Pierre Fabre Médicament
Represented by: Institut de Recherche Pierre Fabre
45, Place Abel Gance
F-92100 Boulogne Cedex

1. TITLE PAGE

ABBREVIATED CLINICAL STUDY REPORT

Pharmacodynamic and clinical assessment of DC982 GE (2, 4 or 6 capsules per day) in patients with chronic venous disorders. Randomised, placebo-controlled, dose effect double blind, parallel group study

Investigational product: DC982 GE/dry extract of *Ruscus aculeatus* (150 mg), hesperidin methyl chalcone (150 mg), ascorbic acid (100 mg)/capsule

Study Design: Randomised, placebo-controlled, dose effect, double-blind, parallel group study

EudraCT number: 2009-014681-25

Protocol number: DC 0982 GE 2 03 1B

Phase of development: Phase IIb

Date of first enrolment: 7 December 2009

Date of last completed: 09 November 2010

Coordinating Investigator: Jean-Jérôme Guex M.D,
32 boulevard Dubouchage
06000 NICE

Sponsor Representatives for study report:
Clinical Study Manager: Sandrine Dalmon. Tel: +33(0)5 34 50 63 62
Medical Study Manager: Richard Roche. Tel: +33(0)5 34 50 63 62
Project Statistician: Sandrine Roye. Tel : +33(0)5 62 24 27 49

Date of report: 09 November 2011

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product:	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***: dry extract of *Ruscus aculeatus* (150 mg), hesperidin methyl chalcone (150 mg), ascorbic acid (100 mg)**	**Vol.: .....Page: .....**	

Title of study:	Pharmacodynamic and clinical assessment of DC982 GE (2, 4 or 6 capsules per day) in patients with chronic venous disorders. Randomised, placebo-controlled, dose effect, double blind, parallel group study	
Coordinating Investigator:	Jean-Jérôme Guex M.D, 32 boulevard Dubouchage 06000 NICE	
Study centres:	Angio-phlebology centres in France (8 centres), Lithuania (1 centre) and Estonia (1 centre)	
Publication (reference):	None	
Studied period: **date of first enrolment:** **date of last completed:**	 7 December 2009 09 November 2010	**Phase of development:** **IIb**
Objectives: Primary:	To assess the dose effect of DC982 GE based on pharmacodynamic parameters after 28 days of treatment	
Secondary:	To assess • the dose effect of DC982 GE based on clinical evaluation of symptoms after 28 days of treatment • the safety and tolerance of DC982 GE	
Methodology:	This was a multicentre, randomised, four arms (3 doses of test product and placebo), 4 weeks double-blind, placebo-controlled, parallel group, phase IIb study.	
Number of patients (planned and analysed):	It was planned that 84 patients would be randomised. In all, 82 patients were screened, and 78 were randomised. All randomised patients completed the study.	

Diagnosis and main criteria for inclusion:	Female patients were eligible for enrolment if they:
	• were non-menopausal, non-sterile and aged over 18 years
	• had primary chronic venous disorder (CVD):
	  • had stage $C_{1.2,S}$, or $C_{2,S}$ of the advanced Clinical signs, Etiological classification, Anatomic distribution, Pathophysiology (CEAP) clinical classification (**Eklöf et al 2004**)
	  • were stable for the 6 months before the Screening visit (Visit 1)
	  • were symptomatic at inclusion with a minimal score of 6 on a visual analogic scale (0 to 10 cm) for at least one of the symptoms: pain/heaviness, paraesthesia/cramps, feeling of swelling
	• had incompetence of Great Saphenous Vein (GSV) characterised by a reverse flow after calf compression release measured in the lower third of the thigh (7 cm to 13 cm upper the femorotibial joint space of the knee) longer or equal to 0.5 seconds with duplex scanning (DS) in a standing position
	• agreed not to use products with the same indication during the study
	• agreed to sign a written Informed Consent Form
	• accepted to attend the planned visits at the investigational centre and to comply with all trial requirements
	• were, (if required by national regulation), registered with a social security or health insurance system
	Woman of childbearing potential were to have:
	• a regular menstrual cycle of 28 days ± 3 days,
	• inclusion performed in the first period of the cycle (1st to 14 th day)
	• a negative urine pregnancy test at inclusion
	• used an efficient method of contraception (implants, injectables, combined oral contraceptives, some intra-uterine devices) for at least 2 months before the study, during the study and one month after the end of the study	

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Test product, **Dose,** **Mode of administration:** **Batch numbers:**	DC982 GE, 1 capsule + placebo, 2 capsules per intake (Group 1) DC982 GE, 2 capsules + placebo, 1 capsule per intake (Group 2) DC982 GE, 3 capsules per intake (Group 3) All patients took 3 capsules at breakfast and 3 capsules at lunch (6 capsules per day). • Oral • G00251 • G00221
Duration of treatment:	4 weeks (28 days ± 3 days).
Reference therapy, **Dose,** **Mode of administration,** **Batch number:**	Placebo 3 capsules per intake (Group 4) All patients took 3 capsules at breakfast and 3 capsules at lunch (6 capsules per day). Oral SB0643
Criteria for evaluation: **Pharmacodynamics:** **Safety:**	**Analysis of effect:** Hemodynamic parameters Venous parameters variation by DS at Day 28. The Peak Reflux Velocity (PRV) was considered the main criterion of interest. Efficacy assessments concerned the change from Baseline (Visit 2, Randomisation visit) to Day 28 (Visit 3) for the following parameters: • PRV • diameter of the GSV in mm (measurement was between 7 cm and 13 cm above the femorotibial articular space of the knee join) • duration of reflux in seconds An examination of the lower limbs (when standing) was performed at each visit to check for signs of venous insufficiency: telangiectasias, oedema, varicoses, skin pigmentation, active ulcer, and healed ulcer. Adverse events (AEs), and vital signs were assessed at each visit.
Statistical methods:	**Primary criteria:** Change in hemodynamic parameters from Randomisation to Day 28. *Main analysis:* • treatment effect on change in each hemodynamic parameter, from Randomisation to Day 28, mean changes and corresponding 95% confidence interval estimated by covariance analysis model (ANCOVA) with treatment, centre and baseline as covariate on the Full Analysis Set (FAS) both within and between treatment groups. • test of a linear trend in changes in each hemodynamic parameter from Randomisation to Day 28 used appropriate contrasts both with and without Placebo group on the previous covariance model on the FAS. *Supportive analysis:* same analysis as main analysis on Per Protocol (PP) dataset. *Sensitivity analysis:* same analysis as main analysis without baseline (ANOVA). *Additional analysis:* ANCOVA model including treatment-by-baseline interaction *Other analysis derived from the primary variable*: description over time of values and changes at Day 28 on PRV, venous diameter and duration of reflux. **Secondary criteria:** For each secondary criteria, descriptive analysis were performed by treatment group on the FAS datasets. For quantitative criteria, treatment effect on change from Baseline, mean changes and corresponding 95% confidence interval was estimated by covariance analysis model with treatment, centre and baseline as covariate on the FAS. Estimates were given both within and between treatment groups. Additionally, Pearson's correlation coefficient was used to measure correlation between each hemodynamic parameters and each symptoms self-assessment separately. ***Safety analysis*** Descriptive statistics were provided summarising AEs, vital signs and physical examination by treatment group

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Summary - Conclusions:

Demography

The median age (min; max) of the 78 patients in the FAS population was 35 years (20; 50): For the FAS population, the median body mass index was 22.7 kg/m^2 (18.1; 29.4) and the median weight 64.0 kg (48.0; 86.0). Overall, the demographic characteristics were similar between treatment groups. The majority of patients were non smokers, with fewer non-smokers in the DC982 Group 2 (45.8%) than in the other treatment groups (71-81%). Overall, alcohol consumption was low (median number of units of alcohol consumed was 0.00 [0.0-0.2]) and 56.4% (44/78) of patients had not practiced sport. Considering the FAS population, 33.3% (26/78) spent long periods in a standing position, 23.1 % (18/78) were standing without rest, 21.8% (17/78) were in a warm environment, and 69.2% (54/78) had a familial history of disease. At Screening, 87.2% (68/78) of the FAS population had Stage $C_{1,2s}$ venous insufficiency and 12.8% (10/78) Stage C_{2s} and the median number of years (min; max) with venous insufficiency was 7 years (1; 25).

Data Set

All randomised patients received at least one dose of study treatment and were included in the FAS population: 22 patients in DC982 treatment Group 1, 14 patients in DC982 treatment Group 2, 24 patients in DC982 treatment Group 3 and 18 patients in the placebo group. 5 patients in the FAS were considered to have a major protocol violation and were excluded from the PP: 2 patients in DC982 treatment Group 1, 1 patient in DC982 treatment Group 3, and 2 patients in the placebo group.

Results

Primary criteria

PRV: There was no statistically significant difference in the pairwise comparison of placebo with any of the DC982 treatment groups (DC982 Group 3: p=0.994, DC982 Group 2: p=0.830 or DC982 Group 1: p=0.539. Baseline effect was statistically significant (p=0.028).

Venous Diameter: There was no statistically significant difference in the pairwise comparison of placebo with any of the DC982 treatment groups (DC982 Group 3: p=0.875), DC982 Group 2: p=0.406) or DC982 Group 1: p=0.127). Baseline effect (p=0.001) and treatment effect (p=0.017) were significant and there was evidence of a difference between centres (p=0.047).

Reflux time: There was no statistically significant difference in the pairwise comparison of placebo with any of the DC982 treatment groups (DC982 Group 3: p=0.564, DC982 Group 2: p=0.809, DC982 Group 1: p=0.987). Baseline effect and treatment effect were not significant and there was no evidence of a difference between centres.

Secondary criteria

From Randomisation to Day 28, there was no statistically significant difference in the pairwise comparison of placebo with any of the DC982 treatment groups, in the change in self-assessment scores for the global symptoms, heaviness/pain, cramp/paresthesia, or swelling. At Day 28 the majority of patients (50/78, 64%) reported the treatment as “very good” and 37/78 (47.4%) patients reported that they were either “very much improved” or “much improved.” At Day 28 no patient in any of the 3 DC982 treatment groups or the placebo group had permanent oedema, skin pigmentation, active ulcer or healed ulcer. Telangiectasia/reticular veins were found in most patients in each group (ranging from 79% to 94%).

Safety results

Considering the 78 patients in the FAS population, the median (min; max) extent of exposure was 28 days (25; 32). In all, 6 patients reported a total of 7 treatment emergent adverse events (TEAEs). At least one TEAE was reported in 4.5% (1/22) of patients in DC982 Group 1, 8.3% (2/24) of patients in DC982 Group 3, and 16.7% (3/18) of patients in the placebo group. No patients in DC982 Group 2 reported a TEAE. TEAEs related to study drug were reported in 4.2% (1/24) of patients in DC982 Group 3 and 5.6% (1/18) of patients in the placebo group and no patient in DC982 Group 1 or DC982 Group 2 had a TEAE related to study drug. No patient had an AE which led to discontinuation and no patient had a serious adverse event.

Of the 7 TEAEs reported, 5 were mild in intensity, 1 was moderate in intensity (cystitis in a patient in the placebo group) and one was severe in intensity (tonsillitis in a patient in the DC982 Group 3). Only 1 patient (DC982 Group 1) reported more than 1 TEAE (headache, 2 events). Two patients reported a TEAE which was suspected to be related to study treatment, one in the DC982 Group 3 (a mild GI disorder which resolved after 3 days) and one in the placebo group (mild diarrhoea which resolved after 25 days). The remaining 5 TEAEs were not suspected to be related to study treatment. Although some patients had values above and/or below predefined limits none were considered clinically significant.

Conclusion

There was no statistically significant difference in the pairwise comparison of placebo with any of the DC982 treatment groups in PRV, venous diameter, reflux time, global symptoms self-assessment scores, heaviness/pain self assessment scores, cramp/paresthesia self assessment scores, or the swelling self assessment scores.

There were few TEAEs reported by patients in the study and safety assessments did not identify any cause for concern.

Date of report: 09 November 2011