



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:

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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 (mm ³) 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: mm ³ | | | | |
| 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 adjustment | |
| 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 occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 52 (0.00%) 0 | |
| Post procedural contusion subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 52 (0.00%) 0 | |
| Vascular disorders Venous insufficiency subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 3 | 4 / 52 (7.69%) 5 | |
| Thrombophlebitis superficial subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 52 (0.00%) 0 | |
| Varicose vein subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 52 (0.00%) 0 | |
| Cardiac disorders Atrial flutter subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 52 (1.92%) 1 | |
| Acute myocardial infarction subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 52 (1.92%) 1 | |
| Nervous system disorders Migraine subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 52 (1.92%) 1 | |
| General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 52 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 52 (1.92%) 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 | <p>This amendment has been implemented:</p> <ul style="list-style-type: none">- 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 | <p>This amendment has been implemented:</p> <ul style="list-style-type: none">- 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. <p>The study completion date is October 2015.</p> |

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.

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|---|
| 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. |
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Notes: