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

Summary

EudraCT number	2015-001890-42
Trial protocol	DE FR DK NL
Global end of trial date	17 August 2017

Results information

Result version number	v1 (current)
This version publication date	22 June 2018
First version publication date	22 June 2018

Trial information

Trial identification

Sponsor protocol code	CLWH090X2202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	Netherlands: 8
Worldwide total number of subjects	64
EEA total number of subjects	27

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	33
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized in a 1:1:2 ratio to LHW090 100 mg, LHW090 200 mg and placebo, respectively.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	LHW090 100 mg

Arm description:

LHW090 100 mg once daily for 28 days

Arm type	Experimental
Investigational medicinal product name	LHW090
Investigational medicinal product code	LHW090
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

LHW090 100 mg once daily for 28 days

Arm title	LHW090 200 mg

Arm description:

LHW090 200 mg once daily for 28 days

Arm type	Experimental
Investigational medicinal product name	LHW090
Investigational medicinal product code	LHW090
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

LHW090 200 mg once daily for 28 days

Arm title	Placebo

Arm description:

Matching placebo to LHW090 oral dose for 28 days

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to LHW090 oral dose for 28 days

Number of subjects in period 1	LHW090 100 mg	LHW090 200 mg	Placebo
Started	17	15	32
Primary Pharmacodynamic Analysis Set	15	14 [1]	29
Pharmacokinetic (PK) analysis set	17	15	0 [2]
Completed	15	15	28
Not completed	2	0	4
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	2	-	-
Protocol deviation	-	-	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number is correct as is

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number is correct as is

Baseline characteristics

Reporting groups	
Reporting group title	LHW090 100 mg
Reporting group description: LHW090 100 mg once daily for 28 days	
Reporting group title	LHW090 200 mg
Reporting group description: LHW090 200 mg once daily for 28 days	
Reporting group title	Placebo
Reporting group description: Matching placebo to LHW090 oral dose for 28 days	

Reporting group values	LHW090 100 mg	LHW090 200 mg	Placebo
Number of subjects	17	15	32
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	10	14
From 65-84 years	8	5	18
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	64.2	61.8	64.4
standard deviation	± 8.42	± 5.16	± 9.56
Sex: Female, Male Units: Subjects			
Female	4	9	13
Male	13	6	19
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	7	14
White	11	7	18
More than one race	0	0	0
Unknown or Not Reported	1	1	0

Reporting group values	Total		
Number of subjects	64		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	33		
From 65-84 years	31		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	26		
Male	38		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	25		
White	36		
More than one race	0		
Unknown or Not Reported	2		

End points

End points reporting groups

Reporting group title	LHW090 100 mg
Reporting group description: LHW090 100 mg once daily for 28 days	
Reporting group title	LHW090 200 mg
Reporting group description: LHW090 200 mg once daily for 28 days	
Reporting group title	Placebo
Reporting group description: Matching placebo to LHW090 oral dose for 28 days	

Primary: Number of participants with reported adverse events (AEs), serious adverse events (SAEs) and deaths

End point title	Number of participants with reported adverse events (AEs), serious adverse events (SAEs) and deaths[1]
End point description: Number of participants with AEs, SAEs and deaths were assessed.	
End point type	Primary
End point timeframe: 6 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis analyzed for this outcome measure

End point values	LHW090 100 mg	LHW090 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	15	32	
Units: Participants				
AEs|	12	3	14	
SAEs|	0	0	0	
Deaths|	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in mean daytime blood pressure

End point title	Change from baseline in mean daytime blood pressure
End point description: Change in the 12 hour average of systolic blood pressure (SBP) measured by ambulatory blood pressure was defined as the 12 hour daytime average SBP on Day 28 minus the 12 hour daytime average SBP on Day -1. monitoring (ABPM). A negative change from baseline indicates improvement.	
End point type	Primary

End point timeframe:
Baseline, day 27

End point values	LHW090 100 mg	LHW090 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	13	28	
Units: mmHg				
arithmetic mean (standard deviation)	-9.41 (± 8.379)	-16.84 (± 7.678)	-0.79 (± 10.555)	

Statistical analyses

Statistical analysis title	Change from baseline in mean daytime BP
Comparison groups	LHW090 100 mg v Placebo
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002 [2]
Method	Longitudinal repeated measures mixed eff
Parameter estimate	Mean difference (net)
Point estimate	-8.555
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.388
upper limit	-2.722
Variability estimate	Standard error of the mean
Dispersion value	2.9077

Notes:
[2] - 1-sided p-value

Statistical analysis title	Change from baseline in mean daytime BP
Comparison groups	LHW090 200 mg v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [3]
Method	Longitudinal repeated measures mixed eff
Parameter estimate	Mean difference (net)
Point estimate	-14.727
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.852
upper limit	-8.602

Variability estimate	Standard error of the mean
Dispersion value	3.0548

Notes:

[3] - 1-sided p-value

Secondary: Pharmacokinetics of LHW090/LHV527 in plasma: observe maximum plasma concentration following LHW090 at steady state in patients (Cmax)

End point title	Pharmacokinetics of LHW090/LHV527 in plasma: observe maximum plasma concentration following LHW090 at steady state in patients (Cmax)[4]

End point description:

Blood samples were collected to assess Cmax.

End point type	Secondary

End point timeframe:

Within 60 min prior to dosing, post dose: +/- 5 min up to 3 hrs, +/- 10 min from ≥3 hrs up to 12 hrs on Day 1 and Day 28

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis analyzed for this outcome measure

End point values	LHW090 100 mg	LHW090 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: ng/mL				
arithmetic mean (standard deviation)				
LHW090, day 1|	3620 (± 1220)	6340 (± 3440)		
LHW090, day 28|	4190 (± 1740)	7340 (± 4300)		
LHV527, day 1|	5040 (± 1770)	6330 (± 3700)		
LHV527, day 28|	5240 (± 1960)	9870 (± 1810)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Pharmacokinetics of LHW090/LHV527 in plasma: time to reach the maximum concentration after administration of LHW090 (Tmax)[5]

End point description:

Blood samples were collected to assess Tmax.

End point type	Secondary

End point timeframe:

Within 60 min prior to dosing, post dose: +/- 5 min up to 3 hrs, +/- 10 min from ≥3 hrs up to 12 hrs on Day 1 and Day 28

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis analyzed for this outcome measure

End point values	LHW090 100 mg	LHW090 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: hour				
median (full range (min-max))				
LHW090, day 1|	2.08 (1.00 to 7.95)	3.00 (2.00 to 8.08)		
LHW090, day 28|	2.00 (1.00 to 3.00)	2.92 (0.383 to 8.08)		
LHV527, day 1|	3.07 (2.08 to 8.03)	4.08 (1.00 to 8.50)		
LHV527, day 28|	3.92 (1.17 to 8.00)	4.00 (2.38 to 8.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of LHW090/LHV527 in plasma: area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration (AUClast)

End point title	Pharmacokinetics of LHW090/LHV527 in plasma: area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration (AUClast)[6]

End point description:

Blood samples were collected to assess AUClast.

End point type	Secondary

End point timeframe:

Within 60 min prior to dosing, post dose: +/- 5 min up to 3 hrs, +/- 10 min from ≥3 hrs up to 12 hrs on Day 1 and Day 28

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis analyzed for this outcome measure

End point values	LHW090 100 mg	LHW090 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: Hr*ng/mL				
arithmetic mean (standard deviation)				
LHW090, day 1|	12300 (± 3870)	24500 (± 16000)		
LHW090, day 28|	13700 (± 4370)	24400 (± 11400)		
LHV527, day 1|	25300 (± 11800)	28700 (± 17900)		
LHV527, day 28|	27700 (± 11600)	52300 (± 14400)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of LHW090/LHV527 in plasma: Last measurable plasma concentration (Clast)

End point title	Pharmacokinetics of LHW090/LHV527 in plasma: Last measurable plasma concentration (Clast)[7]

End point description:

Blood samples were collected to assess Clast.

End point type	Secondary

End point timeframe:

Within 60 min prior to dosing, post dose: +/- 5 min up to 3 hrs, +/- 10 min from ≥3 hrs up to 12 hrs on Day 1 and Day 28

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis analyzed for this outcome measure

End point values	LHW090 100 mg	LHW090 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: ng/mL				
arithmetic mean (standard deviation)				
LHW090, day 1|	404 (± 358)	1710 (± 1600)		
LHW090, day 28|	682 (± 752)	1790 (± 1740)		
LHV527, day 1|	3490 (± 1700)	4670 (± 3050)		
LHV527, day 28|	3430 (± 1340)	7840 (± 3130)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of LHW090/LHV527 in plasma:Tlast

End point title	Pharmacokinetics of LHW090/LHV527 in plasma:Tlast[8]

End point description:

Blood samples were collected to assess Tlast.

End point type	Secondary

End point timeframe:

Within 60 min prior to dosing, post dose: +/- 5 min up to 3 hrs, +/- 10 min from ≥3 hrs up to 12 hrs on Day 1 and Day 28

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis analyzed for this outcome measure

End point values	LHW090 100 mg	LHW090 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: hour				
median (full range (min-max))				
LHW090, day 1|	8.00 (7.07 to 8.08)	8.00 (7.83 to 8.50)		
LHW090, day 28|	8.00 (4.00 to 8.50)	8.00 (7.83 to 8.50)		
LHV527, day 1|	8.00 (7.07 to 8.08)	8.00 (7.83 to 8.50)		
LHV527, day 28|	8.00 (4.00 to 8.50)	8.00 (7.38 to 8.08)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	LHW090 100mg
Reporting group description:	
LHW090 100mg	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	LHW090 200mg
Reporting group description:	
LHW090 200mg	

Serious adverse events	LHW090 100mg	Placebo	LHW090 200mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	LHW090 100mg	Placebo	LHW090 200mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 17 (70.59%)	14 / 32 (43.75%)	3 / 15 (20.00%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Feeling hot			

subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	2 / 17 (11.76%)	3 / 32 (9.38%)	0 / 15 (0.00%)
occurrences (all)	2	3	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Breast discomfort			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Investigations			
Blood cholesterol increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Blood potassium increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Cardiac murmur			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Haematocrit increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Haemoglobin increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0

Weight increased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 17 (5.88%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Fall			
subjects affected / exposed	1 / 17 (5.88%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Photopsia			

subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)	1 / 32 (3.13%)	1 / 15 (6.67%)
occurrences (all)	2	1	1
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Pruritus			

subjects affected / exposed	3 / 17 (17.65%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	4	0	0
Pruritus generalised			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Skin discolouration			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Skin irritation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Renal failure			
subjects affected / exposed	1 / 17 (5.88%)	1 / 32 (3.13%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Urethral pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Arthritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 32 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 17 (0.00%)	2 / 32 (6.25%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Muscular weakness			

subjects affected / exposed	0 / 17 (0.00%)	0 / 32 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Eye infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	2 / 32 (6.25%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 32 (3.13%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 32 (6.25%)	0 / 15 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2015	Amendment 1 issued before study start provided pharmacokinetic based guidance for the initiation of an ACE inhibitor following discontinuation of study medication.
06 January 2016	Amendment 2, issued after inclusion of 1 patient, was generated in response to the following: • to include withdrawal criteria based on an upper limit blood pressure measurement • to add creatine kinase (CK) assessments to safety laboratory evaluations in order to satisfy requirements for CK monitoring • Request from the Health Authority in Germany (BfArM) to clarify extent of ophthalmologic screening for study patients
28 January 2016	Amendment 3 was done to update the eligibility criteria and clarified to exclude women of childbearing potential. Language was also updated throughout the protocol to clarify the allowed anti-hypertensive medications for inclusion in the study.
08 March 2016	Amendment 4 was generated to fulfill request of German Health Authority to add clarification in the protocol to highlight that all patients will be diagnostically evaluated for secondary hypertension according to clinical guidelines as part of screening assessments.
22 August 2016	Amendment 5 was proposed to eliminate the pharmacokinetic monitoring on Day 1. Based on the modeling of PK data obtained in a previous study, the expectation is that the Day 1 profile of LHW090/LHV527 in resistant hypertension patients in the study could be adequately characterized based on prior data and the data obtained to date in the patients that were already enrolled in this study. The protocol was thus amended to eliminate the 8 hours of pharmacokinetic monitoring on Day 1 so that on Day 1 patients could be released from the site after dosing at the Investigator’s discretion. Reducing the frequency of blood sampling also had the effect of reducing patient burden and adding scheduling flexibility which was expected to enhance patient recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported