Multicenter observational program

Evaluation of the efficacy and tolerability of venoactive drugs in combination therapy and their effect on the overall treatment outcomes in patients with chronic venous diseases of CEAP class C4a and C4b in real clinical practice.

VAP-PRO-C4

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Protocol n° IC4-05682-059-RUS

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Background

Chronic venous diseases of clinical class C4 according to the international CEAP classification are characterized by various types of changes in the skin and subcutaneous tissue of the affected limbs. They include skin hemosiderosis, Milian's white atrophy, indurative cellulitis, lipodermatosclerosis, and varicose eczema. Although these conditions are not dangerous, however, they significantly reduce the quality of life of patients [1].

No randomized trials evaluating the regression of trophic changes have been performed to date. However, in patients with clinical class C4, included in several randomized clinical trials, the primary and secondary endpoints were reductions in leg edema, intensity of venous pain, night cramps, feeling of heaviness, and discomfort in the legs [2]. Only the micronized purified flavonoid fraction (MPFF) was found to be effecive in reducing these symptoms in patients with trophic disorders, but without ulcers [2]. At the same time, it was proved that the grade of skin induration in patients, for example, with lipodermatosclerosis, is associated with poor healing of venous ulcers and, accordingly, a worse outcome [3]. Therefore, it is important and clinically useful to obtain additional data on the efficacy of a particular treatment method for these patients with the ability to accurately measure and to objectify the assessment of the results in real clinical practice.

The durometry technique, which has been used in engineering, was adopted for measuring skin density [4,5] and has already been introduced in real clinical practice. Along with this technique of measuring skin density using a durometer, the ultrasound examination and measurement of the area of affected skin are planned to use as objective assessment methods in the present study.

References

1. Ivanov E.V. Assessment of the quality of life of patients with complicated forms of chronic venous insufficiency. Medicinskaja nauka i obrazovanie Urala (Medical science and education of the Urals). 2006; 7 (1): 19–20 [in Russian].
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4. Nemeth AJ, Eaglstein WH, Falang V. Clinical parametrs and transcutaneous oxygen measurements for the prognosis of venous ulcers. AM ACAD Dermatol 1989;20:186-90
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Design

The VAP-PRO-C4 is a multicenter observational program, which is carried out in the frame of routine consultations and follow-up of patients. The program includes patients with chronic venous

diseases (CVDs) of CEAP class C4a and C4b. It is scheduled in Russia for 2019-2020. The program is expected to enroll 90 phlebologists from 60 cities of Russia. The planned number of patients is 500.

First visit of the first patient:	12\2019
Last visit of the last patient:	08\2020
Completion of statistical analysis:	08\2020
Preliminary report:	11\2020
Final report:	12\2020

Aim of the study

The study is aimed at evaluating the efficacy and tolerability of systemic pharmacotherapy as a part of combination treatment, and its influence on the overall treatment outcomes in patients with skin changes (CEAP class C4a and C4b).

Primary goal:
To study the efficacy of systemic pharmacotherapy as part of combination therapy and its impact on the:
- thickness of the skin-fat fold (ultrasound examination);
- change in the venous clinical severity score (VCSS) [1];
- change in the CEAP clinical class of CVD [2];
- evolution of CVD symptoms characteristic for CEAP class C4 (sensations of skin tightening, burning, itching, pain, and exudation) using the Visual Analogue Scale (VAS) [3].

Secondary goals:

1. To study the efficacy of systemic pharmacotherapy as part of combination therapy and its impact on the:

- area of affected skin determined by curvimetry technique (only in selected centers that use this technique routinely) before and after the treatment in patients with skin changes of CEAP class C4a or C4b in real clinical practice;

- skin density determined by durometry technique (only in selected centers that use this technique routinely).

2. To evaluate the changes in the quality of life using the CIVIQ-14 questionnaire (global index score [GIS]) [4].

3. To study the tolerability of systemic pharmacotherapy as part of combination therapy in patients with skin changes of CEAP class C4a or C4b.

References

1. Rutherford RB, Padberg FT Jr, Comerota AJ, Kistner RL, Meissner MH, Moneta GL; American Venous Forum's Ad Hoc Committee on Venous Outcomes Assessment: Venous severity scoring: An adjunct to venous outcome assessment. J Vasc Surg 2000;31:1307-1312.
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3. Huskisson EC. Measurement of pain. Lancet 1974; 2:1127-1131.
4. Launois R, Mansilha A, Jantet G. International Psychometric Validation of the Chronic Venous Disease Quality of Life Questionnaire. Eur J Vasc Endovasc Surg. 2010 ;40: 783-789.

Methodology

Each investigator is planned to include in the program at least 5 patients fulfilling the selection criteria. The enrollment period is 3 months. The treatment will be carried out in accordance to the routine clinical practice, instructions for the medical use of drugs, and a specific clinical situation. To assess the skin changes, the following objective methods will be used:

- measurement of the area of affected skin using the curvimetry technique (only in centers that use this technique routinely);
- measurement of the skin density using the durometry technique (only in centers that use this technique routinely);
- ultrasound exmination.

Curvimetry technique *(only in selected centers)* is carried out using curvimeters

Durometry technique *(only in selected centers)* is carried out using durometers

Ultrasound examination:

1. Thickness of the thickness of the skin-fat fold at the affected skin area;
2. Presence of reflux or occlusion (with an indication of the terrotiry).

- Measurements should be taken in the afternoon at about the same time, at visits V0 and V3.
- The data are recorded only for the limb with the most severe changes.
- Measurements are taken at the site of skin changes.

Management of patients

The present study does not imply any change in the usual management of patients with CVD. In particular, the study will record parameter that are usually evaluated during the examination of patients with CEAP class C4. Particular attention will be paid to determining the changes in skin lesions using the objective methods (measurement of the area of affected skin before and after the treatment, measurement of the skin density, and ultrasound examination).

Treatment

The observational nature of the program assumes that all examinations, procedures and changes in the therapy of a patient, including changes in doses of drugs, should be carried out only on the basis of the decision of attending physician and in full accordance with the current guidelines for management of a particular type of patients under investigation, instructions for medical use of the drugs, as well as in the settings of routine practice.

The treatment is carried out in full accordance with the current guidelines. Participation of a patient in the program, as well as his/her refusal to continue participation, should not affect the current treatment, the availability of diagnostic procedures, or the amount and quality of other necessary medical care. Names and doses of drugs used for the CVD treatment, as well as changes in the doses will be recorded in the case report form (CRF).

Inclusion criteria

- Age 18 years old or above
- Written informed consent
- Patient receives venoactive drug
- Diagnosis of chronic venous disease of CEAP class C4
- No surgical intervention for CVD is planned by a doctor

Exclusion criteria:

- Chronic venous disease of CEAP class C0-C3 or class C4-C6
- History of alcohol or drug abuse or use of narcotic drugs
- Peripheral artery disease
- Lymphatic edema of the lower extremities
- Secondary varicose veins, angiodysplasia, or neoplasia
- Arterial disease (ankle-brachial index <0.9)
- Infection within the past 6 weeks
- Any of the following concomitant diseases, which can affect the results:
    - Connective tissue disease (including rheumatoid arthritis), arthritis
    - Heart failure
    - Chronic kidney disease
    - Decompensated diabetes mellitus
    - Skin diseases of non-venous origin
    - Intermittent claudication (peripheral artery disease)
    - Diseases of the bones or joints of the lower extremities
    - Malignancy

- Treatment with drugs potentially causing leg edema (calcium channel blockers, hormonal drugs, NSAIDs, etc.)
- History of deep vein thrombosis (within the past year)
- History of superficial thrombophlebitis (within the past 3 months)
- History of surgical intervention (within the past 3 months)
- Patient cannot walk (regardless of the cause)
- Predictable poor adherence to treatment
- Participation of a patient in the intervention study within the previous 3 months
- For women: pregnancy or breastfeeding, the desire to become pregnant within at least 2 months after the study
- Patients with a contraindication to diosmin-containing agents, including Detralex
- Patient uses the topical treatments contraindicated in case of skin integrity violation.

Criteria for the assessment of treatment efficacy

1. Venous clinical severity score (VCSS)
2. Clinical class of CVD according to the CEAP classification
3. Changes in the severity of CVD class C4a and C4b CEAP symptoms (sensations of skin tightening, burning, itching, pain, and exudation) using the Visual Analogue Scale (VAS)
4. Changes in the skin status as assessed using the following methods:
   - Skin changes (VAS);
   - Skin lesion area before and after the treatment (curvimetry), only in selected centers;
   - Skin density at the affected area (durometry), only in selected centers;
   - Ultrasound examination (thickness of skin-fat fold).
5. Changes in the quality of life, as assessed by the CIVIQ-14 questionnaire

PLAN OF THE STUDY

Investigator's actions/ assessments	**V0 visit (inclusion)**	**V1 visit (at 2 weeks)**	**V2 phone call (at 3 months)**	**V3 visit (at 6 months)**
Informed consent form	+			
Registration of AEs		+	+	+
Completion of the CRF	+	+	+	+
VCSS	+			+
CEAP class	+			+
Skin changes (VAS)	+	+	+	+
Status localis	**+**	**+**	**+**	**+**
Area of affected skin (curvimetry)	+		-	+
Skin density (durometry)	+		-	+
Skin-fat fold (ultrasound)	+			+
Quality of life (CIVIQ-14)	+			+
Data on the treatment and its change	+	+	+	+
Detralex (VAD) 500 mg 2 tablets or 1000 mg 1 tablet or 1 sachet daily	+	+	+	+

Compression hosiery	+	+	+	+
Topical treatment	+	+	+	+

Safety considerations

1. Definitions

1.1 Pharmacovigilance information

Pharmacovigilance data include any unintended or adverse event associated with the use of a medicinal product in humans, whether or not considered drug related, including the following **special situations** (situations where no adverse event occurred but information needs to be collected):

- exposure during pregnancy or breastfeeding;
- overdose, abuse, misuse, off-label uses, medication error, occupational exposure (including professional one);
- lack of the treatment efficacy of drug;
- suspected transmission via a medicinal product of an infectious agent;
- unintended therapeutic benefit.

1.2. Adverse event (AE)

Adverse event (AE) is any untoward medical occurrence in a patient or clinical-trial participant who received the medicinal product, which does not necessarily have a causal relationship with the use of this medicinal product.

An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered as related to the medicinal product.

1.3. Adverse (drug) reaction (ADR)

Adverse reaction (synonyms: Adverse drug reaction, Suspected adverse (drug) reaction, Adverse effect, Undesirable effect) is a response to a medicinal product which is noxious and unintended.

“Response” in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

1.4. Serious adverse (drug) reaction (SADR)

Serious adverse reaction is an adverse reaction, which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately

life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above.
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.
Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

2. Responsibilities

2.1. Events to be reported

All available information about the following events reported during the study will be recorded:

- All serious adverse drug reactions related to the use of Detralex
- All non-serious adverse drug reactions related to the use of Detralex
- All reports about special situations (see 1.1)
- All adverse events

2.2. Responsibilities of investigator

In prospective studies, at medical visits the investigator will ask a participating patient to indicate whether or not an adverse event (serious or not) has occurred.
Investigator has to assess causal relationship between an adverse event and the investigated drug intake, as well as the seriousness criteria and later on the outcome of the event.
In case of Adverse Events, Adverse Drug Reactions or special situations that occurs during the study (both serious and non-serious), the investigator must complete the "**Adverse event / Adverse drug reaction / Special Situation Reporting Form**" (Appendix 1) without waiting for the clinical outcome or the results of additional investigations.
If the event is serious, it will be notified immediately (same or next working day at the latest) to Servier company in Russia via e-mail to address pvmail.rus@servier.com or by fax to number (495) 937-47-66. The anonymized copies of all the available and relevant laboratory findings, hospitalisation reports or other investigation results performed in connection with the adverse event should be attached to the form.
All other events should be reported by investigator within 2 working days.
The same rules apply for the transferring of additional information about the event.
The investigator must ensure the appropriate follow-up of the patient depending on the nature of event, until it resolves. The investigator will continue to notify follow up data according to timeframes defined above.
If investigator does not follow-up a patients anymore (i.e. in case of hospitalisation followed by the treatment by specialist or the participant's general practitioner,…), he/she will do every effort to contact the specialist or department in charge of follow-up of the patient, so as to have additional information and report it to Servier company in Russia.

2.3. Responsibilities of sponsor/marketing authorization holder (MAH)

Independently of the regulatory obligations of investigator, the sponsor/MAH must report the pharmacovigilance data to the appropriate authorities in accordance with the Good Vigilance Practice and local regulations.

Cases are considered to be closed when an adverse event has recovered or patient's condition was stabilized and the report is deemed sufficiently detailed for adequate medical analysis of the case.

Statistical parameters

Statistical analysis:

Baseline characteristics will be analyzed in all included patients regardless of the adherence to the protocol (intention-to-treat analysis). Analysis of the results of program will be performed using the SPSS 12.0 software package (SPSS Inc., USA). The data entry errors will be corrected before the statistical processing. Quantitative parameters will be presented depending on the distribution of raw data as arithmetic mean ± standard deviation for parametric variables, or as median (25; 75 percentiles) for nonparametric variables. The comparisons of quantitative parameters between the groups with different adherence to treatment will be carried out using the Student's t-test for independent samples or Mann-Whitney U test. Multiple comparisons will include adjustments for continuity.

Changes in the quantitative parameters during the follow-up period will be evaluated using the Student's t-test for paired samples or its nonparametric analogue, Wilcoxon test. Differences on the quantitative parameters, both between the independent groups and during the follow-up, will be evaluated as the standardized mean difference with the corresponding 95% confidence interval.

Intergroup comparisons of changes by VAS scores, VCSS, CIVIC-14, and integral score of the skin changes (lesion area, durometry, and ultrasound data) will be carried out using two-factor analysis of variance (ANOVA) with repeated measures to compare the scores before and after the treatment.

Safety will be assessed in the saall patients who received at least one dose of Detralex during the study.

Adverse events will be recorded and analyzed in patients with the reporting of all the AEs, AEs leading to drug withdrawal, SAEs, ADRs, SADRs and special situations.

Patient's expectations and satisfaction with the treatment

After adjustments for the confounding factors (gender, age, CEAP class, Detralex treatment, type of procedure), subgroup analyzes will be conducted to determine the effect of these variables on expectations and whether there are significant differences for them using the chi-square test. When analyzing data, a common linear model (the SPSS software feature) will be used.

Ethical considerations

The study will be conducted in accordance with the principles of the Declaration of Helsinki, as amended in Fortaleza, Brasil, in 2013.

Patients will be fully informed, and they will need to provide a written consent before participation in the program. The doctor should confirm in the CRF that the patient has provided an informed consent. The "Informed consent" also implies individual discussion with the patient in their national language about the nature and content of the interview and examination to be conducted.

Confidentiality of patient data will be guaranteed by the use of identification (ID) numbers. The relation between ID number and patient's identity will be known only to investigators, which will ensure the anonymity of patients.

Data collection

Please inform patients about their participation in this survey using the patient information sheet attached to this file. All the CRFs that you completed will be sent to Servier. Data anonymity is guaranteed.

Results

The data you obtained will be used to prepare the study reports under supervision of independent scientific experts.

Publications of results

Before being sent for publication, any manuscript, containing the results of the present study, should be provided to Servier company for reviewing. Servier company reserves the right to ask for modifications if needed.

APPENDIX 1.

Adverse event / Adverse drug reaction / Special Situation Reporting Form*

IC4-05682-059-RUS *Please send this form immediately by fax (495) 937-47-66 or by email to pvmail.rus@servier.com, or pass it to the associate of the company.*

Year of birth or **Age**	**Gender**	**Height**	**Weight**	**Patient's ID:**
____ or ___	M / F	___	___	_____

Description of adverse event/reaction/special situation:	**Date of event onset** __ __ ____	**Date of event termination (in case of recovery)** __ __ ____

Criteria of seriousness: ☐ NO
☐ YES (please, specify from stated below)
- ☐ Death
- ☐ Life threatening
- ☐ Hospitalization or prolongation of existing hospitalisation
- ☐ Persistent or significant disability or incapacity
- ☐ Congenital anomaly/birth defect
- ☐ Medically important event

Outcome:
- ☐ Recovered
- ☐ Recovered with consequences (persistent structural or functional impairment)
- ☐ Not yet recovered
- ☐ No recovery
- ☐ Death
- ☐ Unknown

General disease(s) / Concomitant disease(s) (please indicate year when first diagnosed).

Course adverse event/reaction/special situation (please enclose relevant findings, e.g. laboratory, hospital reports, histology, etc.):

Causal relationship with intake of <u>investigational</u> drug: ☐☐
☐ NO ☐ ☐ YES ☐ NOT APPLICABLE

***If «Yes»**, please indicate dates of the use of investigational drug <u>in the first line</u> of the table below:*

***If «No» or «Not applicable»**, please specify whether the adverse event/special situation is related to the medication of Servier company (which is specified in the table below)*:
☐ NO ☐ YES *Please indicate the name of the medication of Servier company: ……*

List of current medications	**Daily dose / route of administration**	**Dates of intake: from to**	**Indication**
		-	
		-	
		-	
		-	
		-	

Name (last, first, patronymic) of doctor:
Speciality:
Work address:
Phone number: _____
(city code)

Date:

Stamp (whenever possible)

Signature:

**Special situations are cases when adverse event was not observed, but the information should be collected: the impact of the drug during pregnancy/breastfeeding, abuse, misuse, medication error, overdose, off-label use, occupational exposure, or treatment failure, suspected*

transmission of infectious agent via a medicinal product, unintended therapeutic benefit…