



## 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           |
| <b>Arm title</b>             | 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

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | 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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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 |

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| Consent withdrawn by subject          | -             | -                 | 1                |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

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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:<br>LHW090 100 mg once daily for 28 days             |               |
| Reporting group title  | LHW090 200 mg |
| Reporting group description:<br>LHW090 200 mg once daily for 28 days             |               |
| Reporting group title  | Placebo       |
| Reporting group description:<br>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<br>Units: Subjects                    |               |               |         |
| In utero  | 0             | 0             | 0       |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0             | 0             | 0       |
| Newborns (0-27 days)                                  | 0             | 0             | 0       |
| Infants and toddlers (28 days-23<br>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<br>Units: Years                        |               |               |         |
| arithmetic mean                                       | 64.2          | 61.8          | 64.4    |
| standard deviation                                    | ± 8.42        | ± 5.16        | ± 9.56  |
| Sex: Female, Male<br>Units: Subjects                  |               |               |         |
| Female  | 4             | 9             | 13      |
| Male  | 13            | 6             | 19      |
| Race (NIH/OMB)<br>Units: Subjects                     |               |               |         |
| American Indian or Alaska Native                      | 0             | 0             | 0       |
| Asian   | 1             | 0             | 0       |
| Native Hawaiian or Other Pacific<br>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<br>Units: Subjects                    |    |  |  |
| In utero  | 0  |  |  |
| Preterm newborn infants<br>(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<br>Units: Years                        |    |  |  |
| arithmetic mean                                       |    |  |  |
| standard deviation                                    | -  |  |  |
| Sex: Female, Male<br>Units: Subjects                  |    |  |  |
| Female  | 26 |  |  |
| Male  | 38 |  |  |
| Race (NIH/OMB)<br>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:<br>LHW090 100 mg once daily for 28 days             |               |
| Reporting group title  | LHW090 200 mg |
| Reporting group description:<br>LHW090 200 mg once daily for 28 days             |               |
| Reporting group title  | Placebo       |
| Reporting group description:<br>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 <sup>[1]</sup> |
| End point description:<br>Number of participants with AEs, SAEs and deaths were assessed. |  |
| End point type  | Primary  |
| End point timeframe:<br>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:<br>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 ( $\pm$ 8.379) | -16.84 ( $\pm$ 7.678) | -0.79 ( $\pm$ 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 <sup>[2]</sup>                   |
| 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 <sup>[3]</sup>                   |
| 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) <sup>[4]</sup> |
|-----------------|--|

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) <sup>[5]</sup> |
|-----------------|---|

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) <sup>[6]</sup> |
|-----------------|--|

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) <sup>[7]</sup> |
|-----------------|--|

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 <sup>[8]</sup> |
|-----------------|--|

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

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



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 17 (0.00%)<br>0 | 1 / 32 (3.13%)<br>1 | 0 / 15 (0.00%)<br>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<br>occurrences (all)   | 0 / 17 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 17 (0.00%)<br>0 | 1 / 32 (3.13%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 17 (0.00%)<br>0 | 1 / 32 (3.13%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Infections and infestations<br>Eye infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 17 (0.00%)<br>0 | 1 / 32 (3.13%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)      | 0 / 17 (0.00%)<br>0 | 2 / 32 (6.25%)<br>2 | 0 / 15 (0.00%)<br>0 |
| Metabolism and nutrition disorders<br>Gout<br>subjects affected / exposed<br>occurrences (all)   | 0 / 17 (0.00%)<br>0 | 1 / 32 (3.13%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 17 (0.00%)<br>0 | 1 / 32 (3.13%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 17 (0.00%)<br>0 | 2 / 32 (6.25%)<br>2 | 0 / 15 (0.00%)<br>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: <ul style="list-style-type: none"><li>• to include withdrawal criteria based on an upper limit blood pressure measurement</li><li>• to add creatine kinase (CK) assessments to safety laboratory evaluations in order to satisfy requirements for CK monitoring</li><li>• Request from the Health Authority in Germany (BfArM) to clarify extent of ophthalmologic screening for study patients</li></ul>  |
| 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported