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An observational, prospective study to assess the outcomes of different treatment options in patients with chronic venous disease in Belgium

Protocol Acronym/short title: Venous Outcome Study (VOS)

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Table of Contents

1. Study Synopsis 5
2. List of abbreviations 10
3. Background and rationale 11
4. Study objectives and Design 12
   - 4.1 Study objectives 12
   - 4.2 Primary endpoints 13
   - 4.3 Secondary endpoints 13
   - 4.4 Study Design 13
   - 4.5 Study diagram 15
   - 4.6 Study Flowchart 15
5. Selection and withdrawal of subjects 17
   - 5.1 Inclusion criteria 17
   - 5.2 Exclusion criteria 17
   - 5.3 Expected duration of study 17
6. Study Variables 18
   - 6.1 By visit 18
   - 6.2 Laboratory tests 19
   - 6.3 Other investigations 19
7. Assessment of effectiveness 19
8. Assessment of safety 20
   - 8.1 Specification, timing and recording of safety parameters 20
   - 8.2 Procedures for recording and reporting adverse events (AE) 21
   - 8.3 Treatment stopping rules 22
9. Statistics 22
   - 9.1 Risk of bias 22
   - 9.2 Sample size 22
   - 9.3 Analysis 23
10. Quality assurance 26
    - 10.1 Study Monitoring 26

10.2 Audit 26
11. Direct access to source data and documents 26
12. Ethics and regulatory approvals 27
13. Data Handling 27
14. Data Management 28
15. Translational research 28
16. Publication Policy 28
17. Insurance/Indemnity 29
18. Financial Aspects 29
19. References 29

1. Study Synopsis

Title of clinical study	An observational, prospective study to assess the outcomes of different treatment options in patients with chronic venous disease in Belgium
Protocol Short Title/Acronym	Venous Outcome Study (VOS)
Sponsor name	KU Leuven
Coordinating Investigator	Sarah Thomis, MD PhD Department of Cardiovascular Sciences Research Unit Vascular Surgery KU Leuven, Leuven, Belgium
Medical condition or disease under investigation	Chronic Venous Disease (CVD)
Purpose of clinical study	This study aims to describe conservative and invasive treatments for patients with CVD in Belgium, and their association with clinical and patient-reported outcomes.
Primary objective	To assess the evolution of the Quality of Life (QoL) after 12 weeks for patients with CVD who underwent conservative or invasive treatment.
Secondary objectives	1. To describe patient characteristics by treatment group, including demographic characteristics, clinical characteristics and specific comorbidities at the inclusion visit (V0), and risk factors and treatment characteristics per visit. 2. To estimate the proportion of patients who received an intervention as secondary/add-on treatment to conservative treatment or who received a re-intervention, and the time to secondary/add-on intervention or re-intervention.

	3. To assess the evolution of the QoL over time by treatment. 4. To assess the evolution of the clinical part of the Clinical Etiological Anatomic Pathophysiologic (CEAP) classification over time by treatment. 5. To assess the evolution of patient's signs through physician-assessed revised Venous Clinical Severity Score (rVCSS) over time by treatment. 6. To assess the evolution of patient's assessment of symptom severity over time by treatment. 7. To assess the evolution of patient satisfaction over time by treatment. 8. To assess QoL, signs, symptoms and patient satisfaction of patients who received an intervention as secondary/add-on treatment to conservative treatment. 9. To assess the safety of treatments in patients with CVD.
Study Design	This study is an observational, prospective, multicentre study to assess the effectiveness of conservative and invasive treatments in patients with CVD in Belgium. The inclusion period of the study will last 6 months. Patients will be followed until 2 years after inclusion into the study. During the inclusion period, after confirmation of eligibility, patients with CVD diagnosed by the General Practitioner (GP) and requiring a treatment will be invited to participate in the study. About 120 GPs across Belgium will be included in the study. During the V0, a treatment strategy will be proposed to the patient by the GP. The treatment can be conservative or invasive, depending on the severity of the disease. Patients awaiting invasive treatment may receive conservative treatment to alleviate symptoms. The choice of treatment modality is left to the discretion of the treating physician, in agreement with the patient and according to local policies. As this is an observational study, there will be no interference in the choice of treatment, and no restrictions will be imposed.

	Patients and their GP may decide to switch at any time between conservative treatments or to undergo an intervention as secondary/add-on treatment to conservative treatment. Baseline data will be collected by the GP on the day of the V0. Follow-up visits will be organized by the GP at defined timepoints after the V0: at 6 weeks, 12 weeks, 6 months, 12 months and 24 months of follow-up (V1-V5). A delay between referral to the venous centre during the V0 and the day of invasive treatment is anticipated. To allow assessment of the primary study objective, GPs will be asked to invite the patients for a follow-up visit 12 weeks after the invasive treatment took place (V-i), provided that it falls within the scope of routine medical practice in terms of visit frequency. Due to the real-world setting, patients might not be assessed exactly at the proposed weeks/months. Therefore, some visits may not take place if they are not within the scope of regular medical practice. Additionally, a time range around the visits will be allowed.
Endpoints	**Primary endpoint**: The primary endpoint is the change in the Global Index Score (GIS) of the ChronIc Venous Insufficiency Quality of life questionnaire (CIVIQ-20) from V0 to a visit realized 12 weeks after the beginning of the treatment (or day of the intervention for patients in the invasive groups). **Secondary endpoints**: 1. Description of patient characteristics by treatment group at V0 (demographics, clinical characteristics, history of CVD, treatment history, specific comorbidities) and description of risk factors and treatment characteristics per visit (type of treatment [initial referral from GP and whether they actually

	received the treatment], concomitant treatment, compliance with conservative treatment) 2. Proportion of patients who received an intervention as secondary/add-on treatment to conservative treatment (in the conservative treatment group). Proportion of patients who received a re-intervention (in the invasive treatment group) and number of re-interventions. Time to secondary/add-on intervention or re-intervention. 3. The change in the GIS of CIVIQ-20 over time from V0 to each follow-up visit. 4. The change in the clinical part of the CEAP classification over time from V0 to each follow-up visit. 5. The change in the rVCSS over time from V0 to each follow-up visit. 6. The change in the symptomatology over time from V0 to each follow-up visit. 7. The change in satisfaction score over time from V1 to each follow-up visit. 8. The change in CIVIQ-20, CEAP, rVCSS, symptomatology and satisfaction scores in patients who received an intervention as secondary/add-on treatment to conservative treatment. 9. Number and proportion of patients with Adverse Events (AEs).
Sample Size	Considering a Minimum Clinically Important Difference (MCID) of 5 points before/after treatment for the primary endpoint, a default correlation of 0.5, and with an expected drop-out of 60% of patients in the conservative group and 25% in the invasive group, we propose the recruitment of 1650 patients (safe margin), to finally include minimally 1590 patients (power 90%). Each investigator (120 GPs) will recruit approximately between 10 and 15 consecutive patients.
Summary of eligibility criteria	**Inclusion criteria** • Patient visiting a GP with complaints related to CVD,

	• Patient aged ≥ 18 years old at inclusion, • Patient receiving the diagnosis of CVD from the GP during the V0, according to international guidelines and made on a clinical basis, • Patient requiring and agreeing to receive conservative or invasive treatment, • French or Dutch speaking patient, • Patient signed informed consent and agrees to take part in the study and follow-up. **Exclusion criteria** • Patient with coagulation disorders such as thrombophilia and/or taking anticoagulation drugs, • Pregnant or breastfeeding patient, • Patient with severe Peripheral Arterial Occlusive Disease (POAD), with Ankle Brachial Index (ABI) < 0.8, • Patient with malignancy, • Patient with neurological disorder or dementia, • Patients taking regular treatment for CVD 3 months prior to inclusion (except painkillers or anti-inflammatory drugs if taken for reasons other than CVD), • Patient in any other clinical study for any pharmaceutical product within 4 weeks preceding study inclusion, • Patient with any comorbidity or situation preventing a follow-up of 2 years.
Maximum duration of treatment of a patient	The duration of treatment is the day(s) of the intervention for the invasive treatment group. The maximum duration of treatment is 24 months for the conservative group.
Version and date of final protocol	Final version of the protocol V1.2 (07-Aug-2023)
Version and date of protocol amendments	Not applicable

2. List of abbreviations

AE	Adverse Event
AS	Analysis Set
BMI	Body Mass Index
CEAP	Clinical Etiological Anatomic Pathophysiologic
CIVIQ-20	ChronIc Venous Insufficiency Quality of life questionnaire
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CVD	Chronic Venous Disease
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
GIS	Global Index Score
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
(I)EC	(Independent) Ethics Committee
IS	Included Set
MCID	Minimum Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
QoL	Quality of Life
RCT	Randomised Controlled Trial
rVCSS	revised Venous Clinical Severity Score
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
V	Visit
V0	Inclusion Visit
VAS	Visual Analogue Scale
VOS	Venous Outcome Study

3. Background and rationale

Chronic Venous Disease (CVD) is one of the most common disorders worldwide, with a total prevalence of more than 50% in the adult population (Vuylsteke 2018). CVD is defined as any morphological and functional abnormality of the venous system. It includes a spectrum of clinical presentations ranging from uncomplicated telangiectasias and varicose veins evolving to skin changes and venous ulceration.[2]

In order to report the extent of the venous disease, a scoring system was introduced in 1994 and updated in 2004 and 2020 (Beebe 1996, Porter 1995, Eklöf 2004, Lurie 2020). This classification is based on clinical manifestations (C), etiological factors (E), anatomic distribution of the disease (A) and underlying pathophysiological findings (P), and is a descriptive classification (CEAP score). In most studies, only the C-classification is used, varying from C0 to C6. The term CVD includes stages C1-C6, whilst Chronic Venous Insufficiency (CVI), usually reserved for more advanced venous disease, includes oedema, skin changes and venous ulcers (C3-C6) (Eklöf 2008, De Maeseneer 2019).

Untreated CVD will evolve into more severe stages. The underlying mechanism of this progression is persistent venous hypertension and local inflammation of the vessel wall. Epidemiological data show an association between several risk factors and CVD progression. Some of them, mostly lifestyle-related, can be modified. However, the most important risk factors are not modifiable, such as having a positive family history, age and sex (Vuylsteke 2018). The progression rate to a higher clinical stage reaches 4% each year (Pannier 2012). Half of the patients with unilateral varicose veins will develop CVD on the contralateral leg in 5 years (Kostas 2010). One third of the patients with varicose veins will develop skin changes over a period of 13 years (Lee 2015). The development of more signs and symptoms impacts patients' health-related Quality of Life (QoL) (Kurz 2001).

Due to its high prevalence, impact on QoL, and morbidity and costs associated with advanced disease, CVD is associated with a large socioeconomic burden. In Western countries, where the prevalence of CVD is highest, it already consumes up to 2% of healthcare budgets (Davies 2019).

With progression to higher clinical stages of the disease, patients will seek appropriate treatment to alleviate symptoms. The treatment options nowadays are extended (Campell 2020) and influenced by the disease severity, reimbursement policies, costs, geography and the preference of the surgeon (Guillaume 2020). Diminishing the signs and the symptoms of the disease, and preventing progression and recurrence are the main objectives for every treatment option. The treatment options range from conservative therapy, such as lifestyle changes, oral or topical venoactive drugs, or compression to more invasive treatments including sclerotherapy, surgery and endovenous techniques. Treatment guidelines have been prescribed according to the severity of the disease (Gloviczki 2011, Gloviczki 2012, Wittens 2015, Rabe 2013, Nicolaides 2018, Nicolaides 2020).

Several RCTs have provided evidence that venoactive drugs and compression therapy may reduce symptoms of CVD (Martinez-Zapata 2020, De Maeseneer 2022). The non-interventional, prospective

"VEIN Act Program" study has shown the effectiveness of conservative therapies to reduce CVD symptoms, but average follow-up was only 2.5 months (Bogachev 2019).

In order to evaluate the efficacy of the possible invasive treatments, a large number of Randomised Controlled Trials (RCTs) and meta-analyses have been conducted (Murad 2011, Siribumrunwong 2012, Hamann 2017). In many studies, anatomical success (occlusion rates) and postoperative side-effects such as pain, paraesthesia, and ecchymosis are the main outcomes. Surrogate outcomes, such as vein occlusion rates, stent patency, and changes in venous haemodynamics do not necessarily relate to a clinical change. In contrast, the number of publications including symptomatology and QoL as an outcome are limited. Only few studies have a long-term follow-up (Murad 2011, Eklöf 2014, Brittenden 2019, Kheirelseid 2018). Some studies with longer follow-up show controversial results: less favourable anatomical results (duplex ultrasound) did not result in any difference in clinical and QoL outcomes (Hamann 2017).

More long-term longitudinal studies are needed, without interfering with current clinical practice, including a sufficient number of patients, investigating the evolution of symptomatology and QoL in patients undergoing treatment for CVD. To obtain in-depth insights into the evolution of outcomes in patients with CVD undergoing treatment in Belgium, we will conduct a longitudinal observational prospective study. This study aims to describe conservative and invasive treatments for patients with CVD in Belgium, and their association with clinical and patient-reported outcomes.

4. Study objectives and Design

4.1 Study objectives

The **primary objective** is to assess the evolution of the QoL after 12 weeks for patients with CVD who underwent conservative or invasive treatment.

The **secondary objectives** are:

1. To describe patient characteristics by treatment group, including demographic characteristics, clinical characteristics and specific comorbidities at the inclusion visit (V0), and risk factors and treatment characteristics per visit.
2. To estimate the proportion of patients who received an intervention as secondary/add-on treatment to conservative treatment or who received a re-intervention, and the time to secondary/add-on intervention or re-intervention.
3. To assess the evolution of the QoL over time by treatment.
4. To assess the evolution of the clinical part of the Clinical Etiological Anatomic Pathophysiologic (CEAP) classification over time by treatment.
5. To assess the evolution of patient's signs through physician-assessed revised Venous Clinical Severity Score (rVCSS) over time by treatment.
6. To assess the evolution of patient's assessment of symptom severity over time by treatment.
7. To assess the evolution of patient satisfaction over time by treatment.

8. To assess QoL, signs, symptoms and patient satisfaction of patients who received an intervention as secondary/add-on treatment to conservative treatment.
9. To assess the safety of treatments in patients with CVD.

4.2 Primary endpoints

The primary endpoint is the change in the Global Index Score (GIS) of the ChronIc Venous Insufficiency Quality of life questionnaire (CIVIQ-20) from V0 to a visit realized 12 weeks after the beginning of the treatment (or day of the intervention for patients in the invasive groups).

4.3 Secondary endpoints

The secondary endpoints are:

1. Description of patient characteristics by treatment group at V0 (demographics, clinical characteristics, history of CVD, treatment history, specific comorbidities) and description of risk factors and treatment characteristics per visit (type of treatment [initial referral from General Practitioner (GP) and whether they actually received the treatment], concomitant treatment, compliance with conservative treatment).
2. Proportion of patients who received an intervention as secondary/add-on treatment to conservative treatment (in the conservative treatment group). Proportion of patients who received a re-intervention (in the invasive treatment group) and number of re-interventions. Time to secondary/add-on intervention or re-intervention.
3. The change in the GIS of CIVIQ-20 over time from V0 to each follow-up visit.
4. The change in the clinical part of the CEAP classification over time from V0 to each follow-up visit.
5. The change in the rVCSS over time from V0 to each follow-up visit.
6. The change in the symptomatology over time from V0 to each follow-up visit.
7. The change in satisfaction score over time from V1 to each follow-up visit.
8. The change in CIVIQ-20, CEAP, rVCSS, symptomatology and satisfaction scores in patients who received an intervention as secondary/add-on treatment to conservative treatment.
9. Number and proportion of patients with Adverse Events (AEs).

4.4 Study Design

This study is an observational, prospective, multicentre study to assess the effectiveness of conservative and invasive treatments of patients with CVD in Belgium. The inclusion period of the study will last 6 months. Patients will be followed until 2 years after inclusion into the study. The study is expected to start in Jan-2024 and be completed by Jul-2026.

During the inclusion period, after confirmation of eligibility, patients with CVD diagnosed by the GP and looking for a treatment will be invited to participate in the study. About 120 GPs will be included in the study.

4.4.1 Physician recruitment

GPs will be selected throughout Belgium, based on their experience of clinical trials and the number of patients they may recruit in the study. The selection and contracting of the GPs will be organized by Keyrus Life Science. Participating GPs will sign an agreement contract and will receive an electronic Case Report Form (eCRF) completion fee. All participating GPs are expected to have undergone accredited training in CVD and CEAP, rVCSS and CIVIQ-20 scoring before the site activation.

4.4.2 Study setting

The GP examines the patient and makes the diagnosis of CVD, based on clinical signs and symptoms. Patients who receive a diagnosis of CVD according to international guidelines who require conservative or invasive treatment can be included in the study. Duplex ultrasound or any other specific examination is not required to make the diagnosis, but could be done if needed according to routine clinical practice and recommendations. Each participating GP (120 GPs) will select approximately between 10 and 15 patients with CVD.

During the inclusion visit (V0), a treatment strategy will be proposed to the patient with confirmed CVD by the GP. The treatment can be conservative or invasive, depending on the severity of the disease. Patients awaiting invasive treatment may receive conservative treatment to alleviate symptoms. The choice of treatment modality is left to the discretion of the treating physician, in agreement with the patient and according to local policies. As this is an observational study, there will be no interference in the choice of treatment, and no restrictions will be imposed.

Commonly proposed conservative treatment options include compression therapy, and oral or topical venoactive drugs. If the GP decides that the patient needs an invasive treatment, then the patient will be referred to a venous centre. The specialist to whom the patient is referred, chooses the type of invasive treatment, as done in standard clinical care. The specialist may also prescribe conservative treatment to the patient, either while awaiting invasive treatment or in case invasive treatment is not deemed necessary.

Patients and their GP may decide to switch at any time between conservative treatments or to undergo an intervention as secondary/add-on treatment to conservative treatment.

Baseline data will be collected by the GP on the day of the V0. Follow-up visits, which are expected to take place within the scope of routine clinical practice, will be organized by the GP at defined timepoints after the V0: at 6 weeks, 12 weeks, 6 months, 12 months and 24 months of follow-up (V1-V5).

A delay between referral to the venous centre during the V0 and the day of invasive treatment is anticipated. To allow assessment of the primary study objective, GPs will be asked to invite the patients for a follow-up visit 12 weeks after the invasive treatment took place (V-i), provided that it falls within the scope of routine medical practice in terms of visit frequency.

Due to the real-world setting, patients might not be assessed exactly at the proposed weeks/months. Therefore, some visits may not take place if they are not within the scope of regular medical practice. Additionally, a time range around the visits will be allowed. The frequency of follow-up visits is upon the discretion of the treating physicians.

4.5 Study diagram

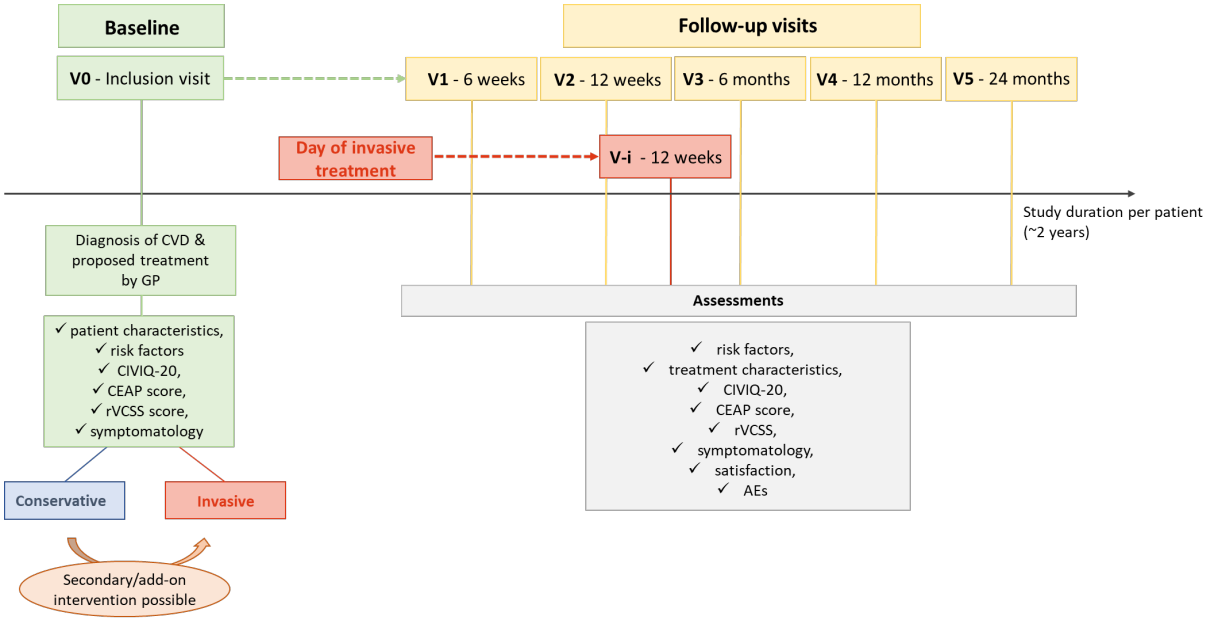

Figure 1. Study diagram

AEs: Adverse Events, CEAP: Clinical Etiological Anatomic Pathophysiologic classification, CIVIQ-20: ChronIc Venous Insufficiency Quality of life questionnaire, CVD: Chronic Venous Disease, GP: General Practitioner, rVCSS: revised Venous Clinical Severity Score.

4.6 Study Flowchart

Table 1. Schedule of assessments

Visits	V0	V1	V2	V3	V4	V5	V-i[a]
	Inclusion visit (Day 0)	Week 6	Week 12	Month 6	Month 12	Month 24	12 weeks after invasive treatment
Informed consent	X						
Inclusion/exclusion criteria	X						

Patient characteristics[b]	X						
Risk factors	X	X	X	X	X	X	X
Treatment characteristics (type/day of treatment initiation)	X[c]	X	X	X	X	X	X
Conservative treatment compliance		X	X	X	X	X	X
Concomitant treatment	X	X	X	X	X	X	X
Treatment changed since last visit/intervention as secondary treatment or re-intervention		X	X	X	X	X	X
CIVIQ-20[d]	X	X	X	X	X	X	X
CEAP	X	X	X	X	X	X	X
rVCSS	X	X	X	X	X	X	X
Symptomatology[d]	X	X	X	X	X	X	X
Satisfaction[d]		X	X	X	X	X	X
AEs		X	X	X	X	X	X
Study discontinuation		X	X	X	X	X	X

AEs: Adverse Events, CEAP: Clinical Etiological Anatomic Pathophysiologic classification, CIVIQ-20: ChronIc Venous Insufficiency Quality of life questionnaire, V: Visit, rVCSS: revised Venous Clinical Severity Score

[a] If the V-i overlaps with another visit (V1-V5) then it will replace this visit.

[b] Patient characteristics include demographics, type of occupational activity, clinical characteristics, history of CVD, treatment history, specific comorbidities.

[c] Date of treatment initiation for the conservative group and date of intervention in the invasive group will be collected retrospectively during a subsequent visit.

[d] The CIVIQ-20 questionnaire, symptomatology visual analogue scale and satisfaction score will be completed by the patients themselves.

5. Selection and withdrawal of subjects

This observational study conducted in real-life setting will include patients with CVD diagnosed by the GP during the V0. To ensure representativity, investigators will be asked to select consecutive patients whenever possible, and based on the inclusion and exclusion criteria. Patients will be managed and treated according to the usual practice.

5.1 Inclusion criteria

Patients must meet all the following criteria to be included in the study:

- Patient visiting a GP with complaints related to CVD,
- Patient aged ≥ 18 years old at inclusion,
- Patient receiving the diagnosis of CVD from the GP during the V0, according to international guidelines and made on a clinical basis,
- Patient requiring and agreeing to receive conservative or invasive treatment,
- French or Dutch speaking patient,
- Patient signed informed consent and agrees to take part in the study and follow-up.

5.2 Exclusion criteria

Patients meeting any of the following criteria will not be eligible for inclusion in the study:

- Patient with coagulation disorders such as thrombophilia and/or taking anticoagulation drugs,
- Pregnant or breastfeeding patient,
- Patient with severe Peripheral Arterial Occlusive Disease (POAD), with Ankle Brachial Index (ABI) < 0.8,
- Patient with malignancy,
- Patient with neurological disorder or dementia,
- Patient taking regular treatment for CVD 3 months prior to inclusion (except painkillers or anti-inflammatory drugs if taken for reasons other than CVD),
- Patient in any other clinical study for any pharmaceutical product within 4 weeks preceding study inclusion,
- Patient with any comorbidity or situation preventing a follow-up of 2 years.

5.3 Expected duration of study

The end of the study is defined as 2 years after the first visit of the last patient included (Last Patient First Visit [LPFV]). The total duration of the study will be 2 years and half (6 months of inclusion + 2 years of follow-up).

Patients have the right to withdraw from the study at any time and for any reason without prejudice for their future medical care. Patients can withdraw their consent without the need to justify their decision. In case of consent withdrawal, data collection will stop from the date of consent withdrawal.

Patients will be considered lost to follow-up if the investigator is not able to contact them despite multiple attempts. In case of study withdrawal, the reason for discontinuation should be recorded. The sponsor has the right to prematurely discontinue the study if the decision is justified.

6. Study Variables

6.1 By visit

During the **V0**, the patient eligibility will be assessed (inclusion/exclusion criteria, informed consent) and several variables will be collected:

- Patient characteristics: demographics (age, sex), type of occupational activity, clinical characteristics (primary/recurrent disease), personal history of CVD, family history of CVD, treatment history, specific comorbidities (diabetes, dysthyroidism, cardiovascular disease)
- Risk factors (weight, height, Body Mass Index [BMI], physical activity, smoking, pregnancy).
- Treatment characteristics: initial prescription/referral from GP, concomitant treatment, date of treatment initiation for the conservative group and date/type of intervention in the invasive group. Dates will be collected retrospectively during a subsequent visit.
- Baseline scores for CIVIQ-20, CEAP, rVCSS, and symptomatology will be collected.

Follow-up visits will be organized by the GP at defined timepoints after the V0: at 6 weeks, 12 weeks, 6 months, 12 months and 24 months of follow-up (V1-V5). Due to the real-world setting, patients might not be assessed exactly at the proposed weeks/months. Therefore, some visits may not take place if they are not within the scope of regular medical practice. Additionally, a time range around the visits will be allowed. The frequency of follow-up visits is upon the discretion of the treating physicians.

A delay between referral to the venous centre during the V0 and the day of invasive treatment is anticipated. To allow assessment of the primary study objective, GPs will be asked to invite the patients for a follow-up visit 12 weeks after the invasive treatment took place (V-i), provided that it falls within the scope of routine medical practice in terms of visit frequency. If the V-i overlaps with another visit (V1-V5) then it will replace this visit. If more than one measurement is available, the value closest to the timepoint assessed will be considered. If two values are equally close, i.e., one value before and one value after, the first one will be taken.

During V1-V5 and V-i the following variables will be collected, if available:

- Risk factors (see V0)
- Treatment characteristics:
    - was the prescribed treatment initiated, type of treatment (conservative: venoactive drugs, compression, or combination; invasive: sclerotherapy, foam sclerotherapy, surgery, thermal ablation (laser or radiofrequency), non-thermal ablation, venous stenting)

    - concomitant treatment
    - compliance with conservative treatment, as reported by the patient
    - change of treatment since the last visit, intervention as secondary/add-on treatment (in case of conservative treatment; if yes: date), re-intervention (in case of invasive treatment; if yes: date)
- CVD-related QoL: CIVIQ-20 score
- Clinical features: CEAP score
- Disease severity: rVCSS
- Patient-reported symptomatology score
- Patient-reported satisfaction score
- AEs: AE type, start date, end date, grade, outcome, lead to drug dose reduction or drug discontinuation (yes/no; only in case of conservative treatment)
- Study discontinuation

The detailed list of variables that will be collected during the conduct of the study will be provided in the eCRF and in the Statistical Analysis Plan (SAP).

6.2 Laboratory tests

Not applicable.

6.3 Other investigations

Not applicable.

7. Assessment of effectiveness

The primary outcome is the patients' QoL, related to the CVD. The CIVIQ-20 (ChronIc Venous Insufficiency quality of life Questionnaire) considers CVD as a whole (Launois 2010, Vuylsteke 2015). It is a reliable, valid, and sensitive instrument applicable to international studies of patients with CVD. The maximal score is 100, with a high score corresponding to lower patient comfort. In order to calculate the GIS, the difference between the final score and the minimum possible score is to be divided by the difference between the theoretical maximum and minimum scores (100-20=80), multiplied by 100.

For the primary endpoint, the CIVIQ-20 score will be collected at V0, and at V2 (12-weeks after V0) for the conservative treatment group and at V-i (12 weeks after the day of invasive treatment) for the invasive treatment group.

The secondary outcomes are:

1. Patient characteristics at V0 as described in Section 6.1 By visit.
2. Treatment characteristics as described Section 6.1 By visit.
3. The **CIVIQ-20** GIS, as described above for the primary outcome.

4. The **CEAP** classification, which is the worldwide standard for describing the clinical features of CVD. In this survey, we only use the C-classification. It is a scale from 0 (C0) to 6 (C6), with a higher score representing more severe disease. However, as a descriptive instrument, the CEAP classification responds poorly to change.
5. The **VCSS** was developed in 2000 and adapted in 2010 (r-VCSS) (Rutherford 2000, Vasquez 2010). The r-VCSS is an evaluative instrument that is responsive to changes in disease severity over time and in response to treatment. It includes 10 items, each scored on a severity scale from 0 to 3 (maximal score: 30; a higher score representing more severe disease). It enables longitudinal outcomes assessment.
6. Patients will evaluate CVD related **symptoms** using a Visual Analogue Scale (VAS) varying from 0 to 10. Symptoms include: having heavy legs, having pain in the legs, sensation of swelling, having night cramps, itching [leg], sensation of burning, sensation of pins and needles, restless legs. This list of symptoms has been validated by the SYM VEIN consensus statement (Perrin 2016). The final list of symptoms will be defined in the eCRF.
7. The patient **satisfaction** rate: the patients provide a score from 0 (not satisfied) to 10 (very satisfied) regarding the result of the treatment offered for their CVD.
8. The CIVIQ-20, CEAP, rVCSS, symptomatology and satisfaction scores, as detailed above, in patients who received an intervention as secondary/add-on treatment to conservative treatment.
9. Assessment of AEs will be described in Section 8.

All of these outcomes, except for treatment failure characteristics, satisfaction, and AEs, will be measured at V0. All outcome measures will be collected V1-V5 (6 weeks, 12 weeks, 6 months, 12 months and 24 months after the V0) and V-i (12 weeks after the day of invasive treatment).

8. Assessment of safety

8.1 Specification, timing and recording of safety parameters

According to the International Conference on Harmonisation (ICH), an **AE** is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Worsening of a pre-existing condition during the study must also be recorded as an AE.

A Treatment Emergent Adverse Event (**TEAE**) is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

A Serious Adverse Event (**SAE**) is defined as any untoward medical occurrence that:

- Results in death,
- Is life-threatening (the term 'life-threatening' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect.

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 AE occurred but information needs to be collected):

- Exposure during pregnancy (maternal and/or transmission of a medicinal product via semen following paternal exposure) or breastfeeding,
- Overdose, abuse, misuse, off label use, medication error, occupational exposure,
- Drug-drug or drug-food interactions,
- Any suspected transmission via a medicinal product of an infectious agent,
- Unintended therapeutic benefit,
- Lack of efficacy.

AEs and special situations will be assessed during each follow-up visit and recorded in the eCRF.

8.2 Procedures for recording and reporting adverse events (AE)

The investigator must record all AEs presented or reported by the patient in the AE section of the eCRF. The start date, the actions taken (concomitant treatments, discontinuation of treatment, dose change, premature withdrawal, none, other) and the outcome (ongoing, not recovered, recovered with / without sequelae, death, unknown) must all be recorded and the investigator must assess the event in terms of seriousness, severity and relationship to the conservative or invasive treatments studied.

When possible, signs and symptoms should be reported as a diagnosis i.e. the investigator should avoid reporting only the signs and symptoms. If there is no medical diagnosis and the signs and symptoms have to be reported, the investigator should record a separate AE for each sign and symptom.

The severity of the AEs will be judged by the investigator(s) and recorded as follows:

- Mild: discomfort noticed but no disruption of normal daily activity,
- Moderate: discomfort sufficient to reduce or affect daily activity,
- Severe: inability to work or perform normal daily activity.

The relationship of the AE to the conservative or invasive treatments will be judged by the investigator(s) and recorded as follows:

- Related: there is reasonable causal relationship between the treatment and the AE,
- Unrelated: there is no reasonable causal relationship between the treatment and the AE.

The proposed study is observational research that makes use of data collected as part of routine care and does not involve alteration of clinical care. Investigators should follow usual reporting rules to fulfil Belgian pharmacovigilance reporting.

Safety evaluations for this study are limited to the specified safety outcomes stated in Section 8.1.

8.3 Treatment stopping rules

Discontinuation or withdrawal of treatment will be decided in accordance with regular medical practice and according to the physician's judgment.

9. Statistics

9.1 Risk of bias

The results obtained during this study may be biased through selection of the treating physicians and the willingness of patients to participate. To minimize the bias related to GP representativity, GPs will be selected throughout Belgium. The GPs will be asked to offer the study to all patients who meet the eligibility criteria, and to select consecutive patients whenever possible. GPs will receive a training before the start of the study.

The statistical model will adjust for the period during which the patients in the invasive treatment group had not yet received the intervention (i.e., the time between inclusion at V0 and the day of the intervention) (See Section 9.3 Analysis).

Patients lost to follow-up may cause attrition bias. To minimize this bias, efforts will be made to contact the patients if they are lost to follow-up.

To minimize the risk of measurement bias, each GP will receive a training on the use of the assessment instruments (CEAP, rVCSS, CIVIQ-20, VAS) before the site activation.

9.2 Sample size

Considering a Minimum Clinically Important Difference (MCID) of 5 points before/after treatment for the primary endpoint (CIVIQ-20 GIS), a default correlation of 0.5, and with an expected drop-out of 60% of patients in the conservative group and 25% in the invasive group, we propose the recruitment of 1650 patients (safe margin), to finally include minimally 1590 patients (power 90%).

Each investigator (120 GPs) will recruit approximately between 10 and 15 consecutive patients.

9.3 Analysis

9.3.1 Statistical hypotheses

All statistical tests will be two-sided at the 5% overall alpha risk level. All Confidence Intervals (CIs) will be two-sided and presented at the 95% confidence level. No alpha risk adjustment is planned.

9.3.2 Population for analyses

The following analysis population will be considered:

- Included Set (IS): This set corresponds to all patients included for the study and with an Informed Consent Form (ICF) signed.
- Analysis Set (AS): This set corresponds to all patients from the IS with at least one follow-up visit (i.e. with at least a date of visit completed for visits V1, V2, V3).

9.3.3 Statistical Analysis

General considerations

The SAP, developed and finalized before the study database lock, will include a description of the statistical methods, analyses planned, and planned tables and figures, in accordance with the objectives of the protocol.

The analyses will be mainly descriptive, and all information will be reported in summary tables. Summary data will be provided for all variables collected and will be done by treatment group (conservative group, invasive group) and overall. Details on rules defining groups will be provided in the SAP. Descriptive statistics could be done by subgroup of conservative treatment (venoactive drugs, compression, combination of both), or by subgroup of invasive treatment (sclerotherapy, foam sclerotherapy, surgery, thermal ablation (laser or radiofrequency), non-thermal ablation, and venous stenting). Any additional subgroup analyses will be defined in the SAP.

Unless specified, missing data will not be imputed and all analyses will be based on observed case. Rules for handling missing score of CIVIQ-20 will be detailed in the SAP. To minimise the number of missing data, a specific query will be generated (automatic or manual) in order to confirm the data are missing and not forgotten in the eCRF.

The statistical package SAS® v.9.4 will be used to perform all statistical analyses.

Descriptive analyses

Continuous variables will be summarised using descriptive statistics (i.e. numbers, means, standard deviations [SD], medians, first and third quartiles, minimum and maximum). The 95% 2-sided CIs of means will be calculated when appropriate using the standard method (standard normal distribution).

Categorical variables will be summarised by numbers and proportions. The 95% 2-sided CIs of proportions will be calculated when appropriate using the Clopper-Pearson exact method.

Within-group comparisons

Within group differences will be evaluated by a paired t-test, a Wilcoxon signed-rank test or a linear mixed model with random intercepts (on the raw data or the rank data depending on the distribution of the variable of interest) for continuous variables. In case of categorical variables, McNemar's test or Cochran's Q test will be used according to the number of modalities of the variable.

Time-to-event endpoints will be expressed in weeks. For the description, Kaplan-Meier estimates (product-limit estimates) will be presented with a summary of associated statistics (number of events, number of censored data / median, Q1 and Q3 survival time / estimate rates of patients not presenting the event of interest at 6 weeks, 12 weeks, 6 months, 12 months and 24 months) including the corresponding two-sided 95% CIs. The Kaplan-Meier curve will also be presented.

Primary endpoint

The analyses will be conducted in the AS.

To evaluate the change in the CIVIQ-20 GIS from V0 to a visit realized 12 weeks after the beginning of the treatment (or day of the intervention for patients in the invasive group) in each treatment group, we will compare the V0 value with the value at 12 weeks with a paired t-test or Wilcoxon signed-rank test depending on the distribution of GIS of CIVIQ-20 in each treatment group.

A mixed model could be conducted, with the GIS of CIVIQ-20 as the dependent variable, the visit as a fixed effect and time between V0 and the day of the intervention as covariate and paired on the patient in the invasive group.

Secondary endpoints

The analyses will be conducted in the AS, overall and by treatment group (conservative group, invasive group). Descriptive statistics and within-group comparative analyses could be done by subgroup of conservative treatment (venoactive drugs, compression, combination of both), or by subgroup of invasive treatment (sclerotherapy, foam sclerotherapy, surgery, thermal ablation (laser or radiofrequency), non-thermal ablation, and venous stenting), if relevant.

Descriptive statistics will be provided for patient characteristics at V0 (in terms of demographics, profession, clinical characteristics, personal and family history of CVD, treatment history, specific comorbidities), risk factors, concomitant treatment and description of treatment characteristics per visit in terms of type of treatment (initial referral from GP and whether they actually received the treatment), concomitant treatment, compliance (for conservative treatment group only).

The proportion of patients who received an intervention as secondary/add-on treatment to conservative treatment (in the conservative treatment group) and the proportion of patients who received a re-intervention (in the invasive treatment group) and number of re-interventions will be provided. If there is enough recurrence (minimum 20% of concerned patients), a Kaplan-Meier analysis could be considered. Time to event will be calculated from the start date of conservative treatment to the date of the secondary/add-on intervention in the conservative treatment group.

Time-to-re-intervention will be calculated from the date of the intervention to the date of the re-intervention in the invasive treatment group.

Patients who will reach the end of the study without receiving an intervention (in the conservative group) or a re-intervention (in the invasive treatment group) will have the time to event censored at the date of treatment discontinuation for any other cause (in the conservative group) or at the date of the end of the study if study ended (in conservative and invasive treatment group).

The change in the CIVIQ-20 GIS over time from V0 to each follow-up visit will be evaluated with the same methods as the primary endpoint.

The change in the clinical part of the CEAP classification over time from V0 to each follow-up visit will be described.

The change in the rVCSS over time from V0 to each follow-up visit will be evaluated with the same methods as the primary endpoint.

The change in the symptomatology over time from V0 to each follow-up visit will be evaluated with the same methods as the primary endpoints.

The satisfaction score over time from V1 to each follow-up visit will be described as a quantitative variable.

Number and proportion of patients with AEs will be described.

Complementary analysis

There is a possibility of carrying out complementary analyses at the end of the study according to the data obtained if they allow this type of analysis.

Interim analyses

Not applicable

10. Quality assurance

10.1 Study Monitoring

In accordance with applicable regulations, Good Clinical Practice (GCP), and Contract Research Organisation (CRO) Standard Operating Procedures (SOPs), an initiation visit will be performed remotely (by session of 5 GPs) before any patients are included in the study. The aim of this visit is to train the investigator on the protocol and data collection procedures as well as to provide a reminder of the investigator responsibilities according to ICH GCP.

During the study, the Clinical Research Associate (CRA) will regularly contact the centres and on-site monitoring visits can be performed. The extent, nature and frequency of on-site visits will be based on the patient inclusion rate and will be discussed with the investigator. The aim of these contacts and visits is to check the progress of the study, discuss recruitment, review collected study data, conduct source document verification and identify any issues and address their resolution. This will be done in order to verify that the data are authentic, accurate and complete, the safety and rights of patients are being protected and the study is being conducted in accordance with the approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the CRA direct access to all relevant documents and to allocate his time and the time of the study personnel to discuss any issues.

Upon completion of the study the CRA, with the collaboration of the investigator, will ensure that:

- All data queries have been finalised,
- The centres' study records are complete.

10.2 Audit

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor or a CRO designated by the sponsor may conduct a quality assurance audit of the investigator centre. Regulatory agencies may also conduct regulatory inspections. Such audits or inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator centre agrees to allow the auditor / inspector direct access to all relevant documents and to allocate his time and the time of the study personnel to the auditor / inspector to discuss findings and any relevant issues.

11. Direct access to source data and documents

According to GCP guidelines, upon request of the CRA, auditor, Independent Ethics Committee (IEC) or regulatory authority, the investigator must provide direct access to all requested source data / documents. The investigator(s) and the institution(s) will permit study-related monitoring, audits, Ethics Committee (EC) review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (ie patients' case sheets, questionnaires etc). This will be defined in a written agreement with the sites.

12. Ethics and regulatory approvals

The study will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to the EC of UZ Leuven. Any modification of the protocol will be made only with the agreement of the sponsor and must be submitted to the EC. No changes in the clinical study protocol will be implemented until the amendment and revised ICF (if applicable) have received approval from the EC.

The study can and will be conducted only on the basis of prior informed consent by the patients, or their legal representatives, to participate in the study. The participating site shall obtain a signed ICF for all patients prior to their enrollment and participation in the study in compliance with all applicable laws, regulations and the approval of the (local) EC, if required. The participating site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigator and the participating site shall treat all information and data relating to the study disclosed to participating site and/or investigator in this study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR") and the Belgian Law of July 30 2018 on the protection of natural persons with regard to the processing of personal data).

13. Data Handling

The files will be checked for completeness. All data will be collected and processed anonymously. The sponsor/organizer/researcher will not have access to the patient's name. Only a patient identification number will appear on the questionnaires/files.

The patient will be informed that all personal details and information will be treated with a strict respect of medical confidentiality and professional secrecy.

Following closure of the study, the investigators must archive, in a safe and secure location, all study records including subject medical files, original ICFs, source documents, eCRFs, copies of the regulatory authorities' approval and all relevant correspondence. Documents will be archived for at least five years after final report or first publication of study results, whichever comes later.

The records must be maintained in a way to allow easy and timely retrieval when needed e.g. for an audit, inspection or any subsequent review of data in conjunction with assessment of the facility,

supporting systems and staff. Where permitted by local laws and regulations, some or all of these records can be maintained in a format other than hard copy e.g. microfiche, scanned, electronic, however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original and meet accessibility and retrieval standards (a hard copy must be regenerated if required). Furthermore, the investigator must ensure that there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator agrees to provide direct access to source documents during monitoring visits.

The investigator must notify the sponsor of any changes in the archiving arrangements, including, but not limited to: archival at an off-site facility and transfer of ownership of the records in the event the investigator leaves the site.

14. Data Management

Data management will be conducted by Keyrus Life Science, a CRO. All data management procedures will be completed in accordance with Keyrus Life Science SOPs. All data will be entered in an eCRF (ENNOV EDC). The data will be validated, and queries will be generated for any inconsistencies according to the data validation plan. The final database will be provided using SAS© software, version 9.4. Coding of AEs will be performed using the Medical Dictionary for Regulatory Activities (MedDRA). Coding of medications will be performed using the World Health Organisation drug dictionary enhanced.

15. Translational research

Not applicable.

16. Publication Policy

It is anticipated that the results of the overall study shall be published in a multicentre publication, involving the data of all clinical sites participating in the study.
The participating site is not allowed to publish any data or results from the study.

Publications will be coordinated by the sponsor. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

17. Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, sponsor shall assume, even without fault, the responsibility of any damages incurred by a study patient and linked directly or indirectly to the participation to the study, and shall provide compensation therefore through its insurance.

18. Financial Aspects

The study will be coordinated by KU Leuven in collaboration with the CRO Keyrus Life Science. The study will be funded (partially) by Servier Affaires Médicales.

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