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 Tanja Kohek, Krka d.d., Novo mesto Dunajska 65 1000 Ljubljana, 00386 14751236, tanja.kohek@krka.biz
Scientific contact	Clinical Trials Information Tanja Kohek, Krka d.d., Novo mesto Dunajska 65 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 to big - difficult swalowing	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 (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 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:

All 389 patients that were enrolled in the trial.

Primary: Percentage of patients with a reduction of leg pain ≥30 % or pain not more than 3 on NS

End point title	Percentage of patients with a reduction of leg pain ≥30 % or pain not more than 3 on NS[1]

End point description:

The primary endpoint of the clinical trial was to determine the percentage of patients in whom leg pain decreased by ≥ 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

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.

End point type	Secondary

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.

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)			

Statistical analyses

No statistical analyses for this end point

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported