Multicenter observational program
VAP-PRO-C3
Protocol n° IC4-05682-055-RUS

NCT03722836

Evaluation of the efficacy and safety of vasoactive drugs as a part of combination treatment, and its influence on the general outcomes of treatment of patients with chronic venous edema (CEAP class C3) in real clinical practice.

01\09\2018

Background

An edema takes a special place among clinical manifestations of varicose veins of the lower extremities. Its occurrence suggests about significant hemodynamic disorders, the consequence of which is a cascade of pathological reactions at the microcirculatory and molecular levels.[1,2] Clinical significance of this sign of the disease is illustrated by the fact that such a widely known term as "chronic venous insufficiency" (CVI) is applied already at the occurrence of venous edema (CEAP class C3).[3] For several decades, the pathogenetic aspects of venous edema, as well as the issues of treatment of CVI patients have been a subject of active investigations worldwide. To date, the mechanisms leading to the development of edema have been explored,[4] the complex of measures for treating patients with C3 clinical class was established, and the efficacy of such a treatment was confirmed. At the same time, studies in CVI are ongoing, and many problems still await their solution. In particular, one of them relates to a search for an optimal method of diagnosis and conservative treatment of the disease.

References

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Design

The VAP-PRO-C3 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 C3. It is scheduled in Russia for 2018-2019. The program is expected to enroll 90 phlebologists from 60 cities of Russia. The planned number of patients is 1350.

First visit of the first patient:	01\10\2018
Last visit of the last patient:	30\03\2019
Completion of statistical analysis:	30\04\2019
Preliminary report:	20\08\2019
Final report:	30\03\2020

Aim of the study

The study is aimed at evaluating the efficacy and safety of systemic pharmacotherapy (Detralex) as a part of combination treatment, and its influence on the general outcomes of treatment of patients with chronic venous edema (CEAP class C3) in real clinical practice.

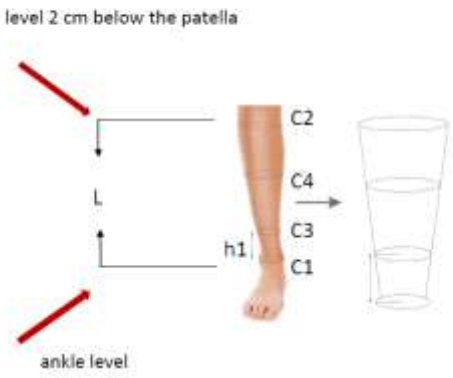
Methodology

Each investigator is planned to include in the program 10 patients fulfilling the inclusion criteria. 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 changes in edema, the method of truncated cones and duplex ultrasound scanning (DUS) will be used.
In the case report form (CRF), only the data for the extremity with most pronounced edema will be recorded.

Method of truncated cones:

Измерение	Заполняется для конечности, где отёк более выражен
L, мм	______\
C1, мм	______\
C2, мм	______\
C3, мм	______\
C4, мм	______\



h1,h2,h3 = L/3
Example of calculating the volume of the lower cone:
V = (p / 12p)²h (C2² + C2XC1 + C1²)=______\ml

The method is based on the assumption that the shape of the lower extremity approaches the shape of several truncated cones connected by bases that coincide in area. The volume of the cone is calculated by measuring the circumference of the upper (C2) and lower (C1) cones and the height (h) between them. For calculating the volume of lower cone, the following formula is used:
V = (p / 12p)²h (C2² + C2XC1 + C1²)=______\ml
The volume of the lower limb is determined by summing the volumes of all the cones. The smaller the height of the segments, the more accurate the result.

Duplex ultrasound scanning:

The thickness of subcutaneous fat in a standard point.
Reflux or occlusion with indication of the pool

- The measurements should provide in the afternoon and, if possible, at the same time. At the Visit 0 (V0) and Visit 4 (V4)
- The examination will be performed on both extremities.
- In the CRF, only the data for the extremity with most pronounced edema will be recorded.
- The standard point is 10 cm higher than medial malleolus

The present study does not imply any change in the usual management of patients with CVD. In particularly, the study will record indicators that are usually evaluated during the

examination of patients with CEAP class C3 of CVD. Particular attention will be paid to determining the changes of edema using the routine methods (geometric method of a truncated cones and duplex ultrasound scanning).

Treatment

The observational nature of the program assumes that all examinations, procedures and changes in the therapy of a patients, 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 CRF.

Inclusion criteria:

- Age 18 years old or above
- Written informed consent
- Patient did not receive treatment with venoactive drugs within the past 4 weeks prior to the inclusion in the study
- Diagnosis of chronic venous disease of class C3 (CEAP)
- Doctor plan to prescribe VADs

Exclusion criteria:

- Age below 18 years old
- Written informed consent is not obtained
- History of alcohol or drug abuse or use of narcotic drugs
- History of allergic reaction to diosmin or any other venoactive agent, or their intolerance
- History of allergic reaction to anesthetics and/or sclerosing agents
- Chronic venous disease of CEAP class C0-C2 or class C4-C6
- 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
    - Intermittent claudication (peripheral artery disease)
    - Diseases of the bones or joints of the lower extremities
    - Malignant growth

- 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)
- Patient cannot walk (regardless of the cause)
- Predictable poor adherence to treatment
- Participation of the 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
- Patient cannot attend a follow-up visit
- Patients with a contraindication to diosmin-containing agents, including Detralex

Criteria for the assessment of treatment efficacy

1. Venous clinical severity score (**VCSS**).[5]
2. Clinical class of CVD according to **CEAP classification**.[6]
3. Changes in the severity of CVD symptoms (leg heaviness, pain, swelling, night cramps and itching), as assessed by the **visual analogue scale (VAS)**.[7]
4. Changes in the severity of edema, as assessed by the method of truncated cones[8] and duplex ultrasound scanning.
5. Changes in the quality of life, as assessed by the **CIVIQ-14 questionnaire**.[9]
6. Satisfaction with treatment, as assessed by the **Darvall self-administered questionnaire**.[10]

References

5. Rutherford R.B., Padberg F.T. Jr, Comerota A.J., Kistner R.L., Meissner M.H., Moneta G.L.; 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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PLAN OF THE STUDY

Procedure	V0 visit	V1 visit	V2 visit	V3 visit	V4 visit

	(Inclusion)	(at 2 weeks)	(at 1 month)	(at 2 months)	(at 3 months)
Informed consent form	+				
Patient's questionnaires	+				+
Completion of the CRF	+	+	+	+	+
VCSS	+				+
CEAP	+				+
Data on the treatment and its change	+	+	+	+	+
Registration of AEs		+	+	+	+
Assessment of edema by the method of truncated cones	+	+	+	+	+
Assessment of edema by duplex ultrasound scanning (DUS)	+				+
Detralex 500 mg 2 times per day 1000 mg daily (1 tablet or 1 sachet)	+	+	+	+	+
Compression hosiery, topical treatment	Compression therapy can be administered on discretion of investigator at any visit				
Surgical intervention	Surgery can be performed on discretion of investigator at any visit				

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.

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 to Detralex
- All non-serious adverse drug reactions related to the use to 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 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 despite adherence to the protocol. 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. 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 mean difference with the corresponding 95% confidence interval.
Intergroup comparisons of changes in VAS scores, global index of CIVIQ questionnaire, Darvall index, and an integral score of the edema severity 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 intention-to-treat population (all 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, 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*

IC4-05682-055-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…*