# Clinical trial results:
# Efficacy and safety of Lorista®, Lorista® H and Lorista® HD in the treatment of mild to moderate arterial hypertension

## Summary

| | |
|---|---|
| EudraCT number | 2004-004933-32 |
| Trial protocol | CZ |
| Global end of trial date | 24 June 2004 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 03 July 2021 |
| First version publication date | 03 July 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | km 55/2004 – LORISTAH/CZ |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | protocol code in SI: km 54/2004 - LORISTAHHD/SI |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Krka, d.d., Novo mesto |
| Sponsor organisation address | Šmarješka cesta 6, Novo mesto, Slovenia, 8501 |
| Public contact | Tanja Kohek, Krka, d.d., Novo mesto<br>Dunajska cesta 65<br>1000 Ljubljana<br>Slovenia, 00386 41 589769, tanja.kohek@krka.biz |
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| Sponsor organisation name | Krka ČR s.r.o. |
| Sponsor organisation address | Sokolovská 192/79, Prague, Czechia, 186 00 |
| Public contact | Martin Sustr, Krka ČR s.r.o.<br>Sokolovská 192/79<br>186 00 Prague<br>Czechia, 00420 602 486846, martin.sustr@krka.biz |
| Scientific contact | Martin Sustr, Krka ČR s.r.o.<br>Sokolovská 192/79<br>186 00 Prague<br>Czechia, 00420 602 486846, martin.sustr@krka.biz |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric | No |

| | |
|---|---|
| investigation plan (PIP) | |
| 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 | 31 March 2006 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 June 2004 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 June 2004 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The aim of this trial is to confirm the antihypertensive effect of Lorista® tablets (50 mg of losartan), Lorista® H tablets (fixed dose combination of 50 mg of losartan and 12,5 mg of hydrochlorothiazide) and Lorista® HD (fixed dose combination of 100 mg of losartan and 25 mg of hydrochlorothiazide) in patients with mild to moderate hypertension:
• previously untreated or
• those with hypertension unsuccessfully treated with monotherapy or combination of antihypertensive drugs (fixed dose or non-fixed dose combinations) or
• in whom antihypertensive therapy needs to be changed due to adverse reactions experienced with previous antihypertensive therapy,
and to establish the tolerance and the effect of therapy on the patient’s quality of life.

Protection of trial subjects:

The patients were divided into two groups with regard to dosing. In the I. group of patients a starting dose was one tablet of Lorista®, after four weeks of treatment those patients, whose blood pressure did not respond properly (140/90 mmHg or less) continued the treatment with 1 tablet of Lorista® H. After eight weeks of treatment, those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with 1 tablet of Lorista® plus 1 tablet of Lorista® H daily. After eleven weeks of treatment, those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with one tablet of Lorista® HD daily.

In the II. group of patients starting dose was one tablet of Lorista® H, after four weeks of treatment, those patients, whose blood pressure did not respond properly (140/90 mmHg or less), continued the treatment with 1 tablet of Lorista® plus 1 tablet of Lorista® H daily. After eight weeks of treatment, those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with 1 tablet of Lorista® HD daily.

| |
|---|
| Background therapy: - |
| Evidence for comparator: - |

| | |
|---|---|
| Actual start date of recruitment | 15 April 2003 |
| 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 | Czechia: 132 |
| Country: Number of subjects enrolled | Slovenia: 221 |
| Worldwide total number of subjects | 353 |
| EEA total number of subjects | 353 |

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) | 211 |
| From 65 to 84 years | 142 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

353 patients enrolled from Slovenia and Czechia. First patient in (FPI) was on 15.4.2003 and Last patient Out (LPO) was on 24.6.2004.

### Pre-assignment

Screening details:

In general:
- Male and female adults from 18-80 years old with AH.
- In I. group were included previously untreated patients and patients with AH unsuccessfully treated with previous monotherapy (inefficacy or AR).
- In II. group were included patients with AH unsuccessfully treated with previous combination AH treatment (inefficacy or AR).

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | All patients |

Arm description:

All patients enrolled in the study. A total of 353 patients were enrolled in the study in Slovenia and Czechia.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Lorista® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One tablet of Lorista® contains 50 mg of losartan. The patient takes one tablet daily.

| | |
|---|---|
| Investigational medicinal product name | Lorista® H |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One tablet of Lorista® H contains 50 mg of losartan and 12.5 mg of hydrochlorothiazid. The patient takes one tablet daily.

| | |
|---|---|
| Investigational medicinal product name | Lorista® HD |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One tablet of Lorista® HD contains 100 mg of losartan and 25 mg of hydrochlorothiazid. The patient takes one tablet daily.

| **Number of subjects in period 1** | All patients |
|---|---|
| Started | 353 |
| Completed | 322 |
| Not completed | 31 |
| Consent withdrawn by subject | 8 |
| Adverse event, non-fatal | 5 |
| Protocol deviation | 18 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall trial |

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|---|---|---|---|
| Number of subjects | 353 | 353 | |
| Age categorical<br>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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 60.3 | | |
| standard deviation | ± 12.0 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 209 | 209 | |
| Male | 144 | 144 | |

## End points

### End points reporting groups

| Reporting group title | All patients |
|---|---|

Reporting group description:

All patients enrolled in the study. A total of 353 patients were enrolled in the study in Slovenia and Czechia.

### Primary: SBP and DBP on each visit

| End point title | SBP and DBP on each visit[1] |
|---|---|

End point description:

In the I. group of patients a starting dose was 1 tablet of Lorista®. After 4 weeks of treatment those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with 1 tablet of Lorista® H. After 8 weeks of treatment, those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with 1 tablet of Lorista® and 1 tablet of Lorista® H daily. After 11 weeks of treatment, those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with one tablet of Lorista® HD daily.
In the II. group of patients starting dose was 1 tablet of Lorista® H, after 4 weeks of treatment, those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with 1 tablet of Lorista® and 1 tablet of Lorista® H daily. After 8 weeks of treatment, those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with 1 tablet of Lorista® HD daily.

| End point type | Primary |
|---|---|

End point timeframe:

Duration of the treatment was 14 weeks. First week from V1 to V2 was a washout period. During washout period patients weren`t taking any AH medications.

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: In order to report statistical analysis it is required to define at least two comparison groups. This was one arm study.
The following data were statistically processed: the largest and the smallest data, arithmetic mean of data with standard deviation of data and standard error of mean and the value of t variable in t-test. Patients prematurely discontinuing the trial due to adverse reactions were also included in the statistical analysis.

| **End point values** | All patients | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 327 | | | |
| Units: mmHG | | | | |
| arithmetic mean (standard deviation) | | | | |
| SBP V1 | 157 (± 13.7) | | | |
| SBP V2 | 159 (± 12.5) | | | |
| SBP V3 | 144.1 (± 13.8) | | | |
| SBP V4 | 138.2 (± 12.5) | | | |
| SBP V5 | 134.8 (± 10.3) | | | |
| SBP V6 | 133.4 (± 9.8) | | | |
| DBP V1 | 93.6 (± 8.2) | | | |
| DBP V2 | 95.4 (± 8) | | | |
| DBP V3 | 86.8 (± 8.7) | | | |
| DBP V4 | 83.3 (± 7.7) | | | |
| DBP V5 | 82 (± 7.1) | | | |
| DBP V6 | 81.4 (± 6.8) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change of SBP and DBP from baseline to visit

| End point title | Absolute change of SBP and DBP from baseline to visit |
|---|---|

End point description:

In the I. group of patients a starting dose was 1 tablet of Lorista®. After 4 weeks of treatment those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with 1 tablet of Lorista® H. After 8 weeks of treatment, those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with 1 tablet of Lorista® and 1 tablet of Lorista® H daily. After 11 weeks of treatment, those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with one tablet of Lorista® HD daily.
In the II. group of patients starting dose was 1 tablet of Lorista® H, after 4 weeks of treatment, those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with 1 tablet of Lorista® and 1 tablet of Lorista® H daily. After 8 weeks of treatment, those patients, whose blood pressure was not 140/90 mmHg or less, continued the treatment with 1 tablet of Lorista® HD daily.

| End point type | Secondary |
|---|---|

End point timeframe:

Duration of the treatment was 14 weeks. First week from V1 to V2 was a washout period. During washout period patients weren`t taking any AH medications.

| **End point values** | All patients | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 327 | | | |
| Units: mmHG | | | | |
| arithmetic mean (standard deviation) | | | | |
| SBP baseline-V3 | -15.5 (± 13.7) | | | |
| SBP baseline-V4 | -21.6 (± 15) | | | |
| SBP baseline-V5 | -25 (± 13.8) | | | |
| SBP baseline-V6 | -26 (± 13.9) | | | |
| DBP baseline-V3 | -8.7 (± 8.9) | | | |
| DBP baseline-V4 | -12.2 (± 8.7) | | | |
| DBP baseline-V5 | -13.7 (± 8.7) | | | |
| DBP baseline-V6 | -14.2 (± 8.8) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of therapeutic effect

| End point title | Assessment of therapeutic effect |
|---|---|

End point description:

At the end of the study, 88.8% of the patients had blood pressure 140/90 mmHg or less (assessed as very good); 6.2% of the patients had the systolic blood pressure reduced by at least 10 mmHg, and the diastolic pressure by at least 5 mmHg (assessed as good); 2.8% of the patients had only the systolic blood pressure reduced by at least 10 mmHg, or only the diastolic pressure by at least 5 mmHg (assessed as satisfactory); 2.2% of the patients had the systolic blood pressure reduced by less than 10 mmHg and the diastolic pressure by less than 5 mmHg (assessed as unsatisfactory).

| End point type | Secondary |
|---|---|

End point timeframe:

Duration of the treatment was up to 14 weeks.

| **End point values** | All patients | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 327 | | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Very Good | 88.8 | | | |
| Good | 6.2 | | | |
| Satisfactory | 2.8 | | | |
| Unsatisfactory | 2.2 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of total clinical effect

| End point title | Assessment of total clinical effect |
|---|---|

End point description:

85.4% of the patients had blood pressure of 140/90 mmHg or less and were without AR (assessed as excellent); 3.7% of the patients had blood pressure of 140/90 mmHg or less and had mild adverse reactions (assessed as very good); 6.5% of the patients had the SBP reduced by at least 10 mmHg and the DBP by at least 5 mmHg and were without adverse reactions (assessed as good); 2.8% of the patients had blood pressure of 140/90 mmHg or less or SBP reduced by at least 10 mmHg or DBP by at least 5 mmHg and were accompanied with moderate adverse reactions or only SBP was reduced by at least 10 mmHg or only DBP by at least 5 mmHg without adverse reactions (assessed as satisfactory); 1.6% of the patients had blood pressure of 140/90 mmHg or less but had very serious adverse reactions that induced withdrawal of the treatment or the SBP was reduced by less than 10 mmHg and DBP by less than 5 mmHg or very serious adverse reactions that induced withdrawal of the treatment (assessed as unsatisfactory)

| End point type | Secondary |
|---|---|

End point timeframe:

Duration of the tratment was up to 14 weeks

| End point values | All patients | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 327 | | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Excellent | 85.4 | | | |
| Very Good | 3.7 | | | |
| Good | 6.5 | | | |
| Satisfactory | 2.8 | | | |
| Unsatisfactory | 1.6 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AE reporting timeline for one patient was up to 14 weeks and was the same for the whole duration of the study (FPI: 15.4.2003, LPO: 24.6.2004).

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 8.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | All patients |

Reporting group description: -

| Serious adverse events | All patients | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 353 (1.13%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 1 / 353 (0.28%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 353 (0.28%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 2 / 353 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| **Non-serious adverse events** | All patients | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 353 (4.25%) | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 10 / 353 (2.83%) | | |
| occurrences (all) | 12 | | |
| Headache | | | |
| subjects affected / exposed | 5 / 353 (1.42%) | | |
| occurrences (all) | 6 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported