Efficacy and Safety of One Dose of Flebaven® (diosmin) 1000 mg per Day in Patients with Chronic Venous Disease

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ABSTRACT

KEY WORDS: micronised diosmin, chronic venous disease, leg pain, efficacy, safety

BACKGROUND. Chronic venous disease is a common chronic non-contagious disease with a global prevalence of more than 80 percent. The disease is clinically defined as a set of symptoms and signs caused by the increased blood pressure in superficial and/or deep veins of the lower limbs. The most common symptoms and signs include leg pain, feeling of heavy legs, and swelling of legs. Flavonoids, in particular micronised diosmin, are medicines with clinically demonstrated efficacy in the treatment of chronic venous disease. The goal of the clinical trial of medicinal product Flebaven® was to confirm the efficacy and safety of one dose of Flebaven® 1000 mg per day in patients with chronic venous disease. METHODS. The clinical trial included 389 patients with primary chronic venous disease and leg pain. The patients were scheduled for three visits at doctors investigators: at the start of treatment (Visit 1), at week 4 of treatment (Visit 2) and at week 12 of treatment (Visit 3). The investigators assessed the efficacy of treatment by evaluating the symptoms (leg pain, feeling of heavy legs, intensity of leg swelling) using the numerical scale, the severity of the disease based on the Clinical Global Impression Scale – Severity (CGI-S) and the improvement of the disease based on the Clinical Global Impression Scale – Improvement (CGI-I). At the start and at the end of the clinical trial, the patients assessed the quality of life using the SF-20 questionnaire. To monitor the safety of the medicinal product, the investigators recorded adverse events at both control visits. RESULTS. Leg pain was reduced by ≥ 30% or Numeric Rating Scale score was not higher than 3 in 52% of patients at 4 weeks of treatment and in 85.4% of patients at 12 weeks of treatment. In addition, statistically significant reductions in leg pain intensity, feeling of heavy legs and leg swelling were observed at 12 weeks of treatment. The results have also shown

statistically significant reduction in the severity of the disease (from the initial value of 3.326 to 2.350 at week 12 of treatment; $p < 0.001$). The mean CGI-I score decreased from 2.262 after 4 weeks of treatment to 1.766 after 12 weeks of treatment. The patients' quality of life improved at the end of treatment, with the highest positive effect observed in the reduction of pain intensity. The patients tolerated the treatment with Flebaven® well and 89% of them were without adverse reactions related to the treatment with Flebaven®. CONCLUSIONS. The results of the clinical trial have demonstrated that one dose of Flebaven® 1000 mg per day is an effective medicine for the treatment of chronic venous disease and is well tolerated in patients.

INTRODUCTION

Chronic venous disease (CVD) involves all stages of the disease from teleangiectasis, varicose veins and oedema to skin ulcerations, while chronic venous insufficiency (CVI) refers to an advanced stage of the disease characterized by persistent swelling and presence of skin changes with ulcer formation (*1, 2*). CVD is clinically defined as a set of symptoms and signs caused by increased blood pressure in superficial and/or deep veins of the lower extremities. Symptoms of CVD may include feeling of heaviness in the legs, dull ache, itching and fatigue of the legs, night cramps, and restless legs. CVD is characterized by the following clinical signs: reticular veins or varicose veins, oedema and skin changes, such as hyperpigmentation, lipodermatosclerosis, hypostatic dermatitis and venous leg ulcer (*1, 2*). CVD is a progressive disease. If not treated in time, it may progress into a more severe form of the disease. (*3*)
Several systems of CVD classification have been developed. A more detailed CEAP scale includes clinical (C), etiologic (E), anatomic (A), and pathophysiologic (P) aspects of the disease (*1, 4*). Clinical classification takes into account clinical signs of CVD and comprises seven groups (Table 1). A subscript letter added to C indicates the presence of symptoms (s) or absence of symptoms (a). The etiology is classified as either congenital (Ec), primary (Ep) or secondary (Es). Anatomic classification is based on the involvement of superficial, deep, or perforator veins. The underlying pathophysiology is related to either reflux (r), obstruction (o), or both (r + o).

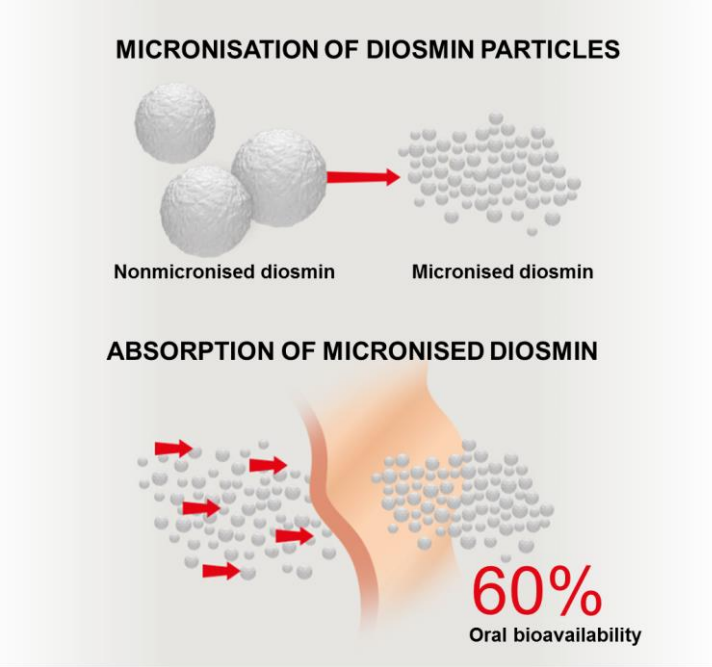
Table 1. CEAP clinical classification, which includes clinical, etiologic, anatomic, and pathophysiologic aspects of the disease. CEAP – clinical, etiologic, anatomic, pathophysiologic (Comprehensive Classification System for Chronic Venous Disorders)

C 0 – no visible or palpable varicose veins
C 1 – telangectasia or reticular veins
C 2 – varicose veins
C 3 – oedema
C 4a – acute skin changes (hyperpigmentation, dermatitis)
C 4d – chronic skin changes (white atrophy, lipodermatosclerosis)
C 5 – skin changes described for class 4, and healed venous leg ulcer
C 6 – above described skin changes and active venous leg ulcer

CVD is a common chronic non-communicable disease with a global prevalence of more than 80%: more than 60% of patients are diagnosed with CVB of CEAP grade C1-C6, and

approx. 20% of patients are diagnosed with primary CVB of CEAP grade C0 (*5*). The medicinal products whose efficacy in the treatment of CVD has been clinically proven are flavonoids, in particular micronised diosmin (*6*). Flebaven® includes the active ingredient micronised diosmin (*7*). The absorption of diosmin in the gastrointestinal tract and consequently a greater bioavailability and clinical efficacy of the formulation is improved by its micronisation to particles with a diameter <10 μm (*8, 9*). The oral bioavailability of micronised diosmin is approx. 60% (*7*).

Figure 1. Diagram of micronised diosmin absorption in the GI tract



Micronised diosmin is indicated for the treatment of signs and symptoms of chronic venous disease in adults, such as leg pain, feeling of heavy legs, tired or restless legs, cramps, oedema and trophic disorders, and the treatment of symptoms related to acute hemorrhoidal disease (*7*). Micronised diosmin has been shown to increase venous tone, and reduce venous capacitance, distensibility, and stasis. Venous occlusion plethysmography with a mercury strain gauge revealed a reduction in venous emptying time. Micronised diosmin also affects venous microcirculation, as it decreases capillary permeability and increases capillary resistance. It exhibits anti-inflammatory properties as it affects the synthesis of prostaglandins. Ultimately, it promotes the reduction of venous hypertension in patients with venous disease (*7*).

The efficacy of micronised diosmin has been tested across different clinical studies. Ziaja et al. have shown that the medicinal product is effective in patients with CVD. Their open label non-comparative clinical study included 6,569 patients monitored in 330 offices of primary care physicians. The study showed that micronised diosmin is effective in the reduction of CVD symptoms, as patients reported statistically significant decrease of leg pain, feeling of heavy and restless legs, cramps, and severity of leg swelling. Micronised diosmin was also effective in decreasing the cural circumference at the ankle and calf levels (*10*).

The goal of the clinical study was to confirm the efficacy and safety of Flebaven® 1000 mg taken once per day in patients with CVD.

METHODS:

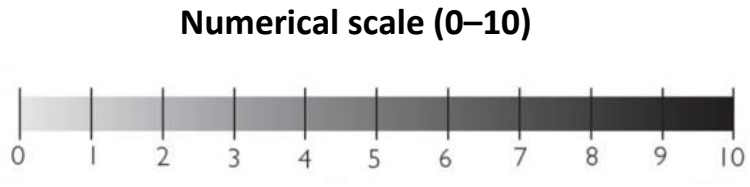
The prospective, open, multi-centre, interventional clinical study was concluded in Slovenia in the period between June 2018 and July 2019. It included patients diagnosed with primary CVD aged 20 to 70, whose average leg pain on the NRS scale was 4 or more (moderate to severe pain), and whose CEAP grade (for the more severely affected leg) was C0 to C4. Exclusion criteria included: hypersensitivity to the active substance or to any of the excipients; CEAP classification (for the more severely affected leg) C5 to C6; concomitant nonpharmacologic therapy (sclerotherapy, varicose vein surgery, angioplasty, endovascular device); and nonpharmacologic therapy concluded less than 3 months before inclusion in this study. Other exclusion criteria included: lymphedema affecting the lower extremities; renal impairment or decompensated heart failure; hepatic impairment; medical history of enterectomy; inadequate diet; malabsorption; active vein thrombosis; and significant chronic deep vein obstruction, which could lead to venous claudication and significant compression therapy, severe inflammatory disease; or other cause of pain in the lower extremities. The clinical study excluded patients receiving concomitant anti-inflammatory treatment (except those receiving antiplatelet dose of acetylsalicylic acid <350 mg per day); systemic corticosteroids; immunosuppressants and venoactive medicinal products; patients receiving concomitant opiate treatment introduced or adjusted in the month prior to inclusion; and pregnant and breastfeeding women or women who recently gave birth (6 months or less prior to inclusion).

Patients who signed a consent statement for clinical study participation and met the inclusion criteria were included in a 12-week treatment with Flebaven®. Patients took 1 tablet of

Flebaven® 1000 mg per day at any time of day, but always at the same time (±3 hours) with a meal.

Patients were scheduled for three visits at doctors investigators – at the start of treatment (Visit 1, baseline), and during treatment (two control visits): at 4 weeks of treatment (Visit 2) and at 12 weeks of treatment (Visit 3). At Visit 1, doctors checked whether the patients met the inclusion and exclusion criteria by reviewing their general medical history, and assessing the severity of leg pain in accordance with the NRS scale (Table 2) and CEAP classification (Table 1).

Table 2. Numerical scale for assessment of one of CVD symptoms – leg pain.



Numerical scale	Verbal scale
0	**No pain**
1	Mild pain Nagging, annoying, interfering with some activities of daily living.
2	
3	
4	Moderate pain Interfering with most activities of daily living.
5	
6	
7	**Severe pain** Disabling, worst imaginable, unable to perform any activities of daily living.
8	
9	
10	**Worst possible pain**

During control visits, investigators assessed the efficacy of treatment by evaluating the symptoms of CVD (leg pain, feeling of heavy legs, severity of leg swelling) using the NRS scale; the severity of the disease using the CGI-S scale (1 = Not ill, 7 = Extremely ill); and the improvement of the disease using the CGI-I scale (1 = Very much improved, 7 = Very much worse).

At the start and at the end of the clinical study, patients assessed their quality of life by filling in the SF-20 survey (20-item short-form survey on health-related quality of life, developed for the Medical Outcomes Study (MOS) by the Rand Corporation: 20-Item Short Form Survey

Instrument, SF-20ct).

Adverse reactions were monitored throughout the duration of the clinical study to evaluate its safety profile. During visits, IMP safety was also evaluated on the basis of data obtained in patient interviews. The assessed and analysed observed safety events were the overall incidence of adverse reactions and the frequency of adverse reactions of the medicinal product according to their type or the percentage of patients who did not discontinue treatment due to adverse reactions. All adverse events were classified according to medicine relation, intensity, severity, time to onset, frequency, need for treatment and degree of adverse event expectation.

The primary endpoint of the clinical study was to determine a proportion of patients with reduced intensity of leg pain by ≥ 30%, (NRS score, Table 2), or a percentage of patients with a NRS score of ≤ 3 (time points: at baseline, at 4 weeks, and at 12 weeks).
Secondary endpoints monitored during the clinical study included the difference in the intensity of reported leg pain, feeling of heavy legs, and severity of leg swelling (evaluated using the NRS scale) from start until end of the clinical study (time points: at baseline, at 4 weeks, and at 12 weeks); the difference in the quality of life (assessed using the SF-20 questionnaire) from start until end of the clinical study (time points: at baseline, and at 12 weeks); the difference in the severity of the disease (evaluated using the CGI-S scale) from start until end of the clinical study (time points: at baseline, at 4 weeks, and at 12 weeks); and the difference in the improvement of the disease (evaluated using the CGI-I scale) from start until end of the clinical study (time period: at 4 weeks, and at 12 weeks). In a subgroup of 25 patients with visible CVD symptoms (varicose veins, oedema) doctors investigators took photographic evidence at the start of the clinical study and at 12 weeks of treatment.

RESULTS

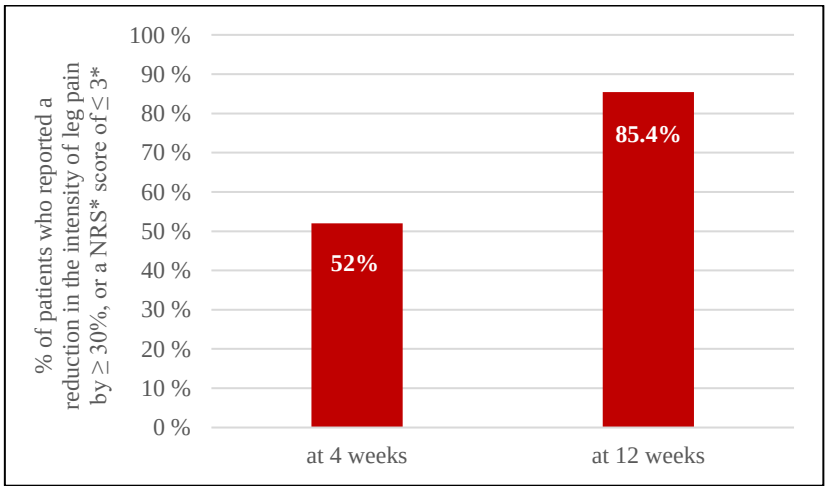
The clinical study included 389 patients; 72 men (18.5%) and 317 women (81.5%). The average age of patients included in the study was 56.3 (1st quartile: 50; 3rd quartile: 65). Based on CEAP classification, the highest number of patients presented with grades C2 (36%) and C3 (30.8%) CVD.

In line with the clinical study plan, CEAP grades C0 to C4 were included. 8.2% of patients received prior CVD treatment.

Efficacy

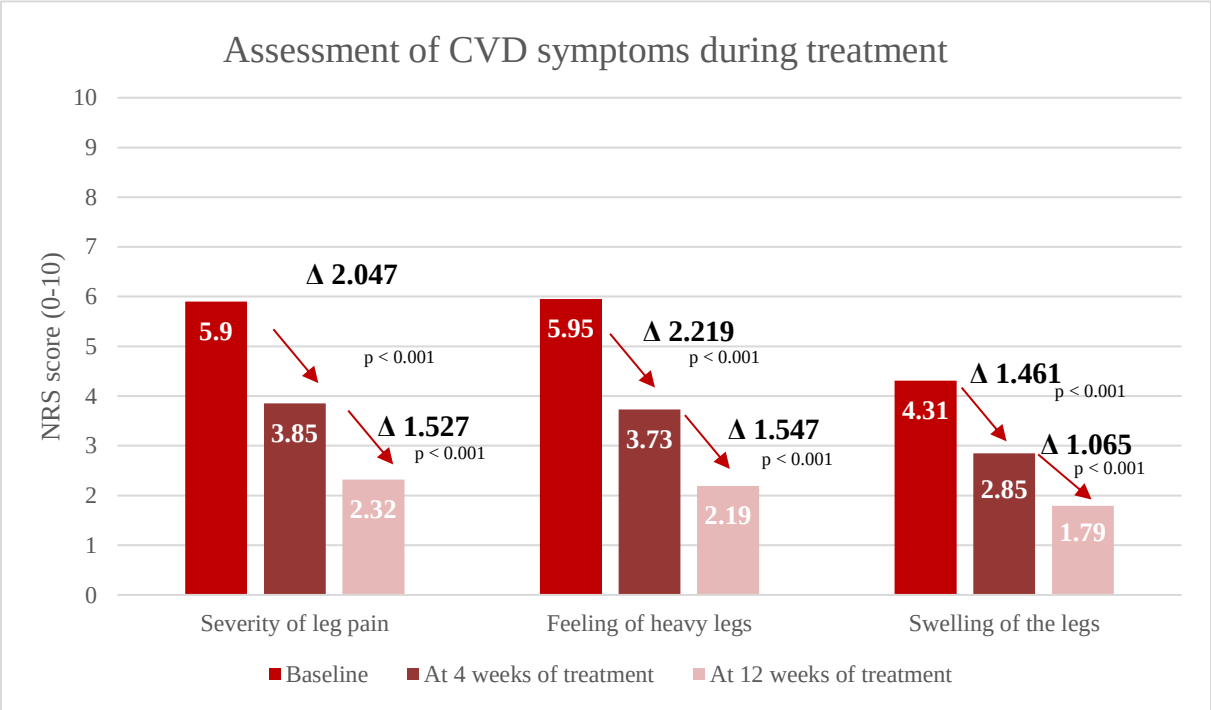
The proportion of patients meeting the primary endpoint (the proportion of patients reporting reduced intensity of leg pain by ≥ 30%, or a NRS score of ≤ 3) at 4 weeks of treatment compared to the baseline was 52%, and at 12 weeks 85.4% (Figure 2).

Figure 2: The proportion of patients meeting the primary endpoint at 4 and 12 weeks of treatment compared to the baseline (NRS)



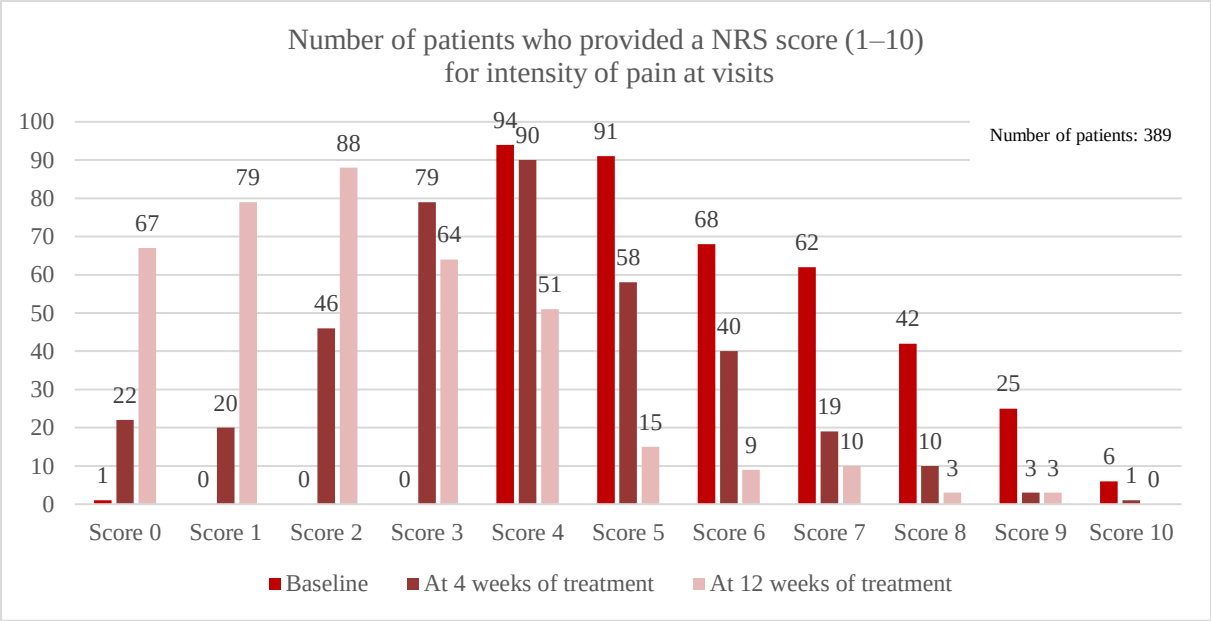
A statistically significant decrease was recorded for severity of leg pain, feeling of heavy legs, and intensity of leg swelling (evaluated using the NRS scale) at 4 and 12 weeks of treatment ($p < 0.001$), as shown on figure 3.

Figure 3: Reduced intensity of CVD symptoms (leg pain, feeling of heavy legs, leg swelling) (NRS)



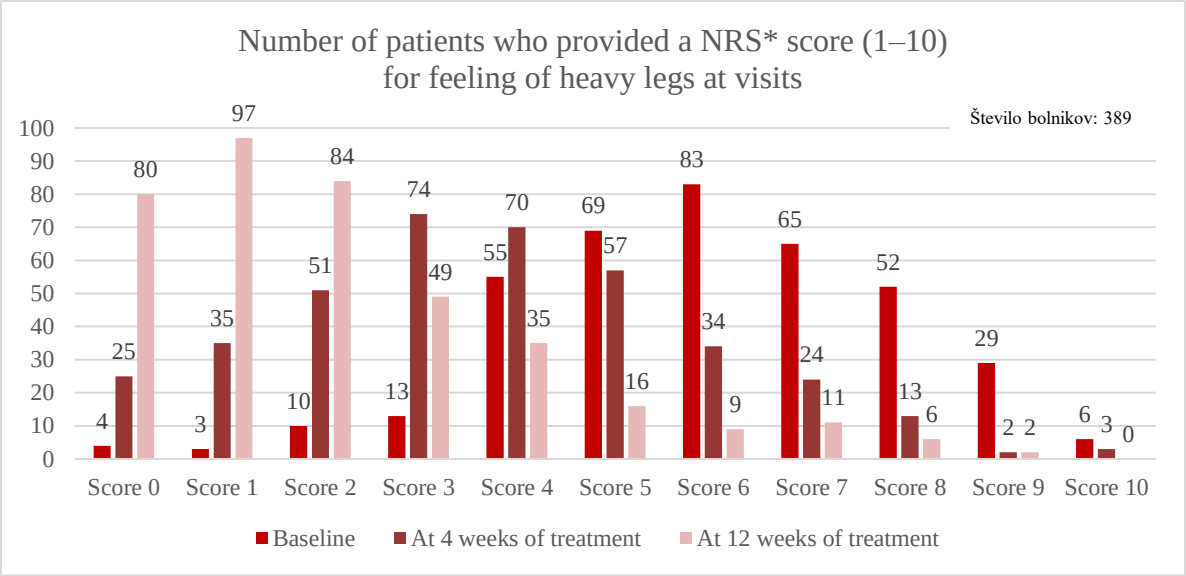
Intensity of leg pain was initially evaluated at 5.897. At 4 weeks of treatment, the intensity of leg pain was evaluated at 3.850, and 2.323 at 12 weeks. At 4 weeks of treatment, 167 (42.9%) patients reported no or mild pain (NRS scores 0–3), and 298 (76.4%) patients at 12 weeks of treatment (figure 4).

Figure 4: The number of patients providing pain intensity scores at their individual visits. NRS – Numerical scale



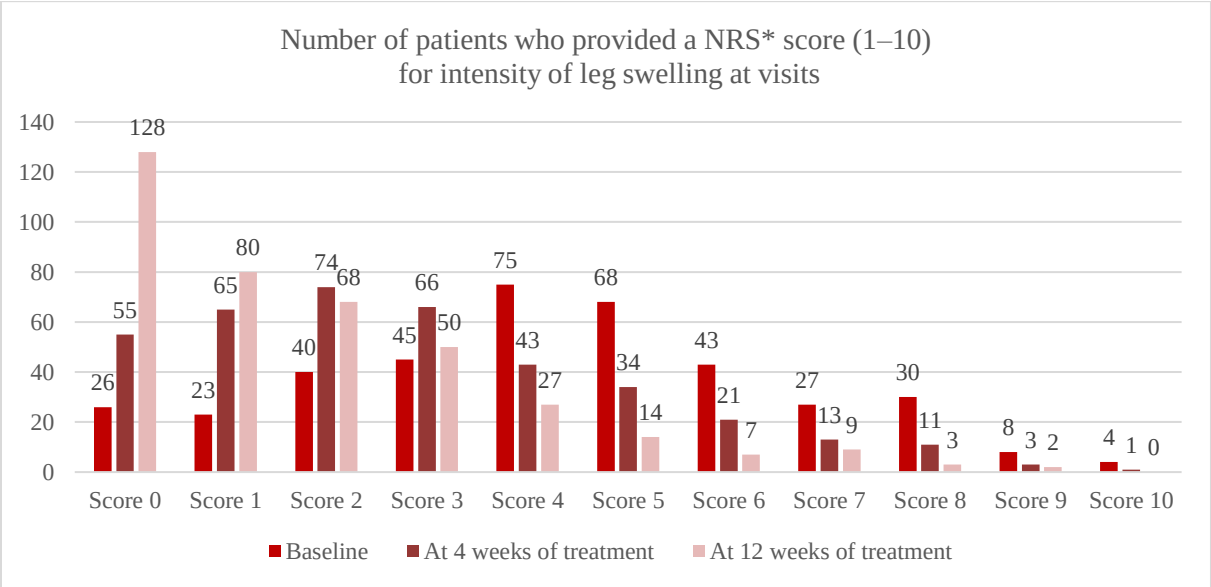
Feeling of heavy legs was evaluated at 5.956 during Visit 1. At 4 weeks of treatment, the intensity of feeling of heavy legs was evaluated at 3.737, and 2.190 at 12 weeks. The distribution of scores based on the NRS scale (0–10) shows that at 4 and 12 weeks of treatment – compared to the baseline – the proportion of scores between 0 and 3 increased (these scores define mild feeling of heavy legs), and the proportion of scores of 4 and above decreased, which means that the number of patients experiencing moderate to severe feeling of heavy legs decreased. At 4 weeks of treatment, 185 (47.5%) patients reported no or mild feeling of heavy legs (NRS scores 1–3), and 310 (79.6%) patients after 12 weeks of treatment.

Figure 5: The number of patients providing intensity scores (1–10) for feeling of heavy legs at their individual visits. NRS – Numerical scale



Severity of leg swelling was evaluated at 4.311 during Visit 1. At 4 weeks of treatment, it was evaluated at 2.850, and 1.785 at 12 weeks. At 4 weeks of treatment, 260 (67%) patients reported no or mild oedema (NRS scores 1–3), and 326 (84%) patients after 12 weeks of treatment (figure 6)

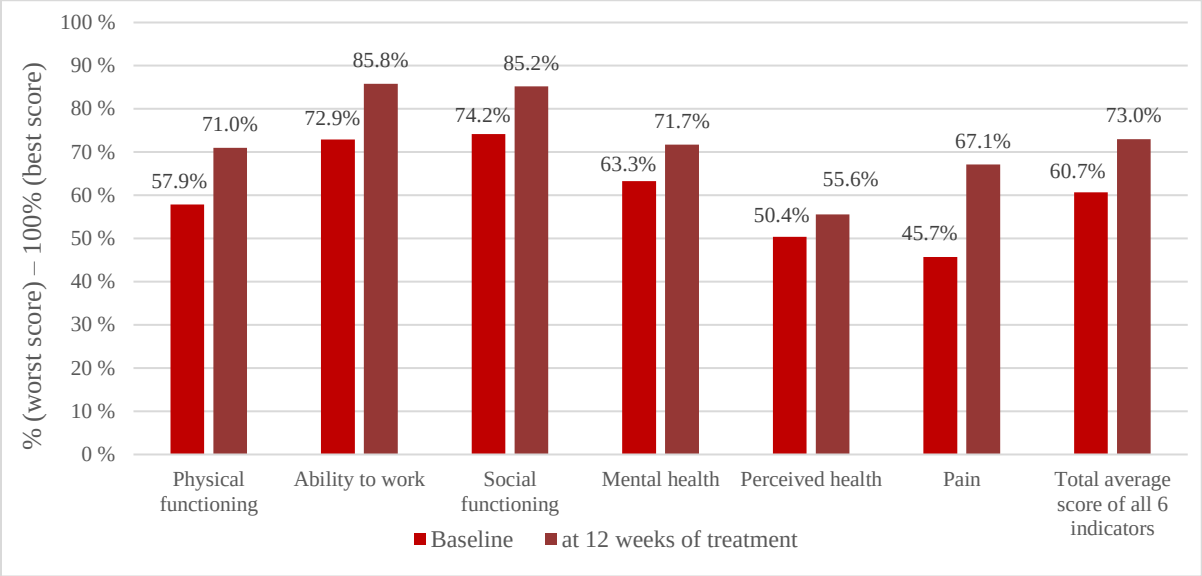
Figure 6: The number of patients providing intensity scores (1–10) for intensity leg swelling at their individual visits. NRS – Numerical scale



At the start and at the end of the clinical study, patients assessed their quality of life by filling in the SF-20 questionnaire. In all indicators related to the quality of life (physical functioning, the ability to work, social functioning, mental health, perceived health, and pain), a statistically significant improvement was recorded at 12 weeks of treatment compared to baseline scores obtained at the start of the study ($p < 0.001$). The six (6) indicators were scored in the 0–100% interval (100% = highest score, 0% = lowest score) (figure 7).

The highest positive effect of the treatment with Flebaven® was observed in the reduction of pain intensity. The score increased by 21.4 percentage points, from 45.7% to 67.1%. A higher score means that patients experienced less pain, or that the pain they experienced had a lesser impact on their quality of life. In total, the quality of life at 12 weeks of treatment (compared to baseline) improved by 11.8 percentage points, from 60.7% to 73%.

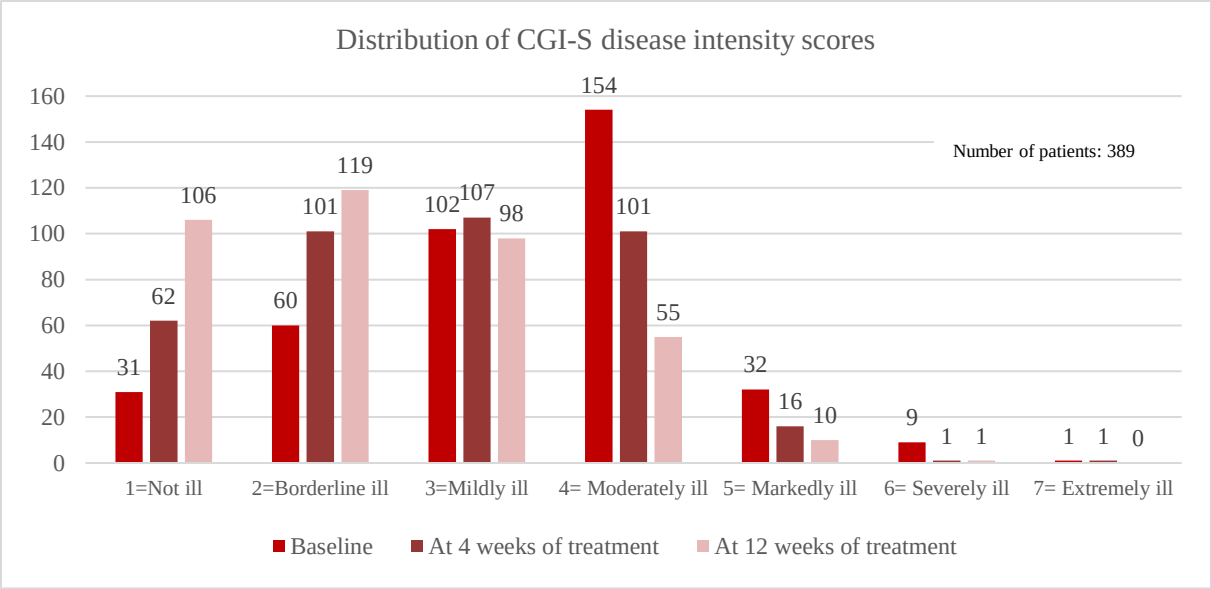
Figure 7: Assessment of quality of life indicators at baseline and at 12 weeks of treatment



The investigators also monitored the difference in the severity of the disease (evaluated using the CGI-S scale) throughout the entire clinical trial. Disease severity statistically significantly reduced at 4 and also at 12 weeks of treatment compared to the baseline ($p < 0.001$). At 4 weeks of treatment, the disease severity score lowered from its baseline at 3.326 to 2.784, and at 12 weeks of treatment to 2.350.

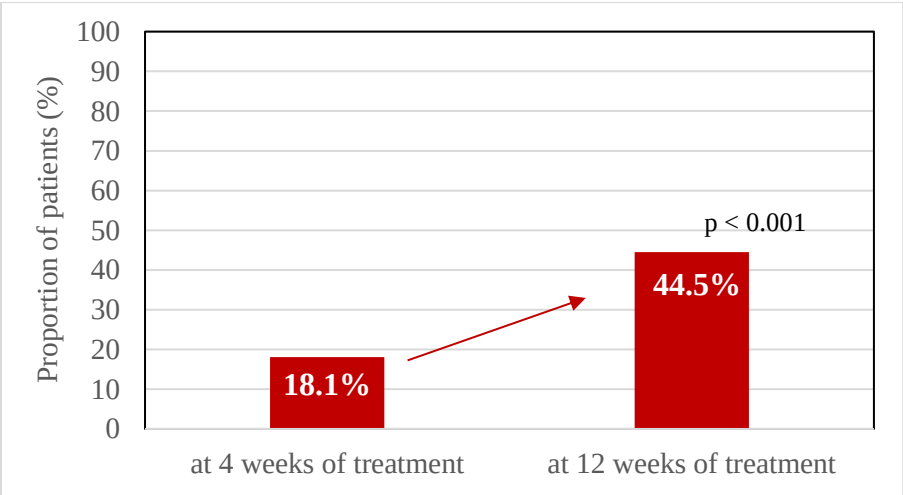
In comparison to the baseline score, the difference between the severity of the disease at 12 weeks evaluated using the CGI-S scale is most prominent in the 'Not ill' category. The baseline for this category was 8% (31 patients). After 12 weeks of treatment, its score increased to 27.1% (106 patients). The difference is statistically significant ($p < 0.001$).

Figure 8: Distribution of severity assessments. CGI-S – Clinical Global Impression Scale for Severity



Investigators also evaluated the difference in the improvement of the disease (using the Clinical Global Impression Scale for Severity, CGI-S) at 4 and 12 weeks of treatment. A statistically significant drop in the mean CGI-S score was recorded between weeks 4 and 12 of treatment ($p < 0.001$). A lower mean score indicates an improvement of the disease. The mean CGI-I score decreased from 2.262 at 4 weeks of treatment to 1.766 at 12 weeks of treatment. A marked difference in the condition of patients recorded during treatment at 4 and 12 weeks of treatment is the most prominent in the 'Very much improved' category, which rose from 18.1% to 44.5% (figure 9). The difference is statistically significant ($p < 0.001$).

Figure 9: Proportion of patients answering 'Very much improved' during treatment



Safety

The safety of Flebaven® was evaluated in all 389 patients. Patients tolerated treatment with Flebaven® well and 346 of them (89% of patients) reported no adverse reactions related to IMP (ADR). Adverse reactions were recorded in 44 (11.3%) patients; an adverse reaction not related to IMP was recorded in one (1) patient; 71 ADRs were recorded in 43 (11%) patients. 54 ADRs were recorded during Visit 2 at 4 weeks of treatment. The reported ADRs were predominantly mild (61.1%) and resolved until Visit 3 at 12 weeks of treatment. At 12 weeks of treatment, only 23 ADRs were recorded. The most common ADRs reported were gastrointestinal problems. Rare ADRs included skin disorders and neurological disorders (headaches, insomnia, restless legs) and common symptoms (malaise).

DISCUSSION

Chronic venous disease is a common non-commutable disease whose most general symptoms and signs include leg pain, feeling of heavy legs, and swelling of legs. This clinical study demonstrated that Flebaven® 1000 mg, taken once daily, is an efficient medicinal product for the treatment of chronic venous disease, as a statistically significant regression of the symptoms and signs of the disease (leg pain, feeling of heavy legs, and swelling of legs) was recorded at 4 and at 12 weeks of treatment. The effect of treatment on the reduction of leg pain intensity and oedema at 12 weeks of treatment was significantly more prominent compared to that at 4 weeks of treatment. It is, therefore, reasonable to extend treatment in particular for patients whose symptoms and signs are more prominent. At the end of treatment, patients reported that their quality of life improved significantly, but the highest positive effect of the treatment was observed in the reduction of pain intensity. Investigators confirmed a statistically significant improvement of the disease at 4 and at 12 weeks of treatment compared to the baseline.

Patients tolerated treatment well as 89% of them reported no adverse reactions related to Flebaven®. A similar prevalence of adverse events with patients most often reporting gastrointestinal and neurological disorders (headaches, vertigo, malaise, insomnia etc.) was also established in other studies (12).

The results of the assessment of micronised diosmin treatment are compliant with the findings of other existing studies of positive effects of this active ingredient on the symptoms and signs of chronic venous disease. The most recent Cochrane meta-analysis of the efficacy of phlebotonics, concluded in 2016, showed that these have a favourable effect on regression of

oedema, cramps, feeling of restless legs and paraesthesia (11). The most recent recommendations for the management of chronic venous disorders of the lower extremities were prepared in 2018 (3). They stress the importance of treatment of symptomatic patients using venoactive medicinal products, which may be prescribed as individual treatment or in combination with other therapies, in particular compression therapy, and in more advanced stages of chronic venous disease invasive therapy methods.

CONCLUSION

This clinical study offers an insight into the efficacy of treatment of chronic venous disease, an extremely prevalent disease, with Flebaven®. It is the first such clinical study conducted in Slovenia. It demonstrated the efficacy and safety of Flebaven® 1000 mg taken once per day in patients with chronic venous disease.

LITERATURE

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