2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Daflon® 500 mg**	**Volume:**	
Name of Active Ingredient: **Micronised purified flavonoid fraction S05682**	**Page:**	

Title of study: Exploratory assessment of the effects of Daflon® 500 mg (2 tablets *i.e.* 1000 mg of micronised purified flavonoid fraction per day for 4 months) on microcirculation parameters and biomarkers in women suffering from chronic venous disease (CEAP class C2, C3 and C4).
Protocol No.: CL2-05682-099

Investigator: [redacted]

Study centre:
Monocentre study: one centre located in Brazil.

Publication: NA

Studied period: Initiation date: 27/07/2009 Completion date: 02/01/2012	**Phase of development of the study:** Phase II

Objective:
The objective of this phase II study was to assess the effects of 1000 mg per day of Daflon® 500 mg on microcirculatory and biological parameters in female patients suffering from chronic venous disease of lower limbs class C2 to C4 of CEAP classification.

Methodology:
Monocentre, double-blind, placebo controlled, parallel group study in women suffering from Chronic Venous Disease (CVD) (CEAP class C2, C3 or C4 on the most affected leg) with randomisation stratified on CEAP class.

Number of patients:
Planned:

- 240 patients including:
  - 180 with regular menstrual cycles (*i.e.* 60 patients C2, 60 patients C3 and 60 patients C4).
  - 60 post-menopausal or ovariectomised patients C4 (added by Amendment No. 4).
  - Within each CEAP subgroup, 30 patients were to be randomised to Daflon® 500 mg group and 30 to placebo group.
- 30 healthy C0a control female volunteers with regular menstrual cycles (added by Amendment No. 4).

Included:

- 261 patients including:
  - 199 with regular menstrual cycles: 65 patients C2 (*i.e.* 33 in the Daflon® group and 32 in the placebo group), 68 patients C3 (*i.e.* 34 in both Daflon® and placebo groups) and 66 patients C4 *(i.e.* 33 patients in both Daflon® and placebo groups)
  - 62 post-menopausal or ovariectomised patients C4 (*i.e.* 31 patients in both Daflon® and placebo groups).
- 30 healthy C0a control female volunteers with regular menstrual cycles.

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Diagnosis and main criteria for inclusion:

The study participants were non-menopausal female with regular menstrual cycles, non-obese (BMI < 30 kg/m^2), outpatients suffering from primary chronic venous disease (CEAP classes C2, C3 or C4 on the most affected leg), 18 to 50 years old (inclusive).

Following Amendment No.4, 2 groups of participants were added to the study:

- Post-menopausal or ovariectomised female, non-obese (BMI < 30kg/m2), outpatients suffering from primary CVD (CEAP class C4 on the most affected leg), 50 to 70 years old (inclusive).
- Female non-menopausal with regular menstrual cycles, non-obese (18 < BMI < 25 kg/m^2), healthy volunteers (HV) presenting with no clinical sign or symptom (C0a) of primary CVD, 18 to 30 years old (inclusive).

Study drug:

Daflon® 500 mg – 2 tablets daily (1000 mg) – per os – at lunchtime.

Batches No.: L0024311, L0029287, L0033129.

Reference product:

Placebo – 2 tablets daily – per os – at lunchtime.

Duration of treatment:

- Run-in period under placebo: 7 to 21 days following Amendment No. 3 (initially, 14 days)
- Double-blind randomised treatment period: about 112 days (4 menstrual cycles) with visits at the same period of each cycle (3 days ± 2 days after the first day of the menstrual cycle) in non-menopausal patients and at 28-day intervals in post-menopausal women (Amendment No.4).

For healthy volunteers in whom participation in the study ended at the inclusion visit, no study drug was administered during the run-in period.

Criteria for evaluation:

Efficacy measurements:

- Microcirculation parameters were assessed on each leg in the perimalleolar area using an OPS Cytoscan then Microscan (Amendment No. 2) at D0, D56 and D112, in the morning for all patients and with additional measurements in the evening for non-menopausal patients with leg oedema. For HV, microcirculation parameters were assessed only at D0. The measurement was performed after a 30-minute-rest in sitting position, without feet up, feet and legs undressed, in air-conditioned room at about 24°C:
  - Functional capillary density.
  - Diameter of dermal papilla.
  - Diameter of capillary bulk.
  - Capillary diameter.
  - Capillary morphology.

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Criteria for evaluation: (Cont'd)
Efficacy measurements: (Cont'd)

- Biomarkers were assessed in fasting conditions at D0, D56 and D112 for all patients and only at D0 for healthy volunteers:
  - Cell adhesion molecules: sE-selectin, sP-selectin and sL-selectin, sICAM-1, sVCAM-1.
  - Matrix metalloproteinases: MMP-2, MMP-3, MMP-9, TIMP-1.
  - Markers of endothelial cell dysfunction or cell damage: von Willebrand factor, Plasminogen Activator Inhibitor-1 (PAI-1), tissue type plasminogen activator (tPA), thrombomodulin.
  - Growth factors: Vascular Endothelial Growth factor (VEGF), Angiopoietin-1 (Ang-1), Angiopoietin-2 (Ang-2), Tie-2.
  - Endoglin.
  - Oxidative stress: Urinary isoprostanes.
  - Pro-inflammatory cytokine: Interleukin 6 (IL-6).

Urinary haemosiderin was deleted by Amendment No. 2.
Biochemical test (C-reactive protein - CRP) was performed in order to detect any acute inflammatory process, which could jeopardize biomarkers evaluation.

- Other evaluation criteria:

Leg ankle and calf circumferences were measured on both legs, at D0, D56 and D112, morning and evening in C3+ non-menopausal patients and only morning in post-menopausal C4 patients, using a Leg-O-Meter II®, 3 cm above the internal malleolus and at the largest diameter of the calf, feet and legs in perfect rest and slackening.

Safety measurements:

- Adverse events (spontaneous reporting at each visit).
- Vital signs: heart rate and blood pressure in sitting position and body weight at each visit.
- Overall acceptability rated by the patient and by the investigator at D112 (or in case of premature withdrawal).

Statistical methods:
The efficacy analyses were carried out firstly in the FAS and secondary in the PPS1 for the microcirculation parameters and in the PPS2 for the biomarkers.

Main analysis:
For each microcirculatory parameter and biomarker, the change within each treatment group between baseline and END value was tested for each subgroup of baseline CEAP class using a two-sided Student's t test for paired samples. The estimate of the mean (standard error) was provided for each treatment group with its 95% Confidence Interval (CI), as well as the corresponding p-value. The analysis was performed on the morning value of the most affected leg at baseline for the microcirculatory parameters.

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Statistical methods: (Cont'd)

Secondary analysis:

The same analysis as the main analysis was performed in overall patients.

For each microcirculatory parameter and biomarker, the following statistical methods were used on the change between baseline and END value to provide an estimate of the difference between Daflon® and placebo and its associated 95% CI:

- In the patients of each subgroup of baseline CEAP class: a General Linear Model with treatment as factor and adjusted on baseline value of the criterion analysed and in addition, for the subgroup of C4 pooled, on the non-menopausal/post-menopausal status.
- In overall patients: a General Linear Model with treatment as factor and adjusted on baseline value of the criterion analysed and baseline CEAP class (non-menopausal/post-menopausal).
- In both legs of all patients of the FAS and the PPS1: a Linear Mixed Model with repeated measures including factor leg, treatment as fixed effects and baseline CEAP class (non-menopausal/post-menopausal) of the most affected leg and baseline value of the criterion analysed as covariates.

For each microcirculatory parameter, biomarker and Leg-O-meter parameter, descriptive statistics were provided by treatment group in the patients of each baseline CEAP class and in overall patients.

SAFETY ANALYSES:

Descriptive statistics were provided in the Safety Set by treatment group and overall.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Overall 332 patients were selected and 261 patients were included and randomly assigned to one of the 2 treatment groups. A well-balanced distribution was reached for each CEAP class subgroup. Table below shows the disposition of included and randomised patients by treatment group.

Disposition of patients

Status	Daflon®	Placebo	All
Included (randomised)	**131**	**130**	**261**
In compliance with the protocol	63	70	133
With a protocol deviation before or at inclusion	68	60	128
Withdrawn from the study due to	**1**	**2**	**3**
Adverse event	-	2	2
Non-medical reason	1	-	1
Completed	**130**	**128**	**258**
In compliance with the protocol	110	115	225

No patient was lost to follow-up.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

The Randomised Set according to baseline CEAP class and the other Analysis Sets are described in the table below.

Analysis Sets

Analysis sets		Daflon®	Placebo	All
Randomised Set	**n**	**131**	**130**	**261**
Randomised Set by CEAP class				
C2 non-menopausal patients	n	33	32	65
C3 non-menopausal patients	n	34	34	68
C4 non-menopausal patients	n	33	33	66
C4 post menopausal patients	n	31	31	62
Safety Set	**n**	**131**	**130**	**261**
Efficacy Sets				
Full Analysis Set (FAS)	n (%)[a]	131 (100)	128 (98.5)	259 (99.2)
Per Protocol Set 1 (PPS-1)	n (%)[b]	102 (77.9)	101 (78.9)	203 (78.4)
Per Protocol Set 2 (PPS-2)	n (%)[b]	107 (81.7)	112 (87.5)	219 (84.6)

[a] *%: % of the Randomised Set*
[b] *%: % of the Full Analysis Set*

At selection, in the Randomised Set, patients were on average 42.4 ± 11.1 years (from 34.3 ± 6.6 years in the C2 non-menopausal subgroup to 58.9 ± 5.4 years in the C4 post-menopausal subgroup). Regarding overall patients, phototypes were mainly cream white (50.2%) and white fair (34.9%). As required in the protocol, all non-menopausal C2, C3 and C4 patients had an effective method of contraception and regular menstrual cycles (around 28 days). No relevant difference between groups was observed regarding deviations, main demographic data and hormonal status.

Regarding characteristics of chronic venous disease, the mean duration of the chronic venous disease was different according to CEAP class subgroups: from 105.3 ± 77.5 months (about 9 years) in the C2 non-menopausal subgroup to 209.8 ± 150.1 months (about 17.5 years) in the C4 post-menopausal subgroup. Mean duration of symptoms increased with the severity of the disease: from 158.8 ± 75.0 months (about 13 years) in the C2 non-menopausal subgroup to 422.0 ± 105.2 months (about 35 years) in the C4 post-menopausal subgroup. Regarding overall patients, the mean duration of the disease was 161.3 ± 119.3 months, median 142, (about 11 years), with a mean duration of the symptoms of 249.0 ± 136.5 months, median 228 (about 21 years). All patients except 2 in the C2 non-menopausal subgroup (one in each group) had at least one risk factor for developing CVD. None of patients had a history of deep vein thrombosis.

Overall 26.8% of the patients had at least one previous drug treatment for CVD with close percentages in CEAP class subgroups except in the C3 non-menopausal subgroup (14.7%). The most frequent previous treatments whatever the CEAP class subgroup, were vasoprotectives without relevant difference between groups. Except C3 subgroup for which previous non-drug treatments were slightly less frequent in the Daflon® group (11 patients, 32.4%) than in the placebo group (16 patients, 47.1%), no relevant difference was observed between groups regarding previous non-drug treatments.

No clinically relevant difference was observed between groups regarding risk factors and duration of the disease or of the symptoms whatever the CEAP class subgroups or overall.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

As expected, the mean total score of Venous Clinical Severity Score (VCSS) as well as the mean total score of symptoms rose with the severity of CVD (3.0 ± 0.9 and 4.9 ± 3.3, respectively in the C2 non-menopausal subgroup to 6.6 ± 1.7 and 8.8 ± 3.5, respectively in the C4 post-menopausal subgroup) without relevant difference between groups. Severe pain was also correlated with the seriousness of CVD (unplanned analysis: $p < 0.05$).

More than 95.0% of patients whichever the CEAP class subgroup presented at least one symptom of CVD at the selection visit. The most frequent symptoms were pain, heaviness and tiredness (more than 80.0% of the patients). Ankle swelling was also one of the most frequent symptoms in the C3 non-menopausal subgroup (92.6%). Except ankle swilling slightly less frequent in the Daflon® group than in the placebo group in C4 patients (34 patients, 53.1% *versus* 46 patients, 71.9%), no clinically relevant differences were observed between groups for symptoms of CVD.

Whichever the subgroup, the diameter of great saphenous vein of the most affected leg was higher than the one of the less affected leg (6.67 ± 3.44 mm *versus* 4.95 ± 2.46 mm, respectively in overall patients). Moreover, the diameter of great saphenous vein of the most affected leg rose with the severity of disease (from 5.26 ± 2.41 mm in the C2 non-menopausal subgroup to 7.44 ± 3.80 mm in the C4 post-menopausal subgroup). No relevant difference was observed between groups regarding duplex ultrasonography evaluation. The mean great saphenous vein diameter rose with the severity of CVD (3.90 ± 1.29 mm in the C1 legs subgroup and 7.05 ± 3.69 mm in the C4 legs) with significant differences between each group of legs (unplanned analysis: $p < 0.05$). Similar results were observed when comparing the diameter of great saphenous vein in the legs of non-menopausal subgroups to the C4 legs post-menopausal subgroup (unplanned analysis: $p < 0.05$).

Regarding CRP value, no relevant difference was observed between Daflon® and placebo groups whatever the CEAP class subgroup, except in the C4 post-menopausal subgroup in which the rate of patients with value in]0.5 ; 5] mg/dL interval was lower in the Daflon® group than in the placebo group at each visit (6.5% *versus* 25.8% at D000). Overall, at D000, 7 (2.7%) patients had a clinically significant abnormal CRP value according to the investigator, with a lower rate in the Daflon® group (1 patient, 0.8%) than in the placebo group (6 patients, 4.6%); at D056 and D112, none patient had clinically significant abnormal value in the Daflon® group *versus* 4 patients (3.2%) and 1 (0.8%) respectively in the placebo group. Mean values of CRP were quite stable over time without relevant difference between groups (from 0.318 ± 0.326 mg/dL, median 0.21 at D000 to 0.314 ± 0.390 mg/dL, median 0.20 at D112 in the overall RS).

As required in the protocol, no patient was smoker. Overall, 11.5% of the patients had a current physical activity, on average 4.3 ± 2.2 hours/week. No clinically relevant difference between treatment groups was observed regarding medical histories, smoking habits and physical activity.

No relevant difference between groups was observed regarding microcirculatory parameters at inclusion, whatever the CEAP class subgroup. No relevant difference between groups was observed regarding most of the biological markers whatever the CEAP class subgroup; however for few parameters, slight differences were noted as follows:

- C2 non-menopausal subgroup: mean angiopoietin-1 value was lower in the Daflon® group (1664.4 ± 1075.4 ng/mL, median 1364.0) than in the placebo group (2231.2 ± 1381.8 ng/mL, median 1913.5).
- C3 non-menopausal subgroup: mean MMP-3 value was higher in the Daflon® group (9.2 ± 3.4 ng/L, median 8.9) than in the placebo group (6.7 ± 2.7 ng/mL, median 6.2).
- C4 post-menopausal subgroup: mean thrombomodulin (mg/mL) value was higher in the Daflon® group (8.2 ± 26.8 mg/mL, median 3.3) than in the placebo group (5.6 ± 12.0 mg/mL, median 3.5) and angiopoietin-1 value was higher in the Daflon® group (2552.0 ± 1670.9 pg/mL, median 1982) than in the placebo group (1755.7 ± 865.8 pg/mL, median 1822).
- Overall C4 patients: angiopoietin-1 value was higher in the Daflon® group (2431.8 ± 1476.0 pg/mL, median 2017) than in the placebo group (1828.3 ± 859.0 pg/mL, median 1778).

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Morning value of ankle circumference and calf circumference were on average 23.2 ± 1.7 cm and 38.2 ± 2.8 cm, respectively at inclusion. BMI was 25.3 ± 2.9 in patients of the RS, ranging from 24.0 ± 2.7 to 26.0 ± 2.2 depending on the CEAP class subgroup. No relevant difference was observed between Daflon® and placebo groups regarding ankle and calf circumference or physical examination and vital signs.

Overall, 78.4% of the patients in the FAS received at least one concomitant treatment during the treatment period, mainly analgesics (23.6%) and sex hormones (23.2%) except in C4 patients for whom the most frequent treatments were all other non therapeutic products (30.8%) and analgesics (24.6%) in non-menopausal patients and lipids modifying agents (22.6%) in menopausal patients. Few between-group differences were observed without clinical relevance.

In the FAS, global study treatment duration ranged between 80 and 152 days with a mean of 112.6 ± 9.7 days; global study treatment period compliance was on average 97.9 ± 4.3 % with close results in each CEAP class subgroup and without relevant between-group differences.

A total of 30 healthy female volunteers were included: they were on average 20.9 ± 2.2 years old. The skin phototype was white, fair for 43.3%. As required by the protocol, the healthy volunteers were all within the C0-C0 CEAP class. In the healthy volunteers group, the mean CRP (± SD) value was: 0.303 ± 0.664 mg / dL ranging from 0.03 mg/dL to 3.41 mg/dL. Overall, 2 healthy volunteers (6.7%) presented clinically significantly abnormal value according to the investigator. Overall, 3 participants reported CRP value in the]0.5 ; 5] range and none of them reported CRP value > 5 mg/dL. Mean BMI was 21.7 ± 1.9 kg/m². No adverse event was reported during the run in study period.

EFFICACY RESULTS

Microcirculatory parameters

In the FAS, no relevant change from baseline to end was observed in the Daflon® group regarding microcirculation parameters whatever the CEAP class subgroup except in C3 non-menopausal patients for which a statistically significant within-group decrease was observed in both Daflon® and placebo groups for capillary diameter (respectively -0.67 ± 1.36 µm, p = 0.008 and -0.87 ± 1.57 µm, p = 0.003) and for functional capillary density (respectively -1.39 ± 3.80 per mm², p = 0.040 and -1.82 ± 4.79 per mm², p = 0.034).

Results on the PPS1 were in agreement with the trends observed on the FAS: no relevant change from baseline to end was observed regarding microcirculation parameters except a statistically significant within-group decrease observed in both Daflon® and placebo groups for capillary diameter in C2 and C3 non-menopausal patients (-0.71 ± 1.50 µm, p = 0.016 and -0.58 ± 1.370 µm, p = 0.034, respectively in the Daflon® group and -1.06 ± 1.35 µm, p < 0.001 and -0.78 ± 1.51 µm, p = 0.007, respectively in the placebo group), and for functional capillary density in C3 non-menopausal patients (respectively -1.54 ± 3.99 per mm², p = 0.047 and -2.00 ± 4.82 per mm², p = 0.028).

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SUMMARY – CONCLUSIONS (cont'd)

EFFICACY RESULTS (Cont'd)

Microcirculation parameters with statistically significant within-group change from baseline to END*
Morning values on the most affected leg at baseline - Subgroups of baseline CEAP class

		Baseline	Change	*Main analysis* *Within-group difference*		Secondary analysis Between-group difference	
	n	Mean ± SD	Mean ± SD	95% CI[1]	p-value[2]	E(SE)[3]	95% CI[1]
FAS							
C3 non-menopausal CEAP class patients							
CD (µm)							
Daflon®	33	9.164 ± 1.298	-0.670 ± 1.359	[-1.15 ; -0.19]	0.008	0.20 (0.26)	[-0.31 ; 0.71]
Placebo	34	9.162 ± 1.210	-0.868 ± 1.566	[-1.41 ; -0.32]	0.003		
FCD (/mm²)							
Daflon®	34	22.982 ± 4.819	-1.394 ± 3.798	[-2.72 ; -0.07]	0.040	-0.10 (0.95)	[-2.00 ; 1.79]
Placebo	34	24.418 ± 5.846	-1.818 ± 4.786	[-3.49 ; -0.15]	0.034		
PPS1							
C2 non-menopausal patients							
CD (µm)							
Daflon®	29	8.993 ± 0.853	-0.714 ± 1.504	[-1.29 ; -0.14]	0.016	0.08 (0.35)	[-0.63 ; 0.78]
Placebo	26	9.354 ± 0.977	-1.058 ± 1.345	[-1.60 ; -0.51]	< 0.001		
C3 non-menopausal patients							
CD (µm)							
Daflon®	28	9.039 ± 1.152	-0.579 ± 1.370	[-1.11 ; -0.05]	0.034	0.17 (0.28)	[-0.39 ; 0.72]
Placebo	31	9.081 ± 1.118	-0.784 ± 1.512	[-1.34 ; -0.23]	0.007		
FCD (/mm²)							
Daflon®	29	23.262 ± 4.644	-1.538 ± 3.989	[-3.06 ; -0.02]	0.047	-0.21 (1.03)	[-2.28 ; 1.86]
Placebo	31	24.958 ± 5.772	-2.000 ± 4.815	[-3.77 ; -0.23]	0.028		

*n: number of patients with a value; * Last post-baseline value (in the FAS)/ last post-baseline value under treatment (in the PPS1)*
(1) 95% Confidence Interval of the estimate; (2) Student t-test for paired samples;
(3) Estimate (Standard Error) of the difference between adjusted mean groups: Daflon® minus placebo, obtained from a General Linear Model with treatment as factor and adjusted on baseline value.
CD: capillary diameter; FCD: functional capillary density

In the overall FAS, no relevant change from baseline to end was observed regarding microcirculation parameters except a statistically significant within-group decrease observed in both Daflon® and placebo groups for capillary diameter (respectively -0.40 ± 1.48 µm, p = 0.004 and -0.70 ± 1.81 µm, p < 0.001) and for functional capillary density (respectively -1.23 ± 4.23 per mm², p = 0.002 and -1.81 ± 4.68 per mm², p < 0.001).
In the overall PPS1, results in all patients in the PPS1 were in agreement with the trends observed on the FAS: no relevant change from baseline to end was observed regarding microcirculation parameters except a statistically significant within-group decrease observed in both Daflon® and placebo groups for capillary diameter (respectively -0.43 ± 1.52 µm, p = 0.009 and -0.73 ± 1.85 µm, p < 0.001), and for functional capillary density (respectively -1.26 ± 4.33 per mm², p = 0.006 and -1.69 ± 4.59 per mm², p < 0.001).

Whatever the microcirculatory parameter in CEAP class subgroups and overall patients of both FAS and PPS1, the statistical analysis showed no relevant difference between groups.
No relevant difference between groups was observed on morning and evening regarding change from baseline to end of microcirculation parameters values.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Biological parameters

Regarding biological parameters in the FAS, the within-group change from baseline to end was relevant and statistically significant in the Daflon® group for sL-selectin in the C2 non-menopausal subgroup (-38.46 ± 103.86 ng/mL, p = 0.041) and for thrombomodulin in both C2 and C3 non-menopausal subgroups (-0.73 ± 0.75 ng/mL, p < 0.001 and -0.84 ± 1.10 ng/mL, p < 0.001, respectively).

In the PPS2, results were close to those observed in the FAS: the within-group change from baseline to end was relevant and statistically significant in the Daflon® group for sL-selectin (-50.4 ± 92.6 ng/mL, p = 0.007) and for thrombomodulin (-0.82 ± 0.80 ng/mL, p < 0.001) in the C2 non-menopausal subgroup and for sVCAM-1 (-30.5 ± 81.2 ng/L, p = 0.049) and thrombomodulin (-0.765 ± 1.110 ng/mL, p < 0.001) in the C3 non-menopausal subgroup.

In the FAS and in the PPS2, no relevant non-statistically significant within-group change from baseline to end was observed in the Daflon® group in both C4 non-menopausal and C4 post-menopausal subgroups whatever the biological parameter.

Biological markers with statistically significant within-group change from baseline to END*
Subgroups of baseline CEAP class

			Baseline	Change	*Main analysis*		Secondary analysis	
					Within-group difference		Between-group difference	
		n	Mean ± SD	Mean ± SD	95% CI[1]	p-value[2]	E(SE)[3]	95% CI[1]
FAS								
C2 non-menopausal CEAP class patients								
sL-selectin								
(ng/mL)	Daflon®	33	963.424 ± 183.400	-38.455 ± 103.862	[-75.28 ; -1.63]	0.041	-15.49 (27.13)	[-69.74 ; 38.76]
	Placebo	31	1008.484 ± 177.900	-27.097 ± 112.269	[-68.28 ; 14.08]	0.189		
Thrombomodulin								
(ng/mL)	Daflon®	33	3.257 ± 0.714	-0.730 ± 0.752	[-1.00 ; -0.46]	< 0.001	0.19 (0.15)	[-0.10 ; 0.48]
	Placebo	31	3.209 ± 0.714	-0.878 ± 0.935	[-1.22 ; -0.53]	< 0.001		
C3 non-menopausal CEAP class patients								
Thrombomodulin								
(ng/mL)	Daflon®	34	3.327 ± 0.971	-0.839 ± 1.097	[-1.22 ; -0.46]	< 0.001	-0.08 (0.16)	[-0.39 ; 0.24]
	Placebo	34	3.556 ± 0.957	-0.951 ± 0.953	[-1.28 ; -0.62]	< 0.001		
PPS2								
C2 non-menopausal CEAP class patients								
sL-selectin								
(ng/mL)	Daflon®	29	968.448 ± 190.912	-50.379 ± 92.576	[-85.59; -15.17]	0.007	-11.69 (26.52)	[-64.85 ; 41.48]
	Placebo	28	1008.786 ± 177.286	-40.786 ± 105.307	[-81.62 ; 0.05]	0.050		
Thrombomodulin								
(ng/mL)	Daflon®	29	3.305 ± 0.731	-0.816 ± 0.799	[-1.12 ; -0.51]	< 0.001	0.15 (0.16)	[-0.18 ; 0.47]
	Placebo	28	3.251 ± 0.690	-0.917 ± 0.918	[-1.27 ; -0.56]	< 0.001		
C3 non-menopausal CEAP class patients								
sVCAM-1								
(ng/L)	Daflon®	30	542.633 ± 150.774	-30.500 ± 81.205	[-60.82 ; -0.18]	0.049	13.89 (18.87)	[-23.89 ; 51.66]
	Placebo	31	525.032 ± 183.511	-36.935 ± 118.632	[-80.45 ; 6.58]	0.093		
Thrombomodulin								
(ng/mL)	Daflon®	30	3.283 ± 0.985	-0.765 ± 1.110	[-1.18 ; -0.35]	< 0.001	-0.02 (0.17)	[-0.36 ; 0.32]
	Placebo	31	3.580 ± 0.953	-0.998 ± 0.983	[-1.36 ; -0.64]	< 0.001		

*n: number of patients with a value; *last post-baseline value (in the FAS)/last-post baseline value under treatment (in the PPS2)*
(1) 95% Confidence Interval of the estimate; (2) Student t-test for paired samples; (3)Estimate (Standard Error) of the difference between adjusted mean groups: Daflon® minus placebo, obtained from a General Linear Model with treatment as factor and adjusted on baseline value

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Regarding overall patients, the within-group change from baseline to end was relevant and statistically significant in the Daflon® group for thrombomodulin in the FAS (-1.16 ± 6.41 ng/mL, p = 0.041) and for sVCAM-1 in the PPS2 (-16.37 ± 72.17 ng/mL, p = 0.021).

Neither statistically significant within-group difference in the Daflon® group nor between-group difference was observed regarding mean change from baseline to end for the other biological parameters in both overall FAS and overall PSS2.

In the FAS subgroups, between-group difference in mean change from baseline to end was observed for:

- PAI-1 in C2 non-menopausal subgroup: E (SE) = -3.07 (1.34), 95% CI = [-5.75 ; -0.40]. A slight decrease was observed in the Daflon® group (-0.53 ± 4.93 IU/mL) whereas an increase was observed in the placebo group (2.64 ± 6.06 IU/mL).
- MMP-9 in C3 non-menopausal subgroup: E (SE) = -15.03 (7.39), 95% CI = [-29.79 ; -0.28]. A slight decrease was observed in the Daflon® group, (-5.67 ± 30.92 ng/mL) whereas an increase was observed in the placebo group (10.52 ± 31.33 ng/mL).
- TIMP-1 in C4 non-menopausal subgroup: E (SE) = 10.09 (3.01), 95% CI = [4.08 ; 16.11]. No relevant change occurred in the Daflon® group (-0.15 ± 13.77 ng/mL) whereas a decrease was observed in the placebo group (-9.53 ± 12.27 ng/mL).
- Endoglin in C4 post-menopausal subgroup: E (SE) = -0.24 (0.11), 95% CI = [-0.46 ; -0.02]. A slight decrease was observed in the Daflon® group (-0.05 ± 0.43 ng/mL) whereas an increase was observed in the placebo group (0.21 ± 0.44 ng/mL).

In the PPS2 subgroups, results were close to those observed in the FAS with between-group difference regarding mean change from baseline to end observed for:

- PAI-1 in C2 non-menopausal subgroup: E (SE) = -3.72 (1.40), 95% CI = [-6.54 ; -0.91]. A slight decrease was observed in the Daflon® group (-0.53 ± 5.05 IU/mL) whereas an increase was observed in the placebo group (3.23 ± 6.03 IU/mL).
- MMP-9 in C3 non-menopausal subgroup: E (SE) = -14.8 (7.2), 95% CI = [-29.25 ; -0.32]. A slight decrease was observed in the Daflon® group (-3.3 ± 22.6 ng/mL) whereas an increase was observed in the placebo group (11.0 ± 32.7 ng/mL).
- TIMP-1 in C4 non-menopausal subgroup: E (SE) = 12.2 (3.43), 95% CI = [5.32 ; 19.13]. No relevant change occurred in the Daflon® group (2.42 ± 12.66 ng/mL) whereas a decrease was observed in the placebo group (-9.42 ± 12.59 ng/mL).
- Tie-2 in C4 non-menopausal subgroup: E (SE) = 1.14 (0.56), 95% CI = [0.02 ; 2.27]. No relevant change occurred in the Daflon® group (0.07 ± 1.80 ng/mL) whereas a decrease was observed in the placebo group (-1.10 ± 2.13 ng/mL). It is to note that, as Tie-2 parameter is an Angiopoietin-1 and Angiopoietin-2 receptor, variations of this parameter is quit difficult to interpretate.

Leg-O-meter parameters

Neither relevant change from baseline nor difference between groups was observed regarding morning and evening values of ankle and calf circumference in the legs C3+ subset of the FAS.

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

- Emergent adverse events

Overall summary of safety results

		Daflon® (N = 131)	Placebo (N = 130)
Patients having reported			
at least one emergent adverse event	n (%)	51 (38.9)	48 (36.9)
at least one treatment-related emergent adverse event	n (%)	2 (1.5)	3 (2.3)
Patients having experienced			
at least one serious adverse event	n (%)	-	1 (0.8)
at least one treatment-related serious adverse event	n (%)	-	-
Patients with treatment withdrawal			
due to an adverse event	n (%)	-	1 (0.8)*
due to a serious adverse event	n (%)	-	1 (0.8)
due to a treatment-related adverse event	n (%)	-	-
Patients who died	n (%)	-	-

** Compared to patient's status, one additional patient was prematurely withdrawn from the study due to adverse event (pregnancy) whereas she had already stopped the study treatment due to menstruation delay, 3 weeks before.*

Overall 99 patients (37.9%) reported at least one emergent adverse event without relevant difference between groups. In the Daflon® group, the most frequently affected system organ classes were infections and infestations (13.0%), nervous system disorders (6.1%), gastrointestinal disorders (5.3%), musculoskeletal and connective tissue disorders (4.6%) and vascular disorders (3.8%). Except infections and infestations less frequent in the Daflon® group than in the placebo group (13.0% *versus* 17.7%, respectively), no relevant difference between groups was observed regarding system organ classes affected.
During the study, the most frequently reported emergent adverse events in the Daflon® group were headache (6 patients, 4.6%), urinary tract infection (4 patients, 3.1%), influenza (4 patients, 3.1%), back pain (4 patients, 3.1%) and dizziness (3 patients, 2.3%). Compared to the placebo, the incidences were higher in the Daflon® group for headache (6 patients, 4.6% *versus* 2 patients, 1.5%) and for dizziness (3 patients, 2.3% *versus* none). In addition, oedema peripheral and phlebitis superficial were both reported by 2 patients in the Daflon® group (1.5%) *versus* none in the placebo group.

No emergent adverse event was rated as severe. Most of emergent adverse events were recovered or improved without relevant difference between Daflon® and placebo groups (92.2% *versus* 93.1%, respectively). Overall, 5 emergent adverse events were not recovered at the end of the study in both groups: venous stasis, anaemia (2), CRP increased and thyroid neoplasm in the Daflon® group and anaemia (2), lymphadenitis, breast calcification and pregnancy in the placebo group.

No death occurred during the study. Overall one patient (in the placebo group) reported 2 serious adverse events (facial palsy and herpes zoster): both were emergent and one (herpes zoster) led to treatment withdrawal. None of those serious adverse events were considered as treatment-related by the investigator.

No patient reported non-serious adverse event leading to premature treatment withdrawal.
In all, 3 patients experienced pregnancy in the placebo group during the study: all but one completed the study. The 3 babies were in good health at birth.

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- Other safety evaluation

Neither relevant changes nor difference between groups over time were detected regarding blood pressure, heart rate and weight.

The overall acceptability score at the end of the study was good without relevant difference between groups: 5.0 ± 0.8 in both groups for overall acceptability rated by the patient and 7.1 ± 1.1 in both groups for overall acceptability rated by the investigator.

CONCLUSION

This phase II monocentre, double-blind, placebo controlled, parallel group study in women suffering from Chronic Venous Disease (CVD) (CEAP class C2, C3 or C4 on the most affected leg) with randomisation stratified on CEAP class did not evidence any MPFF effect of 1000 mg daily dose after 4 months of treatment on selected microcirculation and biological parameters even if for few biological parameters as PAI-1, MMP-9, TIMP-1, Endoglin and Tie-2, a difference was observed between groups, according to CEAP class subgroups. No relevant difference between Daflon® and placebo groups was observed regarding microcirculation or leg-O-meter parameters. MPFF at the daily dose of 1000 mg was well tolerated.

Date of the report: 27 February 2013