Clinical trial results:
Impact of Daflon 500 mg on the progression of chronic venous disease and symptoms in patients operated on for varicose veins with conservation of the great saphenous vein.
A multicentre, double blind randomised, placebo controlled, parallel group study.

Summary

EudraCT number	2010-021270-11
Trial protocol	FR
Global end of trial date	30 June 2014

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	CL2-05682-102

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier (I.R.I.S)
Sponsor organisation address	50 rue Carnot, Suresnes Cedex, France, 92284
Public contact	ITP(Innovation Therapeutic Pole), Institut de Recherches Internationales Servier (I.R.I.S), +33 155724366, clinicaltrials@servier.com
Scientific contact	ITP(Innovation Therapeutic Pole), Institut de Recherches Internationales Servier (I.R.I.S), +33 155724366, clinicaltrials@servier.com

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	30 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2014
Global end of trial reached?	Yes
Global end of trial date	30 June 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of Daflon®500 mg (1000 mg per day) on the progression of chronic venous disease and symptoms after surgical treatment of varicose veins by phlebectomy with conservation of the great saphenous vein (ASVAL method).

Protection of trial subjects:

The reason for premature discontinuation of the study could be:
- Adverse events or any condition incompatible with continuation of either treatment according to the investigator,
- Major deviation from the protocol (unauthorized concomitant treatment, pregnancy or event that could endanger the patient's safety…),
- Decision by the subject to withdraw from the study,
- Non-medical reason,

In case of premature discontinuation of treatment the patient will be withdrawn from the study.
When the investigator has no news of the participant, he must make every effort to contact him/her, to establish the reason for the discontinuation of treatment, and to suggest the participant comes to an end-of-study visit. If all these attempts to contact the participant fail, the investigator can then declare the participant "lost to follow-up". The investigator should document all these attempts in the corresponding medical file.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 April 2011
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	France: 119
Worldwide total number of subjects	119
EEA total number of subjects	119

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)	90
From 65 to 84 years	28
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Demographic characteristics :
-Male or female,
-Outpatient,
-Aged between 18 and 85 years (inclusive),
-For French patient, beneficiary or registered with the French social safety or the social security of Monaco (supressed according to the amendment No. 2).

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, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Daflon

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Daflon 500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage was two tablets daily (at lunchtime) from the day after ASVAL surgery (D1) to M6. The day of surgery (D0), the investigator reminded the patient of beginning the treatment intake the day after (D1).
If the patient forgot to take his treatment at lunchtime, it was recommended to take it as soon as he realized his omission during the same day.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

The dosage was two tablets daily (at lunchtime) from the day after ASVAL surgery (D1) to M6. The day of surgery (D0), the investigator reminded the patient of beginning the treatment intake the day after (D1).
If the patient forgot to take his treatment at lunchtime, it was recommended to take it as soon as he realized his omission during the same day.

Number of subjects in period 1	Daflon	Placebo
Started	59	60
Completed	22	24
Not completed	37	36
Adverse event, non-fatal	2	1
Non-medical reason	32	34
Protocol deviation	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	119	119	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	90	90	
From 65-84 years	28	28	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	91	91	
Male	28	28	

End points

End points reporting groups	
Reporting group title	Daflon
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Saphenous reflux volume	
End point title	Saphenous reflux volume
End point description:	
Volume (mm³) of the reflux of the great saphenous vein : Change from baseline to M3 during the study and between-group comparison - On the most affected leg - FAS (N = 72).	
End point type	Primary
End point timeframe:	
From Baseline to M3	

End point values	Daflon	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	41		
Units: mm³				
arithmetic mean (standard deviation)	-4478.71 (± 4714.756)	-3766.22 (± 3953.772)		

Statistical analyses

Statistical analysis title	Between group difference estimate using an ANCOVA
Statistical analysis description:	
Parametric approach with adjustement	
Comparison groups	Daflon v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-121.976
Confidence interval	
level	95 %
sides	2-sided
lower limit	-891.77
upper limit	647.818
Variability estimate	Standard error of the mean
Dispersion value	385.771

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Daflon
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Daflon	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 46 (2.17%)	1 / 52 (1.92%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	1 / 46 (2.17%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 46 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Daflon	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 46 (21.74%)	6 / 52 (11.54%)	
Injury, poisoning and procedural complications			

Joint dislocation			
subjects affected / exposed	1 / 46 (2.17%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Post procedural contusion			
subjects affected / exposed	1 / 46 (2.17%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Venous insufficiency			
subjects affected / exposed	3 / 46 (6.52%)	4 / 52 (7.69%)	
occurrences (all)	3	5	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 46 (2.17%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Varicose vein			
subjects affected / exposed	1 / 46 (2.17%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 46 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Acute myocardial infarction			
subjects affected / exposed	0 / 46 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 46 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	1 / 46 (2.17%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Nausea			

subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1	0 / 52 (0.00%) 0	
Skin and subcutaneous tissue disorders Pruritus allergic subjects affected / exposed occurrences (all)	 1 / 46 (2.17%) 1	 0 / 52 (0.00%) 0	
Musculoskeletal and connective tissue disorders Osteoarthritis subjects affected / exposed occurrences (all)	 1 / 46 (2.17%) 1	 0 / 52 (0.00%) 0	
Infections and infestations Diverticulitis subjects affected / exposed occurrences (all)	 0 / 46 (0.00%) 0	 1 / 52 (1.92%) 1	
Metabolism and nutrition disorders Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	 0 / 46 (0.00%) 0	 1 / 52 (1.92%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2010	This amendment has been implemented to clarify inclusion criteria with a pregnancy test added, to clarify the main and secondary criteria and to update the statistical method
20 July 2011	This amendment has been implemented: - To modify the beginning of the recruitment. Indeed the initiation date was delayed from December 2010 to April 2011 due to technical problems. - To extend the recruitment period by one year. The observed recruitment rate is only one half of that expected when the study was planned. This is mainly due to the loss of one centre (Monaco), which represents 36 % of the recruitment and to selection criteria. The study completion date is April 2014. - Therefore two modifications are proposed: The modification of the selection criteria regarding phleboactive drugs. The planned period of 3 months without any phleboactive drugs preceding surgery has been changed to one month before the selection of the patient without any impact on the primary criterion. The modification of the duration between the selection (SEL) and inclusion (INCL) visits which were initially planned at D-45 (for SEL) and D-15 to D-1 (for INCL) before surgery. In clinical practice, patients could request to be operated promptly. Therefore, for more flexibility, the duration between the selection and inclusion visits will be between 0 and 90 days with a selection visit scheduled maximum at D-90 and an inclusion visit scheduled at least at D-1 before surgery. The selection / inclusion visits could be realized at the same time. - To modify the number of centres due to the non-participation of Monaco.
23 October 2012	This amendment has been implemented: - To extend the recruitment period by 18 months. The observed recruitment rate is less than one half of that expected when the study was planned (70 included patients instead of 170 at the end of September 2012). This is mainly due to the loss of one centre (Monaco), which represented 36% of the recruitment and to selection criteria. The study completion date is October 2015.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 June 2014	Due to strategic decision, the study has been prematurely terminated with only 119 included patients (instead of 300 patients planned): consequently, only the primary efficacy endpoint (volume of the reflux in the Great Saphenous vein (GSV) was analysed.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The section NSAE presented EAEs on treatment and included SEAEs. The causality and seriousness of reported SAE can be ultimately upgraded by the sponsor. The sponsor took the decisions to be compliant with exiting ICH E3 Clinical Study Report.

Notes: