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**		*(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 between micronized purified flavonoid fraction (MPFF) 1000 mg tablets and micronized purified flavonoid fraction 500 mg tablets after 7 days of treatment followed by a follow-up period of 7 days in patients suffering from acute hemorrhoidal disease (HD).
International, multicenter, double-blind, randomized, parallel group study.

Protocol No.: CL3-05682-108.

The description of the study protocol given hereafter includes the modifications of the substantial amendment No.1 to the protocol.

International coordinator: [redacted]

Study centres:
Overall, 14 centres located in 2 countries included at least one patient: 9 centres in Russia (100 included patients) and 5 centres in Serbia (62 included patients).

Publication (reference): Not Applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 16 December 2013 (date of first visit first patient) Completion date: 14 June 2014 (date of last visit last patient)	phase III

Objectives:
The objective of this phase III study was to compare the clinical acceptability between micronized purified flavonoid fraction 1000 mg tablets and micronized purified flavonoid fraction 500 mg tablets (3 grams per day during 4 days and 2 grams per day during the 3 following days) by oral route in patients suffering from symptoms related to acute hemorrhoidal disease.

Methodology:
International, multicentre, double-blind, randomized, parallel group, phase III study comparing the acceptability of MPFF 1000 mg *versus* MPFF 500 mg in out-patients for an acute haemorrhoidal episode. Method of treatment allocation was balanced non-centralised, non-adaptive; treatment allocation was performed according to the randomisation list using permutation block.
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: 162 (79 patients under MPFF 1000 mg and 83 patients under MPFF 500 mg).

Diagnosis and main criteria for inclusion:
Active male or female patient aged between 18 to 75 years old (included); presenting in out-patient facility with an acute haemorrhoidal episode (internal and/or external) of recent onset (5 days or less before inclusion), with an acute pain with oedema assessed by a VAS and/or bleeding evaluated by a 4 point-scale. The episode should be non-treated and non-complicated.

Test drug:
MPFF, tablets of 1000 mg, 7 days of treatment as follow: 3 tablets per day for the first 4 days taken p.o. (one tablet in the morning, one tablet at midday and one tablet in the evening *i.e.* 3 g/day). Then 2 tablets per day during the 3 following days: one in the morning and one at midday *i.e.* 2 g/day.
Batch No.: L0049608

Comparator (Reference product):
MPFF, tablets of 500 mg, 7 days of treatment as follow: 6 tablets per day for the first 4 days taken p.o. (2 tablets in the morning, 2 tablets at midday and 2 tablets in the evening *i.e.* 3 g/day). Then 4 tablets per day during the 3 following days: 2 in the morning and 2 at midday *i.e*. 2 g/day.
Placebo 1000 mg and placebo 500 mg tablets were also administered to maintain the blind.

Duration of treatment:

- A 7 days double-blind treatment period (P1 from D1 to D4 then P2 from D5 to D7).
- A 7 days follow-up period without treatment (from D8 to D14).

Criteria for evaluation:
Efficacy measurement:
Not applicable.

Safety measurements:

- Adverse events reported at each visit.
- Laboratory tests: biochemical and haematological parameters were performed at selection (D0) and at D7.
- Vital signs: sitting blood pressure and heart rate were assessed at selection (D0) and D7.
- Weight was assessed at selection (D0) and D7.
- Bleeding cessation was to be assessed at selection (D0) and D7 on a 4-point-scale (hematochezia assessment scale and bleeding frequency).
- Pain evaluation: anal pain assessment was performed at selection (D0) and D7 on a VAS.

According to Amendment No. 1: "The safety criteria were assessed only if the patient came with less than 3 days after treatment discontinuation".

Other measurements:

- Score of constipation, score of stools consistency and dietary habits were evaluated at D0 and D7.
- Anuscopy examination was performed at D0; then at D7 if necessary.
- Urinary pregnancy test. Test was sampled, assayed on site and reviewed by the investigator at D0.

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 groups 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**	**79**	**83**	**162**
in compliance with the protocol	n	73	77	150
with a protocol deviation before or at inclusion	n	6	6	12
Withdrawn due to	**n (%)**	**3 (3.8)**	**-**	**3 (1.9)**
adverse event	n	2	-	2
protocol deviation	n	1	-	1
Completed	**n (%)**	**76 (96.2)**	**83 (100)**	**159 (98.1)**
in compliance with the protocol	n	71	80	151
with a protocol deviation after inclusion	n	5	3	8
Safety Set	**n (%)**	**79 (100)**	**83 (100)**	**162 (100)**

%: expressed as percentage of the Randomised Set

A total of 162 patients were included and randomly assigned to one of the 2 groups: 79 patients in the MPFF 1000 mg group and 83 patients in the MPFF 500 mg group. The planned balanced distribution was reached.
In the Randomised Set, 3 patients were withdrawn from the study, all at D007, in the MPFF 1000 mg group: 2 due to non-serious adverse event of mild intensity (lip swelling and dermatitis) and 1 due to protocol deviation (age < 18 years at inclusion).

SUMMARY – CONCLUSIONS (Cont'd)

In all, 12 protocol deviations were observed before or at inclusion (6 in each MPFF group): they all concerned study management, mainly biology (6 deviations in 6 patients, 3.7%) and study treatment dispensation (5 deviations in 5 patients, 3.1%). Similar data were observed in both groups.
After inclusion, 23 protocol deviations were observed with a higher number in the MPFF 1000 mg group (19 deviations in 8 patients) than in the MPFF 500 mg group (4 deviations in 3 patients), all related to study management. The most frequent deviations concerned unauthorized concomitant treatment (6 deviations in 5 patients), dose change (6 deviations in 4 patients), mainly "dose change at D005 morning not done" (4 deviations in 4 patients) and study treatment administration (6 deviations in 4 patients), mainly "overall duration of study < 7 days" (3 deviations in 3 patients).

BASELINE CHARACTERISTICS
Main baseline characteristics in the Randomised Set are summarised in the Table below:

Main baseline characteristics at inclusion in the Randomised Set

			MPFF 1000 mg (N = 79)	MPFF 500 mg (N = 83)	All (N = 162)
Age (years)		n	79	83	162
		Mean ± SD	41.4 ± 12.7	42.6 ± 14.2	42.0 ± 13.5
		Min ; Max	17 ; 68	18 ; 75	17 ; 75
Gender	Male	n (%)	42 (53.2)	48 (57.8)	90 (55.6)
	Female	n (%)	37 (46.8)	35 (42.2)	72 (44.4)
BMI (kg/m^2)		n	79	83	162
		Mean ± SD	25.5 ± 5.3	26.3 ± 5.2	25.9 ± 5.3
		Min ; Max	17.7 ; 48.4	15.1 ; 40.8	15.1 ; 48.4
Race					
	Caucasian	n (%)	79 (100)	83 (100)	162 (100)
Haemorrhoidal disease duration (days)		n	75	79	154
		Mean ± SD	2.5 ± 1.2	2.4 ±1.3	2.5 ± 1.2
		Min ; Max	0 ; 5	0 ; 5	0 ; 5
Previous treatments for haemorrhoidal disease*					
	Yes	n (%)	1 (1.3)	-	1 (0.6)
	No	n (%)	78 (98.7)	83 (100)	161 (99.4)

**Before study.*

At inclusion, the haemorrhoidal disease had been lasted for 2.5 ± 1.2 days, on average; only one patient (in the MPFF 1000 mg group) received a previous treatment for haemorrhoidal disease (not for the current episode): it consisted in local hemostatic (collagen), stopped more than 1 month before the selection. Regarding previous non-drug treatments, as required in the protocol, no patient reported laser therapy, anal surgery or canal radiation (to note, missing data reported for 60 patients (37.0%) regarding laser therapy and canal radiation and 63 patients (38.9%) regarding anal surgery without relevant difference between groups).
Overall, 86 patients (53.1%) reported at least one medical history other than haemorrhoidal disease (37 patients, 46.8% in the MPFF 1000 mg group and 49 patients, 59.0% in the MPFF 500 mg group), mainly related to Vascular disorders (34 patients, 21.0%). At inclusion, 45 patients (27.8%) had taken at least one concomitant treatment (21 patients, 26.6% in the MPFF 1000 mg group and 24 patients, 28.9% in the MPFF 500 mg group). The most frequent were beta blocking agents and agents acting on the renin-angiotensin system (18 patients, 11.1% for both).
On average, at inclusion, sitting SBP was 124.0 ± 13.0 mmHg, sitting DBP was 79.5 ± 9.6 mmHg and sitting HR was 71.7 ± 7.0 bpm.

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

SUMMARY – CONCLUSIONS (Cont'd)

EXTENT OF EXPOSURE/TREATMENT DURATION

In the Randomised Set, global treatment duration ranged between 1 and 7 days with a mean (± SD) of 6.9 ± 0.7 days (median of 7.0 days) with similar results 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.

As Safety Set (SS) was identical to Randomised Set (RS), results in the SS and in the RS were the same.

The compliance was good and similar in both groups, on average 94.2 ± 11.1 %; for 97.5% of patients, 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 = 79)	MPFF 500 mg (N = 83)
Patients having reported			
at least one emergent adverse event	n (%)	15 (19.0)	10 (12.0)
at least one treatment-related emergent adverse event	n (%)	3 (3.8)	2 (2.4)
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 (%)	2 (2.5)	-
due to an emergent serious adverse event	n (%)	-	-
due a treatment-related emergent adverse event	n (%)	2 (2.5)	-
Patients who died	n (%)	-	-

Overall 25 patients reported at least one emergent adverse event with a rate of 19.0% in the MPFF 1000 mg group *versus* 12.0% in the MPFF 500 mg group. No severe emergent adverse event was reported. No death or other serious adverse event was reported during the study.

In the MPFF 1000 mg group, the most frequently affected System Organ Class (SOC) (more than 2 patients affected) were gastrointestinal disorders and nervous system disorders, without relevant difference between groups (8.9% *versus* 6.0% and 5.1% *versus* 2.4%, respectively in the MPFF 1000 mg and 500 mg groups). In addition to gastrointestinal disorders, the most frequently reported SOC in the MPFF 500 mg group was investigations (3.6%), without relevant difference compared to the MPFF 1000 mg group (1.3%).

In the MPFF 1000 mg group, the most frequent (reported by at least 2 patients) emergent adverse event was headache: 3 patients, 3.8% in the MPFF 1000 mg group *versus* one, 1.2% in the MPFF 500 mg group. All other emergent adverse events in the MPFF 1000 mg group were reported by only one patient.

In the MPFF 500 mg group, the most frequent emergent adverse events (at least 2 patients) were diarrhoea and nausea reported by 2 patients, 2.4% for each, with quite similar frequencies in the MPFF 1000 mg group (1 patient, 1.3% for each) and, aspartate aminotransferase increased and dry mouth both reported by 2 patients in the MPFF 500 mg *versus* none in the MPFF 1000 mg group.

Most emergent adverse events were of mild intensity: 76.9% in the MPFF 1000 mg group and all in the MPFF 500 mg group. In the MPFF 1000 mg group, 23.1% of the EAES were reported as moderate.

Overall, 5 patients had 10 emergent adverse events considered as treatment-related according to the investigator, without relevant difference between groups: 3 patients (3.8%) in the MPFF 1000 mg group reported 6 treatment-related EAEs (nausea, hypoaesthesia oral, lip swelling, dermatitis allergic, erythema and dizziness) and 2 patients (2.4%) in the MPFF 500 mg group reported 4 treatment-related EAEs (nausea, dry mouth (2) and diarrhoea). All treatment-related emergent adverse events in the MPFF 1000 mg group were reported once.

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

Overall 2 patients withdrew for EAE (lip swelling and dermatitis allergic) both in the MPFF 1000 mg group. These EAEs were both non-serious, rated as mild intensity and considered as related to the study drug according to the investigator. They resolved within 3 days or less (without treatment for lip swelling).

All emergent adverse events but 2 (24 events, 92.3%) recovered in the MPFF 1000 mg group *versus* 12 events, (75.0%) in the MPFF 500 mg group. Overall, 5 emergent adverse events did not recover: 1 event in the MPFF 1000 mg group (3.8%) and 4 events (25.0%) in the MPFF 500 mg group, none of them was considered as treatment-related according to the investigator.

Overall, 2 patients reported at least one adverse event after the treatment period (last study drug intake + 3 days). One patient in the MPFF 1000 mg group reported 3 adverse events (gamma-glutamyl transferase increased, alanine aminotransferase increased and aspartate aminotransferase increased 11 days after the last study drug intake) and one patient in the MPFF 500 mg group reported haemorrhoidal haemorrhage 5 days after the last study drug intake. All the adverse events were of mild intensity, not serious and resolved.

- **Laboratory tests**

Overall 2 biochemical emergent PCSA (Potentially Clinically Significant Abnormal) values, both in the MPFF 500 mg group, were reported: high gamma glutamyl transferase value and low protein value.
Haematological emergent PCSA values were sparse in both groups: they consisted in low haemoglobin (no patient in the MPFF 1000 mg group *versus* one (1.2%) in the MPFF 500 mg group) and low prothrombin time (1 patient, 1.4% in the MPFF 1000 mg group *versus* 2 patients, 2.4% in the MPFF 500 mg group).

- **Vital signs and clinical examination**

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

- **Bleeding cessation**

The percentage of patients with aggravation of bleeding from baseline to D007 was 4.1% (3 patients) in the MPFF 1000 mg group and 2.4% (2 patients) in the MPFF 500 mg group.
An improvement in bleeding (including patients with complete cessation) was observed for most of the patients in both groups: 55.7% (44 patients) in the MPFF 1000 mg group *versus* 61.5% (51 patients) in the MPFF 500 mg group. A complete cessation of bleeding was observed for about half of the patients: 46.8% (37 patients) in the MPFF 1000 mg group *versus* 54.2% (45 patients) in the MPFF 500 mg group. Of note, the percentage of patients with moderate or severe bleeding at baseline was numerically higher in the MPFF 1000 mg group (46.8%) than in the MPFF 500 mg group (28.9%).
In each group, the percentage of patients without bleeding increased from baseline to D007: from 25.6 % to 73.0% in the MPFF 1000 mg group and from 30.5% to 86.6% in the MPFF 500 mg group.

- **Anal pain**

Anal pain (assessed on VAS), decreased from baseline to D007, in both groups: -2.4 ± 2.0 cm and -2.2 ± 2.2 cm in MPFF 1000 mg and 500 mg groups, respectively.

CONCLUSION

This international multicentre double-blind, randomised phase III study conducted in patients with acute haemorrhoidal episode showed that MPFF 1000 mg was well tolerated. No relevant difference with MPFF 500 mg was observed regarding adverse events, laboratory parameters, vital signs, clinical examination, bleeding and anal pain. In the light of the Reference Safety Information in force (version dated February 2014), no unexpected adverse event was reported.

Date of the report: 23 December 2014

Version of the report: Final version