## 2. SYNOPSIS

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|---|---|---|
| **Name of Sponsors: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France**<br>**L.L.S., 50 rue Carnot - 92284 Suresnes Cedex - France** | | *(For National Authority Use only)* |
| **Test drug**<br>**Name of Finished Product:**<br>Daflon® 1000 mg, chewable tablets<br>**Name of Active Ingredient:**<br>Micronized purified flavonoid fraction, MPFF (S05682) | | |
| **Individual Study Table Referring to Part of the Dossier** | **Volume:** | **Page:** |

**Title of study:** Clinical non-inferiority study between Micronized purified flavonoid fraction (MPFF) 1000 mg, one chewable tablet per day and MPFF 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.: CL3-05682-109
EudraCT No.: 2017-003633-28
The description of the study protocol given hereafter includes the modifications of one substantial amendment to the protocol.

**International coordinator:** [redacted]

**Study countries:**
In all, 9 countries included a total of 611 patients: 125 patients in Argentina, 4 patients in Austria, 78 patients in Brazil, 43 patients in Hungary, 87 patients in Romania, 173 patients in Russia, 32 patients in Vietnam, 55 patients in Thailand and 14 patients in Turkey

**Publication (reference):** Not applicable.

| **Studied period:** | **Phase of development of the study:** |
|---|---|
| Initiation date: 30 July 2018 (date of first visit of the first patient)<br>Completion date: 07 October 2019 (date of the last visit of the last patient) | Phase III |

**Objectives:**
The purpose of this study was to investigate if MPFF 1000 mg chewable tablet had an efficiency close to MPFF 500 mg (non-inferiority study) in relieving patients suffering from chronic venous disease (CVD), and particularly from lower limb discomfort.

**Primary objective**
The primary objective was to demonstrate the clinical non-inferiority of efficacy of MPFF 1000 mg, 1 chewable tablet per day, and MPFF 500 mg, 2 tablets daily, in improving lower limb discomfort assessed by a 10 cm electronic visual analogue scale (eVAS) after 8 weeks of treatment in patients suffering from symptomatic CVD.

**Secondary objectives**
Secondary objectives were to determine the evolution of efficacy during the study according to each symptom (leg pain and leg heaviness assessed by 10 cm eVAS), the quality of life evolution in both groups (assessed by electronic Chronic Venous Insufficiency quality of life Questionnaire [eCIVIQ]), the safety profile, and the acceptability of MPFF 1000 mg chewable tablet as compared to MPFF 500 mg.

**Methodology:**
International, multicentre, double-blind, double dummy, randomised, parallel group, non-inferiority phase III study conducted in adult patients suffering from symptomatic CVD, comparing MPFF chewable tablet 1000 mg to MPFF tablet 2 x 500 mg daily.
The treatment randomisation and allocation were centralised by Interactive Web Response System (IWRS). The treatment (MPFF chewable tablet 1000 mg or MPFF tablet 2 x 500 mg) was assigned at W0 visit by a balanced, non-adaptive randomisation with stratification on the centre, with IWRS.

This study was performed in strict accordance with Good Clinical Practice.

**Number of patients:**
Planned: 570 included patients (285 patients in each group)
Included: 611 patients (309 patients in the MPFF chewable tablet 1000 mg group and 302 in the MPFF tablet 2 x 500 mg group).

**Diagnosis and main criteria for inclusion:**
Male or female patients aged from 20 to 75 years old (included) suffering from primary CVD with lower limb discomfort superior or equal to 4 cm on eVAS and belonging to the Clinical Etiological Anatomic Pathophysiologic (CEAP) class C0s to C4s on the most affected leg. Patients had to be able to fill in a questionnaire or an electronic Patient-Reported Outcome (ePRO) by themselves.

**Test drug:**
MPFF 1000 mg: 1 chewable tablet (once a day) - per os.

**Comparator (Reference product and/or placebo):**
MPFF 500 mg: 2 film-coated tablets (one tablet twice a day) - per os.
Double placebo: placebo chewable tablet and placebo film-coated tablet.

**Duration of treatment:**
**Run-in period** (from selection [W-2, ASSE] to inclusion [W0] visit)**:** open-label period with double placebo (placebo chewable tablet and placebo film-coated tablet) during 14 days.
**Active treatment period** (from W0 to W8)**:** double-blind randomised period of 8 weeks: 1 chewable tablet in the morning + 1 film-coated tablet at midday + 1 film-coated tablet in the evening per day.

**Criteria for evaluation:**
Efficacy measurements:

***Primary criterion:***

- Lower limb discomfort (LLD) related to CVD assessed by eVAS (which evaluate the symptom, *i.e.*, LLD from 0 [no symptom] to 10 cm [extreme symptom]). The primary expression was the change from baseline to W8. Secondary expressions were value at baseline and at each post-baseline visit and change from baseline to W4.

***Secondary criteria:***

- Leg pain assessed by eVAS.
- Leg heaviness assessed by eVAS.
- Quality of life (QoL) assessed by an eCIVIQ-14.

These evaluations were supported by an auto-evaluation performed on an electronic device (ePRO device):

- Every week from ASSE to W8 (at the site during ASSE, and then weekly at home at the same time and same day in the evening, and before the visits W0, W4 and W8 in the evening) for discomfort, pain and heaviness.
- At each visit (ASSE, W0, W4 and W8), at the site, for QoL.

Safety measurements:

- Adverse events (AEs) (all visits).
- Physical examination and vital signs (sitting blood pressure [BP], heart rate [HR] and weight) (all visits).
- Overall acceptability by the patient (sum of well-being and AEs scores) and by the investigator (sum of therapeutic benefit, vital signs and AEs scores) (at the end of the study at W8 or at the withdrawal visit). Each item was scored from 0 (worst acceptability) to 3 (best acceptability).

Other measurements:

- Laboratory tests: haematological, biochemical tests including β Human Chorionic Gonadotropin (ß HCG) blood test available at inclusion visit.
- Laboratory results were not recorded in the electronic Case Report Form (e-CRF) but significant abnormalities were to be reported as AE.
- 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* (FAS, set used for the primary efficacy analysis): In accordance with the intention-to-treat principle and the Section 5.2.1 of International Conference on Harmonization (ICH) E9 guideline, all patients of the randomised set (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 LLD assessed by eVAS.
*Per Protocol Set* (PPS): All patients of the FAS without relevant deviations, which could affect the evaluation of the IMP effect on the LLD assessed by eVAS.

***Efficacy analysis:***
***Primary endpoint:***

- Primary analysis:

To demonstrate the non-inferiority of MPFF chewable tablet 1000 mg as compared to MPFF tablet 2 x 500 mg on lower limb discomfort assessed by eVAS after a 8-week treatment period, MPFF chewable tablet 1000 mg was compared to MPFF tablet 2 x 500 mg in the FAS on the change from baseline to W8, using an analysis of covariance (ANCOVA) model. Non-inferiority margin was set at 1.0 cm.
The analysis included the fixed, categorical effect of treatment, the random categorical effect of centre, as well as the continuous, fixed covariate of baseline.
Missing data were imputed using the multiple imputation approach (MI) considering a monotone missing pattern.

- Sensitivity analysis:

To assess the robustness of the primary analysis results, the following sensitivity analyses were performed:

- *Sensitivity to the method of handling missing data*: to assess robustness to the method for handling missing data, MPFF chewable tablet 1000 mg was compared to MPFF tablet 2 x 500 mg in the FAS on the change from baseline to last post baseline value, using an analysis of covariance (ANCOVA) model (*i.e.* considering the Last Observation Carry Forward (LOCF) method to handle missing data).
- *Sensitivity to the adjustment factors:* to assess the robustness to the adjustment factors, the same strategy as for the primary analysis was used but without baseline and centre adjustment, in the FAS.

- Supplementary analysis:

The primary analysis and sensitivity analysis were repeated for the primary efficacy endpoint in the PPS. Moreover, descriptive statistics were provided by treatment group in the FAS and the PPS.

***Secondary endpoint:***
The same model (*i.e.* ANCOVA) as for primary efficacy endpoint was performed for all secondary efficacy endpoints: leg pain, leg heaviness and eCIVIQ-14 global score and subscores (pain, physical, psychological and social), in the FAS.
Missing data were imputed using the same approach as for the primary efficacy endpoint for leg pain and heaviness, and using the Last Observation Carried Forward (LOCF) approach for eCIVIQ-14.

Sensitivity and supplementary analyses:
Besides, the same sensitivity and supplementary analyse*s* as for the primary efficacy endpoint was expected, in the FAS and the PPS for pain and heaviness, while for eCIVIQ-14 only the following descriptive statistics were provided by treatment group in the FAS and the PPS (value at baseline, at each post-baseline visit, and last post-baseline value as well as change from baseline to each post-baseline visit and to last post-baseline value).

For secondary endpoint analyses, the same statistical elements as for the primary efficacy endpoint were provided, except the p-value. The two-sided 95% confidence interval (CI) of the estimate was given to assess the magnitude of the treatment effect.

***Study patients: disposition baseline characteristics and treatments analysis and Safety analysis:*** Descriptive statistics were provided.

**SUMMARY - CONCLUSIONS**

DISPOSITION OF PATIENTS AND ANALYSIS SETS

**Disposition of patients**

| | MPFF chewable tablet 1000 mg | MPFF tablet 2 x 500 mg | ALL |
|---|---|---|---|
| **Included/Randomised** | **309** | **302** | **611** |
| **Withdrawn due to** | 18 (5.8) | 9 (3.0) | 27 (4.4) |
| - Non-medical reason | 7 (2.3) | 5 (1.7) | 12 (2.0) |
| - Protocol deviation | 6 (1.9) | 2 (0.7) | 8 (1.3) |
| - Adverse event | 5 (1.6) | 2 (0.7) | 7 (1.1) |
| **Completed** | 291 (94.2) | 293 (97.0) | 584 (95.6) |
| **Full Analysis Set (FAS)** | 301 (97.4) | 295 (97.7) | 596 (97.5) |
| **Per Protocol Set (PPS)** | 275 (89.0) | 264 (87.4) | 539 (88.2) |
| **Safety set** | 307 (99.4) | 301 (99.7) | 608 (99.5) |

*%: % of the Randomised Set*
*Data are number and percentage of patients*

In the RS, 27 patients (4.4%) were withdrawn from the study: 18 patients (5.8%) in the MPFF chewable tablet 1000 mg group and 9 patients (3.0%) in the MPFF tablet 2 x 500 mg group. As shown in the table above, this difference was due to slightly higher rates of withdrawal for protocol violations (6 patients, 1.9% *versus* 2 patients, 0.7%, respectively) and for AEs (5 patients, 1.6% *versus* 2 patients, 0.7%, respectively). The other reason of study withdrawal *i.e.*, non-medical reason, showed quite similar frequency between groups (7 patients, 2.3% *versus* 5 patients, 1.7%, respectively).

BASELINE CHARACTERISTICS

Main baseline characteristics in the RS are summarised in the Table below.

Demographic and baseline characteristics of patients included in the study were in line with the target population defined in the study protocol.

At selection, the CVD had lasted for 8.0 ± 10.2 years on average (median = 4.2 years) and a family history of CVD was found in 44.4% of the patients in the RS.

According to the CEAP classification on the most affected leg, the most frequent clinical class (highest class reported) was C2 “varicose veins” (44.8% of the patients) followed by the C3 “oedema” (33.2% of the patients). As required by the protocol, all patients had CEAP classes from C0s to C4s on the most affected leg, at selection.

All randomised patients had duplex scan results at inclusion. No venous obstruction was reported in the patients evaluated. Besides, venous reflux was observed on numerous patients depending on the type of vein.

In all, 2.8% of the patients received at least one previous treatment stopped within 1 month prior to the selection visit or during the run-in period. These previous treatments consisted mostly in paracetamol (1.0%). Overall, 22.3% of the patients had at least one previous non-drug treatment for CVD. These previous non-drug treatments consisted mostly in surgical treatment of varicose veins (12.3%) and compression therapy (11.0%). Of note, all patients having received non-pharmacological treatments for CVD before the study had been treated for the last time 3 months* before the entry in the study (*or one month for the compression therapy/or physical therapy of legs) as required by the protocol, except one patient who was in deviation to the protocol.

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

BASELINE CHARACTERISTICS (Cont'd)

**Main baseline characteristics at selection in the Randomised Set**

| | | MPFF chewable tablet 1000 mg (N = 309) | MPFF tablet 2 x 500 mg (N = 302) | ALL (N = 611) |
|---|---|---|---|---|
| | **n** | **309** | **302** | **611** |
| **Age** (years) | Mean ± SD | 47.7 ± 12.3 | 47.7 ± 12.5 | 47.7 ± 12.4 |
| | Min ; Max | 21 ; 75 | 21 ; 76[$] | 21 ; 76 |
| **Gender** Female | n (%) | 256 (82.85) | 246 (81.46) | 502 (82.16) |
| **Body Mass Index** (kg/m$^2$)[#] | Mean ± SD | 26.4 ± 4.1 | 26.1 ± 4.0 | 26.3 ± 4.0 |
| | Min ; Max | 18 ; 37[$$] | 18 ; 35 | 18 ; 37 |
| **Disease duration** (years) | n | 308 | 300 | 608 |
| | Mean ± SD | 8.19 ± 10.59 | 7.75 ± 9.70 | 7.97 ± 10.15 |
| | Median | 4.15 | 4.10 | 4.15 |
| | Min ; Max | 0.0 ; 52.6 | 0.0 ; 54.6 | 0.0 ; 54.6 |
| **Highest CEAP classification On the most affected leg** | n | 309 | 302 | 611 |
| C0 | n (%) | 1 (0.32) | 1 (0.33) | 2 (0.33) |
| C1 | n (%) | 52 (16.83) | 57 (18.87) | 109 (17.84) |
| C2 | n (%) | 141 (45.63) | 133 (44.04) | 274 (44.84) |
| C3 | n (%) | 102 (33.01) | 101 (33.44) | 203 (33.22) |
| C4A | n (%) | 11 (3.56) | 9 (2.98) | 20 (3.27) |
| C4B | n (%) | 2 (0.65) | 1 (0.33) | 3 (0.49) |
| **Previous non-drug treatment for CVD*** | n | 309 | 302 | 611 |
| No | n (%) | 241 (77.99) | 234 (77.48) | 475 (77.74) |
| Yes | n (%) | 68 (22.01) | 68 (22.52) | 136 (22.26) |

*Percentages are based on n*
*#: Last analysable value prior to the first IMP intake (selection or inclusion)*
**non-pharmacological treatments for CVD (sclerotherapy, surgical treatment of varicose veins, angioplasty, endovascular devices) performed less than 3 months before the entry in the study were considered as a non-selection criterion (compression therapy/or physical therapy of legs was limited to 1 month).*
*$: Two patients were 75 years old at the time of selection but calculated age was rounded to 76.*
*$$: One patient had BMI of 36.6 kg/m$^2$ and was thus in deviation to the protocol.*
*C0: no visible or palpable signs of venous disease; C1: telangiectasies or reticular veins; C2: varicose veins; C3: oedema; C4a: pigmentation or eczema; C4b: lipodermatosclerosis or white atrophy*

At baseline in the RS, body mass index (BMI) was on average 26.3 ± 4.0 kg/m$^2$; sitting systolic blood pressure (SBP)/ diastolic blood pressure (DBP) was 119.0 ± 11.3 / 73.9 ± 7.7 mmHg and sitting heart rate (HR) was 73.4 ± 8.5 beats per minute (bpm). Data were similar in both groups.
Overall, before inclusion, 59.6% of the patients reported at least one medical history other than CVD, mainly menopause (26.4%) and hypertension (10.0%), with no relevant difference between groups regarding these main medical histories.

In the RS, according to eVAS [from 0 cm (no symptom) to 10 cm (extreme symptom)] at baseline, lower limb discomfort was on average 7.3 ± 1.8 cm (7.3 ± 1.8 cm in the MPFF chewable tablet 1000 mg group and 7.3 ± 1.7 cm in the MPFF tablet 2 x 500 mg group), leg pain was 7.0 ± 2.0 cm (7.0 ± 2.0 cm and 7.0 ± 1.9 cm, respectively) and leg heaviness 7.2 ± 1.9 cm (7.2 ± 1.9 cm and 7.1 ± 1.9 cm, respectively).
Regarding QoL evaluated by eCIVIQ-14 [scores calculated from 0 (no impact) to 100 (severe impact)] in the RS at baseline, the mean global score was 44.4 ± 22.2 (43.7 ± 22.7 in the MPFF chewable tablet 1000 mg group and 45.1 ± 21.8 in the MPFF tablet 2 x 500 mg group); mean pain subscore was 52.0 ± 22.5 (51.5 ± 23.3 and 52.5 ± 21.7, respectively); mean physical subscore was 50.1 ± 22.8 (49.0 ± 23.6 and 51.3 ± 22.0, respectively); and mean psychological subscore was 35.8 ± 26.2 (35.4 ± 26.3 and 36.2 ± 26.1, respectively).

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

Baseline characteristics in the FAS (97.5% of the RS) and in the PPS (88.2% of the RS) were similar to those observed in the RS.

EXTENT OF EXPOSURE

In the RS, the mean ± SD treatment duration (days) was 55 ± 8 days (median 56 days) for both the chewable tablet and the film-coated tablet, which was consistent with the planned study treatment period of 8 weeks.
The mean compliance was about 97% for both the chewable tablet and the film-coated tablet. Treatment duration and compliance were similar in both treatment groups in the RS.

Similar data were observed in the SS.

EFFICACY RESULTS

- **Primary efficacy endpoint:** Lower limb discomfort (assessed by eVAS).

In the FAS, the **lower limb discomfort** decreased from baseline in both groups with a mean change from baseline to W8 of -3.6 ± 2.4 cm in the MPFF chewable tablet 1000 mg group *versus* -3.6 ± 2.5 cm in the MPFF tablet 2 x 500 mg group (observed data).
The primary analysis demonstrated the non-inferiority of MPFF chewable tablet 1000 mg once daily *versus* MPFF tablet 2 x 500 mg daily on the improvement of lower limb discomfort after 8-week treatment period in term of change from baseline to W8, with an estimate of the difference (SE) between groups of 0.00 (0.18) cm, 95% CI = [-0.35 ; 0.35] and p-value < 0.0001, using an analysis of covariance (ANCOVA) model and 1.0 cm as pre-defined non-inferiority margin. This result was confirmed by the 2 sensitivity analyses performed; the sensitivity to adjustment factors (E (SE) = -0.06 (0.21), 95% CI -0.46 ; 0.34] and p-value < 0.0001) and the sensitivity to missing data handling (E (SE) = -0.02 (0.18), 95% CI [-0.37 ; 0.33] and p-value < 0.0001).

**Lower limb discomfort measured by eVAS (cm) - Primary analysis: Non-inferiority analysis - Change from baseline to W8 and comparison between groups - FAS**

| | | **MPFF chewable tablet 1000 mg (N = 301)** | **MPFF tablet 2 x 500 mg (N = 295)** |
|---|---|---|---|
| *Descriptive statistics on observed data** | | | |
| Baseline | n | 301 | 295 |
| | Mean ± SD | 7.32 ± 1.71 | 7.25 ± 1.73 |
| | Median | 7.30 | 7.10 |
| | Min ; max | 2.8 ; 10.0 | 2.1 ; 10.0 |
| W8 | n | 266 | 253 |
| | Mean ± SD | 3.64 ± 2.48 | 3.56 ± 2.38 |
| | Median | 3.20 | 3.40 |
| | Min ; Max | 0.0 ; 10.0 | 0.0 ; 10.0 |
| W8 - Baseline | n | 266 | 253 |
| | Mean ± SD | -3.57 ± 2.35 | -3.57 ± 2.50 |
| | Median | -3.40 | -3.40 |
| | Min ; Max | -9.6 ; 1.9 | -9.9 ; 4.1 |
| *Statistical analysis* | | | |
| ***Primary statistical analysis*** | | | |
| | E (SE) (1) | 0.00 (0.18) | |
| | 95% CI (2) | [-0.35 ; 0.35] | |
| | p-value (3) | < 0.0001 | |

**Descriptive statistics are performed on observed data i.e., data without imputation.*
*Non-inferiority tests of MPFF chewable tablet 1000 mg as compared to MPFF tablet 2 x 500 mg / Non-inferiority limit: 1 cm*
*Multiple imputation: All missing data (at each week and) at W8 are imputed by treatment group, using centre and baseline, using MI approach based on the regression method (after a MCMC monotone-data imputation) to generate 100 complete data sets.*
*Resulting complete datasets are modelled using an analysis of covariance model on factors treatment and centre (random effect) with baseline as covariate.*
*Corresponding results are combined to produce final inference:*
*(1) Estimate (Standard Error) of the adjusted difference between treatment group means: MPFF chewable tablet 1000 mg minus MPFF tablet 2 x 500 mg with a multiple imputation approach*
*(2) 95% Confidence interval of the estimate*
*(3) One-sided associated p-value of the non-inferiority (to be compared to 0.025)*

EFFICACY RESULTS (Cont'd)
In addition, this lower limb discomfort improvement observed from baseline to W8 in both groups was clinically relevant.

Similar conclusion could be drawn in the PPS (supplementary analysis), with an estimate of the difference (SE) between MPFF chewable tablet 1000 mg group and MPFF tablet 2 x 500 mg group of -0.03 (0.18) cm, 95% CI = [-0.38 ; 0.32]. This result was also confirmed by the sensitivity analysis to adjustment factors (E (SE) = 0.00 cm (0.21) with 95% CI [-0.42 ; 0.41]) and the sensitivity analysis to missing data handling (E (SE) = -0.07 cm (0.18) with 95% CI [-0.43 ; 0.29]).

- **Secondary efficacy endpoint**

***Leg pain measured by eVAS***
In the FAS, similarly to what was shown for LLD, a clinically relevant decrease of **leg pain,** measured by eVAS (cm), was observed from baseline to W8 in both groups, with similar results between groups (observed data): mean change from baseline to W8 was -3.4 ± 2.3 cm in the MPFF chewable tablet 1000 mg group and -3.5 ± 2.5 cm in the MPFF tablet 2 x 500 mg group, with an estimate of the difference (SE) between groups of 0.00 (0.18) cm (95% CI = [-0.34 ; 0.34]). This result was confirmed by the sensitivity analysis to adjustment factors: E (SE) = -0.04 cm (0.20) with 95% CI [-0.44 ; 0.36] and the sensitivity analysis to missing data handling: E (SE) = -0.03 cm (0.18) with 95% CI [-0.38 ; 0.32].

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

***Leg heaviness measured by eVAS***
In the FAS, similarly to what was shown for LLD, a clinically relevant decrease of the **leg heaviness,** measured by eVAS (cm), was observed from baseline to W8 in both groups with similar results between groups (observed data): mean change from baseline to W8 was -3.5 ± 2.5 cm in the MPFF chewable tablet 1000 mg group and -3.5 ± 2.6 cm in the MPFF tablet 2 x 500 mg group, with an estimate of the difference (SE) between groups of 0.06 (0.18) cm (95% CI = [-0.29 ; 0.41]). This result was confirmed by the sensitivity analysis to adjustment factors (E (SE) = -0.02 cm (0.21) with 95% CI [-0.44 ; 0.39]) and the sensitivity analysis to missing data handling (E (SE) = 0.03 cm (0.18) with 95% CI [-0.32 ; 0.39]).

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

***Quality of life evaluated by eCIVIQ-14 questionnaire***
Scores of QoL were calculated from 0 (no impact) to 100 (severe impact).

In the FAS, whatever the scores, a clinically relevant improvement of QoL was observed in both groups from baseline, without relevant difference between groups: mean changes from baseline to last post-baseline value were respectively in the MPFF chewable tablet 1000 mg group and MPFF tablet 2 x 500 mg group:

- -21.0 ± 17.2 *versus* -22.5 ± 20.1 for global score (E (SE) = 1.03 (1.20), 95% CI = [-1.32 ; 3.38]).
- -25.3 ± 20.0 *versus* -26.0 ± 22.8 for pain subscore (E (SE) = 0.34 (1.36), 95% CI = [-2.33 ; 3.01]).
- -22.5 ± 19.9 *versus* -25.1 ± 22.3 for physical subscore (E (SE) = 1.57 (1.41), 95% CI = [-1.20 ; 4.33]).
- -17.4 ± 19.3 *versus* -18.6 ± 22.7 for psychological subscore (E (SE) = 0.96 (1.22), 95% CI = [-1.45 ; 3.36]).

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

SAFETY RESULTS

- **Emergent adverse events**

**Overall summary for adverse events in the Safety Set**

| | | MPFF chewable tablet 1000 mg (N = 307) | MPFF tablet 2 x 500 mg (N = 301) |
|---|---|---|---|
| **Patients having reported at least one:** | | | |
| Emergent adverse events (EAE) | n (%) | 33 (10.7) | 32 (10.6) |
| Treatment-related EAE | n (%) | 8 (2.6) | 6 (2.0) |
| Serious AE (including death) | n (%) | - | 1 (0.3) |
| Serious EAE (including death) | n (%) | - | 1 (0.3) |
| Treatment-related serious EAE | n (%) | - | - |
| EAE leading to treatment withdrawal | n (%) | 5 (1.6) | 1 (0.3) |
| Serious EAE leading to treatment withdrawal | n (%) | - | - |
| Treatment-related EAE leading to treatment withdrawal | n (%) | 2 (0.7) | - |
| Patients who died | n (%) | - | 1 (0.3) |

*Percentage are based on N*

**EAEs** were reported with similar frequency in the MPFF chewable tablet 1000 mg group and in the MPFF tablet 2 x 500 mg group (10.7% *versus* 10.6% of the patients, respectively).

In the MPFF chewable tablet 1000 mg group, the most frequent EAE (in more than 1% of the patients) was nausea. It was reported in 7 patients (2.3%) in the MPFF chewable tablet 1000 mg group *versus* 3 patients (1.0%) in the MPFF tablet 2 x 500 mg group.
In the MPFF tablet 2 x 500 mg group, the most frequent EAE was headache. It was reported in 3 patients (1.0%) in the MPFF chewable tablet 1000 mg group *versus* 7 patients (2.3%) in the MPFF tablet 2 x 500 mg group.
In both groups, all other EAEs were each reported in 1% of the patients or less.

In addition, one case of pregnancy was reported during the treatment period in the MPFF chewable tablet 1000 mg group and led to the study withdrawal of the patient.

Most of the EAEs were of mild **intensity** in both groups: 58.3% of the EAEs in the MPFF chewable tablet 1000 mg group *versus* 67.4% in the MPFF tablet 2 x 500 mg group. Two EAEs were rated as **severe** in the study; they were both reported in the MPFF tablet 2 x 500 mg group (2 patients, 0.7% of the patients) and consisted in one pneumonia leading to death of the patient and one headache. None of these 2 events were considered as related to the study treatment.

A total of 8 patients (2.6%) in the MPFF chewable tablet 1000 mg group reported at least one EAE considered to be **related to the treatment** *versus* 6 patients (2.0%) in the MPFF tablet 2 x 500 mg group. In both groups, the system organ class most commonly concerned by treatment-related EAEs was gastro-intestinal disorders (1.6% *versus* 1.3%, respectively). The most frequent treatment-related EAE in the MPFF chewable tablet 1000 mg group (in more than 2 patients) was nausea. It was reported in 5 patients (1.6%) in the MPFF chewable tablet 1000 mg group *versus* 1 patient (0.3%) in the MPFF tablet 2 x 500 mg group. None of the nauseas were rated as severe by the investigator. Nausea led to the treatment withdrawal of 2 affected patients in the MPFF chewable tablet 1000 mg group.

Other treatment-related EAEs were sparse (each reported in 2 patients or less in both groups).

Overall, one **serious** EAE was reported in one patient (0.3%) in the MPFF tablet 2 x 500 mg group (none was reported in the MPFF chewable tablet 1000 mg group). This event, pneumonia of severe intensity considered as not related to the treatment by the investigator, led to the death of the patient.

SAFETY RESULTS (Cont'd)
In all, 5 patients (1.6%) in the MPFF chewable tablet 1000 mg group reported at least one EAE **leading to treatment withdrawal** *versus* 1 patient (0.3%) in the MPFF tablet 2 x 500 mg group. These events were mainly nausea (2 patients, 0.7% *versus* none, respectively) and included the case of pregnancy mentioned above.

- **Laboratory tests**

Not applicable.

- **Other tolerance criteria**

***Vital signs***

As regards **vital signs**, neither clinically relevant changes nor differences between groups in mean/median values over time were detected for weight, BMI, blood pressure and heart rate.

***Overall acceptability***

**Acceptability** rated by the patient (total score, well-being and AEs) and by the investigator (total score, therapeutic benefit, vital signs and AEs) at W8 or at withdrawal visit, showed no relevant difference between groups. Total score of acceptability 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 at W8 (or at the withdrawal visit) was judged as good and was similar in both groups: on average 5.4 ± 0.8 in the MPFF chewable tablet 1000 mg group *versus* 5.4 ± 0.7 in the MPFF tablet 2 x 500 mg group for the patient's total score and 7.8 ± 1.0 *versus* 7.9 ± 1.0 respectively for the investigator's total score.

The **comparison between patient's and investigator's opinion** regarding AEs scores showed that the acceptability was similar between investigator and patient judgments: AEs were rated as "none or not related to the treatment" for 94.1% of the patients when assessed by the investigator *versus* 92.5% when assessed by the patient in the MPFF chewable tablet 1000 mg group and 93.4% *versus* 93.0%, respectively in the MPFF tablet 2 x 500 mg group.

**CONCLUSION**

**This international multicentre, double-blind, double dummy, randomised, parallel groups, phase III study conducted in patients suffering from symptomatic chronic venous disease, demonstrated the non-inferiority of MPFF chewable tablet 1000 mg once a day (*o.d.*) *versus* MPFF tablet 500 mg, twice a day (*b.i.d.*) on the improvement of lower limb discomfort (LLD) assessed by a 10 cm electronic visual analogue scale after 8 weeks of treatment. The LLD improvement from baseline to W8 was clinically relevant with similar results between groups. As with LLD, a clinically relevant improvement from baseline to W8 was also observed for leg pain, leg heaviness and quality of life, with similar results between groups. Safety profile of the MPFF chewable tablet 1000 mg *o.d.* was quite similar to the one of the MPFF tablet 500 mg *b.i.d.* MPFF chewable tablet 1000 mg *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 last MPFF Reference Safety Information (January 2019).**

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