Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Clinical non-inferiority study between Daflon® 1000 mg, one oral suspension in a sachet per day and Daflon® 500 mg, 2 tablets daily after eight weeks of treatment in patients suffering from symptomatic Chronic Venous Disease (CVD).** **International, multicenter, double-blind, randomized, parallel group study**
Test drug code	**S 05682** **Micronized purified flavonoid fraction**
Indication	**Chronic venous disease**
Development phase	**Phase III**
Protocol code	**CL3-05682-105**
Study initiation date	**22 July 2013**
Study completion date	**15 December 2014**
Main coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **Les Laboratoires Servier** **50 rue Carnot** **92284 Suresnes Cedex - France** **Laboratorios SERVIER S.L** **Departamento de Investigacion y Desarrollo** **Avenida de los Madronos, 33** **28043 Madrid - Spain**
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	**20 July 2015**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France **Les Laboratoires Servier, 50 rue Carnot - 92284 Suresnes Cedex - France** **Laboratorios SERVIER S.L, Avenida de los Madronos, 33 -28043 Madrid - Spain**		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Daflon® 1000 mg (Argentina, Ecuador) **Name of Active Ingredient:** Micronized purified flavonoid fraction, MPFF (S 05682)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Clinical non-inferiority study between Daflon® 1000 mg, one oral suspension in a sachet per day and Daflon® 500 mg, 2 tablets daily after eight weeks of treatment in patients suffering from symptomatic Chronic Venous Disease (CVD).
International, multicenter, double-blind, randomized, parallel group study.
Protocol No.: CL3-05682-105

EudraCT No.: 2012-003559-13

Universal trial Number: U1111-1135-8530

The description of the study protocol given hereafter includes the modifications of the 4 substantial amendments to the protocol.

International coordinator: [redacted]

Study centres:
83 centres located in 13 countries included 1139 patients: 7 centres in Argentina (146 patients included), 6 centres in Brazil (65 patients included), 9 centres in Czech Republic (94 patients included), 2 centres in Malaysia (3 patients included), 5 centres in Mexico (48 patients included), 11 centres in Romania (194 patients), 13 centres in Russia (255 patients included), 9 centres in Slovakia (94 patients included), 2 centres in Slovenia (53 patients included), 8 centres in Spain (67 patients included), 3 centres in Thailand (47 patients included), 5 centres in Turkey (51 patients included) and 3 centres in Vietnam (22 patients included).

Publication (reference):
Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 22 July 2013 Completion date: 15 December 2014	Phase III

Objectives:
The primary objective was to demonstrate the clinical non-inferiority of efficacy between Daflon® 1000 mg (1 sachet per day) and Daflon® 500 mg (2 tablets per day), in improving lower limb discomfort assessed by a 10 cm visual analog scale (VAS) after eight weeks of treatment in patients suffering from CVD.

Secondary objectives were to determinate the evolution of efficacy during the study of each symptoms (leg pain, leg heaviness assessed by 10 cm VAS), the quality of life evolution in both groups (assessed by CIVIQ-20), and the safety profile and so, the acceptability of Daflon® 1000 mg as compared to Daflon® 500 mg.

Methodology:
International, multicenter, double-blind, randomized, parallel group, non-inferiority phase III study conducted in outpatients suffering from symptomatic primary chronic venous disease, comparing Daflon® 1000 mg o.d. to Daflon® 500 mg b.i.d.
The treatment randomisation and allocation were non-centralised without Interactive Response System (IRS) procedure. The treatment was assigned at inclusion visit by a balance, non-adaptive randomisation with stratification on centre.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:
Planned: 952 patients (476 by treatment group).
Included: 1139 patients (571 patients in the Daflon® 1000 mg o.d. and 568 patients in the Daflon® 500 mg b.i.d. group).

Diagnosis and main criteria for inclusion:
Male or female outpatient aged between 20 to 75 years old (included); Suffering from primary chronic venous disease, with lower limb discomfort superior or equal to 4 cm on the VAS scale and with at least leg pain superior or equal to 3 cm on the VAS [lower limb discomfort ≥ 4 cm and leg pain ≥ 3 cm on the VAS scale] and belonging to the Clinical Etiological Anatomic pathophysiologic (CEAP) class C0s to C4s on the most affected leg. Patient was to be able to fill in a questionnaire and a VAS by himself.

Test drug:
Daflon® 1000 mg (MPFF 1000 mg oral suspension): 1 sachet daily taken *per os* (*p.o.*) in the morning
Batch No.: L0052308, L0048742.

Comparator (Reference product):
Daflon® 500 mg (MPFF 500 mg tablet): 2 tablets daily taken *p.o.* (one at midday and one in the evening)
Batch No.:L0052806, L0044433.

Double placebo: 1 sachet daily taken *p.o.* in the morning or 2 tablets daily taken *p.o.* (one at midday and one in the evening).

Duration of treatment:
Run-in period (from selection to the inclusion visit): open label period under placebo during 14 days
Treatment period (from W0 to W8): double-blind randomised period during 8 weeks

Criteria for evaluation:
Efficacy measurements:

- Primary efficacy criterion: **Lower limb discomfort related to CVD** assessed by a 10 cm visual analog scale (0 = no discomfort and 10 = extreme discomfort) at selection (ASSE), W0, W2, W4 and W8. The primary analysis was the change from baseline to last post baseline visit.
- Leg pain of the disease: assessed on a 10-cm visual analogic scale (0 = no pain and 10 = extreme pain) at the following visits: ASSE, W0, W2, W4 and W8.
- Leg heaviness of the disease: assessed on a 10-cm visual analogic scale (0 = no heaviness and 10 = extreme heaviness) at the following visits: ASSE, W0, W2, W4 and W8.

Lower limb discomfort, leg pain and leg heaviness evaluations were supported by auto-evaluations performed every week the evening before the visit and reported by the patient on a diary.

- Quality of life of the disease: assessed by the patient through the ChronIc Venous Insufficiency Questionnaire CIVIQ-20 scale at the following visits: ASSE, W0, W2, W4 and W8. 20 questions were assessed by the patient from 1 = no impact to 5 = severe impact. This evaluation was filled by the patient the day of the visit under the supervision of the investigator. This scale consists of items that assess pain, physical limitations, social limitations, and psychological limitations. A global score as well as sub-scores were calculated using a formula from 0 = no impact to 100 = severe impact.

In case of premature withdrawal, the efficacy criteria were to be assessed only if the patient came less than 3 days after treatment discontinuation.

Safety measurements:

- Adverse events (AEs) reported at each visit
- Physical examination and vital signs assessed at selection, W0, W2, W4 and W8 visits
  - Sitting blood pressure (mmHg), after 10 minutes of rest, with a sphygmomanometer. Blood pressure was to be assessed in the sitting position.
  - Heart rate (bpm).
  - Body weight (kg).
- Overall acceptability: rated by the patient (sum of well-being and adverse events scores) and by the investigator (sum of therapeutic benefit, vital signs and adverse events scores) at the end of the study W8. Each item was scored from 0 (worst acceptability) to 3 (best acceptability).

Other measurements:

- Laboratory tests: haematological, biochemical tests including ß HCG blood test available at inclusion visit.

Laboratory results in absolute value were not recorded in the e-CRF but significant abnormalities were to be reported as adverse event.
In addition in Argentina, following Amendment No. 2, urinary pregnancy tests were to be performed at visits W0, W2, W4 and W8.

- Clinical CEAP class (C0s to C4s): evaluated at the selection visit
- Duplex ultrasonography (duplex scan): performed on both legs between selection and inclusion visits

Statistical methods:
Analysis Set:
Full Analysis Set (Set used for the primary efficacy analysis): In accordance with the intention-to-treat principle and the section 5.2.1 of ICH E9 guideline, all patients of the RS having taken at least one dose of Investigational Medicinal Product (IMP) and having a value at baseline and at least one post-baseline value for the lower limb discomfort assessed by a VAS.

Efficacy analysis:
Primary efficacy endpoint:

- Primary analysis

To demonstrate the non-inferiority of MPFF 1000 mg o.d. as compared to MPFF 500 mg b.i.d. on lower limb discomfort (VAS) after a 8-week treatment period, the between group difference (MPFF 1000 mg o.d. minus MPFF 500 mg b.i.d.) in the FAS on the change from baseline to last post baseline visit was studied using an ANCOVA model, with 1.0 cm as non-inferiority limit.
Analysis included the fixed, categorical effects of treatment and centre, as well as the continuous, fixed covariate of baseline.

- Secondary analysis

To confirm the main results on the primary endpoint, the difference between MPFF 1000 mg o.d. *minus* MPFF 500 mg b.i.d. was assessed after 8 weeks of treatment using the same analysis strategy as the primary analysis but in the PPS.
Moreover, the lower limb discomfort assessed by a VAS was described in terms of value at W0, at each post baseline visit (including each week) and change from baseline to each post-baseline visit in the FAS and the PPS.

Secondary efficacy endpoints
The same model (*i.e.* ANCOVA) as for primary efficacy endpoint was performed for all secondary efficacy endpoints: leg pain, leg heaviness and CIVIQ-20 global score and subscores (pain, physical, psychological and social). Only the estimate of the between-group difference and the associated standard error and two-sided 95% CI were provided for these analyses.
Besides, descriptive statistics of all secondary efficacy endpoints, at each visit were provided.
Efficacy analyses were carried out in the FAS and in the PPS.

Study outcome and safety analysis: Descriptive statistics were provided.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Disposition of patients

		MPFF sachet 1000 mg o.d.	MPFF tablet 500 mg b.i.d.	All
Included/randomised	**n**	**571**	**568**	**1139**
Withdrawn due to	**n (%)**	**31 (5.4)**	**32 (5.6)**	**63 (5.5)**
- lost to follow-up	n (%)	-	1 (0.2)	1 (0.09)
- adverse event	**n (%)**	6 (1.1)	9 (1.6)	15 (1.3)
- lack of efficacy	n (%)	1 (0.2)	-	1 (0.09)
- non-medical reason	n (%)	9 (1.6)	8 (1.4)	17 (1.5)
- protocol deviation	n (%)	15 (2.6)	14 (2.5)	29 (2.5)
Completed	**n (%)**	**540 (94.6)**	**536 (94.4)**	**1076 (94.5)**
Full Analysis Set (FAS)	n (%)	568 (99.5)	557 (98.1)	1125 (98.8)
Per Protocol Set (PPS)	**n (%)**	496 (86.9)	503 (88.6)	999 (87.7)
Safety Set (SS)	n (%)	**568 (99.5)**	**568 (100)**	**1136 (99.7)**

%: % of the Randomised Set

In all, 152 patients (13.3%) presented 202 protocol deviations before or at inclusion without relevant difference between groups. The most frequent deviations concerned study management (140 patients, 12.3%), mainly related to duplex scan (63 patients, 5.5%) mostly duplex scan result missing (at least one result missing) at W0 visit (61 patients, 5.4%) and study treatment administration (30 patients, 2.6%) mostly run-in compliance ≥ 120% for sachets (20 patients, 1.8%).

SUMMARY - CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

In all, 84 patients (7.4%) presented 218 protocol deviations, after inclusion. The most frequent deviations concerned study management (75 patients, 6.6%), mainly related to study treatment administration (69 patients, 6.1%) mostly compliance during the treatment period less than 80% for sachets (39 patients, 3.4%) and for tablets (45 patients, 4.0%). No relevant difference between groups was observed except a slightly lower frequency of deviations affecting efficacy (related to unauthorised concomitant treatment) in the MPFF 1000 mg o.d. group (one patient, 0.2%) than in the MPFF 500 mg b.i.d. group (11 patients, 1.9%).

BASELINE CHARACTERISTICS

Main baseline characteristic in the Randomised Set are summarised in the Table below.

Main baseline characteristics at selection in the Randomised Set

				MPFF sachet 1000 mg o.d. (N = 571)	MPFF tablet 500 mg b.i.d. (N = 568)	All (N = 1139)
Age (years)			n	571	568	1139
			Mean ± SD	45.9 ± 11.9	46.1 ± 12.2	46.0 ± 12.0
			Median	46.0	46.0	46.0
			Min ; Max	20 ; 74	20 ; 75	20 ; 75
Gender		Male	n (%)	83 (14.5)	79 (13.9)	162 (14.2)
		Female	n (%)	488 (85.5)	489 (86.1)	977 (85.8)
BMI (kg/m^2)*			n	570	568	1138
			Mean ± SD	25.1 ± 3.1	24.9 ± 3.1	25.0 ± 3.1
			Median	25.2	25.0	25.1
			Min ; Max	17.9 ; 30.0	18.1 ; 31.9	17.9 ; 31.9
Race						
		Caucasian	n (%)	525 (91.9)	521 (91.9)	1046 (91.9)
		Black	n (%)	3 (0.5)	-	3 (0.3)
		Asian	n (%)	36 (6.3)	39 (6.9)	75 (6.6)
		Other	n (%)	7 (1.2)	7 (1.2)	14 (1.2)
CVD duration (years)			n	571	568	1139
			Mean ± SD	8.9 ± 10.6	9.5 ± 11.1	9.2 ± 10.8
			Median	5.0	6.0	5.0
			Min ; Max	0 ; 54	0 ; 56	0 ; 56
CEAP class on the most affected leg**			n	569	565	1134
	Right	C0s	n (%)	2 (0.68)	2 (0.71)	4 (0.70)
		C1s	n (%)	63 (21.58)	66 (23.40)	129 (22.47)
		C2s	n (%)	134 (45.89)	124 (43.97)	258 (44.95)
		C3s	n (%)	78 (26.71)	73 (25.89)	151 (26.31)
		C4As	n (%)	14 (4.79)	15 (5.32)	29 (5.05)
		C4Bs	n (%)	1 (0.34)	2 (0.71)	3 (0.52)
		All	n (%)	292 (100)	282 (100)	574 (100)
	Left	C0s	n (%)	4 (1.44)	1 (0.35)	5 (0.89)
		C1s	n (%)	53 (19.13)	65 (22.97)	118 (21.07)
		C2s	n (%)	149 (53.79)	128 (45.23)	277 (49.46)
		C3s	n (%)	58 (20.94)	75 (26.50)	133 (23.75)
		C4As	n (%)	12 (4.33)	12 (4.24)	24 (4.29)
		C4Bs	n (%)	1 (0.36)	2 (0.71)	3 (0.54)
		All	n (%)	277 (100)	283 (100)	560 (100)
Previous treatments for CVD***			n	571	568	1139
		Yes	n (%)	23 (4.0)	20 (3.5)	43 (3.8)
		No	n (%)	548 (96.0)	548 (96.5)	1096 (96.2)

N: Number of patients by group; n: Number of patients in a category; %: n/Nx100

**: last analysable value prior to treatment (selection or inclusion)*

***: C0s:No visible or palpable signs of venous disease; C1s: Telangectasies or reticular veins; C2s: Varicose veins; C3s: Oedema; C4As: Skin changes ascribed to venous disease such as pigmentation and venous eczema; C4Bs: Skin changes ascribed to venous disease such as lipodermatosclerosis and white atrophy*

****: Stopped within at least one month (up to 3 months before the Amendment No. 3) prior to the selection visit*

SUMMARY - CONCLUSIONS (Cont'd)

BASELINE CHARACTERISTICS (Cont'd)

At selection, the CVD had been lasted for 9.2 ± 10.8 years on average (median = 5 years) and a family history of chronic venous disease was found in 61.5% of the patients in the RS.

According to the CEAP classification on the most affected leg, the most frequent class was class 2 "varicose veins" (45.0% of the patients on the right leg and 49.5% on the left leg). As required by the protocol CEAP classes ranged from C0s to C4s.

All, except one, randomised patients had a duplex scan at inclusion. Venous obstruction was observed in 3 patients: 2 patients (one in the MPFF 1000 mg o.d. group and one in the MPFF 500 mg b.i.d. group) had obstructions on both the right GSV above knee and right GSV below knee and one patient (in the MPFF 500 mg b.i.d group) had obstruction on the left small saphenous vein.

Venous reflux was observed on numerous patients depending on the type of vein: from 1.5% of the patients on the left perforators-thigh to 31.6% of the patients on the left great saphenous vein above knee.

Overall, 3.8% of the patients received at least one previous treatment for CVD stopped within at least one month (up to 3 months before the Amendment No. 3) prior to the selection visit, in the RS. These previous treatments consisted mostly in vasoprotective agents (3.5%), mainly bioflavonoids (3.3%).

No clinically relevant difference between groups was observed regarding demographic data and disease characteristics at baseline in the Randomised Set.

At baseline in the RS, BMI was on average 25.0 ± 3.1 kg/m² (weight was 69.3 ± 11.3 kg); sitting SBP was 118.1 ± 11.4 mmHg, sitting DBP was 72.9 ± 8.3 mmHg and sitting HR was 72.3 ± 7.6 bpm. Data were similar in both groups.

Overall, 64.8% of the randomised patients reported at least one medical history other than CVD, mainly menopause (27.1%) and hypertension (11.6%). No clinically relevant difference between groups was observed regarding medical history except a slightly higher rate of dyslipidaemia in the MPFF 1000 mg o.d. group (5.3%) than in the MPFF 500 mg b.i.d. group (2.6%).

Overall, 40.7% of the randomised patients reported at least one surgical or medical procedure history other than CVD without relevant difference between groups: the most frequent were appendectomy (8.9%) and caesarean section (8.3%).

At inclusion, 44.6% of the randomised patients had taken at least one concomitant treatment: the most frequent were sex hormones and modulators of the genital system (10.5%) and agents acting on the renin-angiotensin system (9.0%). No relevant difference between groups was observed regarding concomitant treatments at inclusion except a slightly higher rate of lipid modifying agents in the MPFF 1000 mg o.d. group (7.2%) than in the MPFF 500 mg b.i.d. group (4.2%).

According to a VAS [from 0 cm (no symptom) to 10 cm (extreme symptom)] at baseline, lower limb discomfort was on average 6.7 ± 1.5 cm (6.7 ± 1.5 cm in both MPFF 1000 mg o.d. and MPFF 500 mg b.i.d. groups), leg pain 6.4 ± 1.7 cm (6.4 ± 1.8 cm and 6.4 ± 1.7 cm, respectively) and leg heaviness 6.6 ± 1.8 cm (6.6 ± 1.8 cm and 6.6 ± 1.7 cm, respectively) in the Randomised Set.

Regarding quality of life evaluated by CIVIQ-20 questionnaire [scores from 0 (no impact) to 100 (severe impact)] in the RS at baseline, the mean global index score derived was 39.7 ± 18.4 (39.2 ± 18.3 in the MPFF 1000 mg group and 40.2 ± 18.6 in the MPFF 500 mg group); mean pain subscore was 52.4 ± 17.6 (52.3 ± 17.4 and 52.4 ± 17.8, respectively); mean physical subscore was 43.6 ± 22.7 (42.8 ± 22.9 and 44.4 ± 22.4, respectively); mean psychological subscore was 32.1 ± 21.1 (31.6 ± 20.7 and 32.6 ± 21.6, respectively) and mean social subscore was 40.4 ± 22.4 (39.9 ± 22.3 and 40.9 ± 22.4, respectively).

Data regarding all efficacy criteria at baseline in the Randomised Set were similar in both groups.

Baseline characteristics in the FAS (98.8% of the RS) and in the PPS (88.8% of the FAS) were similar to those observed in the Randomised Set.

EXTENT OF EXPOSURE

In the Randomised Set, global treatment duration ranged between 0 and 71 days with a mean (± SD) of 54.8 ± 7.9 days (median of 56.0 days) for the sachets and from 0 to 71 days with a mean (± SD) of 54.9 ± 7.9 days (median of 56.0 days) for the tablets which was consistent with the planned study treatment period of 8 weeks.

SUMMARY - CONCLUSIONS (Cont'd)

EXTENT OF EXPOSURE (Cont'd)

In the Randomised Set, the mean ± SD overall compliance was of 97.3 ± 10.9 % and ranged from 0% to 126% for the sachets and was of 96.9 ± 11.3 % ranging from 0% to 109% for the tablets. More than 96.0% of the randomised patients had an overall compliance between 80% and 120% for the sachets and for the tablets. Global treatment duration (and compliance) equal to 0 (minimum) was related to 3 randomised patients in the MPFF 1000 mg o.d., group, who did not take any study treatment during the W0-W8 treatment period.

Treatment duration and compliance were similar in both groups.

Similar data were observed in the Safety Set and in the FAS.

EFFICACY RESULTS

- ***Primary assessment criterion:*** lower limb discomfort measured by a VAS (cm)

In the FAS, the **lower limb discomfort** decreased in both groups with a mean change from baseline to last post-baseline value up to W8 of -3.3 ± 2.4 cm in the MPFF 1000 mg o.d. group *versus* -3.3 ± 2.4 cm in the MPFF 500 mg b.i.d. group. The primary statistical analysis demonstrated the statistically significant non-inferiority, with 1.0 cm as non-inferiority limit, of MPFF 1000 mg o.d. *versus* MPFF 500 mg b.i.d. on the improvement of lower limb discomfort with an estimate of the difference (SE) between groups of 0.05 (0.12) cm with 95% CI = [-0.18 ; 0.28] and p-value < 0.0001.

Lower limb discomfort measured by VAS (cm) -
Change from baseline to last post-baseline value up to W8 and comparison between groups -
Non-inferiority analysis in the FAS

		MPFF sachet 1000 mg o.d. (N = 568)	**MPFF tablet 500 mg b.i.d. (N = 557)**
Baseline	n	568	557
	Mean ± SD	6.693 ± 1.537	6.674 ± 1.474
	Median	6.700	6.500
	Min ; max	2.80 ; 10.00	3.40 ; 10.00
Last post-baseline	n	568	557
	Mean ± SD	3.420 ± 2.312	3.343 ± 2.249
	Median	3.100	3.000
	Min ; Max	0.00 ; 10.00	0.00 ; 9.80
Last post-baseline - baseline	n	568	557
	Mean ± SD	-3.272 ± 2.419	-3.330 ± 2.404
	Median	-3.200	-3.300
	Min ; Max	-10.00 ; 2.30	-9.90 ; 2.70
Primary statistical analysis			
	E (SE)	0.05 (0.12)	
	95% CI	[-0.18; 0.28]	
	p-value	< 0.0001	

N: Number of patients in each treatment group.
n: Number of observed values.
Non-inferiority tests of MPFF 1000 mg o.d. as compared to MPFF 500 mg b.i.d.
Non-inferiority limit: 1 cm
One-sided type I error rate: 0.025
E (SE): Estimate (Standard Error) of the adjusted (centre and baseline) difference between treatment group means: MPFF 1000 mg o.d.minus MPFF 500 mg b.i.d.
95% CI: 95% confidence interval of the estimate
p-value: General linear model with baseline and centre as fixed factor

In addition, the lower limb discomfort improvement observed from baseline in both groups was clinically relevant with similar results between groups.

Results in the PPS were similar to those obtained in the FAS with a statistically significant non-inferiority: estimate of the difference (SE) between groups of 0.06 (0.12) cm, 95% CI = [-0.18 ; 0.29] and p-value < 0.0001.

In the FAS, the lower limb discomfort assessed each week by the patient (auto-evaluation) remained stable from the first week after selection to the inclusion visit (from 6.6 ± 1.5 cm to 6.7 ± 1.5 cm in the MPFF 1000 mg o.d. group and from 6.6 ±1.4 cm to 6.7 ± 1.5 cm in the MPFF 500 mg b.i.d. group) then decreased throughout the study up to last weekly measurement before W8 visit (3.4 ± 2.3 cm *versus* 3.3 ± 2.2 cm, respectively) with similar results in both groups. Similar results were observed in the PPS.

SUMMARY - CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

- ***Secondary assessment criteria***

Leg pain measured by a VAS (cm)

In the FAS, a clinically relevant decrease of the **leg pain** was observed from baseline in both groups with similar results between groups: mean change from baseline to last post-baseline value up to W8 was -3.2 ± 2.5 cm in the MPFF 1000 mg o.d. group and -3.3 ± 2.5 cm in the MPFF 500 mg b.i.d. group with an estimate of the difference (SE) between groups of 0.10 (0.12) cm (95% CI = [-0.13 ; 0.34]). Results in the PPS were similar to those obtained in the FAS: estimate of the difference (SE) between groups regarding decrease of leg pain from baseline to last post-baseline value was of 0.10 (0.12) cm with 95% CI = [-0.14 ; 0.34].

Leg heaviness measured by a VAS (cm)

In the FAS, a clinically relevant decrease of the **leg heaviness** was observed from baseline in both groups with similar results between groups: mean change from baseline to last post-baseline value up to W8 was -3.3 ± 2.6 cm in the MPFF 1000 mg o.d. group and -3.4 ± 2.5 cm in the MPFF 500 mg b.i.d. group with an estimate of the difference (SE) between groups of 0.09 (0.12) cm (95% CI = [-0.14 ; 0.33]).

Results in the PPS were similar to those obtained in the FAS: estimate of the difference (SE) between groups regarding decrease of leg heaviness from baseline to last post-baseline value was of 0.10 (0.12) cm with 95%CI = [-0.15 ; 0.34].

Quality of life evaluated by CIVIQ-20 questionnaire

Scores of **quality of life** were calculated from 0 (no impact) to 100 (severe impact).
In the FAS, whatever the scores, a clinically relevant improvement of quality of life was observed in both groups from baseline with similar results between groups: mean changes from baseline to last post-baseline value up to W8 were respectively in the MPFF 1000 mg o.d. and MPFF 500 mg b.i.d. groups:

- -18.5 ± 16.8 *versus* -19.5 ± 17.2 for global index score derived (E (SE) = 0.42 (0.78), 95% CI = [-1.11 ; 1.95]).
- -26.6 ±19.0 *versus* -26.3 ± 20.8 for pain subscore (E (SE) = -0.31 (0.90), 95% CI = [-2.07 ; 1.45]).
- -19.6 ± 20.6 *versus* -20.7 ± 22.0 for physical subscore (E (SE) = 0.06 (0.97), 95%CI = [-1.84 ; 1.95].
- -14.4 ± 18.3 *versus* -15.8 ± 18.1 for psychological subscore (E (SE) = 0.84 (0.79), 95% CI = [-0.71 ; 2.39]).
- -18.7 ± 21.2 *versus* -19.8 ± 21.9 for social subscore (E (SE) = 0.49 (0.98), 95% CI = [-1.43 ; 2.41]).

Results in the PPS were similar to those observed in the FAS.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

- **Adverse events**

Overall summary of adverse events in the Safety Set

		MPFF sachet 1000 mg o.d. (N = 568)	MPFF tablet 500 mg b.i.d. (N = 568)
Patients having reported			
at least one emergent adverse event	n (%)	73 (12.9)	78 (13.7)
at least one treatment-related emergent adverse event	n (%)	24 (4.2)	20 (3.5)
Patients having experienced			
at least one serious adverse event	n (%)	2 (0.4)	3 (0.5)
at least one serious emergent adverse event	n (%)	2 (0.4)	3 (0.5)
at least one treatment-related serious adverse event	n (%)	-	2 (0.4)
Patients with treatment withdrawal			
due to an emergent adverse event	n (%)	6 (1.1)	8 (1.4)
due to an emergent serious adverse event	n (%)	1 (0.2)	2 (0.4)
due a treatment-related emergent adverse event	n (%)	4 (0.7)	6 (1.1)
due a treatment-related emergent serious adverse event	n (%)	-	2 (0.4)
Patients who died	n (%)	-	-

No death occurred during the study. Overall, 5 patients (0.4%) experienced 12 serious adverse events, all emergent: 2 patients in the MPFF 1000 mg o.d. group (0.4%) reported 6 SAEs and 3 patients in the MPFF 500 mg b.i.d. group (0.5%) reported 6 SAEs. None SAE was reported more than once in any group. All serious adverse events but one (asthma) in the MPFF 500 mg b.i.d. group resolved; 5 serious adverse events reported by 2 patients in the MPFF 500 mg b.i.d. group were considered as treatment-related and led to treatment withdrawal (swelling face, urticaria, face oedema, dysphagia and rash). In addition, one serious adverse event (sepsis) led to treatment withdrawal in one patient (0.2%) in the MPFF 1000 mg o.d. group but was considered as not related to the study drug.

Emergent adverse events were reported by 12.9% of the patients in the MPFF 1000 mg o.d. and 13.7% in the MPFF 500 mg b.i.d. group.
In the MPFF 1000 mg o.d. group, the most frequently reported System Organ Classes (SOCs) (more than 2% of the patients affected) were gastrointestinal disorders and infections and infestations without clinically relevant difference compared to the MPFF 500 mg b.i.d. group (4.6% *versus* 4.6% and 4.6% *versus* 3.7%, respectively). Among the other SOCs, injury poisoning and procedural complications were more frequently reported in the MPFF 1000 mg o.d. group than in the MPFF 500 mg b.i.d. group (1.4% *versus* 0.5%, respectively) whereas nervous system disorders and skin and subcutaneous tissue disorders were less frequently reported in the MPFF 1000 mg o.d. than in the MPFF 500 mg b.i.d. group (1.4% *versus* 2.5% and 0.2% *versus* 1.4%, respectively) and psychiatric disorders were not reported in the MPFF 1000 mg o.d. group *versus* 0.5% (3 patients) in the MPFF 500 mg b.i.d. group.
In the MPFF 1000 mg o.d. group, the most frequent emergent adverse events (in more than 1% of the patients) were nausea (1.2%) and abdominal pain upper (1.2%). Abdominal pain upper was more frequently reported in the MPFF 1000 mg o.d. than in the MPFF 500 mg b.i.d. (7 patients, 1.2% *versus* 2 patients, 0.4%).
In the MPFF 500 mg b.i.d. group, the most frequent emergent adverse events were diarrhoea and headache (both reported by 7 patients, 1.2%) without clinically relevant difference with the MPFF 1000 mg o.d. group (5 patients, 0.9% for both events).

Regarding the other emergent adverse events, the following ones were more frequently reported in the MPFF 1000 mg o.d. group than in the MPFF 500 mg b.i.d. group: muscle spasms (5 patients, 0.9%, *versus* none), gastroenteritis (4 patients, 0.7 % *versus* none) and abdominal discomfort (3 patients, 0.5% *versus* none).
Conversely, gastritis was less frequently reported in the MPFF 1000 mg o.d. than in the MPFF 500 mg b.i.d. (none *versus* 4 patients, 0.7%, respectively).
To note an hepatitis acute, reported one month after the first study drug intake in a 54 years old woman (No. 105 764 1003 00742) in the MPFF 1000 mg o.d. group, not serious, not severe, not considered as treatment-related. The adverse event did not lead to study drug withdrawal. The event was unresolved (flatulence still on-going) 3 months after the last study drug intake. The day of the adverse event, ALT was 56 IU/L (normal range: 4 - 36 IU/L), AST was 38 IU/L (normal range: 12 - 32 IU/L), ALP was 202 IU/L (normal range: 42 - 121 IU/L). One and a half month later (3 weeks after the last study drug intake), liver tests showed normal ALT/AST values (20 IU/L and 28 IU/L, respectively) and ALP at 128 IU/L; ultrasonography of upper abdomen showed a mild left hydronephrosis with no other abnormality.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Most of the emergent adverse events were of mild intensity in both groups with a higher rate in the MPFF 1000 mg o.d. group than in the MPFF 500 mg b.i.d. group (79.2% *versus* 66.1%, respectively). The incidence of emergent adverse events rated as severe was lower in the MPFF 1000 mg o.d. group than in the MPFF 500 mg b.i.d. group: 2.1%, 2 events (gastroenteritis and sepsis) *versus* 7.3%, 8 events (osteoarthritis, pain in extremity, headache, hypoaesthesia, dysphagia, face oedema, rash and urticaria), respectively.

No clinically relevant difference between groups was observed regarding the percentage of patients with at least one emergent adverse event considered as treatment-related: 4.2% in the MPFF 1000 mg o.d. group *versus* 3.5% in the MPFF 500 mg b.i.d. group. There were mainly related to gastro-intestinal disorders, more frequently reported in the MPFF 1000 mg o.d. group than in the MPFF 500 mg b.i.d. group (19 patients, 3.3% *versus* 13 patients, 2.3%, respectively).

The following treatment-related adverse events were more frequently reported in the MPFF 1000 mg o.d. group than in the MPFF 500 mg b.i.d. group: nausea (7 patients, 1.2% *versus* 4 patients, 0.7%, respectively), abdominal discomfort (3 patients, 0.5% *versus* none, respectively) and muscle spasms (2 patients, 0.4% *versus* none). Conversely, the followings were less frequently reported in the MPFF 1000 mg o.d. group than in the MPFF 500 mg b.i.d. group: diarrhoea (2 patients, 0.4% *versus* 4 patients, 0.7%), gastritis (none *versus* 2 patients, 0.4%) and paraesthesia (none *versus* 2 patients, 0.4%).

To note that treatment-related events from the SOC "Skin and subcutaneous tissue disorders" were reported by one patient (0.2%) in the MPFF 1000 mg o.d. group *versus* 3 patients (0.5%) in the MPFF 500 mg b.i.d. group.

Overall, emergent adverse events led to treatment discontinuation in 14 patients (1.2%) without clinically relevant difference between groups: 6 patients (1.1%) in the MPFF 1000 mg o.d. group and 8 patients (1.4%) in the MPFF 500 mg b.i.d. group. These events were mainly related to gastrointestinal disorders, without clinically relevant difference between groups: 3 patients (0.5%) in the MPFF 1000 mg o.d. group *versus* 5 patients (0.9%) in the MPFF 500 mg b.i.d. group. The events were mainly nausea (2 patients, 0.4% *versus* 1 patient, 0.2%, respectively) and diarrhoea (one patient, 0.2% *versus* 2 patients, 0.4%, respectively), similarly reported in both groups.

To note that events from the SOC "Skin and subcutaneous tissue disorders" led to treatment discontinuation in 2 patients in the MPFF 500 mg b.i.d. group *versus* none in the MPFF 1000 mg o.d. group.

In both groups, more than 94% of the emergent adverse events resolved. Overall, 3 emergent adverse events were unresolved in the MPFF 1000 mg group (muscle spasms, hypertension and hepatitis acute) *versus* 5 in the MPFF 500 mg b.i.d. group (haemorrhoids, osteoarthritis, tenosynovitis, dysmenorrhoea and asthma).

- **Vital signs and clinical examination**

Neither clinically relevant changes nor differences between groups in mean/median values over time were detected for weight, BMI, blood pressure and heart rate.

- **Acceptability**

Acceptability rated by the patient (well-being and adverse events) showed not clinically relevant difference between groups except, a slightly lower rate of answer "frequent but minor" regarding adverse events in the MPFF 1000 mg o.d. group (7 patients, 1.3%) than in the MPFF 500 mg b.i.d. group (14 patients, 2.6%).
Acceptability rated by the investigator (therapeutic benefit, vital signs and adverse events) showed no clinically relevant difference between groups except for adverse events slightly more frequently rated as "sparse" in the MPFF 1000 mg o.d. group (23 patients, 4.2%) than in the MPFF 500 mg b.i.d. group (13 patients, 2.4%).
In addition, the comparison between patient's and investigator's opinion regarding adverse events, showed that the acceptability was slightly better when rated by the investigator than by the patient without clinically relevant difference between groups: adverse events were rated (taking into account missing data) as "none or not related with the treatment" for 94.2% of the patients when assessed by the investigator *versus* 89.8% when assessed by the patient in the MPFF 1000 mg o.d. group and 96.1% *versus* 89.0%, respectively in the MPFF 500 mg b.i.d. group.

The most frequent common answer between investigator and patient regarding the adverse events was "none or not related with the treatment" with similar data in both groups (88.9% *versus* 88.6% in the MPFF 1000 mg o.d. group and MPFF 500 mg b.i.d. group, respectively).

Global score of acceptability (unplanned analysis) was rated from 0 (worst acceptability) to 6 (best acceptability) by the patient and from 0 (worst acceptability) to 9 (best acceptability) by the investigator. Overall acceptability was good and similar in both groups: on average 5.3 ± 0.8 in the MPFF 1000 mg o.d. group *versus* 5.2 ± 0.8 in the MPFF 500 mg b.i.d. group for the patient's global score and 7.7 ± 1.1 in the MPFF 1000 mg o.d. group *versus* 7.8 ± 1.0 in the MPFF 500 mg b.i.d. group for the investigator's global score.

CONCLUSION

This international multicentre, double-blind, randomised, parallel groups, phase III study conducted in patients suffering from symptomatic chronic venous disease, demonstrated the statistically significant non-inferiority of Daflon® 1000 mg (MPFF 1000 mg oral suspension, one sachet per day) *versus* Daflon® 500 mg (MPFF 500 mg tablet, 2 tablets daily) on the improvement of lower limb discomfort assessed by a 10 cm visual analog scale after 8 weeks of treatment. The lower limb discomfort improvement from baseline was clinically relevant with similar results between groups. Results showed also a clinically relevant improvement from baseline of leg pain, leg heaviness and quality of life with similar results between groups.

Safety profile of Daflon® 1000 mg (MPFF 1000 mg oral suspension o.d.) was similar to the one of Daflon® 500 mg (MPFF 500 mg tablet b.i.d.). MPFF 1000 mg oral suspension o.d. was well tolerated during the 8-weeks treatment period, as well as MPFF 500 mg tablet b.i.d. with emergent adverse events conforming to those described in the MPFF Reference Safety Information (February 2014).

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