SYNOPSIS

EDX09/01

Name of Company:	**OM Pharma SA**
Name of Finished Product:	**Doxium® 500**
Name of Active Ingredients:	**Calcium dobesilate**

Title:	Multicentre, double-blind, placebo-controlled, randomised clinical study to assess the efficacy and safety of Doxium® 500 three times daily in patients suffering from chronic venous insufficiency (CVI) CEAP Class C3 or C4
Short Title:	Doxium® in patients with chronic venous insufficiency
Indication:	Chronic Venous Insufficiency (CVI)
Phase:	IV
Study Code:	EDX09/01
Study Director / Co-ordinating Investigator:	Prof. Dr. med. Eberhard Rabe Hospital and Department of Dermatology - Rheinische Friedrich-Wilhelms University - 53105 Bonn - Germany
Study Centres:	46 European sites of which 32 were active, located in 4 countries: • Germany: 32 sites (7 inactive sites). • Italy: 4 sites (3 inactive sites). • Poland: 5 sites (no inactive site). • Portugal: 5 sites (4 inactive sites).
Objectives:	Primary Objective: • To show the superiority of Doxium® 500 versus placebo in the reduction of oedema of the lower limbs in patients suffering from CVI CEAP Class C3 or C4. Secondary Objectives: To analyse: • The change in calf and ankle circumferences. • The change in the score of a quality of life questionnaire, *i.e.* Chronic Venous Insufficiency Questionnaire (CIVIQ). • The occurrence of six individual symptoms assessed by a specific patient questionnaire. • The assessments of efficacy and tolerability by patients and investigators. • The safety laboratory variables. • The occurrence of Adverse Events (AEs) and Serious Adverse Events (SAEs).

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Design:	Multicentre, randomised, double-blind, parallel, placebo-controlled study
Treatment:	Subjects were allocated to one of the following treatment: Doxium® 500 capsules or placebo. The randomization allocation ratio was 1:1 using a blocked scheme. Doxium® arm (174 subjects): one capsule of powder containing 500 mg of calcium dobesilate. Placebo arm (177 subjects): one capsule containing matched powder. Treatment period: 3 capsules/day, *i.e.* 1 500 mg/day, for 3 months. Follow-up period without treatment: 3 months. Mode of administration: oral route, to be taken during the meals with some water.
Inclusion Criteria:	1. Male or female patient aged from 18 to 70 years. 2. Suffering from unilateral or bilateral CVI CEAP Classes C3 or C4 both at screening and baseline visits, assessed by clinical examination (Visit 1 and Visit 2) and duplex sonography (within one month before Visit 1). 3. Presenting a pitting oedema and at least one of the following two clinical symptoms, discomfort or pain, in at least one leg at both screening and baseline visits. 4. Presenting a chronic oedema at a stable stage. 5. Having signed a written informed consent.
Exclusion Criteria:	1. Diseases/symptoms that imitate the symptomatology of CVI (*i.e.* cardiac, hepatic, renal, orthopaedic, or other causes of leg oedema). 2. Manifest cardiac insufficiency (Stage NYHA III or IV). 3. Diabetes mellitus (Type I or II). 4. Hypertension requiring a change in antihypertensive treatment within 6 weeks before study starts. 5. Operations of the venous system, sclerotherapy during the last 6 months. 6. Compression therapy within the last 6 weeks. 7. Phlebitis or deep leg vein thrombosis in the 3 months preceding inclusion in the study. 8. Any chronic disease which may impair the patient's ability to participate in the study (*i.e.* severe congestive heart failure, active gastric or duodenal ulcer, etc.). 9. Asymptomatic and/or symptomatic peripheral occlusive arterial disease (Ankle/Brachial Index <0.8). 10. Primary or secondary lymphoedema.

	11. Clinical manifest lipoedema. 12. Important obesity (Body Mass Index >40 kg/m^2). 13. Diseases of the gastrointestinal tract, which would impair absorption of the study medication. 14. Competing/interfering systemic or local drug treatments (no new medication with a vascular or cardiovascular effect may be taken /administered during the treatment period). 15. Participation in another clinical trial and/or treatment with an experimental drug within one month before study start. 16. Patients with a known allergy or previous intolerance and/or known hypersensitivity to the study medication. 17. Markedly irregular menstrual cycle (less than 24 or more than 34 days) 18. Female patients who are pregnant, lactating or of childbearing potential and not protected from pregnancy by a sufficiently reliable method (oral contraceptives, Intra Uterine Device) (Pearl-Index <1). 19. Initiation, change or discontinuation of hormone therapy within the past 3 months. 20. Active malignant disease within the last 3 years. 21. Unreliable patients including non-compliant patients, patients with known alcoholism or drug abuse or with a history of a serious psychiatric disorder as well as patients unwilling to give informed consent or to abide by the requirements of the protocol. <u>Specific exclusion criteria to be checked only at Visit 2</u>: 22. Severe renal insufficiency: estimated creatinine clearance rate <50 mL/min (using the Cockroft-Gault-formula). 23. Severe hepatic insufficiency, elevated transaminases, *i.e.* ALAT and ASAT > twice the upper limit of normal. 24. Significant neutropenia, *i.e.* WBC <3.5 G/L. 25. Acute inflammation, *e.g.* leukocytes >10 G/L. 26. Hypoalbuminaemia, *i.e.* albuminaemia <35 g/L.
Primary and Secondary Endpoints:	<u>Primary Endpoint</u>: • Relative volume change of the Most Pathological Leg (MPL) from baseline (Visit 2) to end of treatment period (Visit 5) measured by Water Displacement Volumetry (WDV). <u>Secondary Endpoints</u>: • Relative volume change of the MPL using WDV, from baseline to end of study (Visit 6),

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	• Absolute leg volume change of the MPL using WDV, at Visit 5 and Visit 6, compared with baseline, • Relative leg volume change using the Truncated Cone (TC) method (other volumetric measurement) for the MPL, at Visits 3, 4, 5 and 6, compared with baseline, • Relative change in the circumference of the calf and the ankle of the MPL, at Visits 3, 4, 5 and 6, compared with baseline, • CIVIQ score change between Visit 5 and Visit 2, • Occurrence of six symptoms assessed by a specific patient questionnaire (pain, discomfort, heavy and tired legs, tingling, itching and cramps) within the week before each visit. • Assessments of efficacy and tolerability by patients and investigators. • Safety laboratory variables. • AEs and SAEs.
Procedures:	Six-month study divided in three periods: • a 2-week run-in period, between Visit 1 and Visit 2 (randomisation), • a 3-month double-blind treatment period, between Visit 2 and Visit 5 • then a 3-month follow-up period without treatment, between Visit 5 and Visit 6. The run-in period had to be followed in order to assure a wash-out of previous medications.
Sample Size:	328 subjects planned (147 patients per treatment arm, plus 10% drop rate), number based on standardised difference of at least 0.38 with a level of significance of $\alpha = 5\%$ (two-tailed) and a power of 80%. 397 subjects screened of which 351 were randomised.
Statistical Methods:	A multiple test procedure with a priori ordered hypotheses was carried out. The procedure had to be stopped if at each step the corresponding tested hypothesis could not be rejected. The following hypotheses were tested, *i.e.* H_{01} for primary endpoint and H_{02} to H_{08} for secondary endpoints: • H_{01}: There is no difference between the treatment groups regarding the relative leg volume changes using WDV between Visit 2 and Visit 5. • H_{02}: There is no difference between treatment groups regarding the absolute leg volume changes using WDV between Visit 2 and Visit 5.

	• H_{03}: There is no difference between the treatment groups regarding the relative leg volume changes using TC method between Visit 2 and Visit 5. • H_{04}: There is no difference between the treatment groups regarding the circumference of the calf changes between Visit 2 and Visit 5. • H_{05}: There is no difference between the treatment groups regarding the circumference of the ankle changes between Visit 2 and Visit 5. • H_{06}: There is no difference between the treatment groups regarding the CIVIQ score changes between Visit 2 and Visit 5. • H_{07}: There is no difference between the treatment groups regarding the assessment of efficacy by the patient at Visit 5. • H_{08}: There is no difference between the treatment groups regarding the assessment of efficacy by the investigator at Visit 5. Hypotheses H_{01}, H_{02}, H_{03}, H_{04}, H_{05} and H_{06} were tested using an ANCOVA model including baseline value, centres and interaction treatment*centres as covariates. Hypotheses H_{07} and H_{08} were tested by means of Mann-Whitney-Wilcoxon test (in these cases, no adjustment was performed).
Results:	A total of 397 subjects were screened from April 20th, 2010, to November 10th, 2011, of whom 351 (88.4%) were randomized into the study; 174 patients (49.6%) in the Doxium® treatment arm and 177 patients (50.4%) in the placebo arm. All subjects received at least one dose of study medication and were thus included in the Safety Set (SS), as well as in the Full Analysis Set (FAS). A total of 149 subjects were excluded from the Per Protocol Set (PPS) analysis, mainly due to Visit 5 not done or not evaluable (n=82), duration of treatment period <11 weeks (n=36) or MPL not defined according to the protocol (n=31). <u>Populations of analysis were as follows:</u> • SS = FAS = 351 subjects (174 in the Doxium® group and 177 in placebo group). • PPS = 202 subjects; 57.6% (100 in the Doxium® group and 102 in the placebo group). <u>Baseline demographics and other relevant baseline characteristics:</u> At study entry the two treatment groups were comparable with regard to the baseline and demographic characteristics. Mean age of study population, predominantly female (79.8%), was 54.9 ± 10.7 years old (range, 23 to 70). Pain and discomfort in legs were comparable between the two treatment groups. Almost all subjects (76.4%) had reflux in the superficial veins.

Compliance and treatment exposure:

Overall, compliance to study treatments was good, *i.e.* >80 % of capsules taken, in both treatment arms (92.0% in the Doxium® group and 91.0% in the Placebo group). The mean number of daily capsule intake was 2.91 ± 0.26, close to the theoretical number of 3 capsules. Treatment exposure was of 82.3 ± 16.5 days, with no difference between the treatment groups, and close to the theoretical time of 84 days.

Concomitant medications during the treatment period:

Concomitant medications were comparable between Doxium® and placebo groups, except for thyroid therapy and agents acting on the renin-angiotensin system, for which the medication intake was slightly more important in the Doxium® group (32.2% and 27.0% respectively) compared to the placebo group (21.5% and 21.5% respectively).

A proportion of 12.0% of the subjects had an antithrombotic agent during the study. These therapies consisted mainly in acetylsalicylic acid and phenprocoumon. Additionally, 9.4% of the subjects received analgesics and 4.6% had corticosteroids for systemic use or dermatological preparation.

Of note, a proportion of 17.4% of the subjects received concomitant treatments from Visit 5 to Visit 6, similar in terms of type of treatment (anti-inflammatory and anti-rheumatic products, analgesics…) and of distribution in both groups.

Efficacy results:

Primary efficacy endpoint: relative leg volume change using WDV at Visit 5 compared with baseline

On the FAS, the mean volume of the MPL was:

- At baseline (Visit 2), 2 368.9 ± 414.7 g, comparable in both groups (p=0.8) with 2 352.1 ± 386.5 g in the Doxium® group *vs.* 2 385.5 ± 441.2 g in the placebo group,
- At the end of treatment period (Visit 5), 2 357.3 ± 417.8 g, comparable in both groups (p=0.7) with 2 336.0 ± 389.6 g in the Doxium® group *vs.* 2 378.2 ± 443.9 g in the placebo group.

leading to a relative change of -0.4 ± 4.1%, higher in patients treated with Doxium® (-0.6 ± 4.8%) than in patients treated with placebo (-0.3 ± 3.3%), but the difference was not statistically significant (p=0.09).

Based on the FAS, neither the ANOVA analysis nor the ANCOVA analysis showed a trend in favour of Doxium® compared with placebo. Adjusted on the covariates, the adjusted mean difference in the relative change between end of treatment period and baseline was close to the non-adjusted mean (0.38%), also not significantly different between the 2 treatment groups (p=0.40).

Similar results were observed in the PPS in terms of difference between treatment groups. Indeed, although the relative change between end of treatment period and baseline was slightly higher in the PPS (-0.60%) than in the FAS (-0.35%), the results of the tests comparing the difference between treatment groups was non-statistically significant (p=0.26 for the non-adjusted model, and p=0.34 for the adjusted model).

The hypothesis H_{01} was then not rejected, and no difference was observed regarding the relative leg volume changes using WDV between Visit 2 and Visit 5.

Secondary efficacy endpoints:

Secondary endpoints were analysed in an exploratory way. The results are summarized below:

- On the FAS, the mean absolute leg volume change using WDV between Visit 5 and baseline was of -16.1 ± 109.5 g in the Doxium® group, not statistically different from the placebo group (-7.2 ± 84.0 g, p=0.08). Based on the FAS, neither the ANOVA analysis nor the ANCOVA analysis showed a trend in favour of Doxium® compared with placebo. The mean difference in the absolute change between end of treatment period and baseline was not significantly different between the 2 treatment groups (p=0.39). Adjusted on the covariates, the adjusted mean difference in the absolute change between end of treatment period and baseline was close to the non-adjusted mean, also not significantly different between the 2 treatment groups (p=0.36).
- On the FAS, at Visit 6, the relative leg volume change using WDV in the Doxium® group (-1.01 ± 5.4%) was statistically different from the relative volume change in the placebo group (-0.08 ± 3.5%, p=0.002). This result was also confirmed in the PPS (p<0.001). Also, the mean absolute change in the volume between Visit 6 and baseline was of -25.7 ± 127.4 g in the Doxium® group, significantly higher compared with -1.1 ± 88.3 g in the placebo (p=0.002).
- At baseline, on the FAS, the mean leg volume using the TC method was almost identical between the two treatment groups (1 249.4 ± 352.9 cm^3 for Doxium® group, 1 266.7 ± 342.3 cm^3 for placebo group), and then decreased up to 1 229.1 ± 341.8 cm^3 at Visit 5, with comparable volumes in both treatment groups (p=0.67). The relative changes in the volume of the MPL was fairly similar between treatment groups leading to a non-adjusted difference of 0.19% (p=0.79) (ANOVA analysis). The ANCOVA adjusted on the covariates led to similar results.

- At baseline, on the FAS, the mean circumference of the calf or the ankle was almost identical between the two treatment groups (respectively, 40.7 ± 4.9 cm or 24.8 ± 3.1 cm for Doxium® group, 41.0 ± 4.5 cm or 25.2 ± 3.3 cm for placebo group), and then; remained steady up to Visit 5 (respectively, 40.5 ± 4.7 cm or 24.8 ± 3.1 cm), with comparable data in both treatment groups. The relative changes in the circumference of the calf or the ankle was fairly similar between treatment groups leading to a non-adjusted difference of, respectively, 0.13% (p=0.71) or 0.14% (p=0.84) (ANOVA analysis). The ANCOVA adjusted on the covariates led to similar results (p=0.65 or p=0.95).
- At baseline, on the FAS, the mean total CIVIQ score was almost identical between the two treatment groups (50.5 ± 14.8 for Doxium® group, 51.0 ± 14.7 for placebo group), and then decreased up to Visit 5 (39.9 ± 14.9), with comparable data in both treatment groups (p=0.9). The relative changes in the total CIVQ score was fairly similar between treatment groups with a mean decrease of 20.1 ± 23.3% in patients treated with Doxium® *vs.* a decrease of 21.4 ± 24.6% in patients treated with placebo, leading to a non-adjusted difference of 1.3% (ANOVA analysis). Adjusted on the covariates "total CIVIQ score at baseline" and "centre" in the ANCOVA analysis, the adjusted mean difference in the relative change in total CIVIQ score between Visit 5 and baseline was higher than the non-adjusted mean (1.98%), also not significantly different between the 2 treatment groups (p=0.49).
- Focusing on the 2 symptoms "pain" and "discomfort" of the patient questionnaire, it was to note that the pain and the discomfort decreased from Visit 2 to Visit 5, in both groups. Also, the severity of the pain/discomfort decreased during the study. These results were consistent with the evaluation of the investigator on the CIVIQ questionnaire.
- During study treatment period, the scores evaluating the efficacy according to the patient or the investigator tended to increase from Visit 3 up to Visit 5 and then decreased at Visit 6 (period without study treatment). Of note, over time, the scores in each treatment group were comparable between the two treatment groups. Thus, at Visit 5, no significant difference between Doxium® and placebo was noticed.

<u>Safety analysis:</u>

Overall the safety profile of Doxium® was good.

Of the 351 included subjects included in the SS analysis, 188 subjects (53.6%) presented 427 Treatment-Emergent Adverse Events (TEAEs) during the study, 91 subjects (52.3%) with 210 TEAEs in the Doxium® group and 97 subjects (54.8%) with 217 TEAEs in the placebo group.

The most frequently reported TEAEs involved infections and infestations (19.1%), musculoskeletal and connective tissue disorders (14.5%), gastrointestinal disorders (10.3%), nervous system disorders (7.1%), skin and subcutaneous tissue disorders (6.8%), vascular disorders (6.3%) and investigations (5.1%).

Seventy TEAEs leading to permanent treatment discontinuation were reported for 40 subjects (11.4%), distributed in 17 subjects (9.8%, 35 TEAEs) in the Doxium® group and 23 subjects (13.0%, 35 TEAEs) in the placebo group. Of note, 24 treatment-related TEAEs leading to permanent treatment discontinuation were reported for 13 subjects (3.7%), distributed in 6 subjects (3.4%, 12 TEAEs) in the Doxium® group and 7 subjects (4.0%, 12 TEAEs) in the placebo group.

One subject in the Doxium® group experienced 2 TEAEs leading to dose reduction (corresponding to temporary discontinuation). The corresponding TEAEs reported were, by SOC (PT): gastrointestinal disorders (Gastric disorder) and nervous system disorders (Headache).

In the Doxium® and placebo groups respectively, the majority of TEAEs were of mild (32.2% and 28.2%) to moderate (29.3% and 32.2%) intensity. It is to note that the proportion of subjects who experienced at least one severe event in the Doxium® group (6.9%) was lower than proportion of subjects who experienced at least one severe event in the placebo group (11.3%).

A total of 16 severe treatment-related AEs occurred in 10 subjects (2.8%); distributed in 4 subjects (2.3%) in the Doxium® group (8 AEs involved) and 6 subjects (3.4%) in the placebo group (8 AEs involved). The most frequently reported severe AEs occurred in the SOC of musculoskeletal and connective tissue disorders.

A total of 26 subjects (14.9%, 128 events) in the Doxium® group experienced at least one AE that was considered by the investigator to be related to treatment, compared with 23 subjects (13.0%, 131 events) in the placebo group. The most commonly reported treatment-related events (SOC) in the Doxium® group were gastrointestinal disorders (12 subjects, 6.9%), followed by skin and subcutaneous tissue disorders (6 subjects, 3.4%), and in the placebo group, most frequently reported related AEs concerned gastrointestinal disorders (8 subjects, 4.5%), followed by skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders and nervous system disorders (4 subjects, 2.3%, each).

Twenty-three Treatment-Emergent Serious Adverse Events (TESAEs) were reported in 15 subjects during the study: 6 subjects (3.4%) treated with Doxium® experienced 13 TESAEs and 9 subjects (5.1%) treated with placebo experienced 10 TESAEs.

	The most commonly reported TESAEs in the Doxium® group were infections and infestations (2 patients: gastroenteritis and peritonsillar abscess), general disorders and administration site conditions (2 patients: chills and death), and surgical and medical procedures (2 patients: tonsillectomy and venous operation). The most commonly reported TESAEs in the placebo group were infections and infestations (2 patients: 2 erysipelas), musculoskeletal and connective tissue disorders (2 patients: ankle fracture and sciatica), skin and subcutaneous tissue disorders (2 patients: eczema and skin erosion), and vascular disorders (2 patients: aortic aneurysm and lymphoedema). No treatment-related SAE was reported during the study. One death was reported during the course of the study, in a patient treated with Doxium®. The event was assessed by the investigator as not related to study medication (complications after gastroscopy).
Conclusion	This randomised double-blind placebo controlled Phase IV study was designed to investigate efficacy and safety of Doxium® in a large population of ambulatory patients suffering from CVI CEAP class C3 and C4, using a method considered as the new gold standard to measure the oedema on the MPL, *i.e.* WDV. This study was also the first one to evaluate Doxium® on a longer duration of treatment period (*i.e.* 12 weeks of treatment period followed by a 12 weeks follow-up period) in terms of efficacy and long-term tolerability (assessed as secondary study objective). The study failed to demonstrate a statistically significant effect of Doxium® in the reduction of the oedema of the leg in this population of patients, although a trend for a decrease of the oedema and a better improvement in the CVI symptoms and global scores of CIVIQ questionnaire were observed in patients treated with Doxium®. Interestingly, there was a statistically significant reduction of the oedema of the leg after the 12-week follow-up period in the Doxium® group compared to the placebo group. The clinical significance of this would warrant further exploration. The study has shown that when given in a 12 weeks treatment period, Doxium® was safe and well tolerated, with low incidences of treatment-related AEs and SAEs.