mg MAD N=6	LHW090 25mg MAD N=6	LHW090 50mg MAD N=6	LHW090 100mg MAD N=6	LHW090 200mg MAD N=6	LHW090 400mg MAD N=6	Pooled placebo N=12	Total N=48
Age (years)	Mean(SD)	35.2 (5.31)	28.7 (3.50)	31.5 (8.60)	31.3 (6.74)	37.7 (7.92)	29.7 (7.50)	31.5 (7.06)	32.1 (7.00)
	Median	34.0	27.5	31.0	30.0	39.0	28.5	31.0	33.0
	Range	29-42	25-33	18-42	23-39	24-45	21-42	18-40	18-45
Height (cm)	Mean(SD)	178.08 (5.635)	181.52 (6.868)	171.92 (10.466)	175.17 (6.547)	182.40 (6.630)	169.50 (4.864)	175.53 (8.806)	176.20 (8.200)

		LHW090 5mg MAD N=6	LHW090 25mg MAD N=6	LHW090 50mg MAD N=6	LHW090 100mg MAD N=6	LHW090 200mg MAD N=6	LHW090 400mg MAD N=6	Pooled placebo N=12	Total N=48
Weight (kg)	Median	177.20	178.85	172.85	175.00	183.00	169.60	177.40	175.75
	Range	172.0- 187.4	175.2- 190.5	160.0- 189.0	166.5- 184.5	174.4- 190.0	162.8- 176.4	156.5- 191.0	156.5-191.0
	Mean(SD)	83.95 (7.517)	92.12 (21.760)	78.78 (15.430)	88.30 (18.653)	97.97 (13.698)	80.05 (11.205)	89.03 (14.170)	87.40 (15.324)
	Median	84.00	83.85	77.75	92.45	96.10	82.25	87.30	87.30
	Range	75.7- 93.6	69.0- 128.4	57.1- 102.2	60.0- 112.6	79.8- 122.1	61.4- 90.6	66.5- 112.0	57.1-128.4
	Mean(SD)	26.47 (1.953)	27.83 (5.490)	26.46 (3.098)	28.55 (4.592)	29.35 (2.692)	27.87 (3.895)	28.80 (3.215)	28.02 (3.567)
Body mass index (kg/m ²)	Median	26.45	26.73	27.17	28.57	29.21	28.61	30.03	28.53
	Range	23.23- 28.97	22.35- 35.68	22.30- 29.37	21.64- 34.75	26.24- 33.82	21.70-32.88	20.82- 32.00	20.82-35.68
Sex - n (%)	Male	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	12 (100)	48 (100)
Predominant race - n (%)	Caucasian	5 (83.3)	2 (33.3)	2 (33.3)	1 (16.7)	5 (83.3)	2 (33.3)	6 (50.0)	23 (47.9)
	Black	1 (16.7)	4 (66.7)	3 (50.0)	5 (83.3)	0 (0.0)	1 (16.7)	6 (50.0)	20 (41.7)
	Asian	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	2 (4.2)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (33.3)	0 (0.0)	3 (6.3)
Ethnicity - n (%)	Hispanic/La tino	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	2 (4.2)

		LHW090 5mg MAD N=6	LHW090 25mg MAD N=6	LHW090 50mg MAD N=6	LHW090 100mg MAD N=6	LHW090 200mg MAD N=6	LHW090 400mg MAD N=6	Pooled placebo N=12	Total N=48
	Indian (India subcontine nt)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (2.1)
	Mixed ethnicity	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
	Other	6 (100)	6 (100)	6 (100)	5 (83.3)	5 (83.3)	4 (66.7)	12 (100)	44 (91.7)

Demographic summary by treatment group - Stage 4 (safety analysis set)

		LHW090 5mg SAD N=6	LHW090 12.5mg SAD N=9	LHW090 25mg SAD N=9	LHW090 2mg SAD N=9	LHW090 5mg SAD N=9	Total N=42
Age (years)	Mean (SD)	68.2 (2.86)	68.4 (5.83)	61.2 (8.29)	66.3 (7.25)	62.1 (11.56)	65.0 (8.17)
	Median	68.0	69.0	59.0	69.0	65.0	67.0
	Range	65-73	56-75	53-75	54-74	44-75	44-75
Height (cm)	Mean (SD)	166.28 (11.024)	168.13 (8.273)	163.37 (10.398)	168.71 (11.207)	166.81 (10.705)	166.69 (9.997)
	Median	168.00	169.70	159.40	170.00	169.00	169.25
	Range	147.0-177.0	156.6-183.0	153.5-183.4	147.0-183.3	154.0-189.0	147.0-189.0
Weight (kg)	Mean (SD)	74.75 (12.134)	84.98 (14.260)	84.61 (12.943)	89.62 (15.640)	88.07 (13.176)	85.10 (13.931)
	Median	74.70	84.20	85.10	89.00	85.00	85.05
	Range	56.8-90.3	66.7-108.1	66.5-111.7	58.4-113.7	69.5-111.9	56.8-113.7
Body mass index (kg/m ²)	Mean (SD)	26.97 (2.990)	29.85 (2.600)	31.63 (3.126)	31.25 (2.631)	31.56 (2.758)	30.49 (3.117)
	Median	26.74	28.75	32.00	31.49	31.33	30.00
	Range	22.34-31.25	27.19-34.69	28.22-36.00	27.03-35.65	28.12-35.63	22.34-36.00
Sex - n (%)	Male	5 (83.3)	5 (55.6)	4 (44.4)	6 (66.7)	5 (55.6)	25 (59.5)
	Female	1 (16.7)	4 (44.4)	5 (55.6)	3 (33.3)	4 (44.4)	17 (40.5)

		LHW090 5mg SAD N=6	LHW090 12.5mg SAD N=9	LHW090 25mg SAD N=9	LHW090 2mg SAD N=9	LHW090 5mg SAD N=9	Total N=42
Predominant race - n (%)	Caucasian	4 (66.7)	7 (77.8)	8 (88.9)	9 (100)	5 (55.6)	33 (78.6)
	Black	2 (33.3)	2 (22.2)	1 (11.1)	0 (0.0)	4 (44.4)	9 (21.4)
Ethnicity - n (%)	Hispanic/Latino	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)	1 (11.1)	4 (9.5)
	Mixed ethnicity	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.4)
	Other	6 (100)	9 (100)	7 (77.8)	7 (77.8)	8 (88.9)	37 (88.1)
Creatinine (umol/L)	Mean(SD)	173.3 (60.88)	155.6 (57.47)	142.7 (40.85)	132.1 (26.03)	164.8 (41.92)	
	Median	155	129	138	133	164	
	Range	126-284	100-279	99-232	97-170	102-246	
eGFR (mL/min)	Mean (SD)	34.8 (13.99)	31.0 (8.00)	44.2 (9.99)	42.6 (12.80)	36.0 (7.75)	
	Median	30	31	45	42	35.5	
	Range	19-50	23-39	26-55	28-61	27-47	

Demographic summary by treatment group - Stage 5 (safety analysis set)

		LHW090 5mg MAD N=9	Pooled placebo N=3	Total N=12
Age (years)	Mean(SD)	63.4 (9.25)	65.7 (9.07)	64.0 (8.84)
	Median	67.0	67.0	67.0
	Range	48-74	56-74	48-74
Height (cm)	Mean(SD)	166.08 (11.255)	164.83 (16.024)	165.77 (11.795)
	Median	170.20	156.60	169.75
	Range	146.5-177.0	154.6-183.3	146.5-183.3
Weight (kg)	Mean(SD)	81.73 (14.987)	80.17 (26.235)	81.34 (17.000)
	Median	84.80	66.70	84.30
	Range	52.3-101.4	63.4-110.4	52.3-110.4
Body mass index (kg/m ²)	Mean(SD)	29.60 (4.541)	28.86 (3.477)	29.41 (4.160)
	Median	30.30	27.20	29.77

		LHW090 5mg MAD N=9	Pooled placebo N=3	Total N=12
Sex - n (%)	Range	21.07-35.18	26.53-32.86	21.07-35.18
	Male	6 (66.7)	1 (33.3)	7 (58.3)
	Female	3 (33.3)	2 (66.7)	5 (41.7)
Predominant race - n (%)	Caucasian	6 (66.7)	3 (100)	9 (75.0)
	Black	3 (33.3)	0 (0.0)	3 (25.0)
Ethnicity - n (%)	Mixed ethnicity	4 (44.4)	1 (33.3)	5 (41.7)
	Other	5 (55.6)	2 (66.7)	7 (58.3)
Creatinine (umol/L)	Mean(SD)	176.0 (65.95)	105.7 (6.03)	
	Median	154	105	
	Range	104-290	100-112	
eGFR (mL/min)	Mean(SD)	42.6 (13.99)	55.0 (11.31)	
	Median	44	55	
	Range	19-60	47-63	

Summary of Efficacy**Primary Outcome Result(s)**

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)**Summary statistics of plasma PD markers – Stage 1 PD analysis set**

Treatment	Day	Scheduled time (hr)	Statistics	-----Results-----		-Change from baseline-	
				ANP (pg/mL)	cGMP (nmol/L)	ANP (pg/mL)	cGMP (nmol/L)
LHW090 1mg	Day -1	Pre-Dose	n	3	3		
			Mean	110.4333	4.9300		
			SD	15.82287	1.22282		
			Min	97.300	4.160		
			Median	106.0000	4.2900		
			Max	128.000	6.340		
	Day 1	1 hr Post-Dose	n	3	3	3	3
			Mean	119.3333	3.4133	8.9000	-1.5167
			SD	6.11010	1.32085	11.37673	1.27033
			Min	114.000	1.890	-2.000	-2.270
			Median	118.0000	4.1100	8.0000	-2.2300
			Max	126.000	4.240	20.700	-0.050
		4 hr Post-Dose	n	3	3	3	3
			Mean	130.0000	4.4700	19.5667	-0.4600
			SD	9.53939	2.32697	25.02725	2.29406
			Min	121.000	1.890	-7.000	-2.270

				Median	129.0000	5.1100	23.0000	-1.2300
				Max	140.000	6.410	42.700	2.120
LHW090 1mg	Day 1	8 hr Post-Dose	n	3	3	3	3	
			Mean	103.9333	6.5200	-6.5000	1.5900	
			SD	20.06024	2.12981	11.15303	2.82491	
			Min	86.800	5.110	-19.200	-0.860	
			Median	99.0000	5.4800	-2.0000	0.9500	
			Max	126.000	8.970	1.700	4.680	
	Day 2	24 hr Post-Dose	n	2	3	2	3	
			Mean	112.0000	4.1600	-5.0000	-0.7700	
			SD	7.07107	2.01785	8.48528	1.96924	
			Min	107.000	1.890	-11.000	-2.270	
			Median	112.0000	4.8400	-5.0000	-1.5000	
			Max	117.000	5.750	1.000	1.460	
	Day 3	48 hr Post-Dose	n	3	3	3	3	
			Mean	111.3333	2.5333	0.9000	-2.3967	
			SD	7.02377	1.11429	14.87380	0.12503	
			Min	104.000	1.890	-16.000	-2.520	
			Median	112.0000	1.8900	6.7000	-2.4000	
			Max	118.000	3.820	12.000	-2.270	

Summary statistics of plasma PD markers – Stage 2

Treatment	Day	Scheduled time(hr)	Statistics	-----Results-----			-----Change from baseline-----		
				CYS (ng/mL)	ANP (pg/mL)	cGMP (nmol/L)	CYS (ng/mL)	ANP (pg/mL)	cGMP (nmol/L)
LHW090 1mg SAD	Day -1	Pre-Dose	n	8	2	8			

			Mean	988.5000	47.4500	3.2375			
			SD	133.68299	31.46625	1.96732			
			Min	789.000	25.200	1.890			
			Median	976.0000	47.4500	1.8900			
			Max	1180.000	69.700	6.420			
LHW090 1mg SAD	Day 1	0 hr Pre-Dose	n	8	3	8	8	0	8
			Mean	964.0000	101.0000	3.6775	-24.5000		0.4400
	SD	101.74478	32.79863	2.21736	123.79245		1.03193		
	Min	837.000	75.500	1.890	-200.000		-0.380		
	Median	951.0000	89.5000	2.8900	26.0000		0.0000		
	Max	1130.000	138.000	7.630	146.000		2.410		
	1 hr Post-Dose	n	8	2	8	8	1	8	
		Mean	930.2500	101.7000	2.8450	-58.2500	50.2000	-0.3925	
	SD	88.85261	37.19382	1.35923	76.84260		1.51882		
	Min	789.000	75.400	1.890	-180.000	50.200	-2.490		
	Median	940.5000	101.7000	1.8900	-72.0000	50.2000	0.0000		
	Max	1040.000	128.000	5.130	79.000	50.200	2.360		
	4 hr Post-Dose	n	8	2	8	8	1	8	
		Mean	889.0000	79.0000	4.2012	-99.5000	62.5000	0.9638	
LHW090 1mg SAD	Day 1	4 hr Post-Dose	SD	126.89366	12.30366	2.16709	116.17843		1.11069
			Min	730.000	70.300	1.890	-306.000	62.500	0.000
	Median	907.0000	79.0000	4.3950	-94.0000	62.5000	0.5850		
	Max	1100.000	87.700	7.430	71.000	62.500	2.520		
	8 hr Post-Dose	n	8	4	8	8	1	8	
		Mean	828.0000	87.0500	4.7000	-160.5000	68.9000	1.4625	
	SD	90.24570	7.46436	2.29090	117.53054		1.20292		
	Min	726.000	80.500	1.890	-411.000	68.900	0.000		
	Median	809.5000	86.8000	4.6100	-122.5000	68.9000	1.5500		

			Max	1010.000	94.100	8.400	-50.000	68.900	3.260
		12 hr Post-Dose	n	8	4	8	8	1	8
			Mean	754.5000	61.6750	5.2187	-234.0000	-5.0000	1.9813
			SD	111.42711	26.03528	3.08089	124.17499		2.10417
			Min	590.000	25.200	1.890	-507.000	-5.000	-2.240
			Median	770.0000	67.4500	4.5750	-203.5000	-5.0000	2.6850
			Max	960.000	86.600	10.300	-114.000	-5.000	4.400
LHW090 1mg SAD	Day 2	24 hr Post-Dose	n	8	2	8	8	1	8
			Mean	778.2500	141.6500	4.1087	-210.2500	62.1000	0.8713
			SD	97.40160	76.86251	2.63362	93.89926		1.06892
			Min	673.000	87.300	1.890	-362.000	62.100	0.000
			Median	744.0000	141.6500	3.2850	-209.0000	62.1000	0.4200
			Max	943.000	196.000	8.050	-46.000	62.100	2.790
	Day 4	72 hr Post-Dose	n	8	4	8	8	0	8
			Mean	659.3750	86.5250	5.4075	-329.1250		2.1700
			SD	93.52148	60.15909	3.52602	88.75236		1.99896
			Min	550.000	25.200	1.890	-496.000		0.000
			Median	657.5000	75.9500	5.3550	-294.5000		2.3450
			Max	841.000	169.000	10.900	-239.000		4.480
	Day -1	Pre-Dose	n	8	8	8			
			Mean	763.2500	131.3750	5.3387			
			SD	96.37686	16.66423	3.50138			
			Min	613.000	108.000	1.890			
			Median	793.5000	134.5000	5.0300			
			Max	864.000	160.000	13.100			
LHW090 5mg SAD	Day 1	0 hr	n	8	8	8	8	8	8

LHW090 5mg SAD	Day 1	Pre-Dose	Mean	778.8750	124.1250	6.2937	15.6250	-7.2500	0.9550
			SD	124.44096	8.32273	6.58463	73.84141	17.66150	6.93059
			Min	610.000	112.000	1.890	-81.000	-33.000	-7.820
			Median	812.5000	124.0000	4.9000	10.0000	-6.5000	0.0650
			Max	908.000	135.000	21.800	157.000	18.000	16.510
		1 hr Post-Dose	n	8	8	8	8	8	8
			Mean	746.5000	124.0000	6.8437	-16.7500	-7.3750	1.5050
			SD	103.99863	10.99350	6.82720	108.02612	14.07061	7.23692
			Min	610.000	109.000	1.890	-113.000	-30.000	-8.040
			Median	746.5000	125.0000	4.8550	-64.5000	-1.5000	0.1200
			Max	955.000	138.000	23.100	204.000	7.000	17.810
		4 hr Post-Dose	n	8	8	8	8	8	8
			Mean	733.7500	121.2750	7.3750	-29.5000	-10.1000	2.0362
			SD	103.39211	41.89960	6.48588	80.10885	42.24919	6.32782
			Min	551.000	25.200	1.890	-133.000	-104.800	-5.100
			Median	730.0000	140.5000	6.9050	-40.0000	-4.0000	0.5200
			Max	881.000	149.000	21.300	130.000	31.000	16.010
		8 hr Post-Dose	n	8	7	8	8	7	8
			Mean	679.1250	134.1429	7.6187	-84.1250	0.7143	2.2800
			SD	89.47695	15.12645	3.89217	61.24293	24.44527	3.07694
			Min	541.000	111.000	1.890	-150.000	-28.000	-1.900
			Median	698.5000	135.0000	7.1750	-100.0000	-7.0000	2.1450
			Max	795.000	152.000	13.900	44.000	44.000	8.610
		12 hr Post-Dose	n	8	8	8	8	8	8
			Mean	679.1250	133.1250	7.2587	-84.1250	1.7500	1.9200
			SD	99.50368	8.59298	5.07527	98.19432	18.78259	4.93893
			Min	544.000	116.000	1.890	-246.000	-23.000	-4.150
			Median	681.0000	134.5000	6.8750	-95.0000	-4.0000	1.8050

			Max	840.000	146.000	17.500	89.000	28.000	12.210
LHW090 5mg SAD	Day 2	24 hr Post-Dose	n	8	8	8	8	8	8
			Mean	754.5000	131.0000	5.4700	-8.7500	-0.3750	0.1313
			SD	122.48382	9.30438	3.02232	72.92805	16.73267	3.97190
			Min	559.000	118.000	1.890	-142.000	-16.000	-7.470
			Median	814.5000	130.5000	5.3900	-13.0000	-8.5000	0.3600
			Max	867.000	145.000	11.400	116.000	23.000	6.110
	Day 4	72 hr Post-Dose	n	8	8	8	8	8	8
			Mean	714.0000	119.1250	4.3175	-49.2500	-12.2500	-1.0213
			SD	115.56074	12.86676	2.77751	66.62850	18.62218	4.22856
			Min	564.000	101.000	1.890	-131.000	-38.000	-9.240
			Median	736.0000	120.5000	4.2250	-52.0000	-11.5000	-0.6900
			Max	867.000	139.000	10.200	70.000	21.000	4.910
LHW090 25mg SAD	Day -1	Pre-Dose	n	8	8	8			
			Mean	818.7500	132.0000	4.6437			
			SD	170.00231	46.20065	2.92305			
			Min	556.000	87.500	1.890			
			Median	852.0000	119.0000	4.0400			
			Max	1040.000	212.000	9.860			
	Day 1	0 hr Pre-Dose	n	8	8	8	8	8	8
			Mean	846.7500	104.1500	3.6175	28.0000	-27.8500	-1.0263
			SD	130.73501	24.71922	1.98204	164.74222	29.09438	1.98923
			Min	647.000	73.600	1.890	-251.000	-83.000	-4.970
			Median	833.0000	103.9500	3.0950	18.5000	-17.5000	-0.0500
			Max	1030.000	153.000	6.870	290.000	7.000	1.280
		1 hr	n	8	8	8	8	8	8

				Post-Dose										
				Mean	780.0000	123.7750	4.2650	-38.7500	-8.2250	-0.3788				
				SD	106.63154	31.09753	3.00626	193.70578	28.16253	2.09145				
				Min	626.000	80.400	1.890	-329.000	-67.000	-4.150				
				Median	769.0000	119.5000	3.1200	-93.0000	-4.0000	0.0000				
				Max	928.000	176.000	10.100	277.000	30.000	3.130				
LHW090 25mg SAD	Day 1	4 hr	n	8	8	8	8	8	8	8				
		Post-Dose												
				Mean	782.5000	149.4375	7.9237	-36.2500	17.4375	3.2800				
				SD	72.45886	53.73442	4.26806	224.33569	16.32141	3.07208				
				Min	661.000	97.500	1.890	-379.000	-10.000	-1.070				
				Median	791.5000	126.0000	8.9800	-53.0000	23.0000	4.7900				
				Max	881.000	235.000	13.100	299.000	38.000	6.130				
				8 hr	n	8	7	8	8	7	8			
				Post-Dose										
				Mean	763.2500	139.3714	9.3075	-55.5000	1.8714	4.6638				
				SD	91.52166	43.39085	4.56234	180.00952	15.47091	4.09219				
				Min	561.000	75.600	5.130	-313.000	-13.000	-3.370				
				Median	777.5000	139.0000	7.3250	-86.5000	-5.0000	4.0050				
				Max	853.000	199.000	17.100	187.000	24.000	10.130				
				12 hr	n	8	6	8	8	6	8			
				Post-Dose										
				Mean	776.8750	122.4500	10.2963	-41.8750	-13.8833	5.6525				
				SD	134.55263	45.72692	3.44433	212.33426	27.84094	2.19858				
				Min	475.000	95.800	5.050	-355.000	-65.000	1.840				
				Median	816.0000	99.8500	11.1000	-101.5000	-2.0000	6.1600				
				Max	900.000	212.000	15.100	224.000	9.700	8.130				
LHW090 25mg SAD	Day 2	24 hr	n	8	7	8	8	7	8					
		Post-Dose												
				Mean	817.2500	111.5286	7.1900	-1.5000	-22.9000	2.5463				
				SD	165.29087	18.54191	2.16082	164.51227	34.71575	1.54702				
				Min	599.000	82.100	4.570	-213.000	-74.000	-1.010				
				Median	836.5000	118.0000	6.7850	-49.5000	-6.0000	2.7850				
		Max	1090.000	138.000	10.900	265.000	9.500	3.930						

LHW090 50mg SAD	Day 4	72 hr Post-Dose	n	8	6	8	8	6	8
			Mean	814.0000	101.1167	4.3400	-4.7500	-36.5500	-0.3037
			SD	145.86001	39.86258	2.03383	278.29622	34.84450	2.39662
			Min	585.000	58.200	1.890	-317.000	-88.000	-4.970
			Median	834.5000	101.2000	4.4400	-56.0000	-36.6500	0.2900
			Max	1080.000	157.000	8.320	429.000	10.000	2.370
	Day -1	Pre-Dose	n	8	7	8			
			Mean	974.6250	118.5286	4.1675			
			SD	137.26402	39.48691	2.25840			
			Min	742.000	64.300	1.890			
			Median	1035.0000	124.0000	4.3050			
			Max	1090.000	177.000	8.300			
	Day 1	0 hr Pre-Dose	n	8	7	8	8	6	8
			Mean	935.1250	85.1714	4.2325	-39.5000	-19.3167	0.0650
			SD	110.32735	39.19025	1.59228	63.82118	24.62490	2.06625
			Min	739.000	25.200	1.890	-133.000	-46.200	-2.540
			Median	952.5000	92.5000	4.5900	-21.0000	-22.2500	0.0950
			Max	1100.000	139.000	5.770	42.000	18.000	3.630
		1 hr Post-Dose	n	8	7	8	8	7	8
			Mean	856.3750	123.8429	4.2662	-118.2500	5.3143	0.0988
			SD	121.03357	37.71330	1.57874	48.10034	24.13955	2.42059
			Min	673.000	61.700	1.890	-218.000	-35.000	-3.280
			Median	900.0000	131.0000	4.5100	-115.0000	10.0000	0.1250
			Max	972.000	167.000	5.990	-68.000	38.000	4.100
	Day 1	4 hr Post-Dose	n	8	4	8	8	4	8
			Mean	827.8750	151.5000	6.6163	-146.7500	37.1750	2.4488
			SD	92.92153	22.88376	1.78846	83.46043	31.63736	2.47474
			Min	678.000	128.000	4.230	-254.000	-8.000	-1.990

LHW090 50mg SAD	Day 2	8 hr Post-Dose	Median	833.5000	152.0000	6.5300	-154.5000	46.5000	2.2650
			Max	989.000	174.000	10.300	5.000	63.700	6.050
		8 hr Post-Dose	n	8	7	8	8	7	8
			Mean	779.1250	112.2000	8.3187	-195.5000	-6.3286	4.1513
			SD	78.34072	40.50593	3.87596	101.08836	40.70654	3.73167
			Min	621.000	57.500	1.890	-318.000	-55.000	0.000
			Median	798.0000	108.0000	8.2200	-211.0000	-17.0000	3.6400
			Max	859.000	191.000	15.600	-15.000	70.000	11.350
		12 hr Post-Dose	n	8	7	7	8	6	7
			Mean	701.0000	101.0857	6.8329	-273.6250	-5.2500	2.6771
			SD	129.50124	41.97171	1.58123	97.29475	28.45064	2.34591
			Min	531.000	25.200	4.320	-458.000	-39.100	0.170
			Median	713.5000	96.0000	6.8500	-259.0000	-8.5000	2.4300
			Max	871.000	156.000	8.520	-140.000	35.000	6.630
	Day 4	24 hr Post-Dose	n	8	6	8	8	5	8
			Mean	821.3750	85.2833	7.5863	-153.2500	-26.9800	3.4188
			SD	103.92296	40.49209	2.17397	108.26786	50.67052	2.36453
			Min	682.000	25.200	4.670	-384.000	-94.200	-0.750
			Median	852.0000	85.0500	7.1700	-150.0000	-31.0000	4.1050
			Max	944.000	150.000	10.800	-52.000	29.000	6.550
		72 hr Post-Dose	n	8	7	8	8	6	8
			Mean	834.0000	80.5000	4.9750	-140.6250	-28.4000	0.8075
			SD	136.41533	35.39195	1.59762	127.35209	19.16319	1.86847
			Min	644.000	25.200	1.890	-260.000	-50.400	-3.120
			Median	817.5000	82.8000	5.1450	-169.5000	-31.6000	1.4750
			Max	1090.000	134.000	6.590	129.000	-4.700	2.520
LHW090 100mg	Day -1	Pre-Dose	n	8	8	8			

SAD

			Mean	927.0000	90.6875	3.5275			
			SD	114.44899	11.63142	1.81461			
			Min	796.000	74.000	1.890			
			Median	887.0000	89.5000	3.1800			
			Max	1160.000	105.000	5.830			
LHW090 100mg SAD	Day 1	0 hr Pre-Dose	n	8	8	8	8	8	8
			Mean	974.2500	85.2125	4.2387	47.2500	-5.4750	0.7113
			SD	161.63694	11.49552	2.82882	107.78119	6.08223	1.49018
			Min	735.000	67.600	1.890	-122.000	-14.900	-0.490
			Median	1003.0000	86.8500	2.9350	47.0000	-5.9500	0.0000
			Max	1150.000	101.000	8.680	210.000	2.300	4.080
		1 hr Post-Dose	n	8	8	8	8	8	8
			Mean	880.5000	94.3750	4.1862	-46.5000	3.6875	0.6588
			SD	162.93820	19.93939	2.05910	123.76475	13.49809	1.02591
			Min	671.000	65.500	1.890	-186.000	-11.900	-0.040
			Median	899.5000	91.2000	4.6000	-63.0000	4.2500	0.0650
			Max	1090.000	125.000	6.940	190.000	24.000	2.340
		4 hr Post-Dose	n	8	8	8	8	8	8
			Mean	867.5000	109.5375	6.8125	-59.5000	18.8500	3.2850
			SD	129.94504	21.42728	3.27824	84.97899	14.41646	2.31134
			Min	675.000	82.400	1.890	-182.000	-6.400	0.000
			Median	876.5000	108.5000	7.3500	-67.0000	17.4000	4.6200
			Max	1030.000	144.000	10.700	54.000	42.000	5.290
		8 hr Post-Dose	n	8	8	8	8	8	8
			Mean	837.5000	110.7625	9.1538	-89.5000	20.0750	5.6263
			SD	122.55494	20.43400	2.69467	109.04652	12.95870	2.42315
			Min	643.000	83.800	4.490	-239.000	1.500	2.600
			Median	825.5000	114.5000	9.8050	-73.5000	18.9000	5.2900
			Max	1010.000	146.000	13.000	79.000	44.000	8.910

			12 hr Post-Dose	n	8	8	8	8	8	8
				Mean	874.2500	104.4875	8.2625	-52.7500	13.8000	4.7350
				SD	130.59397	17.04209	2.95415	112.10295	8.41954	2.55164
				Min	652.000	80.500	4.560	-201.000	-1.500	1.770
				Median	900.5000	106.5000	8.6050	-69.0000	15.1000	4.0800
				Max	1040.000	128.000	13.100	140.000	27.000	8.610
LHW090 100mg SAD	Day 2	24 hr Post-Dose		n	8	8	8	8	8	8
				Mean	926.7500	90.3125	7.9725	-0.2500	-0.3750	4.4450
				SD	115.08848	10.41173	2.86174	104.05184	6.78312	2.68083
				Min	754.000	76.200	3.830	-103.000	-10.800	1.310
				Median	938.5000	93.6000	7.2050	-4.5000	1.7500	4.0050
				Max	1070.000	104.000	13.100	201.000	8.600	9.110
	Day 4	72 hr Post-Dose		n	8	7	8	8	7	8
				Mean	944.7500	87.7000	4.7612	17.7500	-5.3714	1.2338
				SD	142.49185	22.07291	2.44500	142.34540	18.32327	1.79067
				Min	711.000	67.000	1.890	-150.000	-21.800	-1.370
				Median	970.5000	86.1000	4.5600	7.5000	-10.3000	1.1450
				Max	1130.000	133.000	8.590	271.000	31.000	3.990
LHW090 0.1mg SAD	Day -1	Pre-Dose		n		8	8			
				Mean		92.5000	5.1862			
				SD		21.86641	2.32882			
				Min		67.600	1.890			
				Median		85.1000	5.4450			
				Max		133.000	8.070			
	Day 1	0 hr Pre-Dose		n		7	8		7	8
				Mean		75.2571	4.1025		-13.6000	-1.0838
				SD		44.78612	1.63913		32.30062	1.18680
				Min		25.200	1.890		-65.700	-3.540

			Median	66.0000	4.2500	-14.4000	-1.0100
			Max	150.000	6.780	27.000	0.000
LHW090 0.1mg Day 1 SAD	1 hr Post-Dose	n		8	8	8	8
		Mean		79.0375	3.6812	-13.4625	-1.5050
		SD		18.26417	1.60566	24.74637	1.58714
		Min		52.700	1.890	-49.100	-4.150
		Median		80.6500	4.0900	-9.6000	-1.0150
		Max		97.700	6.000	13.900	0.000
	4 hr Post-Dose	n		8	8	8	8
		Mean		87.8375	3.3750	-4.6625	-1.8113
		SD		35.18875	1.69380	23.02576	1.46255
		Min		71.400	1.890	-40.400	-3.640
		Median		73.7000	2.8850	-7.8000	-1.8650
		Max		174.000	6.000	41.000	0.000
	8 hr Post-Dose	n		7	8	7	8
		Mean		81.4000	5.0487	-14.6571	-0.1375
		SD		21.13078	2.42865	25.85362	1.91010
		Min		57.300	1.890	-60.700	-3.640
		Median		77.2000	5.0750	-5.4000	-0.0700
		Max		112.000	9.160	21.100	3.140
	12 hr Post-Dose	n		8	8	8	8
		Mean		80.8875	4.7937	-11.6125	-0.3925
		SD		29.61112	1.93113	39.45060	0.95528
		Min		25.200	1.890	-92.800	-1.690
		Median		81.9500	5.3700	-2.9500	-0.3450
		Max		121.000	6.560	39.000	1.060
LHW090 0.1mg Day 2 SAD	24 hr Post-Dose	n		8	8	8	8
		Mean		92.3000	4.6475	-0.2000	-0.5388

			SD	12.56321	2.30787	23.70256	1.05310
			Min	72.300	1.890	-45.700	-2.260
			Median	95.9500	4.5950	7.7000	-0.2550
			Max	106.000	9.030	22.600	1.080
Day 4	72 hr	n		8	8	8	8
	Post-Dose						
		Mean		78.4000	4.9687	-14.1000	-0.2175
		SD		26.81892	1.85133	20.16914	1.73581
		Min		25.200	1.890	-42.400	-3.100
		Median		79.9500	4.6600	-13.1500	-0.1450
		Max		108.000	7.780	19.000	2.420
LHW090 200mg SAD	Day -1	Pre-Dose	n	8	8		
		Mean		823.7500	4.2900		
		SD		140.09053	2.53043		
		Min		594.000	1.890		
		Median		799.5000	4.3550		
		Max		1080.000	9.260		
Day 1	0 hr	n		8	8	8	8
	Pre-Dose						
		Mean		907.0000	4.0237	83.2500	-0.2662
		SD		96.18286	1.36192	65.96915	2.32523
		Min		767.000	1.890	-10.000	-3.940
		Median		900.0000	4.5650	98.5000	-0.5850
		Max		1070.000	5.320	173.000	3.110
	1 hr	n		8	8	8	8
	Post-Dose						
		Mean		889.6250	3.5012	65.8750	-0.7888
		SD		96.09956	1.36636	99.03309	1.96864
		Min		768.000	1.890	-83.000	-4.780
		Median		896.0000	4.1250	73.5000	-0.4350
		Max		997.000	5.000	209.000	2.050

LHW090 200mg SAD	Day 1	4 hr Post-Dose	n	8	8	8	8
			Mean	859.7500	7.4513	36.0000	3.1613
			SD	91.74304	2.19418	98.69868	1.68878
			Min	732.000	4.330	-85.000	1.290
			Median	866.0000	7.6850	25.5000	2.4400
			Max	995.000	11.700	208.000	5.980
		8 hr Post-Dose	n	8	8	8	8
			Mean	813.2500	10.3188	-10.5000	6.0288
			SD	81.74656	3.53098	112.78678	2.10875
			Min	683.000	6.720	-223.000	3.140
			Median	828.0000	9.4550	-19.0000	5.8850
			Max	912.000	16.200	137.000	9.620
		12 hr Post-Dose	n	8	8	8	8
			Mean	771.2500	9.7563	-52.5000	5.4663
			SD	103.07799	3.72248	91.16547	2.82838
			Min	634.000	5.310	-220.000	1.400
			Median	768.0000	8.2100	-42.0000	5.6100
			Max	958.000	16.500	40.000	10.820
LHW090 200mg SAD	Day 2	24 hr Post-Dose	n	8		8	
			Mean	882.3750		58.6250	
			SD	102.59760		94.78689	
			Min	771.000		-50.000	
			Median	854.0000		26.5000	
			Max	1030.000		232.000	
	Day 4	72 hr Post-Dose	n	8		8	
			Mean	906.0000		82.2500	
			SD	81.31245		86.75046	
			Min	809.000		-60.000	
			Median	912.0000		63.0000	

				Max	1020.000	215.000			
LHW090 400mg SAD	Day -1	Pre-Dose	n	8	5	8			
			Mean	1064.7500	46.3800	3.3025			
			SD	196.79631	23.46097	1.58283			
			Min	689.000	13.900	1.890			
			Median	1100.0000	42.8000	2.9700			
			Max	1300.000	71.700	5.670			
	Day 1	0 hr Pre-Dose	n	8	8	8	8	5	8
			Mean	1084.3750	36.9500	2.6962	19.6250	-7.3600	-0.6063
			SD	158.25832	17.96886	1.50850	119.13011	9.29882	1.03080
			Min	822.000	13.900	1.890	-240.000	-21.400	-2.380
			Median	1110.0000	36.0500	1.8900	30.0000	-2.0000	-0.0750
			Max	1240.000	65.500	5.520	140.000	0.000	0.000
		1 hr Post-Dose	n	8	8	8	8	5	8
			Mean	971.1250	60.4375	3.0050	-93.6250	14.0400	-0.2975
SD			140.02289	13.10997	1.61566	106.66896	15.23821	0.77106	
Min			743.000	35.800	1.890	-270.000	-1.000	-2.160	
Median			1020.0000	64.5500	1.8900	-97.0000	15.8000	0.0000	
Max			1140.000	77.200	5.670	54.000	34.400	0.190	
LHW090 400mg SAD		4 hr Post-Dose	n	8	8	8	8	5	8
			Mean	918.3750	91.2625	6.7775	-146.3750	45.0800	3.4750
			SD	106.10364	6.50647	2.26457	106.30272	19.00610	2.01660
			Min	776.000	82.000	3.940	-259.000	26.300	0.960
			Median	927.5000	91.3000	6.8050	-164.5000	49.7000	3.1850
			Max	1070.000	101.000	9.650	87.000	71.900	7.760
	8 hr Post-Dose	n	8	5	8	8	4	8	
		Mean	869.5000	65.9400	10.9925	-195.2500	14.8500	7.6900	
		SD	125.54680	9.30554	3.07060	156.99932	18.19826	3.11595	

					Min	731.000	52.300	6.590	-378.000	-5.300	4.700
					Median	825.0000	69.4000	11.8000	-228.5000	16.1500	6.9400
					Max	1130.000	76.100	15.300	122.000	32.400	13.410
LHW090 400mg SAD	Day 2	12 hr Post-Dose	n	8	3	8	8	3	8		
			Mean	794.0000	55.4000	9.3275	-270.7500	-4.9333	6.0250		
		SD	120.91674	6.42106	1.30117	173.18260	14.88836	2.26320			
		Min	684.000	51.300	7.080	-450.000	-20.400	2.780			
		Median	748.0000	52.1000	9.4150	-326.5000	-3.7000	5.4600			
		Max	1000.000	62.800	11.500	67.000	9.300	9.610			
		Day 4	24 hr Post-Dose	n	8			8			
	Mean			823.2500			-241.5000				
	SD		118.98950			168.36270					
	Min		720.000			-412.000					
	Median		776.5000			-302.0000					
	Max		1070.000			86.000					
	Day 4	72 hr Post-Dose	n	8			8				
			Mean	858.6250			-206.1250				
		SD	132.12217			174.69029					
		Min	748.000			-352.000					
		Median	807.5000			-272.0000					
		Max	1120.000			156.000					
LHW090 800mg SAD	Day -1	Pre-Dose	n	8		8					
			Mean	781.1250		3.1200					
		SD	74.86070		1.77678						
		Min	636.000		1.890						
		Median	789.5000		1.8900						
		Max	868.000		6.300						

LHW090 800mg SAD	Day 1	0 hr Pre-Dose	n	8	8	8	8
			Mean	805.2500	2.4937	24.1250	-0.6263
			SD	63.63231	1.70766	128.46393	1.29794
			Min	735.000	1.890	-103.000	-2.790
			Median	793.5000	1.8900	-1.0000	0.0000
			Max	926.000	6.720	290.000	0.420
		1 hr Post-Dose	n	8	8	8	8
			Mean	850.8750	3.9712	69.7500	0.8513
			SD	141.32176	1.86832	200.54764	1.71958
			Min	746.000	1.890	-99.000	-1.110
			Median	796.5000	4.2800	21.0000	0.0000
			Max	1170.000	6.250	534.000	4.210
		4 hr Post-Dose	n	8	8	8	8
			Mean	833.8750	8.4862	52.7500	5.3663
			SD	192.84223	3.75043	253.97849	2.74471
			Min	669.000	1.890	-199.000	0.000
			Median	765.5000	9.2600	11.5000	6.0600
			Max	1260.000	12.700	624.000	8.170
		8 hr Post-Dose	n	8	8	8	8
			Mean	710.2500	10.8363	-70.8750	7.7163
			SD	96.51462	4.20053	112.78353	3.91034
			Min	573.000	5.180	-264.000	3.290
			Median	719.5000	10.8000	-52.0000	7.7050
			Max	872.000	17.900	81.000	16.010
		12 hr Post-Dose	n	8	8	8	8
			Mean	771.1250	9.5825	-10.0000	6.4625
			SD	106.97188	3.26627	93.77024	3.07844
			Min	660.000	6.280	-177.000	1.720
			Median	710.5000	8.8100	-7.0000	6.9200

			Max	912.000	14.200	121.000	12.310
LHW090 800mg SAD	Day 2	24 hr Post-Dose	n	8		8	
			Mean	707.0000		-74.1250	
			SD	74.35629		135.61125	
			Min	656.000		-190.000	
			Median	684.0000		-109.0000	
			Max	881.000		245.000	
	Day 4	72 hr Post-Dose	n	8		8	
			Mean	779.0000		-2.1250	
			SD	163.52108		226.62583	
			Min	662.000		-155.000	
			Median	719.5000		-91.5000	
			Max	1170.000		534.000	
LHW090 400mg SAD (Japanese ethnicity)	Day -1	Pre-Dose	n		8		
			Mean		1.8900		
			SD		0.00000		
			Min		1.890		
			Median		1.8900		
			Max		1.890		
	Day 1	0 hr Pre-Dose	n		8		8
			Mean		1.8900		0.0000
			SD		0.00000		0.00000
			Min		1.890		0.000
			Median		1.8900		0.0000
			Max		1.890		0.000

LHW090 400mg SAD (Japanese ethnicity)	Day 1	1 hr Post-Dose	n			8	8
			Mean			1.8900	0.0000
			SD			0.00000	0.00000
			Min			1.890	0.000
			Median			1.8900	0.0000
			Max			1.890	0.000
		4 hr Post-Dose	n			8	8
			Mean			2.8725	0.9825
			SD			1.88878	1.88878
			Min			1.890	0.000
			Median			1.8900	0.0000
			Max			6.770	4.880
		8 hr Post-Dose	n			8	8
			Mean			3.3737	1.4838
			SD			2.27880	2.27880
			Min			1.890	0.000
			Median			1.8900	0.0000
			Max			7.840	5.950
		12 hr Post-Dose	n			8	8
			Mean			3.0525	1.1625
			SD			2.18667	2.18667
			Min			1.890	0.000
			Median			1.8900	0.0000
			Max			7.260	5.370
Pooled placebo	Day -1	Pre-Dose	n	16	13	20	
			Mean	884.0000	102.9154	3.8120	
			SD	175.91589	35.28935	1.97159	
			Min	582.000	36.100	1.890	

			Median	899.5000	111.0000	3.8700			
			Max	1140.000	166.000	6.920			
Pooled placebo	Day 1	0 hr Pre-Dose	n	16	14	20	16	13	20
			Mean	902.8125	91.2429	3.3030	18.8125	-6.5923	-0.5090
			SD	150.03165	35.81673	1.73865	123.65070	19.47496	1.29601
			Min	633.000	25.200	1.890	-159.000	-37.900	-3.620
			Median	874.5000	93.2500	1.8900	10.0000	-1.0000	0.0000
			Max	1150.000	165.000	6.980	264.000	21.900	2.250
		1 hr Post-Dose	n	16	13	20	16	12	20
			Mean	887.8125	91.7462	2.6255	3.8125	-6.5333	-1.1865
			SD	132.59322	42.34180	1.33724	144.10192	24.77199	1.43327
			Min	687.000	48.300	1.890	-224.000	-50.100	-5.030
			Median	891.0000	80.6000	1.8900	10.0000	4.2000	-0.6450
			Max	1150.000	195.000	5.490	310.000	29.000	0.000
	Day 1	4 hr Post-Dose	n	16	12	20	16	11	20
			Mean	878.8750	90.3583	3.7210	-5.1250	-7.0182	-0.0910
			SD	141.26895	32.57809	3.21579	160.21272	16.26209	2.67393
			Min	624.000	48.500	1.890	-238.000	-29.400	-3.620
			Median	889.5000	87.8500	1.8900	2.5000	-6.6000	0.0000
			Max	1080.000	150.000	14.400	313.000	19.300	9.080
		8 hr Post-Dose	n	16	13	20	16	12	20
			Mean	850.6875	91.0077	3.5455	-33.3125	-11.9917	-0.2665
			SD	82.67907	30.16188	1.61010	161.77751	24.00149	1.45745
			Min	724.000	25.200	1.890	-398.000	-58.000	-3.620
			Median	858.0000	91.0000	4.0550	-15.0000	-8.5500	0.0000
			Max	979.000	147.000	5.850	220.000	22.600	2.830
		12 hr Post-Dose	n	16	13	20	16	12	20
			Mean	818.8125	82.3231	3.6455	-65.1875	-21.4000	-0.1665

			SD	128.27950	24.11705	1.74112	208.44703	26.93342	1.58966
			Min	532.000	25.200	1.890	-444.000	-81.500	-3.620
			Median	840.0000	84.5000	3.9000	-45.5000	-16.3500	0.0000
			Max	1020.000	124.000	6.310	237.000	13.900	3.730
Pooled placebo	Day 2	24 hr Post-Dose	n	16	12	12	16	11	12
			Mean	874.4375	98.0667	3.6750	-9.5625	-10.7182	-0.3658
			SD	117.23763	25.77907	1.73155	203.53901	24.48485	1.67068
			Min	640.000	52.900	1.890	-355.000	-65.000	-3.620
			Median	878.5000	97.2500	3.9200	9.5000	-10.0000	-0.0200
			Max	1050.000	145.000	6.330	361.000	15.000	2.120
	Day 4	72 hr Post-Dose	n	16	11	12	16	10	12
			Mean	818.1875	93.5909	3.6017	-65.8125	-20.3200	-0.4392
			SD	128.83851	18.88234	1.88761	232.38021	18.81901	0.70401
			Min	588.000	58.600	1.890	-403.000	-55.000	-2.010
			Median	813.5000	93.1000	2.8800	-69.5000	-15.1000	0.0000
			Max	1020.000	128.000	6.310	415.000	5.200	0.270

Summary statistics of plasma PD markers – Stage 3

Treatment	Day	Scheduled time(hr)	Statistics	-----Results-----			-----Change from baseline-----		
				CYS (ng/mL)	ANP (pg/mL)	cGMP (nmol/L)	CYS (ng/mL)	ANP (pg/mL)	cGMP (nmol/L)
LHW090 5mg MAD	Day 1	Pre-Dose	n			6			
			Mean			4.4650			
			SD			1.42102			
			Min			1.890			
			Median			5.0750			
			Max			5.500			
	Day 2	Pre-Dose	n			6			6
			Mean			5.6817			1.2167
			SD			1.31618			1.11002

			Min	3.820	-0.360
			Median	5.6750	1.6100
			Max	7.840	2.340
	Day 5	Pre-Dose	n	6	6
			Mean	5.7067	1.2417
			SD	2.33717	2.45716
			Min	1.890	-3.530
			Median	5.6900	1.8950
			Max	8.470	3.100
LHW090 5mg MAD	Day 14	Pre-Dose	n	6	6
			Mean	5.9017	1.4367
			SD	2.02781	1.53402
			Min	4.070	-0.010
			Median	5.0850	1.2000
			Max	9.550	4.050
	Day 17	72 hr Post-Dose	n	6	6
			Mean	4.0167	-0.4483
			SD	1.68644	1.55281
			Min	1.890	-3.560
			Median	4.6950	0.0600
			Max	5.540	0.740
LHW090 25m g MAD	Day 1	Pre-Dose	n	6	
			Mean	5.5117	
			SD	5.27491	
			Min	1.890	
			Median	3.9350	
			Max	15.900	
	Day 2	Pre-Dose	n	5	5

			Mean	7.3020	3.8680
			SD	4.99563	3.78619
			Min	4.060	1.380
			Median	5.3400	2.4900
			Max	16.100	10.580
	Day 5	Pre-Dose	n	6	6
			Mean	10.5750	5.0633
			SD	12.23508	14.43990
			Min	1.890	-14.010
			Median	4.9350	3.0150
			Max	34.300	30.390
LHW090 25m g MAD	Day 14	Pre-Dose	n	6	6
			Mean	7.2467	1.7350
			SD	4.85508	7.78604
			Min	4.230	-11.670
			Median	4.7400	2.7200
			Max	16.500	12.590
	Day 17	72 hr Post-Dose	n	6	6
			Mean	6.0600	0.5483
			SD	5.26727	7.57293
			Min	1.890	-11.610
			Median	4.1450	1.0550
			Max	15.500	11.590
LHW090 50m g MAD	Day 1	Pre-Dose	n	6	
			Mean	3.6483	
			SD	2.10391	
			Min	1.890	

			Median	3.0900	
			Max	6.890	
	Day 2	Pre-Dose	n	6	6
			Mean	6.0200	2.3717
			SD	4.14314	2.51655
			Min	1.890	-0.280
			Median	4.4950	2.5350
			Max	13.600	6.710
	Day 5	Pre-Dose	n	6	6
			Mean	6.5167	2.8683
			SD	2.79765	2.46629
			Min	1.890	0.000
			Median	7.2800	2.8350
			Max	9.190	6.680
LHW090 50m g MAD	Day 14	Pre-Dose	n	6	6
			Mean	5.8150	2.1667
			SD	2.77675	1.72327
			Min	1.890	0.000
			Median	5.7400	2.3900
			Max	9.520	4.760
	Day 17	72 hr Post-Dose	n	6	6
			Mean	4.4717	0.8233
			SD	2.11554	1.63424
			Min	1.890	-1.550
			Median	5.0950	0.8250
			Max	6.920	2.960
LHW090 100 mg MAD	Day 1	Pre-Dose	n	6	
			Mean	2.9200	

			SD	1.59812			
			Min	1.890			
			Median	1.8900			
			Max	5.120			
	Day 2	Pre-Dose	n	6		6	
			Mean	7.1367		4.2167	
			SD	1.30546		2.57349	
			Min	5.550		0.430	
			Median	6.8600		4.6250	
			Max	8.950		7.060	
	Day 5	Pre-Dose	n	6		6	
			Mean	9.4433		6.5233	
			SD	2.44948		3.25988	
			Min	6.960		2.270	
			Median	9.0450		5.6500	
			Max	12.800		10.910	
LHW090 100 mg MAD	Day 14	Pre-Dose	n	6		6	
			Mean	5.1700		2.2500	
			SD	1.87117		2.37320	
			Min	1.890		-0.680	
			Median	5.8800		2.3750	
			Max	6.700		4.810	
	Day 17	72 hr Post-Dose	n	6		6	
			Mean	5.5650		2.6450	
			SD	1.31049		1.39684	
			Min	4.690		-0.150	
			Median	5.1550		3.1050	
			Max	8.160		3.630	
LHW090 200 mg	Day 1	Pre-Dose	n	6	5	6	

MAD

			Mean	887.3333	33.5600	2.6917		
			SD	187.57896	18.84630	1.25006		
			Min	659.000	13.900	1.890		
			Median	878.5000	39.0000	1.8900		
			Max	1200.000	55.200	4.520		
	Day 2	Pre-Dose	n	6	6	6	5	6
			Mean	936.8333	43.8333	6.1400	49.5000	3.4483
			SD	85.45506	9.62843	1.96944	205.28395	1.28250
			Min	864.000	31.800	3.980	-250.000	2.090
			Median	908.5000	41.8500	6.1850	30.0000	3.3600
			Max	1100.000	59.400	8.290	335.000	5.640
	Day 3	Pre-Dose	n	6		6		
			Mean	1010.3333		123.0000		
			SD	238.90556		301.85493		
			Min	638.000		-305.000		
			Median	1080.0000		142.0000		
			Max	1280.000		501.000		
LHW090 200 mg MAD	Day 5	Pre-Dose	n	6	6	6	5	6
			Mean	887.3333	38.3833	6.5500	0.0000	3.8583
			SD	226.79212	16.14514	1.43629	357.29428	1.52349
			Min	621.000	13.900	4.590	-477.000	2.350
			Median	865.5000	38.6500	6.3600	-76.5000	3.7350
			Max	1270.000	58.300	8.560	505.000	6.670
	Day 9	Pre-Dose	n	6		6		
			Mean	923.0000		35.6667		
			SD	249.80312		225.31282		
			Min	754.000		-178.000		
			Median	794.5000		-8.5000		
			Max	1380.000		439.000		
	Day 14	Pre-Dose	n	6	6	6	5	6

				Mean	996.6667	29.8833	4.3450	109.3333	-0.4800	1.6533
				SD	184.93530	12.93003	1.25502	187.59815	15.16301	1.22114
				Min	790.000	13.900	1.890	-77.000	-14.400	0.000
				Median	963.0000	34.2500	4.7650	44.5000	0.0000	1.7650
				Max	1210.000	42.100	5.250	401.000	23.200	2.900
LHW090 200 mg MAD	Day 17	72 hr Post-Dose	n		6	6	6	6	5	6
				Mean	1005.0000	38.7833	2.3933	117.6667	10.2000	-0.2983
				SD	319.05109	13.83783	1.23291	295.80309	14.30944	2.01274
				Min	693.000	13.900	1.890	-250.000	-10.400	-2.630
				Median	892.0000	42.9500	1.8900	154.5000	7.8000	0.0000
				Max	1520.000	53.600	4.910	485.000	27.200	3.020
LHW090 400 mg MAD	Day 1	Pre-Dose	n				6			
				Mean			2.4367			
				SD			1.33905			
				Min			1.890			
				Median			1.8900			
				Max			5.170			
	Day 2	Pre-Dose	n				6			6
				Mean			5.0400			2.6033
				SD			3.55456			2.41272
				Min			1.890			0.000
				Median			4.7400			2.8500
				Max			11.600			6.430
	Day 5	Pre-Dose	n				6			6
				Mean			3.8750			1.4383
				SD			3.35601			2.24927
				Min			1.890			0.000
				Median			1.8900			0.0000
				Max			9.970			4.800

LHW090 400 mg MAD	Day 14	Pre-Dose	n			6			6
			Mean			3.1433			0.7067
			SD			2.14464			1.10205
			Min			1.890			0.000
			Median			1.8900			0.0000
			Max			7.090			2.320
	Day 17	72 hr Post-Dose	n			6			6
			Mean			2.5900			0.1533
			SD			1.08445			1.07025
			Min			1.890			-1.190
			Median			1.8900			0.0000
			Max			4.000			2.110
Pooled placebo	Day 1	Pre-Dose	n	2	2	12			
			Mean	1065.5000	39.8000	4.5542			
			SD	133.64318	9.05097	2.72463			
			Min	971.000	33.400	1.890			
			Median	1065.5000	39.8000	4.4800			
			Max	1160.000	46.200	11.300			
	Day 2	Pre-Dose	n	2	2	12	2	2	12
			Mean	631.0000	43.1000	4.3420	-434.5000	3.3000	-0.2121
			SD	56.56854	0.56569	2.76726	77.07464	8.48528	1.10371
			Min	591.000	42.700	0.095	-489.000	-2.700	-1.950
			Median	631.0000	43.1000	4.1500	-434.5000	3.3000	0.0000
			Max	671.000	43.500	10.300	-380.000	9.300	2.210
	Day 3	Pre-Dose	n	2			2		
			Mean	816.5000			-249.0000		
			SD	72.83200			60.81118		
			Min	765.000			-292.000		
			Median	816.5000			-249.0000		
			Max	868.000			-206.000		

Pooled placebo	Day 5	Pre-Dose	n	2	2	12	2	2	12
			Mean	854.0000	47.5000	4.9617	-211.5000	7.7000	0.4075
			SD	121.62237	1.97990	3.00164	255.26555	11.03087	1.71172
			Min	768.000	46.100	1.890	-392.000	-0.100	-1.860
			Median	854.0000	47.5000	4.9750	-211.5000	7.7000	0.0000
			Max	940.000	48.900	11.200	-31.000	15.500	5.210
	Day 9	Pre-Dose	n	2			2		
			Mean	947.5000			-118.0000		
			SD	74.24621			207.88939		
			Min	895.000			-265.000		
			Median	947.5000			-118.0000		
			Max	1000.000			29.000		
	Day 14	Pre-Dose	n	2	2	12	2	2	12
			Mean	637.0000	33.7000	4.2533	-428.5000	-6.1000	-0.3008
			SD	60.81118	2.68701	2.89613	72.83200	11.73797	1.29818
			Min	594.000	31.800	1.890	-480.000	-14.400	-2.490
			Median	637.0000	33.7000	3.0350	-428.5000	-6.1000	0.0000
			Max	680.000	35.600	9.750	-377.000	2.200	2.460
Pooled placebo	Day 17	72 hr Post-Dose	n	2	2	12	2	2	12
			Mean	807.5000	38.5000	5.7958	-258.0000	-1.3000	1.2417
			SD	51.61880	5.37401	3.47321	82.02439	3.67696	1.54831
			Min	771.000	34.700	1.890	-316.000	-3.900	-0.300
			Median	807.5000	38.5000	4.8100	-258.0000	-1.3000	0.7700
			Max	844.000	42.300	13.500	-200.000	1.300	5.210

Summary statistics of plasma PD markers – Stage 4

Treatment	Day	Scheduled time (hr)	Statistics	-----Results-----			-----Change from baseline-----		
				CYS (ng/mL)	ANP (pg/mL)	cGMP (nmol/L)	CYS (ng/mL)	ANP (pg/mL)	cGMP (nmol/L)
LHW090 5mg	Day -1	Pre-Dose	n	6	6	6			

SAD
(cohort 1)

			Mean	1973.3333	235.8500	10.0583			
			SD	704.17801	81.97765	5.92542			
			Min	1000.000	141.000	5.370			
			Median	2050.0000	216.0000	7.9000			
			Max	3050.000	340.100	20.900			
	Day 1	0 hr Pre-Dose	n	6	5	6	6	5	6
			Mean	1921.6667	191.4200	8.5383	-51.6667	-48.0000	-1.5200
			SD	528.18242	89.36013	4.94001	253.17320	73.82073	2.54945
			Min	1190.000	105.000	5.210	-500.000	-148.000	-6.160
			Median	2130.0000	182.0000	6.5250	10.0000	-67.0000	-0.7250
			Max	2550.000	340.100	18.300	190.000	45.000	0.600
		1 hr Post-Dose	n	6	6	6	6	6	6
			Mean	1691.3333	208.0167	8.7283	-282.0000	-27.8333	-1.3300
			SD	504.90659	72.28888	6.10671	255.01373	52.90526	2.32327
			Min	998.000	138.000	1.890	-570.000	-111.000	-4.090
			Median	1675.0000	193.5000	7.8300	-250.0000	-2.0000	-1.1600
			Max	2480.000	340.100	19.800	-2.000	23.000	1.820
LHW090 5mg SAD (cohort 1)	Day 1	4 hr Post-Dose	n	5	5	5	5	5	5
			Mean	1540.0000	243.4200	15.2600	-218.0000	28.4200	7.3700
			SD	386.52296	86.68698	3.88690	170.79227	84.93516	3.07160
			Min	1030.000	133.000	10.100	-410.000	-81.000	4.120
			Median	1710.0000	246.0000	17.5000	-210.0000	12.0000	6.4000
			Max	1890.000	340.100	18.700	30.000	122.100	12.130
		8 hr Post-Dose	n	5	5	5	5	5	5
			Mean	1420.4000	230.2200	15.7000	-337.6000	15.2200	7.8100
			SD	393.40920	93.15950	4.11886	250.79633	82.21339	4.11519
			Min	942.000	122.000	10.600	-740.000	-92.000	4.290

LHW090 5mg SAD (cohort 1)	Day 2	12 hr Post-Dose	Median	1510.0000	208.0000	17.1000	-280.0000	-3.0000	6.9300
			Max	1800.000	340.100	20.500	-58.000	122.100	14.520
			n	5	4	5	5	4	5
			Mean	1433.0000	184.0750	14.5660	-325.0000	-30.1750	6.6760
			SD	336.11010	107.18841	5.24145	191.50718	66.83554	4.62420
			Min	915.000	84.300	8.230	-550.000	-129.700	1.920
			Median	1640.0000	158.0000	13.7000	-410.0000	-1.0000	5.7300
			Max	1700.000	336.000	20.100	-85.000	11.000	14.120
		24 hr Post-Dose	n	5	5	5	5	5	5
			Mean	1840.0000	175.7800	11.7400	82.0000	-39.2200	3.8500
			SD	577.79754	79.83008	3.46958	490.42838	52.85160	1.23562
			Min	1310.000	82.900	7.200	-630.000	-131.100	1.830
			Median	1620.0000	154.0000	11.2000	130.0000	-18.0000	4.1000
			Max	2680.000	296.000	16.400	630.000	1.000	5.220
		72 hr Post-Dose	n	5	5	5	5	5	5
			Mean	1894.0000	209.0400	8.5360	136.0000	-5.9600	0.6460
			SD	516.94294	119.87954	2.30793	448.69812	83.39486	1.52467
			Min	1380.000	115.000	5.590	-560.000	-99.000	-1.200
			Median	1690.0000	134.0000	8.1300	330.0000	-7.0000	1.1100
			Max	2510.000	340.100	11.100	510.000	122.100	2.150
LHW090 12.5mg SAD	Day -1	Pre-Dose	n	9		9			
			Mean	1661.1111		8.9133			
			SD	309.85660		5.86448			
			Min	1410.000		1.890			
			Median	1600.0000		5.8500			
			Max	2440.000		20.800			
	Day 1	0 hr	n	9		9	9		9
			Mean						
			SD						
			Min						
			Median						

LHW090 12.5m Day 1 g SAD	Pre-Dose	Mean	1552.2222	7.2156	-108.8889	-1.6978
		SD	251.03674	4.97697	159.17321	1.83282
		Min	1210.000	1.890	-310.000	-3.610
		Median	1510.0000	6.0500	-110.0000	-2.7000
		Max	2130.000	17.700	190.000	1.410
	1 hr Post-Dose	n	9	9	9	9
		Mean	1580.0000	7.9878	-81.1111	-0.9256
		SD	231.40873	5.63138	178.98634	1.40675
		Min	1230.000	1.890	-380.000	-4.050
		Median	1520.0000	6.2700	-100.0000	-0.5100
		Max	2060.000	20.600	130.000	0.490
	4 hr Post-Dose	n	9	9	9	9
		Mean	1528.8889	16.3878	-132.2222	7.4744
		SD	250.32201	9.54604	203.94716	4.90864
		Min	1230.000	8.090	-440.000	-0.440
		Median	1490.0000	12.8000	-140.0000	7.5000
		Max	2080.000	38.100	170.000	17.300
	8 hr Post-Dose	n	9	8	9	8
		Mean	1283.6667	19.0275	-377.4444	9.2363
		SD	524.81997	9.45869	467.92230	5.28286
		Min	33.000	7.380	-1567.000	1.600
		Median	1390.0000	19.4000	-260.0000	10.5000
		Max	2000.000	36.400	-30.000	15.600
	12 hr Post-Dose	n	9	9	9	9
		Mean	1402.2222	18.0222	-258.8889	9.1089
		SD	194.40793	9.03196	146.66667	5.18912
		Min	1130.000	8.640	-580.000	0.960
		Median	1380.0000	20.2000	-250.0000	8.7000

			Max	1860.000	35.100	-90.000	15.400
LHW090 12.5m g SAD	Day 2	24 hr Post-Dose	n	9	9	9	9
			Mean	1462.2222	13.8256	-198.8889	4.9122
			SD	180.19280	8.76320	197.89167	4.14068
			Min	1110.000	4.260	-630.000	-0.600
			Median	1450.0000	12.8000	-190.0000	3.8300
			Max	1810.000	31.100	20.000	10.500
	Day 4	72 hr Post-Dose	n	9	9	9	9
			Mean	1525.5556	10.8133	-135.5556	1.9000
			SD	275.59532	6.36838	201.74929	1.34932
			Min	1300.000	4.950	-370.000	0.090
			Median	1440.0000	8.5500	-220.0000	1.5700
			Max	2170.000	24.000	310.000	3.800
LHW090 25mg SAD	Day -1	Pre-Dose	n	9	9		
			Mean	2296.6667	7.9111		
			SD	708.69599	3.59330		
			Min	1350.000	1.890		
			Median	2570.0000	7.0700		
			Max	3650.000	14.000		
	Day 1	0 hr Pre-Dose	n	9	9	9	9
			Mean	2138.8889	5.9756	-157.7778	-1.9356
			SD	333.55826	3.07887	498.06570	2.11039
			Min	1630.000	1.890	-1230.000	-6.390
			Median	2100.0000	5.1100	-50.0000	-1.4000
			Max	2560.000	12.600	430.000	0.020
		1 hr Post-Dose	n	9	9	9	9
			Mean	2167.7778	6.8233	-128.8889	-1.0878

				SD	418.32337	5.83801	482.27182	4.02516
				Min	1490.000	1.890	-980.000	-6.650
				Median	2250.0000	4.8500	-190.0000	-0.1100
				Max	2670.000	20.600	640.000	6.600
LHW090 25mg SAD	Day 1	4 hr Post-Dose	n	9		9	9	9
			Mean	2231.1111	14.4900	-65.5556		6.5789
			SD	436.93376	10.29138	500.62738		7.93492
			Min	1550.000	6.450	-1210.000		-0.900
			Median	2220.0000	12.4000	80.0000		5.9300
			Max	2900.000	39.800	520.000		25.800
		8 hr Post-Dose	n	9		9	9	9
			Mean	2272.2222	15.1489	-24.4444		7.2378
			SD	504.94499	9.69270	499.40242		7.24101
			Min	1670.000	5.460	-860.000		0.760
			Median	2120.0000	12.5000	20.0000		5.7000
			Max	3280.000	37.400	610.000		23.400
		12 hr Post-Dose	n	9		9	9	9
			Mean	2145.5556	14.2911	-151.1111		6.3800
			SD	333.65818	8.65109	523.93808		6.22136
			Min	1720.000	6.280	-1170.000		1.060
			Median	2120.0000	12.3000	-70.0000		4.3000
			Max	2640.000	35.100	550.000		21.100
LHW090 25mg SAD	Day 2	24 hr Post-Dose	n	9		9	9	9
			Mean	2213.3333	10.9189	-83.3333		3.0078
			SD	418.59885	5.78872	593.14838		4.41193
			Min	1790.000	5.290	-1200.000		-1.110
			Median	2140.0000	8.6300	20.0000		0.9800
			Max	3050.000	22.700	580.000		11.640
	Day 4	72 hr	n	9		9	9	9
			Mean					
			SD					
			Min					
			Median					

		Post-Dose						
			Mean	2174.4444	8.7078	-122.2222	0.7967	
			SD	433.62170	5.74997	580.08141	4.16736	
			Min	1520.000	4.550	-1310.000	-3.470	
			Median	2200.0000	6.4200	50.0000	-1.1200	
			Max	2910.000	23.100	650.000	9.100	
LHW090 2mg SAD	Day -1	Pre-Dose	n	9	9			
			Mean	1405.4444	4.6922			
			SD	317.26452	2.38123			
			Min	889.000	1.890			
			Median	1460.0000	5.3900			
			Max	1910.000	8.300			
	Day 1	0 hr Pre-Dose	n	9	9	9	9	
			Mean	1417.1111	3.1167	11.6667	-1.5756	
			SD	435.29658	1.90245	180.88256	2.41610	
			Min	876.000	1.890	-150.000	-6.410	
			Median	1410.0000	1.8900	-13.0000	0.0000	
			Max	2360.000	6.570	450.000	0.140	
		1 hr Post-Dose	n	9	9	9	9	
			Mean	1386.7778	3.4633	-18.6667	-1.2289	
			SD	372.84842	1.55469	124.07558	2.90866	
			Min	926.000	1.890	-220.000	-6.410	
			Median	1420.0000	4.1100	-20.0000	-0.1000	
			Max	2120.000	5.460	210.000	3.570	
LHW090 2mg SAD	Day 1	4 hr Post-Dose	n	9	9	9	9	
			Mean	1380.7778	7.5444	-24.6667	2.8522	
			SD	429.80396	3.13788	167.07558	1.91006	
			Min	756.000	1.890	-250.000	0.000	
			Median	1400.0000	7.1900	-99.0000	2.5000	
			Max	2200.000	11.900	290.000	6.060	

LHW090 2mg SAD	Day 2	8 hr Post-Dose	n	9		9	9	9
			Mean	1316.6667		8.6311	-88.7778	3.9389
			SD	383.68314		2.56734	92.47132	1.45234
			Min	689.000		5.880	-210.000	1.870
			Median	1320.0000		7.7100	-110.0000	3.9900
			Max	1950.000		13.200	40.000	6.630
		12 hr Post-Dose	n	9		9	9	9
			Mean	1434.7778		7.2978	29.3333	2.6056
			SD	484.07948		1.67926	253.44427	2.25640
			Min	743.000		4.680	-146.000	-1.120
			Median	1340.0000		7.4700	-90.0000	3.4500
			Max	2260.000		9.450	570.000	5.550
	Day 4	24 hr Post-Dose	n	9		9	9	9
			Mean	1399.4444		4.7400	-6.0000	0.0478
			SD	413.33616		2.50911	167.23935	1.74243
			Min	819.000		1.890	-150.000	-3.300
			Median	1370.0000		4.7200	-70.0000	0.0000
			Max	2290.000		8.610	380.000	2.180
		72 hr Post-Dose	n	9		9	9	9
			Mean	1437.6667		3.1678	32.2222	-1.5244
			SD	422.66594		1.64547	169.39435	2.05654
			Min	829.000		1.890	-140.000	-6.410
			Median	1410.0000		1.8900	-30.0000	-1.2800
			Max	2330.000		6.330	420.000	0.000
LHW090 5mg SAD (cohort 5)	Day -1	Pre-Dose	n	9	7	9		
			Mean	1564.6667	135.0714	7.5678		
			SD	435.44345	127.87503	4.77326		

			Min	982.000	37.500	1.890			
			Median	1570.0000	83.6000	5.2500			
			Max	2340.000	412.000	16.400			
LHW090 5mg SAD (cohort 5)	Day 1	0 hr Pre-Dose	n	9	9	9	9	7	9
			Mean	1527.3333	151.3778	5.8278	-37.3333	-5.7143	-1.7400
		SD	358.88578	144.21408	4.92283	211.52778	17.15696	1.60702	
		Min	996.000	38.600	1.890	-400.000	-31.000	-3.460	
		Median	1510.0000	97.4000	4.5200	-60.0000	-3.9000	-2.1300	
		Max	1940.000	412.000	17.000	370.000	22.400	0.600	
		1 hr Post-Dose	n	9	9	9	9	7	9
			Mean	1490.3333	117.2333	6.3178	-74.3333	-25.9286	-1.2500
	SD		309.47294	68.61988	4.53346	182.15790	58.97352	2.80954	
	Min		923.000	38.300	1.890	-420.000	-149.000	-6.830	
	Median		1550.0000	95.1000	7.0200	-59.0000	0.4000	-1.1000	
	Max		1920.000	263.000	15.300	150.000	24.500	2.710	
	Day 1	4 hr Post-Dose	n	9	8	9	9	6	9
			Mean	1475.5556	145.8250	12.8133	-89.1111	-9.9833	5.2456
			SD	331.32730	81.25165	7.44572	111.99157	57.86351	4.75203
			Min	1030.000	55.100	4.410	-280.000	-111.000	-2.760
			Median	1490.0000	109.5000	10.3000	-80.0000	15.3500	5.5700
			Max	2060.000	301.000	24.900	48.000	39.000	11.850
		8 hr Post-Dose	n	9	7	9	9	5	9
			Mean	1423.2222	171.3714	12.6611	-141.4444	3.9000	5.0933
	SD		344.83901	116.65856	5.12280	150.51006	45.97260	4.08169	
	Min		891.000	59.600	5.990	-450.000	-75.000	0.710	
	Median		1510.0000	127.0000	11.9000	-110.0000	22.0000	3.7700	
	Max		1890.000	337.000	20.600	110.000	43.400	14.710	
12 hr	n	9	8	9	9	7	9		

				Post-Dose							
				Mean	1413.5556	129.5375	12.1422	-151.1111	-7.1714	4.5744	
				SD	308.99640	88.54871	5.76825	165.86474	49.37292	4.58163	
				Min	922.000	48.800	5.760	-440.000	-78.000	-2.960	
				Median	1440.0000	109.1500	9.8800	-60.0000	1.0000	4.8000	
				Max	1900.000	334.000	23.500	0.000	75.000	13.310	
LHW090 5mg SAD (cohort 5)	Day 2	24 hr Post-Dose	n		9	8	9	9	7	9	
			Mean		1493.3333	106.7875	8.0011	-71.3333	-24.3571	0.4333	
			SD		331.70017	62.11697	4.98074	165.45694	69.36293	1.93624	
			Min		1040.000	56.900	1.890	-400.000	-173.000	-2.130	
			Median		1580.0000	82.7000	6.7400	-50.0000	-6.1000	0.5000	
			Max		1940.000	239.000	17.500	180.000	30.000	3.380	
	Day 4	72 hr Post-Dose	n		9	8	9	9	7	9	
			Mean		1546.6667	117.6375	5.7800	-18.0000	-18.4857	-1.7878	
			SD		403.05087	105.06182	4.34545	98.92421	30.17242	2.44764	
			Min		1040.000	36.100	1.890	-180.000	-70.700	-5.030	
			Median		1560.0000	93.1500	4.8400	-40.0000	-10.0000	-2.4500	
			Max		2290.000	367.000	15.600	120.000	19.400	2.950	

Summary statistics of plasma PD markers – Stage 5

Treatment	Day	Scheduled time(hr)	Statistics	-----Results-----			-----Change from baseline-----		
				CYS (ng/mL)	ANP (pg/mL)	cGMP (nmol/L)	CYS (ng/mL)	ANP (pg/mL)	cGMP (nmol/L)
LHW090 5mg MAD	Day -1	Pre-Dose	n	4	9	9			
			Mean	1662.5000	95.4222	11.7389			
			SD	260.81603	34.86731	5.51249			
			Min	1310.000	54.800	5.740			
			Median	1700.0000	93.1000	11.3000			
			Max	1940.000	159.000	21.500			

LHW090 5mg MAD	Day 2	0 hr Pre-Dose	n	4	9	9	4	9	9
			Mean	1542.5000	92.3778	16.8811	-120.0000	-3.0444	5.1422
			SD	278.37325	25.18476	6.47716	53.54126	32.00770	5.89913
			Min	1140.000	59.300	9.860	-170.000	-52.000	-8.000
			Median	1625.0000	88.8000	15.7000	-125.0000	-3.5000	4.8000
			Max	1780.000	140.000	29.500	-60.000	41.300	12.400
		12 hr Post-Dose	n	4	9	9	4	9	9
			Mean	1537.5000	99.9667	19.3444	-125.0000	4.5444	7.6056
			SD	282.76905	37.73231	5.83355	80.20806	27.33025	4.97574
			Min	1130.000	72.400	10.600	-180.000	-46.600	-2.100
			Median	1630.0000	88.4000	19.4000	-155.0000	17.9000	8.7000
			Max	1760.000	194.000	28.200	-10.000	35.000	14.600
	Day 3	0 hr Pre-Dose	n	4	9	9	4	9	9
			Mean	1535.0000	90.5556	16.2500	-127.5000	-4.8667	4.5111
			SD	257.48786	26.90326	6.60085	63.44289	34.57362	5.42709
			Min	1160.000	52.800	7.350	-200.000	-66.200	-6.600
			Median	1620.0000	93.1000	14.9000	-130.0000	0.2000	6.0600
			Max	1740.000	137.000	30.400	-50.000	30.900	11.700
		12 hr Post-Dose	n	4	5	9	4	5	9
			Mean	1567.5000	91.2600	16.0167	-95.0000	-11.9400	4.2778
			SD	267.87746	24.70208	6.67168	89.62886	17.51065	5.36636
			Min	1210.000	64.300	5.300	-180.000	-33.100	-1.090
			Median	1625.0000	85.9000	18.2000	-115.0000	0.3000	2.0500
			Max	1810.000	130.000	23.800	30.000	1.500	15.960
	Day 4	24 hr Post-Dose	n	4	9	9	4	9	9
			Mean	1540.0000	83.4667	13.1856	-122.5000	-11.9556	1.4467
			SD	250.19992	23.62144	4.97327	42.72002	34.28823	3.82175
			Min	1180.000	55.200	4.550	-180.000	-63.800	-6.900
			Median	1610.0000	78.7000	14.0000	-110.0000	-2.4000	2.7000

			Max	1760.000	126.000	22.500	-90.000	32.900	5.780
Pooled placebo	Day -1	Pre-Dose	n	2	3	3			
			Mean	1310.0000	74.9000	5.5567			
			SD	127.27922	24.06180	1.01214			
			Min	1220.000	53.600	4.390			
			Median	1310.0000	70.1000	6.0800			
			Max	1400.000	101.000	6.200			
	Day 2	0 hr Pre-Dose	n	2	3	3	2	3	3
			Mean	1275.0000	68.7333	6.3067	-35.0000	-6.1667	0.7500
			SD	162.63456	19.63398	1.25261	35.35534	5.08167	1.99592
			Min	1160.000	49.800	4.870	-60.000	-12.000	-1.210
			Median	1275.0000	67.4000	6.8800	-35.0000	-3.8000	0.6800
			Max	1390.000	89.000	7.170	-10.000	-2.700	2.780
		12 hr Post-Dose	n	2	2	3	2	2	3
			Mean	1165.0000	65.2500	6.8467	-145.0000	3.4000	1.2900
			SD	219.20310	4.31335	0.72528	91.92388	7.35391	1.65928
			Min	1010.000	62.200	6.110	-210.000	-1.800	0.030
			Median	1165.0000	65.2500	6.8700	-145.0000	3.4000	0.6700
			Max	1320.000	68.300	7.560	-80.000	8.600	3.170
Pooled placebo	Day 3	0 hr Pre-Dose	n	2	3	3	2	3	3
			Mean	1270.0000	75.5667	6.4400	-40.0000	0.6667	0.8833
			SD	197.98990	15.96381	1.53353	70.71068	8.50078	2.46529
			Min	1130.000	60.000	4.970	-90.000	-9.100	-1.110
			Median	1270.0000	74.8000	6.3200	-40.0000	4.7000	0.1200
			Max	1410.000	91.900	8.030	10.000	6.400	3.640
		12 hr Post-Dose	n	2	3	3	2	3	3
			Mean	1215.0000	69.9000	7.2400	-95.0000	-5.0000	1.6833

		SD	205.06097	24.41782	1.96924	77.78175	6.01082	2.93643
		Min	1070.000	44.500	5.390	-150.000	-9.100	-0.810
		Median	1215.0000	72.0000	7.0200	-95.0000	-7.8000	0.9400
		Max	1360.000	93.200	9.310	-40.000	1.900	4.920
Day 4	24 hr Post-Dose	n	2	3	3	2	3	3
		Mean	1265.0000	55.2000	6.0967	-45.0000	-19.7000	0.5400
		SD	205.06097	14.01820	1.47025	77.78175	11.70427	2.35023
		Min	1120.000	40.100	4.560	-100.000	-33.200	-1.520
		Median	1265.0000	57.7000	6.2400	-45.0000	-13.5000	0.0400
		Max	1410.000	67.800	7.490	10.000	-12.400	3.100

Summary of plasma pharmacokinetic parameters of LHW090 following single dose administration (0.1-800 mg) of LHW090 to healthy subjects (PK analysis set)-Stage 1 and 2

Dose	Statistic	Cmax (ng/mL)	Tmax ¹ (hr)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUC0-24h (hr*ng/mL)	T1/2 (hr)	CL/F (L/hr)	LHW090 %Hydrolysis (%)
1 mg (Stage 1)	n	3	3	3	3	3	3	3	3
	Mean (SD)	60.7 (11.4)	1.50 (1.00;2.00)	153 (28.3)	155 (29.5)	155 (30.5)	1.69 (0.922)	6.63 (1.26)	63.0 (3.60)
	CV% mean	18.7		18.6	19.1	19.7	54.4	19.1	5.7
0.1 mg	n	8	8	8	6	8	6	6	8
	Mean (SD)	7.24 (2.26)	1.00 (1.00;1.00)	14.6 (5.09)	17.0 (5.72)	15.5 (5.13)	1.38 (0.728)	6.77 (3.46)	45.3 (9.49)
	CV% mean	31.2		34.8	33.5	33.1	52.7	51.1	20.9
1 mg	n	8	8	8	8	8	8	8	8
	Mean (SD)	57.1 (22.2)	1.25 (0.967;3.00)	128 (34.9)	130 (35.2)	129 (35.8)	1.33 (0.618)	8.12 (1.77)	68.6 (5.05)
	CV% mean	38.8		27.2	27.2	27.6	46.3	21.8	7.4
5 mg	n	8	8	8	8	8	8	8	8

Dose	Statistic	Cmax (ng/mL)	Tmax ¹ (hr)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUC0-24h (hr*ng/mL)	T1/2 (hr)	CL/F (L/hr)	LHW090 %Hydrolysis (%)
25 mg	Mean (SD)	290 (88.1)	1.00 (0.500;3.00)	716 (150)	722 (152)	723 (151)	3.26 (1.28)	7.22 (1.65)	65.8 (4.99)
	CV% mean	30.4		20.9	21.0	20.9	39.3	22.9	7.6
	n	8	8	8	8	8	8	8	8
50 mg	Mean (SD)	1580 (465)	2.00 (1.00;3.00)	4060 (1040)	4070 (1040)	4050 (1030)	4.55 (0.369)	6.46 (1.42)	66.0 (5.76)
	CV% mean	29.5		25.6	25.5	25.4	8.1	22.0	8.7
	n	8	8	8	8	8	8	8	8
100 mg	Mean (SD)	2540 (425)	3.00 (1.00;4.00)	7880 (1510)	7890 (1510)	7850 (1490)	5.42 (1.29)	6.57 (1.38)	67.1 (3.75)
	CV% mean	16.7	49.7	19.2	19.2	19.0	23.8	21.1	5.6
	n	8	8	8	8	8	8	8	8
200 mg	Mean (SD)	3960 (1250)	3.00 (1.00;6.00)	14100 (4070)	14100 (4070)	14000 (4070)	5.81 (0.985)	8.31 (4.95)	70.2 (6.60)
	CV% mean	31.5		28.9	28.9	29.2	17.0	59.5	9.4
	n	8	8	8	8	8	8	8	8
400 mg	Mean (SD)	6630 (1600)	3.50 (1.50;4.00)	25100 (5410)	25200 (5410)	24800 (5380)	6.35 (1.25)	8.26 (1.66)	65.7 (6.59)
	CV% mean	24.1		21.5	21.5	21.6	19.7	20.1	10.0
	n	8	8	8	8	8	8	8	8
400mg (Jap.)	Mean (SD)	17100 (2640)	3.00 (2.00;4.00)	63400 (17100)	63400 (17100)	62500 (16700)	10.5 (1.28)	6.72 (1.80)	67.6 (4.13)
	CV% mean	15.5		27.0	27.0	26.8	12.2	26.7	6.1
	n	8	8	8	8	8	8	8	8
800 mg	Mean (SD)	17700 (3300)	3.00 (1.50;4.00)	69300 (16600)	69300 (16600)	68700 (16500)	10.4 (1.18)	6.02 (1.24)	66.1 (5.68)
	CV% mean	18.7		23.9	23.9	24.0	11.4	20.6	8.6
	n	8	8	8	8	8	8	8	8

Dose	Statistic	Cmax (ng/mL)	Tmax ¹ (hr)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUC0-24h (hr*ng/mL)	T1/2 (hr)	CL/F (L/hr)	LHW090 %Hydrolysis (%)
	Mean (SD)	20000 (5050)	3.00 (2.00;4.00)	96000 (21600)	96100 (21600)	95300 (21400)	11.3 (2.07)	8.70 (1.92)	70.9 (6.36)
	CV% mean	25.2		22.5	22.5	22.5	18.4	22.1	9.0

Statistics presented include: n, arithmetic mean (standard deviation) and CV% arithmetic mean

¹For Tmax, Median (Minimum;Maximum) are presented

Summary of plasma pharmacokinetic parameters of LHV527 following single dose administration (0.1- 800 mg) of LHW090 to healthy subjects (PK analysis set)-Stage 1 and 2

Dose	Statistic	Cmax (ng/mL)	Tmax ¹ (hr)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUC0-24h (hr*ng/mL)	T1/2 (hr)
1 mg (Stage 1)	n	3	3	3	3	3	3
	Mean (SD)	34.8 (4.12)	3.00 (2.00;3.00)	258 (19.8)	309 (37.7)	204 (14.4)	47.2 (9.34)
	CV% mean	11.8		7.7	12.2	7.1	19.8
0.1 mg	n	8	8	8	8	8	8
	Mean (SD)	3.34 (1.05)	1.50 (1.50;2.00)	11.5 (1.96)	13.6 (2.17)	12.1 (1.93)	2.48 (0.852)
	CV% mean	31.4		17.1	16.0	16.0	34.4
1 mg	n	8	8	8	8	8	8
	Mean (SD)	40.0 (10.4)	2.50 (1.50;4.00)	277 (32.0)	327 (38.9)	217 (31.7)	42.2 (7.35)
	CV% mean	25.9		11.6	11.9	14.6	17.4
5 mg	n	8	8	8	8	8	8
	Mean (SD)	193 (41.7)	3.00 (1.50;4.00)	1390 (279)	1430 (275)	1260 (261)	27.4 (6.60)
	CV% mean	21.6		20.1	19.2	20.8	24.0
25 mg	n	8	8	8	8	8	8
	Mean (SD)	1180 (189)	3.00 (1.50;4.00)	7970 (2010)	8020 (2010)	7540 (1880)	16.1 (3.44)
	CV% mean	15.9		25.2	25.1	25.0	21.3
50 mg	n	8	8	8	8	8	8

Dose	Statistic	Cmax (ng/mL)	Tmax ¹ (hr)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUC0-24h (hr*ng/mL)	T1/2 (hr)
100 mg	Mean (SD)	2280 (454)	4.00 (2.00;4.00)	16100 (3000)	16200 (3000)	15400 (2910)	15.1 (3.24)
	CV% mean	19.9		18.6	18.5	18.9	21.5
	n	8	8	8	8	8	8
200 mg	Mean (SD)	4210 (770)	4.00 (3.00;6.00)	32500 (5320)	32600 (5330)	30600 (4960)	10.7 (2.29)
	CV% mean	18.3		16.4	16.4	16.2	21.4
	n	8	8	8	8	8	8
400 mg	Mean (SD)	5830 (1730)	4.00 (4.00;6.00)	49200 (11800)	49300 (11800)	46000 (10900)	9.96 (2.41)
	CV% mean	29.7		23.9	23.8	23.8	24.2
	n	8	8	8	8	8	8
400mg (Jap.)	Mean (SD)	17000 (2740)	4.00 (3.00;6.00)	131000 (25600)	131000 (25700)	122000 (24100)	8.75 (1.37)
	CV% mean	16.1		19.5	19.5	19.7	15.6
	n	8	8	8	8	8	8
800 mg	Mean (SD)	16000 (4000)	4.00 (3.00;6.00)	136000 (30600)	136000 (30700)	127000 (27500)	10.4 (1.74)
	CV% mean	24.9		22.5	22.5	21.7	16.7
	n	8	8	8	8	8	8
800 mg	Mean (SD)	26300 (4830)	4.00 (4.00;6.00)	237000 (48700)	237000 (48800)	222000 (43700)	9.03 (0.610)
	CV% mean	18.4		20.5	20.5	19.7	6.8

Statistics presented include: n, arithmetic mean (standard deviation) and CV% arithmetic mean

¹For Tmax, Median (Minimum;Maximum) are presented

Summary of plasma pharmacokinetic parameters of LHW090 following multiple ascending dose administration of LHW090 to healthy subjects (PK analysis set)-Stage 3

Dose	Day	Statistic	Cmax (ng/mL)	Tmax ¹ (hr)	AUCtau (hr*ng/mL)	AUClast (hr*ng/mL)	Racc	T1/2 (hr)	CLss/F (L/hr)	LHW090 % Hydrolysis (%)
5 mg	1	n	6	6	6					6
		Mean (SD)	256 (71.2)	1.50 (1.00;3.00)	672 (242)					68.5 (3.10)
		CV% mean	27.8		36.0					4.5
	14	n	6	6	6	6	6	6	6	6
		Mean (SD)	341 (144)	1.25 (0.500;2.00)	741 (261)	740 (263)	1.11 (0.117)	4.59 (1.97)	7.47 (2.58)	71.2 (3.42)
		CV% mean	42.1		35.3	35.6	10.5	42.9	34.6	4.8
25 mg	1	n	6	6	6					6
		Mean (SD)	1490 (501)	1.00 (1.00;3.00)	3730 (1440)					68.5 (9.16)
		CV% mean	33.6		38.7					13.4
	14	n	6	6	6	6	6	6	6	6
		Mean (SD)	1810 (339)	1.25 (1.00;3.00)	4470 (934)	4500 (956)	1.27 (0.230)	5.71 (0.730)	5.80 (1.24)	68.5 (6.68)
		CV% mean	18.7		20.9	21.3	18.1	12.8	21.4	9.7
50 mg	1	n	6	6	6					6
		Mean (SD)	3410 (944)	2.00 (1.00;3.00)	7190 (1100)					68.3 (3.37)
		CV% mean	27.6		15.3					4.9
	14	n	6	6	6	6	6	6	6	6
		Mean (SD)	2810 (1070)	3.00 (1.00;4.00)	8470 (1220)	8520 (1230)	1.19 (0.172)	6.43 (0.885)	6.00 (0.850)	66.8 (3.55)
		CV% mean								

Dose	Day	Statistic	Cmax (ng/mL)	Tmax ¹ (hr)	AUCtau (hr*ng/mL)	AUClast (hr*ng/mL)	Racc	T1/2 (hr)	CLss/F (L/hr)	LHW090 % Hydrolysis (%)
100 mg	1	CV% mean	38.0		14.4	14.4	14.5	13.8	14.2	5.3
		n	6	6	6					6
		Mean (SD)	5150 (2300)	3.00 (1.50;4.00)	14900 (3580)					66.3 (3.06)
	14	CV% mean	44.6		23.9					4.6
		n	6	6	6	6	6	6	6	6
		Mean (SD)	5510 (1200)	1.75 (1.50;3.00)	17000 (2580)	17100 (2620)	1.16 (0.187)	10.9 (5.27)	6.03 (1.03)	67.5 (2.30)
200 mg	1	CV% mean	21.7		15.2	15.3	16.1	48.3	17.1	3.4
		n	6	6	6					6
		Mean (SD)	7650 (2930)	2.75 (1.00;4.00)	24500 (7410)					67.9 (5.51)
	14	CV% mean	38.3		30.3					8.1
		n	6	6	6	6	6	6	6	6
		Mean (SD)	8230 (1690)	1.75 (1.00;4.00)	27900 (4470)	28100 (4550)	1.20 (0.288)	14.7 (4.85)	7.36 (1.52)	70.9 (5.99)
400 mg	1	CV% mean	20.6		16.0	16.2	24.0	32.9	20.7	8.5
		n	6	6	6					6
		Mean (SD)	15700 (5120)	3.00 (1.50;4.00)	57600 (9560)					65.5 (2.40)
	14	CV% mean	32.5		16.6					3.7
		n	6	6	6	6	6	6	6	6
		Mean (SD)	15200 (5270)	3.00 (2.00;6.00)	65300 (13800)	66000 (13800)	1.13 (0.0694)	11.6 (2.45)	6.35 (1.31)	65.5 (3.77)
		CV% mean	34.6		21.1	20.9	6.2	21.1	20.6	5.8

Statistics presented include: n, arithmetic mean (standard deviation) and CV% arithmetic mean

¹For T_{max}, Median (Minimum; Maximum) are presented

Summary of plasma pharmacokinetic parameters of LHV527 following multiple ascending dose administration of LHW090 to healthy subjects (PK analysis set) - Stage 3

Dose	Day	Statistics	Cmax (ng/mL)	Tmax ¹ (hr)	AUCtau (hr*ng/mL)	AUClast (hr*ng/mL)	Racc	T1/2 (hr)
5 mg	1	n	6	6	6			
		Mean (SD)	227 (31.0)	2.50 (1.50;4.00)	1420 (314)			
		CV% mean	13.7		22.1			
	14	n	6	6	6	6	6	6
		Mean (SD)	281 (40.1)	2.50 (2.00;3.00)	1770 (347)	1940 (389)	1.26 (0.082)	29.6 (2.10)
		CV% mean	14.3		19.6	20.1	6.5	7.1
25 mg	1	n	6	6	6			
		Mean (SD)	1280 (195)	2.50 (2.00;4.00)	7940 (1180)			
		CV% mean	15.2		14.9			
	14	n	6	6	6	6	6	6
		Mean (SD)	1490 (346)	3.00 (2.00;4.00)	9820 (1570)	10600 (1760)	1.24 (0.078)	14.2 (4.13)
		CV% mean	23.1		16.0	16.6	6.3	29.0
50 mg	1	n	6	6	6			
		Mean (SD)	2830 (573)	3.00 (2.00;4.00)	15600 (2510)			
		CV% mean	20.3		16.1			
	14	n	6	6	6	6	6	6
		Mean (SD)	2630 (625)	4.00 (1.50;6.00)	17100 (2360)	18000 (2420)	1.10 (0.0583)	13.8 (3.29)
		CV% mean	23.8		13.8	13.5	5.3	23.8
100 mg	1	n	6	6	6			
		Mean (SD)	4460 (1350)	4.00 (2.00;4.00)	29100 (5080)			
		CV% mean	30.3		17.4			
	14	n	6	6	6	6	6	6
		Mean (SD)	5090 (1530)	3.50 (3.00;4.00)	35500 (6940)	38000 (7190)	1.22 (0.138)	10.2 (1.84)
		CV% mean	30.1		19.6	18.9	11.3	18.1

Dose	Day	Statistics	Cmax (ng/mL)	Tmax ¹ (hr)	AUCtau (hr*ng/mL)	AUClast (hr*ng/mL)	Racc	T1/2 (hr)
200 mg	1	n	6	6	6			
		Mean (SD)	6610 (1660)	3.50 (1.50;6.00)	51600 (11900)			
		CV% mean	25.1		23.0			
	14	n	6	6	6	6	6	6
		Mean (SD)	8200 (2920)	3.50 (2.00;6.00)	70100 (19100)	75400 (20300)	1.39 (0.337)	9.44 (1.80)
		CV% mean	35.7		27.3	26.9	24.2	19.1
400 mg	1	n	6	6	6			
		Mean (SD)	14900 (2940)	4.00 (3.00;4.00)	109000 (17100)			
		CV% mean	19.7		15.7			
	14	n	6	6	6	6	6	6
		Mean (SD)	14200 (3450)	4.00 (4.00;6.00)	124000 (22300)	133000 (23700)	1.13 (0.075)	9.33 (1.25)
		CV% mean	24.3		18.0	17.8	6.6	13.4

Statistics presented include: n, arithmetic mean (standard deviation) and CV% arithmetic mean

¹For Tmax, Median (Minimum;Maximum) are presented

Summary of plasma pharmacokinetic parameters of LHW090 following SAD administration to subjects with CRI (PK analysis set)- Stage 4

Dose	Statistic	Cmax (ng/mL)	Tmax ¹ (hr)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUC0-24h (hr*ng/mL)	T1/2 (hr)	CL/F (L/hr)	LHW090 %H ydrolysis (%)
2 mg	n	9	9	9	9	9	9	9	9
	Mean (SD)	147 (70.0)	1.00 (0.500;2.00)	271 (89.6)	273 (89.8)	274 (90.6)	2.09 (0.714)	8.24 (3.31)	82.0 (6.99)
	CV% mean	47.6		33.1	32.9	33.0	34.2	40.2	8.5
5 mg	n	5	5	5	5	5	5	5	5
	Mean (SD)	411 (205)	1.00 (1.00;1.50)	869 (256)	875 (257)	878 (257)	2.71 (0.699)	6.17 (2.01)	82.7 (5.21)
	CV% mean	49.8		29.5	29.4	29.3	25.8	32.6	6.3
5mg (repeat)	n	9	9	9	9	9	9	9	9
	Mean (SD)	276 (102)	1.00 (0.500;1.50)	653 (181)	658 (181)	660 (179)	2.14 (0.682)	8.02 (1.77)	84.3 (6.87)
	CV% mean	37.0		27.6	27.5	27.1	31.9	22.0	8.2
5mg (pooled)	n	14	14	14	14	14	14	14	14
	Mean (SD)	324 (154)	1.00 (0.500;1.50)	730 (228)	735 (228)	738 (228)	2.34 (0.719)	7.36 (2.00)	83.7 (6.16)
	CV% mean	47.6		31.2	31.1	30.8	30.7	27.2	7.4
12.5 mg	n	9	9	9	9	9	9	9	9
	Mean (SD)	980 (383)	1.53 (1.00;3.00)	1900 (499)	1910 (499)	1900 (496)	3.51 (1.05)	6.93 (1.64)	82.8 (7.43)
	CV% mean	39.1		26.2	26.2	26.1	29.8	23.6	9.0
25 mg	n	8	8	8	8	8	8	8	8
	Mean (SD)	1570 (443)	1.76 (1.00;4.00)	3670 (1110)	3680 (1110)	3660 (1100)	4.39 (1.50)	7.58 (3.15)	85.4 (4.25)
	CV% mean	28.3		30.3	30.2	30.1	34.1	41.5	5.0

Statistics presented include: n, arithmetic mean (standard deviation) and CV% arithmetic mean

¹For Tmax, Median (Minimum;Maximum) are presented

Summary of plasma pharmacokinetic parameters of LHV527 following SAD administration to subjects with CRI (PK analysis set)- Stage 4

Dose	Statistic	Cmax (ng/mL)	Tmax (hr) ¹	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUC0-24h (hr*ng/mL)	T1/2 (hr)
2 mg	n	9	9	9	9	9	9
	Mean (SD)	110 (37.6)	3.00 (1.50;4.00)	1370 (680)	1500 (712)	1030 (452)	27.6 (10.0)
	CV% mean	34.3		49.5	47.6	43.9	36.5
5 mg	n	5	5	5	5	5	5
	Mean (SD)	336 (77.9)	3.00 (1.50;4.00)	4310 (1350)	4450 (1390)	3440 (921)	18.3 (5.20)
	CV% mean	23.2		31.3	31.2	26.8	28.4
5mg (repeat)	n	9	9	9	9	9	9
	Mean (SD)	284 (112)	3.00 (1.50;10.0)	3890 (1520)	4020 (1640)	3050 (1010)	14.8 (4.07)
	CV% mean	39.2		39.1	40.7	33.0	27.4
5mg (pooled)	n	14	14	14	14	14	14
	Mean (SD)	303 (101)	3.00 (1.50;10.0)	4040 (1420)	4170 (1510)	3190 (961)	16.1 (4.64)
	CV% mean	33.3		35.2	36.3	30.1	28.8
12.5 mg	n	9	9	9	9	9	9
	Mean (SD)	887 (316)	4.00 (1.50;4.00)	10300 (3940)	10400 (3970)	8520 (3050)	13.5 (2.32)
	CV% mean	35.6		38.4	38.2	35.9	17.2
25 mg	n	8	8	8	8	8	8
	Mean (SD)	1930 (497)	4.00 (2.00;4.00)	22500 (8530)	22800 (8860)	18200 (5400)	10.7 (1.74)
	CV% mean	25.8		38.0	38.9	29.6	16.2

Statistics presented include: n, arithmetic mean (standard deviation) and CV% arithmetic mean

¹For Tmax, Median (Minimum;Maximum) are presented

Pharmacokinetic parameter summary for LHW090 and LHV527 following four 5 mg doses every 12 hr in subjects with chronic renal insufficiency (PK analysis set)-Stage 5

Analyte	Statistic	Cmax (ng/mL)	Tmax ¹ (hr)	AUCtau (hr*ng/mL)	AUClast (hr*ng/mL)	T1/2 (hr)	CLss/F (L/hr)	LHW090 %H ydrolysis (%)
LHW090	n	9	9	9	9	9	9	9
	Mean (SD)	355 (194)	1.50 (1.00;3.00)	835 (257)	865 (264)	9.38 (5.50)	6.45 (1.75)	86.0 (4.25)
	CV% mean	54.7		30.8	30.6	58.7	27.1	4.9
LHV527	n	9	9	9	9	9		
	Mean (SD)	639 (232)	3.00 (2.00;4.00)	5600 (2460)	11400 (6450)	15.4 (2.25)		
	CV% mean	36.4		43.9	56.5	14.7		

Statistics presented include: n, arithmetic mean (standard deviation) and CV% arithmetic mean

¹For Tmax, Median (Minimum;Maximum) are presented

Summary of Safety

Safety Results

Incidence of AEs by primary system organ class - n(percent) of subjects - Stage 1 (safety analysis set)

	LHW090 1mg N=3 n (%)
Subjects with AEs	1 (33.3)
System organ class	

	LHW090 1mg N=3 n (%)
Gastrointestinal disorders	1 (33.3)

Incidence of AEs by primary system organ class - n(percent) of subjects - Stage 2 (safety analysis set)

	LHW090 1mg SAD N=8 n (%)	LHW090 5mg SAD N=8 n (%)	LHW090 25mg SAD N=8 n (%)	LHW090 50mg SAD N=8 n (%)	LHW090 100mg SAD N=8 n (%)	LHW090 0.1mg SAD N=8 n (%)	LHW090 200mg SAD N=8 n (%)	LHW090 400mg SAD N=8 n (%)	LHW090 800mg SAD N=8 n (%)	LHW090 400mg SAD (Japanese ethnicity) N=8 n (%)	Pooled placebo N=20 n (%)	Total N=100 n (%)
Subjects with AEs	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (37.5)	1 (12.5)	3 (37.5)	1 (12.5)	2 (10.0)	11 (11.0)
	System organ class											
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)	2 (25.0)	1 (12.5)	1 (5.0)	6 (6.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	2 (2.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (1.0)
Injury, poisoning and procedural complications	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (1.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (1.0)

	LHW090 1mg SAD N=8 n (%)	LHW090 5mg SAD N=8 n (%)	LHW090 25mg SAD N=8 n (%)	LHW090 50mg SAD N=8 n (%)	LHW090 100mg SAD N=8 n (%)	LHW090 0.1mg SAD N=8 n (%)	LHW090 200mg SAD N=8 n (%)	LHW090 400mg SAD N=8 n (%)	LHW090 800mg SAD N=8 n (%)	LHW090 400mg SAD (Japanese ethnicity) N=8 n (%)	Pooled placebo N=20 n (%)	Total N=100 n (%)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (1.0)

Arranged in descending order of frequency (in total group) and by system organ class.

Incidence of AEs by primary system organ class – n (percent) of subjects - Stage 3 (safety analysis set)

	LHW090 5mg MAD N=6 n (%)	LHW090 25mg MAD N=6 n (%)	LHW090 50mg MAD N=6 n (%)	LHW090 100mg MAD N=6 n (%)	LHW090 200mg MAD N=6 n (%)	LHW090 400mg MAD N=6 n (%)	Pooled placebo N=12 n (%)	Total N=48 n (%)
Subjects with AEs	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	5 (83.3)	3 (50.0)	3 (25.0)	15 (31.3)
System organ class								
Nervous system disorders	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	2 (33.3)	1 (16.7)	3 (25.0)	8 (16.7)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	2 (33.3)	1 (16.7)	0 (0.0)	4 (8.3)
Skin and subcutaneous tissue disorders	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	4 (8.3)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	2 (4.2)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (2.1)

Arranged in descending order of frequency (in total group) and by system organ class.

Incidence of AEs by primary system organ class – n (percent) of subjects - Stage 4 (safety analysis set)

	LHW090 5mg SAD N=6 n (%)	LHW090 12.5mg SAD N=9 n (%)	LHW090 25mg SAD N=9 n (%)	LHW090 2mg SAD N=9 n (%)	LHW090 5mg SAD N=9 n (%)	Total N=42 n (%)

	LHW090 5mg SAD N=6 n (%)	LHW090 12.5mg SAD N=9 n (%)	LHW090 25mg SAD N=9 n (%)	LHW090 2mg SAD N=9 n (%)	LHW090 5mg SAD N=9 n (%)	Total N=42 n (%)
Subjects with AEs	0 (0.0)	3 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	5 (11.9)
System organ class						
Gastrointestinal disorders	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (2.4)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.4)
Nervous system disorders	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)

Arranged in descending order of frequency (in total group) and by system organ class.

Incidence of AEs by primary system organ class – n (percent) of subjects - Stage 5 (safety analysis set)

	LHW090 5mg MAD N=9 n (%)	Pooled placebo N=3 n (%)	Total N=12 n (%)
Subjects with AE(s)	0 (0.0)	1 (33.3)	1 (8.3)
System organ class			
Gastrointestinal disorders	0 (0.0)	1 (33.3)	1 (8.3)

Arranged in descending order of frequency (in total group) and by system organ class.

Incidence of AEs by preferred term – n (percent) of subjects - Stage 1 (safety analysis set)

	LHW090 1mg N=3 n (%)
Subjects with AE(s)	1 (33.3)
Preferred term	
Dry mouth	1 (33.3)

Incidence of AEs by preferred term – n (percent) of subjects - Stage 2 (safety analysis set)

	LHW090 1mg SAD N=8 n (%)	LHW090 5mg SAD N=8 n (%)	LHW090 25mg SAD N=8 n (%)	LHW090 50mg SAD N=8 n (%)	LHW090 100mg SAD N=8 n (%)	LHW090 0.1mg SAD N=8 n (%)	LHW090 200mg SAD N=8 n (%)	LHW090 400mg SAD N=8 n (%)	LHW090 800mg SAD N=8 n (%)	LHW090 400mg SAD (Japanese ethnicity) N=8 n (%)	Pooled placebo N=20 n (%)	Total N=100 n (%)
Subjects with AE(s)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (37.5)	1 (12.5)	3 (37.5)	1 (12.5)	2 (10.0)	11 (11.0)
	Preferred term											
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	2 (25.0)	1 (12.5)	1 (5.0)	5 (5.0)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (1.0)
Allergy to chemicals	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (1.0)
Contusion	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (1.0)
Dermatitis contact	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (1.0)
Infusion site vesicles	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Muscle spasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (1.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (1.0)

Arranged in descending order of frequency (in total group) and by preferred term.

Incidence of AEs by preferred term – n (percent) of subjects - Stage 3 (safety analysis set)

	LHW090 5mg MAD N=6 n (%)	LHW090 25mg MAD N=6 n (%)	LHW090 50mg MAD N=6 n (%)	LHW090 100mg MAD N=6 n (%)	LHW090 200mg MAD N=6 n (%)	LHW090 400mg MAD N=6 n (%)	Pooled placebo N=12 n (%)	Total N=48 n (%)
Subjects with AE(s)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	5 (83.3)	3 (50.0)	3 (25.0)	15 (31.3)
Preferred term								
Diarrhea	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	3 (6.3)
Dizziness	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	3 (6.3)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	1 (8.3)	3 (6.3)
Tension headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	1 (8.3)	3 (6.3)
Oropharyngeal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	2 (4.2)
Blepharospasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (2.1)
Chronic pigmented purpura	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Dermatitis contact	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (2.1)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (2.1)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (2.1)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (2.1)

Arranged in descending order of frequency (in total group) and by preferred term.

Incidence of AEs by preferred term – n (percent) of subjects - Stage 4 (safety analysis set)

	LHW090 5mg SAD N=6 n (%)	LHW090 12.5mg SAD N=9 n (%)	LHW090 25mg SAD N=9 n (%)	LHW090 2mg SAD N=9 n (%)	LHW090 5mg SAD N=9 n (%)	Total N=42 n (%)
Subjects with AE(s)	0 (0.0)	3 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	5 (11.9)
Preferred term						
Abdominal pain upper	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Catheter site related reaction	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (2.4)

	LHW090 5mg SAD N=6 n (%)	LHW090 12.5mg SAD N=9 n (%)	LHW090 25mg SAD N=9 n (%)	LHW090 2mg SAD N=9 n (%)	LHW090 5mg SAD N=9 n (%)	Total N=42 n (%)
Dry mouth	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Dysgeusia	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.4)

Arranged in descending order of frequency (in total group) and by preferred term.

Incidence of AEs by preferred term – n (percent) of subjects - Stage 5 (safety analysis set)

	LHW090 5mg MAD N=9 n (%)	placebo N=3 n (%)	Total N=12 n (%)
Subjects with AE(s)	0 (0.0)	1 (33.3)	1 (8.3)
Preferred term			
Abdominal pain upper	0 (0.0)	1 (33.3)	1 (8.3)
Nausea	0 (0.0)	1 (33.3)	1 (8.3)

Arranged in descending order of frequency (in total group) and by preferred term.

Serious Adverse Events and Deaths

No deaths or severe AEs were reported. None of the AEs led to the discontinuation of the subjects from the study.

Other Relevant Findings

Not applicable.

Conclusion:

- Safety: LHW090 was safe and well tolerated when given as single oral doses up to 800 mg and once daily multiple doses up to 400 mg in healthy subjects. LHW090 was safe and well tolerated when given as single oral doses up to 25 mg in subjects with chronic renal insufficiency.
- Pharmacodynamics: Administration of LHW090 increased plasma cGMP and urinary cGMP excretion rates.
- Pharmacokinetics:
 - Following single (0.1-800 mg) and multiple (5-400 mg) once daily doses of LHW090 to healthy subjects; LHW090 Tmax ranged from 1-3.5 hr and terminal elimination T1/2 from 1.33 - 14.7 hr. Accumulation in AUCtau was minor ranging from 1.11-1.27 and in-line with the T1/2, steady-state was achieved by approximately 4 days. Hydrolysis of LHW090 to the active moiety LHV527 was high, ranging from 63-70%. LHV527 Tmax was similar to LHW090 ranging from 1.5-4 hr with terminal elimination T1/2 from 2.5 - 47 hr after single doses and 9.33 -29.6 hr after multiple once daily doses. Accumulation in AUCtau was minor, ranging from 1.1- 1.39 and in-line with T1/2,

steady-state was achieved by approximately 4 days. Approximately 29-54% and 35.8-49% of the dose after single doses and multiple doses, respectively, was excreted in urine as LHV527.

- After single and multiple dose administration C_{max} and AUC of LHW090 and LHV527 increased with increase in dose, however not in a dose-proportional manner over the investigated dose range.
- For CRI subjects, T_{max} of LHW090 and LHV527 was in the range of the healthy subjects. The T_{1/2} ranged from 2.09-4.39 hr for LHW090 and 10.7-27.6 hr for LHV527. At 5 and 25 mg single doses the C_{max} and AUC_{inf} of LHV527 were approximately 1.6 fold and 2.9 fold higher compared to healthy subjects, which, may be attributed to the reduced renal clearance of LHV527 in subjects with CRI. Following single (2-25 mg) or multiple (four 5 mg doses administered 12 hr apart) doses, the % hydrolysis of LHW090 to LHV527 was also high, ranging from 82-86%.
- The pharmacokinetics of LHW090 and LHV527 was similar between Japanese and non-Japanese subjects after administration of LHW090 at a 400 mg single dose.

Date of Clinical Trial Report

12 May 2015