



## Clinical trial results:

### The efficacy and safety of a single dose Flebaven® (Diosmin) of 1000 mg per day in patients with chronic venous disease (LIGHTEN-UP)

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2017-004804-23 |
| Trial protocol           | SI             |
| Global end of trial date | 08 July 2019   |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 15 August 2020 |
| First version publication date | 15 August 2020 |

#### Trial information

##### Trial identification

|                       |                        |
|-----------------------|------------------------|
| Sponsor protocol code | KCT13/2017-FLEBAVEN/SI |
|-----------------------|------------------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Krka, d.d., Novo mesto   |
| Sponsor organisation address | Dunajska 65, Ljubljana, Slovenia, 1000   |
| Public contact               | Clinical Trials Information<br>Tanja Kohek, Krka d.d., Novo mesto<br>Dunajska 65<br>1000 Ljubljana, 00386 14751236, tanja.kohek@krka.biz |
| Scientific contact           | Clinical Trials Information<br>Tanja Kohek, Krka d.d., Novo mesto<br>Dunajska 65<br>1000 Ljubljana, 00386 14751236, tanja.kohek@krka.biz |

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 January 2020 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 08 July 2019    |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 08 July 2019    |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of the study was to confirm efficacy and safety of Flebaven 1000 mg once daily on:

- reduction of leg pain,
- reduction the feeling of heavy legs,
- reduction of swelling of the legs and
- improving the quality of life.

Protection of trial subjects:

There were three visits for each patient - first or screening visit and two control visits. Second visit was after 4 weeks of treatment and third visit was after 12 weeks of treatment. On second and third visit the researchers assessed efficacy of the treatment by assessing the symptoms on a numerical scale (leg pain, feeling of heavy legs, the extend of swelling of the legs) and the clinical global indicator of disease severity (CGI-S) and the clinical global indicator of disease improvement (CGI-I ). At the beginning and the end of the clinical trial, patients assessed their quality of life with the SF-20 questionnaire. To monitor safety, the researchers recorded adverse events at both control visits.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 26 June 2018 |
| 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 | Slovenia: 389 |
| Worldwide total number of subjects   | 389           |
| EEA total number of subjects         | 389           |

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) | 297 |
| From 65 to 84 years  | 92  |
| 85 years and over    | 0   |

## Subject disposition

### Recruitment

Recruitment details:

In general, patients aged 20 to 70 years with a diagnosis of primary Chronic Venous Disease (CVD) were eligible for inclusion in the trial.

### Pre-assignment

Screening details:

Clinical trial was performed on adult patients aged 20 to 70 years with a diagnosis of primary CVD and leg pain rated 4 or more on a numeric scale, which corresponds to at least moderate pain intensity. In CT were included patients who were classified according to CEAP into clinical classes C0s to C4s on the most affected leg and who signed an ICF.

### Period 1

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

### Arms

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

Arm description:

All 389 patients that were enrolled in the trial.

|  |                |
|--|----------------|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Flebaven® 1000 |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Tablet         |
| Routes of administration               | Oral use       |

Dosage and administration details:

One tablet of Flebaven® 1000 contains 1000 mg of micronised Diosmin.

| Number of subjects in period 1        | All patients |
|---------------------------------------|--------------|
| Started                               | 389          |
| Completed                             | 356          |
| Not completed                         | 33           |
| Consent withdrawn by subject          | 4            |
| Adverse event, non-fatal              | 15           |
| Tablet too big - difficult swallowing | 3            |
| Other illness                         | 1            |
| Lost to follow-up                     | 8            |
| Lack of efficacy                      | 2            |



## Baseline characteristics

### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

| Reporting group values                                | Overall trial | Total |  |
|---|---------------|-------|--|
| Number of subjects                                    | 389           | 389   |  |
| Age categorical                                       |               |       |  |
| 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<br>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  |               |       |  |
| Units: years  |               |       |  |
| arithmetic mean                                       | 56.3          |       |  |
| inter-quartile range (Q1-Q3)                          | 50 to 65      | -     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female  | 317           | 317   |  |
| Male  | 72            | 72    |  |

## End points

### End points reporting groups

|   |              |
|---|--------------|
| Reporting group title   | All patients |
| Reporting group description:<br>All 389 patients that were enrolled in the trial. |              |

### Primary: Percentage of patients with a reduction of leg pain $\geq 30$ % or pain not more than 3 on NS

|                 |  |
|-----------------|--|
| End point title | Percentage of patients with a reduction of leg pain $\geq 30$ % or pain not more than 3 on NS <sup>[1]</sup> |
|-----------------|--|

End point description:

The primary endpoint of the clinical trial was to determine the percentage of patients in whom leg pain decreased by  $\geq 30$  % (estimated according to numeric scale) or the percentage of patients whose assessment of pain according to NS did not exceed number 3 (assessed at baseline, after 4 weeks and after 12 weeks).

The percentage of patients who achieved primary endpoint after 4 weeks of treatment was 52.0 %, and after 12 weeks 85.4 %.

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

End point timeframe:

Timeframe was the whole duration of the study (from the day the first patient entered (26.6.2018) to the day the last patient concluded the study (8.7.2019)). Timeframe for one patient was 12 weeks.

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: Statistical analysis could not be entered because the interface insisted on selecting at least two arms.

Due to a large sample, an asymptotic z-test was used to determine the statistically significant difference between the averages of two measurements in the same population, and an asymptotic 95% confidence interval was used for interval estimates of the mean.

| End point values                          | All patients        |  |  |  |
|---|---------------------|--|--|--|
| Subject group type                        | Reporting group     |  |  |  |
| Number of subjects analysed               | 389                 |  |  |  |
| Units: percentage                         |                     |  |  |  |
| arithmetic mean (confidence interval 95%) |                     |  |  |  |
| % of patients after 4 weeks               | 52.0 (47.0 to 57.0) |  |  |  |
| % of patients after 12 weeks              | 85.4 (81.8 to 89.1) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Arithmetic mean of assessed leg pain at baseline, after 4 and after 12 weeks

|                 |  |
|-----------------|--|
| End point title | Arithmetic mean of assessed leg pain at baseline, after 4 and after 12 weeks |
|-----------------|--|

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**End point description:**

The severity of leg pain decreased statistically significantly after 4 and 12 weeks of treatment ( $p < 0.001$ ). Wilcoxon's Signed rank test was used to determine the statistically significant differences between the averages of two measurements in the same population because the dependent variables do not have a normal distribution. The arithmetic mean of leg pain intensity assessed on a numeric scale from 0 to 10 was 5,897. After 4 weeks of treatment, the assessed leg pain intensity was 3,850, and after 12 weeks of treatment, 2,323.

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

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**End point timeframe:**

Timeframe was the whole duration of the study (from the day the first patient entered (26.6.2018) to the day the last patient concluded the study (8.7.2019)). Timeframe for one patient was 12 weeks.

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| End point values                          | All patients           |  |  |  |
|---|------------------------|--|--|--|
| Subject group type                        | Reporting group        |  |  |  |
| Number of subjects analysed               | 389                    |  |  |  |
| Units: score on numeric scale             |                        |  |  |  |
| arithmetic mean (confidence interval 95%) |                        |  |  |  |
| leg pain at baseline                      | 5.897 (5.734 to 6.061) |  |  |  |
| leg pain after 4 weeks                    | 3.850 (3.654 to 4.046) |  |  |  |
| leg pain after 12 weeks                   | 2.323 (2.129 to 2.518) |  |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE reporting for one patient was 12 weeks and was the same for the whole duration of the study (from the day the first patient entered (26.6.2018) to the day the last patient concluded the study (8.7.2019)).

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 22.1   |

### Reporting groups

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

Reporting group description:

All 389 patients that were enrolled in the study.

| Serious adverse events                            | All patients    |  |  |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events |                 |  |  |
| subjects affected / exposed                       | 0 / 389 (0.00%) |  |  |
| number of deaths (all causes)                     | 0               |  |  |
| number of deaths resulting from adverse events    |                 |  |  |

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                           | 43 / 389 (11.05%) |  |  |
| Nervous system disorders                              |                   |  |  |
| Headache  |                   |  |  |
| subjects affected / exposed                           | 8 / 389 (2.06%)   |  |  |
| occurrences (all)                                     | 8                 |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Asthenia  |                   |  |  |
| subjects affected / exposed                           | 4 / 389 (1.03%)   |  |  |
| occurrences (all)                                     | 4                 |  |  |
| Gastrointestinal disorders                            |                   |  |  |
| Dyspepsia   |                   |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed            | 9 / 389 (2.31%) |  |  |
| occurrences (all)                      | 9               |  |  |
| Nausea                                 |                 |  |  |
| subjects affected / exposed            | 9 / 389 (2.31%) |  |  |
| occurrences (all)                      | 9               |  |  |
| Diarrhoea                              |                 |  |  |
| subjects affected / exposed            | 8 / 389 (2.06%) |  |  |
| occurrences (all)                      | 8               |  |  |
| Abdominal pain                         |                 |  |  |
| subjects affected / exposed            | 7 / 389 (1.80%) |  |  |
| occurrences (all)                      | 7               |  |  |
| Skin and subcutaneous tissue disorders |                 |  |  |
| Pruritus                               |                 |  |  |
| subjects affected / exposed            | 7 / 389 (1.80%) |  |  |
| occurrences (all)                      | 7               |  |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported