2. SYNOPSIS

Name of Sponsors: **I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex – France** **Les Laboratoires Servier, 50 rue Carnot - 92284 Suresnes Cedex – France**		*(For National Authority Use only)*
Test drug **Name of Finished Product:** NA **Name of Active Ingredient:** Micronized purified flavonoid fraction (S 05682)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Clinical acceptability study of Micronized purified flavonoid fraction 1000 mg, one tablet per day compared to Micronized Purified Flavonoid Fraction 500 mg, 2 tablets daily after eight weeks of treatment in patients suffering from symptomatic Chronic Venous Disease (CVD).
International, multicentre, double-blind, randomised, parallel group study.

Protocol No.: CL3-05682-107.

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

International coordinator: [redacted]

Study centres:
Overall, 11 centres located in 2 countries included at least one patient: 8 centres in Russia (122 included patients) and 3 centres in Serbia (52 included patients).

Publication (reference): Not Applicable

Studied period:	**Phase of development of the study:**
Initiation date: 19 December 2013 (date of first visit first patient) Completion date: 03 July 2014 (date of last visit last patient)	Phase III

Objectives:
The objective was to demonstrate clinical acceptability of MPFF 1000 mg, one tablet per day compared to MPFF 500 mg, 2 tablets daily after eight weeks of treatment in patients suffering from symptomatic Chronic Venous Disease (CVD).

Methodology:
International, multicentre, double-blind, randomized, parallel group phase III study comparing the acceptability of Micronized Purified Flavonoid Fraction (MPFF) 1000 mg *versus* MPFF 500 mg in out-patients suffering from primary symptomatic CVD. Method of treatment allocation was balanced with non-centralised randomisation at W0.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:
Planned: 150 (75 patients under MPFF 1000 mg and 75 patients under MPFF 500 mg).
Included: 174 (87 patients under MPFF 1000 mg and 87 patients under MPFF 500 mg).

Diagnosis and main criteria for inclusion:
Male or female patient aged between 20 to 70 years old (included); treated in out-patients facility and suffering from primary symptomatic CVD with leg pain superior or equal to 4 cm on visual analogue scale (VAS) and belonging to the Clinical Etiological Anatomic Pathophysiologic (CEAP) class C0s to C4s. Patients were not to have causes of leg pain in lower limbs other than CVD symptoms.

Test drug:
MPFF 1000 mg: 1 tablet daily taken *per os* (*p.o.*) in the morning.
Batch No.: L0049608

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

Placebo 1000 mg and placebo 500 mg tablets were administrated to maintain the blind.

Duration of treatment:

- **Run-in period from selection (ASSE) to inclusion (W0):** open label period under double placebo (1000 mg and 500 mg) during 14 days
- **Active treatment period from W0 to W8**: double-blind randomised period of 8 weeks.

Criteria for evaluation:
Efficacy measurement:
Not applicable

Safety measurements:

- Adverse events reported at each visit.
- Laboratory tests: biochemical and haematological parameters were performed at inclusion and at W8.
- Sitting blood pressures (systolic and diastolic blood pressure *i.e.* SBP and DBP) and heart rate (HR) were assessed at each visit.
- Weight was assessed at each visit.
- Leg pain evaluated by VAS at each visit.

Other measurements:

- Duplex ultrasonography performed between ASSE and W0 visits.
- Urinary pregnancy test. Test was to be done at ASSE visit.

Statistical methods:
Analysis Set:
Safety analyses were performed in the Safety Set, *i.e.* all included patients having received at least one study treatment intake.
Efficacy analysis:
Not applicable.
Study outcome and safety analysis: Descriptive statistics were provided by treatment group and overall.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Disposition of patients

Status		MPFF 1000 mg	MPFF 500 mg	All
Included and randomised	**n**	**87**	**87**	**174**
in compliance with the protocol	n (%)	74 (85.1)	76 (87.4)	150 (86.2)
with a protocol deviation before or at inclusion	n (%)	13 (14.9)	11 (12.6)	24 (13.8)
Withdrawn due to	**n (%)**	**3 (3.4)**	**-**	**3 (1.7)**
adverse event	n	1	-	1
protocol deviation	n	1	-	1
non-medical reason	n	1	-	1
Completed W0-W8 period	**n (%)**	**84 (96.6)**	**87 (100)**	**171 (98.3)**
in compliance with the protocol	n	74	78	152
with a protocol deviation after inclusion	n	10	9	19
Safety Set	**n (%)**	**87 (100)**	**87 (100)**	**174 (100)**

n: number of patients; %: expressed as percentage of the Randomised Set

A total of 174 patients were included and randomly assigned to one of the 2 groups: 87 patients in the MPFF 1000 mg group and 87 patients in the MPFF 500 mg group. The planned balanced distribution was reached.
In the Randomised Set, 3 patients (1.7%) were withdrawn from the study (all were in the MPFF 1000 mg group) due to: adverse event (dyspepsia), protocol deviation (Body Mass Index = 31.1 kg/m^2) and non-medical reason (consent withdrawal).

SUMMARY – CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

In all, 25 protocol deviations were observed in 24 patients (13.8%) before or at inclusion: they all concerned study management, mainly study treatment dispensation (7 deviations in 7 patients, 4.0%) and biology (5 deviations in 5 patients, 2.9%). After inclusion, 23 protocol deviations were observed in 20 patients (11.5%): they all concerned study management, mainly biology (blood sample not taken within the 7 days before W8 visit): 17 deviations in 17 patients (9.8%). No relevant difference between groups was observed regarding protocol deviations.

BASELINE CHARACTERISTICS

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

Main baseline characteristics at selection in the Randomised Set

			MPFF 1000 mg (N = 87)	MPFF 500 mg (N = 87)	All (N = 174)
Age (years)		n	87	87	174
		Mean ± SD	49.1 ± 12.2	47.1 ± 12.5	48.1 ± 12.4
		Min ; Max	23 ; 70	23 ; 68	23 ; 70
Gender	Male	n (%)	16 (18.4)	13 (14.9)	29 (16.7)
	Female	n (%)	71 (81.6)	74 (85.1)	145 (83.3)
BMI (kg/m^2)		n	87	87	174
		Mean ± SD	25.1 ± 3.1	25.3 ± 3.0	25.2 ± 3.1
		Min ; Max	19.0 ; 31.6	19.0 ; 29.9	19.0 ; 31.6
Race	Caucasian	n (%)	87 (100)	87 (100)	174 (100)
CVD duration (years)		n	87	87	174
		Mean ± SD	14.6 ± 10.9	14.5 ± 11.3	14.5 ± 11.1
		Min ; Max	1 ; 48	0 ; 43	0 ; 48
CEAP class		n	87	87	174
on the most affected leg*	C0	n (%)	-	1 (1.2)	1 (0.6)
	C1	n (%)	18 (20.7)	16 (18.4)	34 (19.5)
	C2	n (%)	34 (39.1)	33 (37.9)	67 (38.5)
	C3	n (%)	29 (33.3)	33 (37.9)	62 (35.6)
	C4A	n (%)	6 (6.9)	2 (2.3)	8 (4.6)
	C4B	n (%)	-	2 (2.3)	2 (1.2)
Previous treatments for CVD**		n	87	87	174
	Yes	n (%)	24 (27.6)	31 (35.6)	55 (31.6)
	No	n (%)	63 (72.4)	56 (64.4)	119 (68.4)

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

**: C0:No visible or palpable signs of venous disease; C1: Telangectasias or reticular veins; C2: Varicose veins; C3: Oedema; C4A: Skin changes ascribed to venous disease such as pigmentation and venous eczema; C4B: Skin changes ascribed to venous disease such as lipodermatosclerosis and white atrophy*

***: Before study*

At selection, the CVD had been lasted for 14.5 ± 11.1 years, on average. According to the CEAP classification on the most affected leg, the most frequent classes were class 2 "varicose veins" (38.5% of the patients) and class 3 "oedema" (35.6% of the patients). As required by the protocol, all randomised patients suffering from CVD had leg pain score superior or equal to 4 cm on VAS at selection, and no patient had presence of venous obstruction according to the Duplex ultrasonography results at inclusion.

One third of patients (31.6%) received at least one previous treatment for CVD before the study (27.6% in the MPFF 1000 mg group *versus* 35.6% in the MPFF 500 mg group). These previous treatments consisted mostly in vasoprotective agents (22 patients, 25.3% in the MPFF 1000 mg group *versus* 31 patients, 35.6% in the MPFF 500 mg group), mainly bioflavonoids (21 patients, 24.1% *versus* 28 patients, 32.2%, respectively).

On average, at inclusion, sitting SBP was 118.8 ± 8.5 mmHg, sitting DBP was 73.8 ± 7.4 mmHg and sitting HR was 70.6 ± 7.2 bpm.

SUMMARY – CONCLUSIONS (Cont'd)

BASELINE CHARACTERISTICS (Cont'd)

Overall, 128 patients (73.6%) reported at least one medical history other than CVD (65 patients, 74.7% in the MPFF 1000 mg group and 63 patients, 72.4% in the MPFF 500 mg group). The most frequent medical histories (more than 10% of the patients) were menopause (59 patients, 33.9%) and hypertension (26 patients, 14.9%). At inclusion, 57 patients (32.8%) had taken at least one concomitant treatment (27 patients, 31.0% in the MPFF 1000 mg group and 30 patients, 34.5% in the MPFF 500 mg group). The most frequent (more than 10.0% in any group) were agents acting on the renin-angiotensin system (22 patients, 12.6%) mainly Angiotensin Converting Enzyme (ACE) inhibitors (17 patients, 9.8%), and all other non-therapeutic products (18 patients, 10.3%). Data on concomitant treatments during the treatment period were similar to those at inclusion.

No clinically relevant difference between groups was observed regarding demographic data, disease characteristics and other baseline characteristics.

EXTENT OF EXPOSURE / TREATMENT DURATION

In the Randomised Set, global treatment duration ranged between 14 and 64 days with a mean (± SD) of 56.3 ± 5.1 days (median of 57.0 days) with similar data in both groups. Global exposure to treatment (days), defined as global treatment duration minus the number of days of interruption, was similar to the global treatment duration: none of the patients reported temporary interruption of the treatment ≥ 3 days.

The compliance to study treatment was good with similar data in both groups, on average 98.4 ± 3.8%; for all patients except one, the compliance was included in the [80 ; 120]% range.

SAFETY RESULTS

- **Adverse events**

Overall summary of adverse events in the Safety Set

		MPFF 1000 mg (N = 87)	MPFF 500 mg (N = 87)
Patients having reported			
at least one emergent adverse event	n (%)	12 (13.8)	11 (12.6)
at least one treatment-related emergent adverse event	n (%)	3 (3.4)	-
Patients having experienced			
at least one serious adverse event (including death)	n (%)	-	-
at least one treatment-related serious adverse event	n (%)	-	-
Patients with treatment withdrawal			
due to an emergent adverse event	n (%)	1 (1.1)	-
due to an emergent serious adverse event	n (%)	-	-
due a treatment-related emergent adverse event	n (%)	1 (1.1)	-
Patients who died	n (%)	-	-

Emergent adverse events were reported by 13.8% of the patients in the MPFF 1000 mg group *versus* 12.6% in the MPFF 500 mg group.

No severe emergent adverse event was reported in any group. No death or other serious adverse event was reported during the study.

In the MPFF 1000 mg group, the most frequently affected System Organ Classes (**SOCs**) (more than 2 patients affected) were nervous system disorders and gastrointestinal disorders, with a slightly higher rate in the MPFF 1000 mg group than in the MPFF 500 mg group (6.9% *versus* 2.3% and 5.7% *versus* 1.1 %, respectively).

In the MPFF 500 mg group, the most frequently affected SOC (more than 2 patients) was infections and infestations, with a slightly lower rate in the MPFF 1000 mg group (1.1%) than in the MPFF 500 mg group (5.7%).

No relevant difference between groups was observed regarding the other SOCs.

In the MPFF 1000 mg group, the most frequent (reported by at least 2 patients) emergent adverse event was headache, with a slightly higher rate in the MPFF 1000 mg group than in the MPFF 500 mg group (5 patients, 5.7% *versus* 1 patient, 1.1% respectively): all the headaches were considered by the investigator as not related to the study drug, were of mild intensity with rapid recovery (within 2 days in the 1000 mg group and within 5 days in the 500 mg group). The other most frequent emergent adverse event was nausea, reported by 2 patients (2.3%) in the MPFF 1000 mg group *versus* none in the MPFF 500 mg group.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Adverse events (Cont'd)**

In any group, other emergent adverse events were each reported by only one patient except respiratory tract infections reported by 4 patients (4.6%) in the MPFF 500 mg group *versus* none in the MPFF 1000 mg group.

All emergent adverse events reported in both groups on treatment were of mild intensity.

Overall, 3 patients (3.4%) in the MPFF 1000 mg group experienced 3 emergent adverse events considered as treatment-related according to the investigator *versus* none in the MPFF 500 mg group. These 3 treatment-related EAEs (constipation, dyspepsia, and dermatitis allergic) were neither of severe intensity nor serious, and recovered after treatment period.

In all, one emergent adverse event "dyspepsia" (one patient, 1.1%) in the MPFF 1000 mg group led to treatment withdrawal. This non-serious EAE was considered as related to the study drug according to the investigator, and the patient recovered after Investigational Medicinal Products treatment withdrawal.

In both groups, all emergent adverse events (30 EAEs *i.e.* 15 EAEs in each group**) recovered**. Most of them (90.0% of the overall EAEs) recovered while the patient was still under treatment (80.0% in the MPFF 1000 mg group *versus* 100% in the MPFF 500 mg group). The EAEs that recovered after the treatment period (all in the MPFF 1000 mg group) were constipation, dyspepsia and dermatitis allergic.

- **Laboratory tests**

No emergent biochemical potentially clinically significant abnormal value (PCSA) on treatment was reported in any group. One patient (1.2%) in the MPFF 500 mg group reported one haematological emergent PCSA value on treatment (low haemoglobin value), not reported as adverse event by the investigator.

- **Vital signs and clinical examination**

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

- **Leg pain**

Leg pain (assessed on VAS), decreased from baseline to each post-baseline visit (W2, W4 and W8) in both groups, without clinically relevant difference between groups (mean change from baseline to W8: -4.2 ± 1.7 cm in the MPFF 1000 mg group *versus* -4.0 ± 1.9 cm in the MPFF 500 mg group).

CONCLUSION

This international multicentre double-blind, randomised phase III study conducted in patients suffering from symptomatic chronic venous disease (CVD) showed that MPFF 1000 mg was well tolerated. No clinically relevant difference with MPFF 500 mg was observed regarding adverse events, laboratory parameters, vital signs, clinical examination and leg pain, except a slightly higher rate of mild headaches in the MPFF 1000 mg group. In the light of the Reference Safety Information in force (version dated February 2014), no unexpected adverse event was reported.

Date of the report: 16 January 2015

Version of the report: Final version