Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**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.**
Test drug code	**S 05682** **Micronised purified flavonoid fraction (MPFF)** **Daflon® 500 mg**
Indication	**Chronic Venous Disease**
Development phase	**Phase II**
Protocol code	**CL2-05682-102**
Study initiation date	**29 April 2011**
Study completion date	**30 June 2014**
Main coordinator	[redacted]
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**16 April 2015**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** **Daflon® 500 mg** **Name of Active Ingredient:** **Micronised purified flavonoid fraction (MPFF)** **S 05682**		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: 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.

Protocol No.: CL2-05682-102
EudraCT No.: 2010-021270-11
The description of the study protocol given hereafter includes the modifications of the 3 substantial amendments to the protocol.

National coordinator: [redacted]

Study centres:
Two (2) centres, located in France, included at least one patient.

Publication:
Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 29/04/2011 Completion date: 30/06/2014	Phase II

Objectives:
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 (Ambulatory Selective Varicose veins Ablation under Local anesthesia (ASVAL) method).
Primary and secondary objectives were hierarchized according to the Amendment No. 1.
The primary objective was to assess the treatment-effect on the volume of the reflux of the Great Saphenous Vein (GSV).
The secondary objective was to assess the treatment-effect on the volume of the reflux at the SaphenoFemoral Junction (SFJ), durations and the speeds of the reflux of the GSV and at the SFJ.

Methodology:
Multicentric, double-blind randomised, placebo-controlled, parallel group phase II study in patients suffering from primary chronic venous disease on the leg to be operated on.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.
Due to strategic decision, the study has been prematurely terminated, with only 119 included patients (instead of 300 patients planned, so about 40% of expected patients).
Consequently, there were several changes between the Statistical Analysis Plan and analyses planned in the protocol and an abbreviated report was written. The main modification was about endpoint: only the primary efficacy endpoint was analysed (Volume of the reflux in the Great Saphenous Vein).

Number of patients:
Planned: 300 patients (150 per group)
Included: 119 (59 in the Daflon® group and 60 in the placebo group)
The number of patients included was much lower than planned, as the study was prematurely stopped.

Diagnosis and main criteria for inclusion:
Male or female outpatients, without any contra-indication to a treatment with Daflon® 500 mg, aged between 18 and 85 (inclusive), suffering from primary chronic venous disease, CEAP C2 to C6 on the leg to be operated on (or, if both legs are to be operated on the same day, on the most affected leg), for whom the ASVAL surgery was indicated according to the investigator's judgment and presenting with a reflux on the great saphenous vein (> 0.5 sec). Patient should not have received any phleboactive drugs during at least 3 months, amended to 1 month (Amendment No. 2) preceding the selection visit.

Test drug:
Daflon® 500 mg: 2 tablets daily per os at lunchtime.
Batch No. L0044433

Comparator (Reference product and/or placebo):
Placebo: 2 tablets daily per os at lunchtime

Duration of treatment:
From Selection visit to ASVAL surgery (D0): about 1 month ½ amended to "up to 3 months" according to the Amendment No. 2, without treatment.
Treatment period: from D1 to M6 (about 6 months after surgery)
Follow-up period: from M6 to M12 (about 6 months) without treatment

Criteria for evaluation:
Efficacy measurements:

- ***Duplex ultrasound examination*** performed before surgery at the selection visit, during the treatment period (on M3 and M6 visits) and at the end of the follow-up period (M12 visit), to measure:
  - Hemodynamic parameters:
    - Duration (sec), speed (mm/sec) and **volume (mm³) of the reflux of the great saphenous vein (GSV) as primary criterion (according to the amendment No. 1)** measured at the level of the first refluxing collateral vein,
    - Duration (sec), speed (mm/sec) and volume (mm³) of the reflux at the SaphenoFemoral Junction (SFJ) between the pre-terminal valve and the terminal valve.
  - *Anatomic measurements*: Diameter (mm) of the GSV just above the level of the first refluxing collateral vein and Diameter of the saphenofemoral junction at the level of saphenous vein where the venous walls were parallel.
- ***Other efficacy measurements:*** Modified Venous Clinical Severity Score, Clinical symptoms, Ankle circumference, Cosmetic improvement and ecchymosis evaluation of the operated leg, Quality of life CIVIQ-14 questionnaire, Number of zones to be treated and Analgesic intake were assessed during the study.

In the context of an abbreviated report, the only criterion analysed in the report was the **volume (mm³) of the reflux of the great saphenous vein (GSV)**.

Safety measurements:
Adverse events reported at each visit.

Statistical methods:
Analysis Set:
The main analysis of the primary efficacy criterion was performed on the FAS: based on the intention-to-treat principle, this set corresponded to randomised patients who have taken at least one dose of study treatment and who have a change from baseline to M3 available for the volume of the reflux of the GSV.

Efficacy analysis:
Primary criterion (defined according to the Amendment No. 1): volume (mm³) of the reflux of the great saphenous vein (GSV).

- Main analysis: To estimate the treatment-groups difference of the change from baseline to M3 value of volume (mm³) of the reflux of the great saphenous vein (GSV), an analysis of covariance (ANCOVA) model was performed. Analysis included the fixed categorical effects of treatment and centre, as well as the continuous fixed covariate of baseline.
- Secondary analysis: The same model was performed for the change from baseline to M6.

Study outcome and safety analyses: descriptive statistics were provided in the RS/FAS and SS, respectively.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Disposition of patients and analysis sets

		Daflon® (N = 59)	Placebo (N = 60)	All (N = 119)
Included/randomised	n	**59**	**60**	**119**
Withdrawn due to	n (%)	**37 (62.7)**	**36 (60.0)**	**73 (61.3)**
- lost to follow-up	n (%)	-	-	-
- adverse event	n (%)	2 (3.4)	1 (1.7)	3 (2.5)
- non-medical reason	n (%)	32 (54.2)	34 (56.7)	66 (55.5)
- protocol deviation	n (%)	3 (5.1)	1 (1.7)	4 (3.4)
Completed	n (%)	**22 (37.3)**	**24 (40.0)**	**46 (38.7)**
FAS	n (%)	31 (52.5)	41 (68.3)	72 (60.5)
Safety Set	n (%)	46 (78.0)	52 (86.7)	98 (82.4)

**FAS: Full Analysis Set*

One patient, in the placebo group, had one protocol deviation before or at inclusion: consent signed after first visit. Overall, 29 patients had at least one protocol deviation after inclusion until visit M12: 15 patients (25.4%) in the Daflon® group and 14 patients (23.3%) in the placebo group. In all, 47 protocol deviations were observed after inclusion until visit M12. The most frequent deviations concerned deviations affecting efficacy (30 deviations in 19 patients), mainly compliance with prescription (24 deviations in 14 patients). No relevant difference between groups was observed regarding the number of patients with deviations.

BASELINE CHARACTERISTICS

Main baseline characteristics in the Randomised Seta are summarised in the table below:

Main baseline* characteristics in the Randomised Set

			Daflon® (N = 59)	Placebo (N = 60)	All (N = 119)
Age (years)		n	59	60	119
		Mean ± SD	55.4 ± 12.7	51.9 ± 12.2	53.6 ± 12.5
		Median	56.0	50.5	53.0
		Min ; Max	30 ; 85	25 ; 76	25 ; 85
Sex	Men	n (%)	16 (27.1)	12 (20.0)	28 (23.5)
	Women	n (%)	43 (72.9)	48 (80.0)	91 (76.5)
BMI		n	59	60	119
		Mean ± SD	23.78 ± 3.22	23.32 ± 3.58	23.55 ± 3.40
		Median	23.3	23.6	23.4
		Min ; Max	18.3 ; 32.0	16.9 ; 32.0	16.9 ; 32.0
CEAP	C2	n (%)	51 (86.4)	48 (80.0)	99 (83.2)
on the most affected leg	C3	n (%)	7 (11.9)	10 (16.7)	17 (14.3)
	C4a	n (%)	-	2 (3.3)	2 (1.7)
	C4b	n (%)	1 (1.7)	-	1 (0.8)

** selection*

At selection, 84.0% of the randomised patients were planned for unilateral ASVAL operation and 16.0% for bilateral operation without relevant difference between groups. The most affected leg was the right one for half (49.6%) and the left one for half (50.4%).

Overall, 81 patients (68.1%) had a family history of chronic venous disease. Previous venous thrombosis was reported by 8 patients (6.7%): for 3 of them, a superficial venous thrombosis and for 6 of them a deep venous thrombosis (one patient in the placebo group had both superficial and deep venous thrombosis). The daily duration of standing position was on average 5.63 ± 3.24 hours. For most of the patients (74.8%), daily physical activities consisted in more than 30 min fast walking per day. One patient (in the placebo group) had a current intake of anticoagulant treatment at selection. Overall 10 women (11.0%) reported a current intake of hormonology at the selection visit: 3 (7.0%) in the Daflon® group and 7 (14.6%) in the placebo group. Regarding pregnancies, 16.5% of the women had not experienced pregnancy, 23.1% one pregnancy, 41.8% 2 pregnancies and 18.7% more than 2 pregnancies. Results of pregnancy tests were negative in all women for whom a test was performed (30 women).

SUMMARY – CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

Within 3 months before selection, 10 patients (8.4%) had received at least one previous non-drug treatment for CVD: 7 (11.9%) in the Daflon® group and 3 (5.0%) in the placebo group. They consisted in varicose vein surgery (1 patient (14.3%) in the Daflon® group *versus* none in the placebo group) and compression therapy (6 patients (85.7%) in the Daflon® group *versus* 3 (100%) in the placebo group).

Except a trend for older patients in the Daflon® group than in the placebo group, no relevant difference between groups was observed regarding above baseline characteristics including disease factors, in the Randomised Set.

Overall in the Randomised Set, 78 patients (65.5%) reported at least one medical history and 53 patients (44.5%) at least one surgical or medical procedure history. Except a higher rate of patients with varicose vein surgery in the Daflon® group (11 patients, 18.6%) than in the placebo group (4 patients, 6.7%), no clinically relevant difference between groups was observed regarding medical or surgical histories in the Randomised Set.

In the FAS, baseline characteristics were similar to those observed in the RS. Mean age (54.0 ± 12.7 years old) was similar to the one observed in the RS, with however a more marked difference between groups: patients were 57.6 ± 11.9 years old (median = 61 years) in the Daflon® group and 51.4 ± 12.8 years old (median = 50 years) in the placebo group.

Before treatment period, 60 patients (50.4%) in the Randomised Set had taken at least one treatment. The most frequently reported (at least 10 patients) were antithrombotic agents (11.8%), agents acting on the renin-angiotensin system (8.4%) and sex hormones and modulators of the genital system (8.4%). Except antithrombotic agents less reported in the Daflon® group (4 patients, 6.8%) than in the placebo group (10 patients, 16.7%), no relevant difference was observed between groups. Concomitant treatments received during treatment period were similar to those received before treatment period.

On the most affected leg in the Randomised Set, volume of the reflux of the great saphenous vein (main efficacy criterion) at baseline was on average 5231 ± 4981 mm^3, median = 3837 mm^3 (ranging between 141 and 29019 mm^3) with higher values in the Daflon® group than in the placebo group: mean values were 5451 ± 4943 mm^3 in the Daflon® group (median = 4044 mm^3) *versus* 5010 ± 5051 mm^3 in the placebo group (median = 2956 mm^3).

EXTENT OF EXPOSURE

In the Randomised Set, mean treatment duration was 132.8 ± 96.2 days (median 182 days) with a mean value slightly shorter in the Daflon® group (119.3 ± 97.9 days) than in the placebo group (146.1 ± 93.3 days) and without difference on median values (180 days and 182 days, respectively). Overall, 13 patients (22.0%) in the Daflon® group and 8 patients (13.3%) in the placebo group had never taken study treatment (mainly related to consent withdrawal for personal reasons).

The mean ± SD overall compliance was of 73.8 ± 40.1% (median 92.5%) with slightly lower value in the Daflon® group (69.1 ± 43.3%) than in the placebo group (78.5 ± 36.4%) and without difference on median values (92.0% and 94.0%, respectively).

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Primary assessment criterion

Saphenous reflux volume (1rst coll*) (mm^3): value at baseline, at M3, change from baseline to M3 during the study and between-group comparison - On the most affected leg - FAS (N = 72)

		Daflon® (N = 31)	Placebo (N = 41)
Baseline	n	31	41
	Mean ± SD	5079.097 ± 5470.326	4535.195 ± 4093.982
	Median	3754.00	3532.00
M3	n	31	41
	Mean ± SD	600.387 ± 1495.928	768.976 ± 1827.150
	Median	0.00	0.00
M3 - baseline	n	31	41
	Mean ± SD	-4478.710 ± 4714.756	-3766.220 ± 3953.772
	Median	-3341.00	-2956.00
Main statistical analysis			
Parametric approach with adjustment (difference)	E(SE) (1)	-121.976 (385.771)	
	95% CI (2)	[-891.770 ; 647.818]	

**: first refluxing collateral vein*
N: Number of patients in each treatment group.
n: Number of observed values.
(1): E (SE): Estimate (Standard Error) of the difference between adjusted mean groups: Daflon® minus placebo using a General Linear Model with baseline and centre (fixed effects) as covariates.
(2): 95% CI: 95% confidence interval of the estimate.

The saphenous reflux volume (primary efficacy criterion) decreased in both groups from baseline to M3 (main analysis) with an estimated between-group difference of: E (SE) = -122.0 (385.8) mm^3 with a 95% CI [-891.8 ; 647.8] mm^3. It is to note that the number of patients in the FAS (72 patients) was much lower than the one expected (286 patients) and therefore, results should be carefully interpreted.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

- **Adverse events**

Overall summary for adverse events in the Safety Set

		Daflon® (N = 46)	Placebo (N = 52)
Patients having reported			
at least one emergent adverse event	n (%)	10 (21.7)	6 (11.5)
at least one treatment-related emergent adverse event	n (%)	2 (4.3)	-
Patients having experienced			
at least one serious adverse event	n (%)	1 (2.2)	1 (1.9)
at least one serious emergent event	n(%)	1 (2.2)	1 (1.9)
at least one treatment-related serious adverse event	n (%)	-	-
Patients with treatment withdrawal			
due to an emergent adverse event	n (%)	2 (4.3)	1 (1.9)
due to an emergent serious adverse event	n (%)	-	-
due a treatment-related emergent adverse event	n (%)	2 (4.3)	-
Patients who died	n (%)	-	-

During the study, the rate of patients who reported at least one emergent adverse event was higher in the Daflon® group (21.7%) than in the placebo group (11.5%) without relevant difference between groups as regards system organ classes or preferred terms.

The most frequently reported system organ class in the Daflon® group was vascular disorders similarly reported in both groups (4 patients in each group *i.e.* 8.7% and 7.7% in the Daflon® and placebo groups, respectively). The most frequent emergent adverse event was venous insufficiency reported by 3 patients (6.5%) in the Daflon® group and 4 patients (7.7%) in the placebo group. All other emergent adverse events were each reported by one patient in any group.

No death occurred during the study.

Two severe emergent adverse events (joint dislocation and myocardial infarction) were reported, both were serious: see description below. The other emergent adverse events were of mild (11/22 events, 50.0%) or moderate (9/22 events, 40.9%) intensity.

Two patients (2.0%) had 2 emergent adverse events considered as treatment-related: nausea and pruritus allergic, both in the Daflon® group (4.3%). There were both non-serious adverse events having led to treatment withdrawal.

During the study, 3 emergent adverse events led to study treatment withdrawal in 3 patients (3.1%): 2 (4.3%) in the Daflon® group (pruritus allergic and nausea) and one (1.9%) in the placebo group (abdominal pain). In addition, one event (acute myocardial infarction in the placebo group) led to temporarily interruption of study treatment.

All emergent adverse events were resolved except one which has been resolving (thrombophlebitis superficial). Among these EAEs, 3 resolved after treatment (*i.e.* after last intake + 2 days): injection site reaction and post-procedural contusion in the Daflon® group and abdominal pain in the placebo group.

Overall, 3 patients reported 3 adverse events after the treatment period (*i.e.* after last intake + 2 days): varicose vein and venous insufficiency reported respectively, 84 days and 186 days after the last Daflon® intake, and venous insufficiency 49 days after the last placebo intake.

Two patients (2.0%) experienced 2 serious adverse events during the study, both emergent and rated as severe: joint dislocation in one patient (2.2%) in the Daflon® group and acute myocardial infarction in one patient (1.9%) in the placebo group. These events were not considered as treatment-related according to the investigator and did not lead to study treatment withdrawal.

CONCLUSION

This multicentric, double-blind randomised, placebo-controlled, parallel group phase II study, conducted in patients suffering from primary chronic venous disease on the leg to be operated on with ASVAL method has been prematurely terminated due to strategic decision. The number of patients included in the study was much lower than the one expected and the results should thus be carefully interpreted. The study showed no effect of Daflon® 500 mg (1000 mg/day) on the volume of the reflux of the great saphenous vein (GSV) after surgical treatment of varicose veins by ASVAL method. Daflon® was well tolerated with no unexpected adverse events or relevant difference between Daflon® and placebo groups in the nature of the reported adverse events.

Date of the report: 16 April 2015

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