Document title	**AMENDED CLINICAL STUDY PROTOCOL**
Study official title	**Dose-response relationship study of S42909 on leg ulcer healing after oral repeated administration in patients with active venous leg ulcer.** **A 10-week randomised, double-blind, placebo-controlled, prospective, international, multicentre, phase IIa study.**
Study brief title	**Dose-response relationship study of 42909 on leg ulcer healing**
Test drug code	**S42909**
Indication	**Venous leg ulcer**
Development phase	**Phase IIa**
Protocol code	**CL2-42909-016**
EudraCT Number	**2016-004143-36**
Universal Trial Number	
Sponsor	**ILKOS THERAPEUTIC INC**
International Coordinator	**Professor Eberhard RABE** **Department of Dermatology University of Bonn** **Sigmund-Freud-Str. 25** **53105 Bonn, Germany** **Tel.: +49-228-287-16630** **Fax : +49-228-287-14333** **E-mail : eberhard.rabe@ukb.uni-bonn.de**
Date of the document	**05-March-2018**
Version of the document	**Final version**

Substantial Amendment integrated

No	Final version date	Countries concerned
1	19-May-2017	ALL
2	29-Jun-2017	CAN, SVK, USA
3	29-Jun-2017	AUT, CZE, DNK, DEU, ESP, ITA
4	05-Mar-2018	ALL

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FOLLOW-UP OF VERSIONS

	Substantial amendment No	Final version date	Countries concerned	Nature of modifications
Initial protocol	NA	30-Jan-2017	ALL	Not Applicable
Amended protocol	1	19-May-2017	ALL	This substantial amendment has been implemented in order to adapt selection/inclusion criteria to new medical data, to clarify wording relative to selection/inclusion criteria, to add withdrawal criteria, to precise items regarding standard of care, to adjust the investigation schedule during the selection period, and to correct errors of typology. It also addresses safety comments and recommendations raised by the FDA in their May Proceed Letter to the Sponsor dated May 5, 2017.
Amended protocol	2	29-Jun-2017	CAN, USA, SVK	This substantial amendment has been implemented to tighten up the eligibility criteria by removing the investigator's judgement on the arterial duplex scan from the non-selection criterion N°26, since it has become apparent that there is variability in methodology and assessment of the arterial network by arterial duplex scan between countries and investigators. Protocol Appendix 2 has been modified accordingly in order to capture the data from the arterial duplex scan based on the different methods used in the participating sites and countries. CEAP classification at ASSE visit has been added (Table (4.4.2) 1 – Investigation schedule). A typo has been corrected in the wording of criterion N°34 (suppression of a reference to hepatic enzymes measured at ASSE). A sentence has been added in the statistical paragraph to anticipate the need to perform some

				exploratory analyses.
Amended protocol	3	29-Jun-2017	AUT, CZE, DNK, DEU, ESP, ITA	This amendment has been implemented to integrate prior amendments N°1 and N°2 (for European countries, where amendment N°1 had not yet been submitted for Regulatory and Ethic review at the time of amendment N°2 issuance).
Amended protocol	4	05-Mar-2018	ALL	This substantial amendment has been implemented in order to adapt selection/inclusion criteria to new considerations and new medical data; to clarify new timelines of the study; to add a 3D picture of the reference ulcer on the day of the inclusion visit after randomisation; to clarify wording; and to broaden the study population.

STUDY SUMMARY SHEET

Name of the sponsor: ILKOS THERAPEUTIC INC	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
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Title of study:
Dose-response relationship study of S42909 on leg ulcer healing after oral repeated administration in patients with active venous leg ulcer. A 10-week randomised, double-blind, placebo-controlled, prospective, international, multicentre, phase IIa study
Protocol No.:CL2-42909-016

Coordinator
International Coordinator: Professor Eberhard Rabe (Bonn, Germany)
National coordinators and investigators: listed in a separate document

Study centre(s):
Total number of centres: around 55
Total number of countries: 10

Study period:	**Study development phase: IIa**
- Study duration for the participant: up to 10 weeks - Study initiation date: July 2017 - Study completion date: Q1 2020	

Objective(s):

Primary objective:
To detect the existence of an overall dose-response relationship with S42909 on improving healing of venous leg ulcers on top of standard of care (compression and local wound care) after 4 weeks of treatment.

Secondary objectives:

- To determine a dose window for the Minimal Effective Dose (MED) on improving healing of venous leg ulcers.
- To explore the effect of S42909 on improving healing of venous leg ulcers on top of standard of care (compression and local wound care) after 6 weeks of treatment.
- To explore the effect of S42909 on improving pain related to venous leg ulcer over 6 weeks.
- To explore the effect of S42909 in decreasing analgesic drug consumption related to venous leg ulcer over 6 weeks.
- To assess the safety profile of each tested dose of S42909 (adverse events, biochemistry, haematology, ECG, vital signs, body weight and standard urinalysis).
- To assess the pharmacokinetics of S42909 and its metabolites in patients after repeated administration of S42909.

Additional objectives

- To assess any potential PK/PD relationship (mainly on improving healing of venous leg ulcers and pain related to venous leg ulcers).
- Genomic assessment of S42909:
  - To evaluate associations between polymorphisms in relevant genes and the pharmacokinetics of S42909.
  - To identify subgroups of patients with genomic susceptibility to develop non healing venous leg ulcer or to identify novel genes that may play a critical role in the treatment response
- To collect the blood non genomic biomarkers which can be related to venous leg ulcer healing, underlying chronic venous disease, response to S42909 treatment (bio-collection in a bio-repository).

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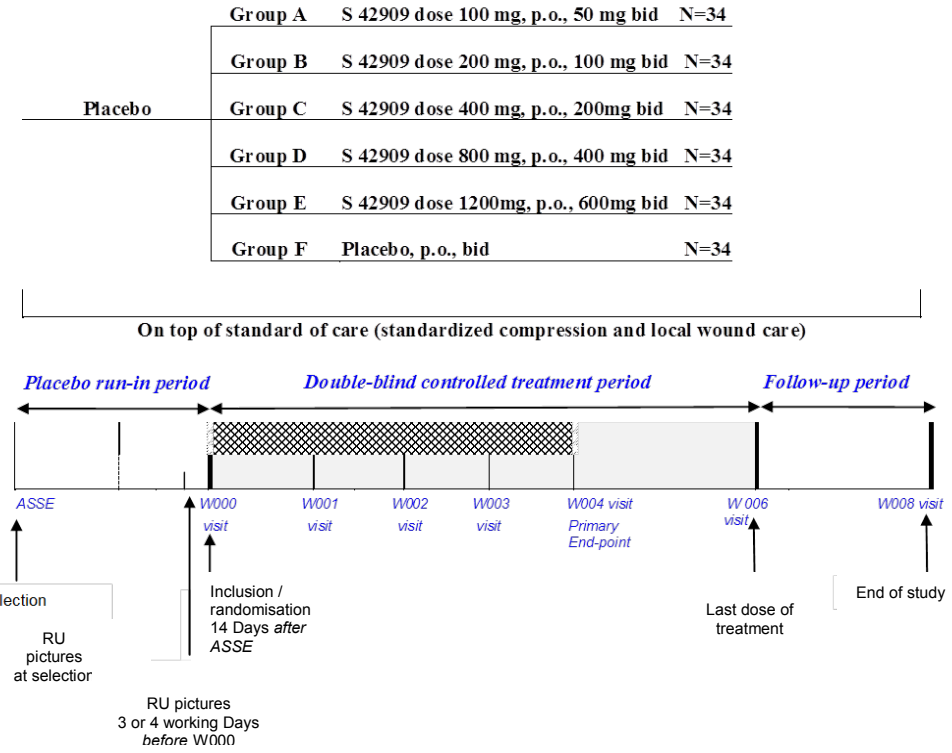
Methodology:

Study design



Phase IIa, prospective, international, multicentre, randomised, double-blind, placebo-controlled, parallel group, dose-finding study in patients with venous leg ulcer.

Patients suffering from chronic venous disease and having at least one active venous leg ulcer will be selected at the selection visit (ASSE). One Reference Ulcer (RU) defined as the largest ulcer in size that is fitting the area selection criteria will be established. At ASSE, a first picture will be taken before cleansing and debridement and a second picture will be taken after cleansing and debridement. The investigator will check that the selection RU area is compliant with the selection criteria. Patients will start the selection period and will be switched from their current pharmacological and/or local treatment (if any) for venous leg ulcer to local wound care with sterile saline solution or sterile water, "non-active" dressings and standardized compression (same strength and type of compression). They will be administrated the placebo selection treatment for a period of fourteen days.

Three (or four) working days before the inclusion visit, the participants will come to the site for a RU picture in order to get the RU area central measurement for inclusion visit (W000).
At W000, the investigator will check that the inclusion RU area is compliant with the inclusion criteria. The relative change of Reference Ulcer area compared with the RU area measured at the selection visit must be less or equal to 20% in order for patients to be eligible. The investigator will also check that the participant is compliant with the selection treatment and stockings wearing. Patients found to be eligible for randomisation will have a 3D picture of the RU on the day of W000, taken after randomisation and after wound bed preparation. This picture (W000-B) will be the baseline measure for comparison with all subsequent pictures taken at following visits.

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All participants found to be eligible for inclusion will be randomised to one of the following six groups – S42909: 100, 200, 400, 800 or 1200 mg per day- or placebo, using a centralised, dynamic, balanced with 1:1:1:1:1:1 ratio, stratified randomisation according to the country, a combined prognosis criteria (size and age of ulcer)), and diabetic status (yes/no), by Interactive Web Response System (IWRS).
The combined prognosis criteria (size and age of ulcer) for ulcer healing are:

- A : ≤ 10 cm² and ≤ 6 months
- B : > 10 cm² or > 6 months

The participants will enter a 6 weeks ambulatory Investigational Medicinal Product (IMP) treatment period on top of standard of care (standardized compression and local wound care with sterile saline solution or sterile water and "non-active" dressing) followed by a 2 weeks follow-up period of standard of care only. During this period the participants will return to the investigator's site for intermediate visits after one week (W001), two weeks (W002), three weeks (W003), four weeks (W004), six weeks (W006) and eight weeks (W008). Participants will continue receiving standardized compression therapy and local wound care (sterile saline solution or sterile water and "non-active" dressing) until the end of the study (W008).

At each visit, the clinical features of the RU will be recorded and a 3D picture of the RU will also be taken after wound bed preparation except at ASSE visit where a 3D picture of the RU will be taken before and after wound bed preparation and where an additional picture of entire leg will also be taken. All 3D pictures will be recorded and uploaded for central review, measurement of ulcer area, perimeter and volume for the primary and secondary endpoints of the study. Independent experts from patients, CRO, and investigators, will review the 3D pictures centrally at selection (and inclusion, if applicable) as well as the clinical aspect of the RU and will confirm or not the selection (or the inclusion, if applicable). At W000, W004 and W006, the pain level will be assessed before the recording of clinical features of RU.

The primary endpoint will be assessed at 4 weeks.

Four PK samples will be collected at the W000, W004 and W006 visits and one predose PK sample will be taken at W001and W002 visits in all participants. Participants who agreed to participate in the optional PK analysis in participating centres will have 9 PK samples collected over 12 hours at the W000 visit and 13 PK samples collected over 24 hours at the W004 visit.

Number of participants:
Planned selected: 250 participants
Planned included participants: 204 included participants (34 participants per group)

Diagnosis and main criteria for inclusion:

Main selection criteria:
Caucasian (defined for this study as having 2 Caucasian parents) men or women ≥ 18 years of age who have given their written informed consent, with chronic venous disease documented by duplex ultrasonography and with at least one active venous leg ulcer (CEAP C6 stage) diagnosed or reoccurred for more than 6 weeks and less than 2 years at selection. The Reference Ulcer (RU) should be 3 cm away from other ulcers.

- The size of Reference Ulcer (defined as the largest ulcer in size that is fitting the area selection criteria) should be ≥ 5 cm² and ≤ 100 cm^2
- Ankle Brachial Pressure Index (ABPI) should be ≥ 0.8 and ≤ 1.3

Main non-selection criteria:

- Ulcer bed with black necrotic tissue
- Infected ulcer that require local or systemic antibiotherapy
- Recent history of lower extremity deep venous thrombosis within the last 3 months

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- Other non-venous leg ulcer or other associated skin conditions which may influence healing
- Inadequately controlled type 1 and type 2 diabetes, treated or not treated, with an HbA1c > 8% either from the result of a test done within the 3 months before selection or from a result discovered at the laboratory test done within the 5 calendar days prior to the W000 visit.
- Contra-indication to lower limb compression with an applied pressure of approximately 45 mmHg
- Participants who are undergoing treatments known to affect healing within the month prior to selection: pentoxifylline, immunosuppressive drugs, immunomodulators, cytotoxic chemotherapy or oral corticosteroids
- Topical corticosteroids application on and around the ulcer within 15 days prior to selection
- Acetylsalicylic acid treatment started within the last 6 weeks prior to the selection or during the study. Acetylsalicylic acid is allowed if started more than 6 weeks before the selection and remaining stable until the end of the study (i.e.: low dose prophylactic acetylsalicylic acid at antiaggregant dose ≤ 350 mg daily)
- Drugs known to be Breast Cancer Resistance Protein (BCRP) substrates (e.g.: rosuvastatine, sulfasalazine…).
- Participants treated with oral anticoagulant treatments known to be BCRP substrates such as acenocoumarol, fluindione, apixaban, rivaroxaban
- Venoactive drugs within the month prior to selection
- Participants on oral or parenteral antibiotherapy. Long-term, low dose prophylactic antibiotherapy started at least one month before the selection is however acceptable if there is no change in the treatment during the study.
- NSAIDs on long-term chronic treatment within last month, except if taken for less than one week within the last month.

Main inclusion criteria:

- Still eligible as per requirement of selection/non-selection criteria (except for reference ulcer area which should be ≥ 4.5 cm^2 and ≤ 100 cm^2)
- Presence of venous disease characterized by imaging methods (duplex ultrasonography) to detect a venous disorder on both sub- and extra-fascial venous systems. The disorder may be a combination of different manifestations such as venous reflux, venous dilation, thickening of venous wall, etc. The results of the examinations should be available for the inclusion visit
- No clinically significant change in the ulcer healing process available and confirmed by central reading (size and clinical features if applicable).

Main non inclusion criteria:

- Tablet compliance < 80% and > 120 % during the placebo selection period.
- Compliance with the standardized compression regimen < 80% during the placebo selection period.
  - standardized compression regimen: one understocking and one overstocking. The understocking to be worn 24/7. The overstocking applied over the understocking during the day must be removed during the night.
- Clinically significant change in the ulcer healing process showing a change in reference ulcer area of more than 20% or showing unstable evolution or complications (i.e. by infection, erosion) between selection and inclusion.
- Clinically significant abnormalities in laboratory examination (haematology, biochemistry) sampled within the 5 calendar days prior to W000 visit, with the results available at W000 visit (at the latest) before randomisation:

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- Serum albumin < 20g/l
- eGFR <30 ml/min calculated with MDRD formula
- AST or ALT > 3ULN (Upper Limit of normal laboratory range)
- GGT > 3 ULN
- Total bilirubin > 2 ULN
- Clinically significant anaemia (i.e. Hb <10 g/dL)
- HbA1c > 8% in an available result from the previous 3 months in a known diabetic patient or discovered between selection and inclusion (HbA1c > 8% in the laboratory test done within the 5 calendar days prior to the W000 visit).
  Note: If a patient is discovered with hyperglycaemia (fasting blood sugar ≥7 mmol/L) and/or with an elevated HbA1c ≥ 6.5% but ≤ 8% between selection and inclusion, the patient can be included in the study and will be stratified as a diabetic.

Test drug: S42909
S42909 50 mg and 200 mg tablets per os administration, 3 tablets twice a day taken at the end of the morning and evening meals

Comparator: placebo
Matching placebo tablets, per os administration, 3 tablets twice a day taken at the end of the morning and evening meals

Duration of treatment:
- Selection period: 14 days
- Active treatment period: 6 weeks
- Follow-up period: 2 weeks

Criteria for evaluation:
Efficacy measurements:

- Primary endpoint:
  Relative reduction of Reference Ulcer area after 4 weeks of treatment on top of standard of care compared with baseline Reference Ulcer area assessed during study visits using a digital 3D imaging device.

- Secondary endpoints:
  - Reference Ulcer area (ASSE, W000, W001, W002, W003, W004, W006 and W008 visits): relative reduction of Reference Ulcer area after each visit on top of standard of care compared with baseline Reference Ulcer area.
  - Linear advance of the wound margin towards the wound centre (ASSE, W000, W001, W002, W003, W004, W006 and W008 visits) (Gilman, 1990) to measure healing progress at each visit on top of standard of care compared with baseline Reference Ulcer area
  - Reference Ulcer volume (ASSE, W000, W001, W002, W003, W004, W006 and W008 visits): relative reduction of Reference Ulcer volume at each visit on top of standard of care compared with baseline Reference Ulcer volume.
  - Pain assessment (W000, W004, W006 visits): change in intensity and in the characteristics compared with baseline (W000), using a questionnaire including a Visual Analog Scale (VAS).
  - Analgesic drug consumption: dose and/or duration (patient using analgesic drug for Venous Leg Ulcer (VLU) during the study)
  - Safety measurements:
    - Physical examination (ASSE, W000, W001, W002, W003, W004, W006, W008).

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. 6 or 12-leads electrocardiogram (within 5 calendar days prior to W000, W001, W002, W003, W004, W006, W008).
. Laboratory assessments (within 5 calendar days prior to W000, W001, W002, W003 (INR only, if applicable), W004, W006, W008).
. Adverse events (from ASSE to W008).

Other measurements

- Pharmacokinetic measurements

The concentrations of S42909 and its metabolites (S45015, S45236 and S55113) in plasma will be assayed according to validated methods.

- Genomics assessment (W000) (optional):
  . To evaluate potential associations between polymorphisms in relevant genes and the pharmacokinetics of S42909.
  . To identify subgroups of participants with genetic susceptibility to develop non healing venous leg ulcer or to identify novel genes that may play a critical role in the treatment response.

- Non genomic biomarkers assessment (optional):

Plasma and serum samples for assessment of non genomic biomarkers related to venous leg ulcer healing, underlying chronic venous disease and response to S42909 treatment will be collected at the W000 and W004 visits.

Statistical methods:

Study Outcome

Study outcome analyses will be carried out on the RS (Randomised Set).

Main efficacy analysis: Detection of an overall dose-response effect

The objective of the main analysis will be to detect the existence of a dose-response relationship according to the ulcer area reduction expressed as the relative change from baseline to W004 (%) and using the MCP-Mod Method.

Study participants (disposition, baseline characteristics and follow-up) and Safety analysis:

The doses 0 mg (placebo), 100 mg, 200 mg, 400 mg, 800 mg and 1200 mg will be assessed in the study and the following set of 7 candidate models: M = (Linear, Emax (2), Sigmoïd Emax, Logistic, Exponential (2)) will be considered for the main analysis.

For each model in M, optimal contrasts will be defined in order to evaluate the global relevance of model.

Then, a test of contrast will be performed on each model to detect the existence of dose-response relationship with control of the Family Wise Error Rate. The model with the minimum p-value (the one with the strongest statistical test and greater than an appropriate critical value q) will be chosen as the "best" fit model.

As secondary analysis, after reassessment of the parameters of the model selected in the main analysis and considering an hypothesis of clinically relevant difference that is equal to 6.5% (as compared to placebo), a dose window for the Minimal Effective Dose (MED) will be estimated.

Pharmacokinetic analysis

A population PK analysis will be performed in order to describe the pharmacokinetics of S42909 and its metabolites in participants suffering from active venous leg ulcers, to quantify and qualify the sources of PK variability (*i.e.,* covariate analysis), and to provide individual secondary PK parameter estimates (*e.g.,* exposure, terminal half-life).

To further investigate any potential PK/PD relationship, the correlation between S42909 and its metabolites PK and the potential biological markers and clinical outcome (mainly on improving healing of Venous Leg Ulcers and pain related to venous leg ulcers) will be explored. If relevant, population PK/PD analysis will be performed. In addition, the correlation between drug exposure and any evidence of safety signal will be

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studied.
The population PK analysis (and PK/PD analysis, if any) will be described more precisely in a separate data analysis plan.

Biomarkers analysis
The association between healing and plasma biomarkers could be investigated with prognostic approaches e.g. regression models, Receiver Operator Characteristic (ROC) curve.

Contractual signatories

I, the undersigned, have read the foregoing amended protocol and the "Amendment to the Participant information and consent form" document attached to the amended protocol and agree to conduct the study in compliance with such documents, Good Clinical Practice (GCP) and the applicable regulatory requirements.

	NAME	**DATE**	**SIGNATURE**
COORDINATOR / INVESTIGATOR :			

CENTER NUMBER	

Sponsor

MONIQUE CHAMPAGNE 06 MAR 2018

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List of abbreviations

ABPI	:	Ankle Brachial Pressure Index
ADME	:	Absorption Distribution Metabolism Elimination
AE	:	Adverse Event
ALT	:	ALanine AminoTransferase
Anti HCV		Anti Hepatite C virus
AST	:	ASpartate AminoTransferase
ASSE	:	Selection visit
BCRP	:	Breast Cancer Resistance Protein
β-HCG	:	β-Human Chronic Gonadotropine
bid	:	bis in die (twice a day)
BMI	:	Body Mass Index
BUN	:	blood urea nitrogen
CEAP	:	Clincial, Ethiological, Anatomic and Physiopathologic
Cl	:	Chlore
cm	:	Centimetre
cm/mV	:	Centimetre per millivolt
Cmax	:	Maximum Concentration
CPK	:	Creatine Phosphokinase
CRF	:	Case Report Form
CRP	:	C-Reactive Protein
CRO	:	Contract Research Organisation
CSU	:	Clinical Supply Unit
CV	:	Curriculum Vitae
CVD	:	Chronic Venous Disease
CVI	:	Chronic Venous Insufficiency
CWD	:	Continuous Wave Doppler
CYP	:	Cytochrome P
D	:	Day
3 D	:	three-dimensional
DDI		drug-drug interaction
DNA	:	Deoxyribonucleic acid
e.g.	:	exempli gratia (for example)
ECG	:	ElectroCardioGram
e-CRF	:	Electronic Case Report Form
EDTA		EthyleneDiamineTetraacetic Acid
eGFR		Estimated Glomerular Filtration Rate
ERIN	:	Event Requiring Immediate Notification
EWMA	:	European Wound Management Association
FAS	:	Full Analysis Set
FGF-β1	:	Fibroblast Growth Factor
FSH	:	Follicle Stimulating Hormone
FWER	:	Family Wise Error Rate
g	:	Gram
g/dL	:	Gram per decilitre
GCP	:	Good Clinical Practice
GGT	:	Gamma-Glutamyl Transferase (Gamma-Glutamyl Transpeptidase)
h	:	Hour
Hb	:	Hemoglobin
HbA1c	:	Glycosylated Hemoglobin
Hbs	:	Surface antigen of Hepatitis B virus
HCG	:	Human Chorionic Gonadotrophin
HDL	:	High-Density Lipoprotein
HFHC	:	High Fat High Calorie
Hg	:	Mercury
HIV	:	Human Immunodeficiency Virus

HPMC-AS	:	HydroPropyl Methyl Cellulose
HR	:	Heart Rate
HUVEC	:	Human Umbilical Vein Endothelial Cells
i.e.	:	id est (that is)
I.E.C.	:	Independent Ethics Committee
IRB.	:	Institutional Review Board
I.R.I.S.	:	Institut de Recherches Internationales Servier
ICAM	:	IntraCellular Adhesion Molecule
ICH	:	International Conference on Harmonisation
IMP	:	Investigational Medicinal Product (test drug / placebo)
INR		International Normalized Ratio
IWRS	:	Interactive Web Response System
K	:	Potassium
Kcal	:	Kilocalory
K/DOQI	:	Kidney Disease Outcomes Quality Initiative
kg	:	Kilogram
LDL	:	Low-Density Lipoprotein
MCH	:	Mean Corpuscular Haemoglobin
MCHC	:	Mean Corpuscular Haemoglobin Concentration
MCP	:	Monocyte Chemo-attractant Protein
MCP-Mod	:	Multiple Comparisons and Modeling
MCV	:	Mean Corpuscular Volume
MDRD	:	Modification of Diet in Renal Disease
MED	:	Minimal Effective Dose
MedDRA	:	Medical Dictionary for Regulatory Activities
mg	:	Milligram
min	:	Minute
ml	:	Milliliter
mm	:	Millimeter
mm/s	:	Minimeter per seconde
mmHg	:	Millimeter of mercury
MMP	:	Matrix Metalloproteinase
Na	:	Sodium
NA	:	Not Applicable
NADPH	:	Nicotinamide Adenine Dinucleotide Phosphate
NKF	:	National Kidney Foundation
NOSF	:	Nano-Oligosaccharide Factor
NSAIDs	:	NonSteroidal Anti-inflammatory Drugs
NYHA	:	New York Heart Association
PAI	:	Plasminogen Activator Inhibitor
Pcr	:	Plasma Creatinine
PD	:	PharmacoDynamics
PK	:	PharmacoKinetics
p.o	:	Per os
PPS	:	Per Protocol Set
QTc	:	QT interval corrected for heart rate
QTcF		QTc calculated using Fridericia formula
ROC	:	Receiver Operating Characteristic
ROS	:	Reactive Oxygen Species
RS	:	Randomised Set
RT	:	Room Temperatur
RU	:	Reference Ulcer
SAE	:	Serious Adverse Event
SGOT	:	Serum glutamic oxaloacetic transaminase
SGPT	:	Serum glutamic pyruvic transaminase
SNP	:	Single Nucleotide Polymorphisms
SS	:	Safety Set
TGF-β	:	Transforming Growth Factor
tmax	:	time corresponding to Cmax
TNF	:	Tumor Necrosis Factor

TU	:	Therapeutic Units
UGT	:	UDP-Glucuronyl transferase
ULN	:	Upper Limit of Normal reference range
VAS	:	Visual Analog Scale
VCAM	:	Vascular Cell Adhesion Molecule
VEGF	:	Vascular Endothelial Growth Factor
VLU	:	Venous Leg Ulcer
WHO-DD	:	World Health Organization, Drug Dictionary
WMA	:	World Medical Association

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

Non sponsor parties, sponsor parties and CRO responsible for local management of the study are described in a separate document entitled Administrative part of clinical study protocol.

The list of investigators for each country is given in separate documents attached to the protocol and entitled "List of investigators" for Austria, Canada, Czech Republic, Germany, Denmark, Italy, Slovakia, Spain, and the United States of America.

2. BACKGROUND INFORMATION

Venous disease is considered as extremely common and a major cause for seeking medical assistance in Western countries ((Fowkes, 2001); (Beebe-Dimmer, 2005)) costing society more than ten million Euros/year per million people (Carpentier , 2004). Several studies based on the Clinical, Etiological, Anatomic and Physiopathologic (CEAP) classification have shown that a large portion of the general population suffers from symptoms related to venous insufficiency in the lower limbs ((Criqui, 2003); (Jawien, 2003); (Chiesa, 2005)). Epidemiological surveys have suggested that 15% to 20% of the general population have early symptoms, indicative of the disease onset, but without any visible or detectable sign of chronic venous disease (C0s on the CEAP classification) (Andreozzi, 2006).

A more recent epidemiologic study, the Vein Consult Program (VCP), aimed to collect global epidemiological data on chronic venous disorders (CVD) based on the CEAP classification. The range of CVD is from no visible or palpable signs of venous disease (C0) to leg ulcers (C6). Having enrolled 91 545 patients worldwide followed by 6232 general practitioners, results showed that the CVD prevalence is high worldwide: 19,7% of C0s (patients reporting symptoms but without objective signs), 21,7% of C1, 17,9% of C2 and 24,3% from C3 to C6, with C0s to C3 stages predominant whatever the country, and confirmed that CVD affects significant part of the populations worldwide (Rabe, 2012).

Patients with chronic venous insufficiency are prone to develop venous leg ulcers in the ankle and the lower leg (Valencia, 2001).

The annual prevalence of venous leg ulcer is estimated to be between 1.65% and 1.74% in adults aged 65 years and older (Margolis, 2002) and this is expected to grow substantially during the next several decades. In Europe, the prevalence of leg ulcers varies between 0.2 to 1% of the general population ((Ruckley, 2000). Leg ulcer is associated with aging with peak prevalence between 60 and 80 years old (Brem, 2003). In addition, recent studies have shown that one percent of the population developed at least one episode of venous ulcer during a life-time with a higher prevalence in the elderly (Ramelet, 2008).

Chronic wounds result in high morbidity as treatment of leg ulcers requires frequent visits to dispense topical dressings, debridement, compression therapy and skingraft and may needs hospitalisation for complications, mostly leg infections. Despite attempts to improve ulcer healing, this pathology represents an unresolved clinical problem as healing may be slow or never be achieved in a subset of patients. In addition, leg ulcer is characterized by a high incidence rate of recurrent ulcerations reported to be 37% and 48%, 3 and 5 years respectively after wound healing (Brem, 2004).

Chronic venous disease is the result of a multi-factorial pathological process that finally leads to venous stasis and profound deterioration of the microcirculation (Bergan, 2006).

Several modifications in the microcirculation are observed in patients suffering from venous disease. These modifications are initially characterised by a capillary dilatation secondary to raised blood pressure in the microvascular bed and microedema formation leading to worsened skin nutrition. With the evolution of the pathology, a reduced number of functional capillaries are observed due to microthrombosis and/or trapping of white cells, and lymphatic microangiopathy that is characterised by destruction of the micro lymphatic network (Scurr, 1994).

The disruption of the microcirculation induces a cascade of events which may explain ulcer formation: 1) development of oedema responsible for parenchymal cells ischemia by limiting the diffusion of oxygen and nutriments; 2) extravasation and degradation of red blood cells leading to hemosiderin deposition; 3) formation of pericapillary fibrin cuff; 4) accumulation and adhesion of leukocytes in the dermal matrix and release of toxic metabolites (TNFα), proteolytic enzymes (MMPs), and growth factors (TGF-β and its receptor endoglin, FGF-β1, VEGF) ((Korthuis, 2000); (Perrin, 2011); (Raffetto, 2011)).

Vascular Endothelial Growth Factor (VEGF), a potent angiogenic factor, enhances endothelial proliferation and the vascular permeability in the same time with inducing the expression of adhesion molecules such as ICAM-1, VCAM-1 and E-selectin ((Kim, 2001), (Verbeuren, 2000)).
The importance of matrix metalloproteinases (MMPs) has also been discussed due to their involvement in both inflammatory reaction and cutaneous tissue remodeling. Recent studies showed an increased expression of MMP2 in liposclerotic skin (Tarlton, 1999)

Venous hypertension is responsible for the progression of the inflammatory cascade. An inflammatory process is triggered when there is an increased adhesion of circulating leukocytes to the vascular endothelium ((Jacob, 2002); (Howlader, 2003); (Kappelmayer, 2004)) leading to the release of inflammatory mediators. Leukocyte involvement in the process of chronic venous disease (CVD) is supported by the hypothesis of "leukocyte trapping". It refers to the leukocyte adhesion to the endothelium and its migration through the altered endothelium of venous wall and venous valve, possibly leading to valve incompetence and reflux (Bergan, 2007).

Leukocyte activation is followed by synthesis and release of many inflamatory molecules such as leukotrienes, prostaglandins, bradykinin, free oxygen radicals and cytokines. Cytokines act to regulate and perpetuate the inflammatory reaction and thus leading to delayed re-epithelisation and liposlerotic skin remodelling.

In addition, prolonged inflammation generates reactive oxygen species (ROS) by inflammatory cells and vascular cells through the NADPH oxidase pathway. Mechanical stress also promotes the inflammatory response by increasing the expression of other pro-inflammatory molecules, such as monocyte chemo-attractant protein-1 (MCP-1), endothelin-1 and ICAM-1 and secondarily exacerbates ischemia of the surrounding tissue.

The combination of all these pathophysiological factors leads to cellular and tissue dysfunction resulting in dermal changes such as skin fibrosis and ulceration.

S42909 is a synthetic benzo (b) pyran-4-one derivative proposed for the treatment of venous and mixed leg ulcers.

Data available on pharmacology, safety and toxicology on S42909 are detailed in the brochure for clinical investigators. Non-clinical pharmacological studies carried out with S42909 show that it could be a potential new medicine in the treatment of chronic venous disease. By correcting the microcirculatory disturbances related to venous disease, S42909 may represent a powerful leg ulcer treatment.

Pharmacological properties of S42909 may be summarised as follows:

Mechanism of action: S42909 is an inhibitor of leukocyte adhesion to human endothelial cells stimulated with TNF-α, via an inhibition of cell surface adhesion molecules (E-selectin and VCAM-1) expression.
S42909 reduces the oxidative stress through the inhibition of the vascular NADPH oxidase activity. It also decreases the expression of the markers of endothelial cell dysfunction (PAI-1) in HUVEC (human umbilical vein endothelial cells) and MMP-2 activity in venous smooth muscle cells from varicose veins. S42909 shares its pharmacology properties with two of its glucuronides, S45015 and S45236.

- Microcirculation:
  S42909 inhibits hyperpermeability and leukocyte adhesion to endothelial cells induced by ischemia/reperfusion in the microcirculation of the hamster cheek pouch. It protects the microcirculation against ischemic damage and presents an anti-oedema activity in mice and dogs.
- Venous reactivity:
  In rabbits, S42909 prevents the vasodilatation in a pathological model and reinforces the saphenous vein constriction in response to noradrenaline.
- Lymphatic vessels:
  In rats, S42909 reinforces the contractility of the mesenteric lymphatic vessels which should result in an increase in lymphatic flow.
- Healing of ischemia-reperfusion ulceration:
  In a rat model of cutaneous ulcer, S42909 significantly reduces the intensity of ulceration at macro- and microscopic levels and decreases time to heal.

Pharmacokinetics and metabolism in humans

In clinical and non-clinical studies, the absolute bioavailability of S42909 is low after oral administration; however, the rate and extent of absorption was markedly improved by using several different absorbtion-enhancing formulations.

After single oral administration of S42909 (Formulation R, formulation to be used in this study), t_{max} is observed between 3.0 and 4.5 h. UGT-mediated metabolism occurs in the intestine and/or the liver leading to two mono-glucuronides (S45015, S45236) and a di-glucuronide (S55113). The non-clinical data regarding metabolism and drug elimination was confirmed in the human excretion-balance study (PKH-42909-005) in which the majority of the radioactivity was recovered in faeces (94% of the dose) and less than 0.1% of the radioactivity was excreted in urine. S42909 and its three metabolites suffice to account for the total radioactivity in plasma. The highest C_{max} and exposures are reached for S45236.

Overall, after single oral administration of S42909 (in fasting conditions) in young healthy male volunteers, the data suggest a more than proportional increase in exposure with the dose for both S42909 and S45015 and less than the proportional with the dose for S45236.

After repeated oral administration of S42909, steady-state is reached by Day 4, with no accumulation of the parent drug after 10 days of repeated administration of S42909 at 600, 1200 and 1800 mg (with standard meals). Food intake (High Fat High Calorie (HFHC) or standard breakfast) increases Cmax and exposure for S42909 and S45015. S45236 C_{max} and exposure are decreased at 600 mg after a HFHC breakfast.

Results of one combined study (PKH-42909-003) investigating the S42909 drug-drug interactions with a CYP2C9 substrate (warfarin) and with a CYP3A4 substrate (midazolam) showed that S42909 at the dose of 210 mg q.d does not interact with the elimination of warfarin or midazolam, in accordance with circulating concentrations much lower than K_i and supporting a low risk of drug-drug interaction with S42909.

Safety data in clinical studies

Overall, 278 subjects have been enrolled into the S42909 clinical studies; out of these, 203 have received at least one administration of S42909.

S42909 was administered in doses ranging from:

- 105 mg to 840 mg in oral single dose administration and 210 mg to 630 mg in oral repeated dose administration for periods between 5 and up to 14 days, in the Gelucire® 44/14 formulation (currently discontinued),
- 600 mg/day to 2100 mg/day in single oral dose administration and repeated dose administration with the newly developed formulation for 10 days.

Overall, S42909 was well tolerated up to the dose of 1800 mg in oral single dose and 1200 mg in oral repeated dose administration. There were no clinically relevant abnormalities concerning biologic and hematologic parameters, physical examination, vital signs or on ECG tracings.
The majority of the reported Treatment Related Emergent Adverse Events were mild or moderate, mainly diarrhoea probably due to the laxative effect of main excipient a cellulosic derivative.
During the conduct of the CL1-42909-013 dose-escalation study, diarrheic episodes were reported in several subjects starting from the daily dose of 1200 mg of S42909. The episodes increased in frequency, duration and severity when escalating the dose and at the same dose when passing from single dose administration to repeated dose administration. Typically, the episodes were mild to moderate in intensity occurring rapidly after study drug intake and resolved spontaneously the same day.

The tolerability of S42909 in a b.i.d. schedule of administration was investigated and allowed to reduce the frequency of the diarrhoea.

Study design and population

This study will be a parallel group, dose-finding study. 204 participants with an active venous leg ulcer (CEAP C6 classification) occuring in the presence of documented pure venous disease in a limb with 0.8 ≤ Ankle Brachial Pressure Index (ABPI) ≤ 1.3 and no other significant medical disease preventing the use of high compression therapy (Position Document EWMA, 2003) will be included.

The participants will be randomised into one dose group or placebo group. The placebo arm will allow the evaluation of the effect of treatment in addition to the standard existing therapy.

Participants will be treated on top of the standard of care in all treatment arms with compression and local wound care. Compression therapy is the current standard treatment for venous ulcers. Compression is directed at lowering venous hyperpressure. Numerous studies have confirmed that the proportion of complete ulcer healing is improved when high compression is used (O'Meara, 2012). To apply uniform standard care procedures, high compression stockings (approximately 45 mmHg working pressure) with individually adapted-sizes will be provided to all participants selected in the study.

Justification of the treatments, doses to be administrated

The dose selection was based on the safety and pharmacokinetic data from Phase 1 studies. Considering the variability in exposure of the parent compound and its metabolites and in order to avoid overlap of exposure between dose groups a factor 2 between two consecutive doses has been chosen (except for the last step). Consequently the doses to be investigated in this study will be 100, 200, 400, 800 and 1200 mg of S42909 per day.

The highest dose of S42909 to be administrated during this study will be 1200 mg/day as this dose was administrated in the CL1-42909-013 study and showed a good tolerability after single and repeated administration. At this dose level no safety concerns were raised. Mild to moderate intermittent diarrhoeic episodes have been reported which stopped after 6 days of administration.
Taking into account the positive food effect on drug absorption (CL1-42909-013), the IMP treatment will be taken at the end of the meals.

Participants will start a 14-days placebo selection treatment period to check their compliance with the IMP treatment and compression stockings, then start a 6-weeks IMP treatment being randomised equally in each treatment group (one dose or placebo) taking into account stratification factors. Finally, the participants will be followed-up during 2 weeks after the last intake of study treatment.

Patients will be assigned to one of the six treatment arms by an algorithm of randomisation meant to ensure balanced allocation in all respective arms of treatment. Participants in the optional PK will be randomised too, in order to ensure balanced allocation in all arms of treatment. Standard wound care treatment and baseline ulcer characteristics generally have a significant effect on progression of healing. Therefore it is planned to consider the following stratification factors:

- 1. Country - to account for the variation in wound care from one country to another
- 2. A prognostic factor for healing based on the wound characteristics (wound size and duration).
- 3. Diabetic status (yes/no)

Efficacy assessment

The evaluation of therapeutic response in patients with venous leg ulcers is difficult due to the long time needed to observe complete wound healing.
Whereas the complete healing remains the final goal for treating these patients (Guidance FDA, 2006), it would be of a great value to clinicians as well as to patients to have a reliable estimate of the time to total healing based on early progress in a given treatment regimen. This is especially important for chronic leg ulcers where the expected healing time with standard care may be 6 months or more. Today, the standard practice for the treatment of chronic wounds includes monitoring of the wound size at regular intervals.

A reliable qualification of the percentage of change in wound area over time is a significant prognostic measure of complete healing (Kantor, 2000). A study using a large cohort of venous leg ulcer patients has demonstrated that the percentage of change in wound area after 4 weeks of treatment can be a valid surrogate marker of healing at 12 or 24 weeks of care (Gelfand, 2002).

Consequently, in the current study, the primary efficacy endpoint will be the relative reduction of the reference ulcer area after 4 weeks of treatment. In order to establish a dose-response relationship between S42909 and the relative reduction of ulcer area, the "MCP-Mod" statistical methodology (Bretz and Al, 2005) will be applied. Based on a set of candidate models, the existence of an overall dose-response relationship will be assessed and, if observed, the best model will be used, after re-estimation of parameters and convergence, to evaluate the dose window able to produce a clinically significant effect.

Measurements of the ulcer area will be performed using a 3D imaging device and the accompanying software. The same equipment will be provided to all centres in order to standardize the ulcer measurement methodology: images will be recorded using the same type of camera with automatic adjustment of light, focus and color reproduction according to distance to the ulcer and measurements will be performed centrally on the provided images.

The study will be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

3. STUDY OBJECTIVES AND PURPOSE

The purpose of this study is to investigate if S42909 at any dose has an effect on healing of venous leg ulcer (proof of concept) and to explore the relationship between dose and effect of S42909 on venous leg ulcer healing on top of standardized compression and local wound care.

Assessment of efficacy will be performed on the relative reduction of the reference ulcer area after 4 weeks of treatment as compared to baseline using a digital 3D imaging device, a

surrogate endpoint which is positively correlated with chances to heal after 12 or 24 weeks of treatment.

3.1. Primary objective

The primary objective of the study is:

- To detect the existence of an overall dose-response relationship with S42909 on improving healing of venous leg ulcers on top of standard of care (compression and local wound care) after 4 weeks of treatment.

3.2. Secondary objectives

The secondary objectives of the study are:

- To determine a dose window for the Minimal Effective Dose (MED) on improving healing of venous leg ulcers.
- To explore the effect of S42909 on improving healing of venous leg ulcers on top of standard of care (compression and local wound care) after 6 weeks of treatment.
- To explore the effect of S42909 on improving pain related to venous leg ulcer over 6 weeks.
- To explore the effect of S42909 on decreasing analgesic drug consumption related to venous leg ulcer over 6 weeks.
- To assess the safety profile of each tested dose of S42909 (adverse events, laboratory parameters, physical examination, body weight, vital signs (blood pressure, heart rate), 6 or 12-lead electrocardiogram (ECG). and standard urinalysis).
- To assess the pharmacokinetics of S42909 and its metabolites in patients after repeated administration of S42909.

3.3. Additional objectives

- To assess any potential PK/PD relationship (mainly on improving healing of venous leg ulcers and pain related to venous leg ulcer).
- Genomic assessment of S42909:
  - To evaluate potential associations between polymorphisms in relevant genes and the pharmacokinetics of S42909.
  - To identify subgroups of patients with genomic susceptibility to develop non healing venous leg ulcer or to identify novel genes that may play a critical role in the treatment response
- To collect the blood non genomic biomarkers which can be related to venous leg ulcer healing, underlying chronic venous disease, response to S42909 treatment (bio-collection in a bio-repository).

4. STUDY DESIGN

4.1. Endpoint(s)

Table (4.1) 1 – Endpoints

	Endpoints
Primary	Relative reduction of Reference Ulcer area after 4 weeks of treatment
Secondary	Relative reduction of Reference Ulcer area after each visit
	Linear advance of the wound margin towards the wound centre
	Reference reduction of Reference Ulcer volume at each visit
	Pain assessment by VAS
	Analgesic daily dose
	Safety assessment
	Adverse event
	Laboratory parameters
	Physical examination, body weight, vital signs
	6 or 12-leads electrocardiogram
Exploratory	Pharmacokinetics in plasma
	Genomic in blood
	Non genomic biomarkers in plasma and serum

4.1.1. Primary Efficacy Endpoint

- Relative reduction of Reference Ulcer area after 4 weeks of treatment on top of standard of care compared with baseline Reference Ulcer area assessed during study visits using a digital 3D imaging device.

4.1.2. Secondary Endpoints

- Reference Ulcer Area using a digital 3D imaging device: Relative reduction of Reference Ulcer area after each visit on top of standard of care compared with baseline Reference Ulcer area.
- Linear advance of the wound margin towards the wound center (Gilman, 1990) to measure healing progress at each visit on top of standard of care compared with baseline (see section 10 for more details)
- Reference Ulcer volume using a digital 3D imaging device: relative reduction of Reference Ulcer volume at each visit on top of standard of care compared with baseline Reference Ulcer volume.

- Pain assessment (W000, W004, W006): change in intensity and in the characteristics at each visit compared with baseline (W000), using a questionnaire including a VAS scale
- Analgesic drug consumption (W0, W4, W6): change in daily dose of analgesic taken for VLU at each visit compared with baseline (W000) (patient using analgesic drug for VLU during the study)
- Safety measurements
    - Adverse events occurring during the double-blind period of the study.
    - Assessment of laboratory parameters, physical examination, body weight, Vital signs (blood pressure, heart rate), 6 or 12-lead electrocardiogram (ECG).

4.1.3. Other Endpoints

- PK assessment: PK of S42909 and its metabolites will be measured in patients with venous leg ulcer at W000, W001, W002, W004 and W006 and will be analysed by population PK approach.
- Sample collection and storage for genomic exploratory analysis of samples collected at W000.
- Sample collection and storage for non genomic biomarker analysis of samples collected at W000 and W004.

4.2. Experimental design

4.2.1. Study plan

This is a phase IIa, prospective, international, multicentre, randomised, double-blind, placebo-controlled, parallel group, dose-finding study in patients with venous leg ulcer.

The study will consist of 3 periods as follows:

- A selection period of 14 days of placebo treatment in which participants will be investigated for documenting the presence of Chronic Venous Disease and assessment of type and size of Reference Leg Ulcer. Their clinical and biological status will be documented prior to inclusion. From the selection visit, standard of care will be changed to standardized compression and local wound care with sterile saline solution or sterile water and “non active” dressings.
- A double-blind controlled period of 42 days: 6 weeks of treatment with one dose of S42909 or placebo on top of standardized compression and wound local care.
- A follow-up period of 2 weeks with standard of care only after the last dose of S42909 (from W006 to W008).

An Interactive Web Response System (IWRS) will be set up for participant selection/inclusion randomisation and allocations of the therapeutic units pack numbers.

About 250 patients suffering from chronic venous disease and having at least one active venous ulcer matching with the selection criteria (CEAP classification C6 stage) will be selected at the selection visit (ASSE) to include 204 participants at W000 visit.

During the ASSE visit, the underlying chronic venous disease will be documented and recorded in the participant medical file according to CEAP classification. To document the chronic venous disease, a duplex ultrasonography should have been performed within the previous 6 months or will have to be performed during ASSE or the placebo selection period

of 14 days to have the results before inclusion and allow verification of compliance with the inclusion criteria. If data of the duplex ultrasonography report performed in the previous 6 months doesn't permit to fill in the e-CRF and/or to rule out an acute venous thrombosis, a duplex ultrasonography must be performed before inclusion. The presence of a peripheral arterial component of the disease must be ruled out by measuring and calculating the ankle-brachial pressure index (ABPI) ideally by continuous waves Doppler, otherwise by duplex ultrasonography (see Appendix 5) before applying high level compression (Mosti, 2009).

During the selection visit (ASSE), one Reference Ulcer (RU) defined as the largest ulcer in size that is fitting the area selection criteria will be established for each participant.

At ASSE visit, the clinical aspect of the RU will be documented by the investigator by recording the clinical features of the wound on the clinical assessment document.

The investigator (or a designated person) will take two 3D pictures of the RU using the digital 3D devices provided to the site. Only at ASSE, a first picture will be taken before cleansing and debridement and a second picture will be taken after cleansing and debridement. In addition, only at ASSE, the investigator will take a 3D picture of the leg where the RU is located, fully covering the gaiter area. The 3D pictures will be uploaded on a secured website and recorded using a standardized procedure. From W000 to W008, 3D pictures will be performed only after cleansing and debridement. The same procedure will be used to send the pictures to the RU central reviewer. The investigators (or a designated person) will be trained to use the device.
The investigator or a designee will use a transparent sheet that will be provided to trace the RU outlines and measure the RU area at the selection visit after cleansing and debridement. The investigator or designated person will record the measured RU area of this outline and check that the area is fitting the selection criteria. The selection will be based on the investigator's RU area measurement and the compliance with the selection/non selection criteria.

The participants successfully selected will start the selection period and will be switched from their current pharmacological and/or local treatment (if any) for venous leg ulcer to standardized compression stockings provided to the sites and local wound care with sterile saline solution or sterile water, "non-active" dressings (see section 4.4.1). They will be given the placebo selection treatment for a period of fourteen days. Prior to first dispensation supply, the participants will be trained on the use of stockings.
The RU area will also be centrally measured by the CRO within the 3 working days following the selection visit and the measurement will be sent back to the investigator. The picture performed at selection after cleansing and debridement will be the reference for measurement of changes between the selection (ASSE) and inclusion (W000) pictures.

Following the selection, an independent expert will review centrally the clinical aspect of RU. The expert will give an opinion on the RU selection by reviewing the clinical aspect of the RU. The review will be based on the clinical analysis of the two 3D pictures taken by the investigator (or a designated person) at selection visit (before and after cleansing and debridement). In addition, the expert will also review the 3D picture of the leg where the RU is located, taken at the selection visit. The expert will confirm the selection if RU clinical pictures are consistent with a venous aetiology, or give a recommendation for study continuation. In case of doubt on the venous aetiology of the ulcer, the expert can send the picture to another expert for double review.

If the central measurement of the RU area is not fitting the RU area selection criteria and/or if the RU clinical aspect is not suitable for the study according to the independent expert, the participant who has been selected must be withdrawn before inclusion in the double-blind phase of the study.

Three (or four) working days before the inclusion visit (W000) at the latest, the participants will come to the site for a RU picture: after wound cleansing and debridement, the investigator (or a designated person) will take a 3D picture of the RU using the digital 3D imaging device provided to the site and upload this picture on the same day to a secured website for central review. As the local wound care is done at the same time, he will also perform RU clinical assessment, and pain will be assessed by VAS during W000 visit.

In case of persistent doubt after double review of the picture taken at selection, the independent expert will recheck the features of the RU and its venous aetiology with the help of the 3D picture taken before the inclusion visit. The result of the independent expert review will be given within three working days. If the doubt persists at the review of the picture taken at inclusion, the patient will not be included.

The CRO in charge of the central reading of pictures will perform RU area measurement before W000 and send it back to the investigator within 3 working days together with the central RU area measured at ASSE and the change between ASSE and W000 area measurements.

At the end of the placebo selection period, participants will return to the investigator site for inclusion visit and randomisation (W000).

At W000, the investigator will check that the RU area measured centrally at ASSE is consistent with his/her measurement, that independent experts validation is done, and will re check the selection criteria.

- If the central measurement of ASSE RU area is not fitting the selection criteria, the participant will not be included.
- If the central measurement of ASSE RU area confirm the RU area selection criteria, the investigator will check that the participant complies with the inclusion criteria, the recommendations for compression (stockings wearing ≥ 80% of the time according to diary information) and is compliant with placebo selection treatment (between 80 and 120%). The relative change of RU area compared with the RU area measured at ASSE visit must be less or equal to 20% in order for the participant to be eligible for inclusion. This relative change calculated centrally will be used to check the compliance with the inclusion criteria.
- Patients found to be eligible for randomisation will have a 3D picture of the RU on the day of W000, taken after randomisation and after wound bed preparation. This picture (W000-B) will be the baseline measure for comparison with all subsequent pictures taken at following visits.

All participants found to be eligible for inclusion will be randomised to one of the following six groups - S42909 100, 200, 400, 800 or 1200 mg per day - or placebo. The randomisation will be performed using a centralised, dynamic, balanced with 1:1:1:1:1:1 ratio, stratified randomisation according to the country, a combined prognosis criterion (age and size of ulcer, using the RU area measured centrally at W000), and diabetic status (yes/no) by the IWRS. For stratification purposes, will be considered diabetic patients those with an already

confirmed diagnosis of diabetes as well as previously unknown diabetic patients with a fasting blood sugar ≥7mmol/L and/or an elevated HbA1c value between 6.5 and 8% on pre-inclusion laboratory results.
The participants will enter a 6-week ambulatory IMP treatment period on top of standard of care (standardized compression and local wound care with sterile saline solution or sterile water and "non-active" dressing) followed by a 2-weeks follow-up period with standard of care only. During this period the participants will return to the investigator's site for intermediate visits after one week (W001), two weeks (W002), three weeks (W003), four weeks (W004), six weeks (W006) and eight weeks (W008). Participants will continue to receive standardized compression therapy and local wound care (sterile saline solution or sterile water and "non-active" dressing) until the end of the study (W008). At W000, W004 and W006 visits, pain assessment will be performed at the beginning of the visit using a questionnaire with VAS. At each visit, the clinical features of the RU will be recorded and a 3D picture of the RU will be taken after wound bed preparation. All 3D pictures will be recorded and uploaded for central review, measurement of ulcer area, perimeter and volume for the primary and secondary endpoints of the study.

Four PK samples will be taken at W000, W004 and W006 visits and one predose PK sample will be taken at W001 and W002 visits in all participants. The participants who agreed to participate in the optional PK analysis in participating centres (7 patients per dose group) will have 9 PK samples collected over 12 hours at W000 visit and 13 PK samples collected over 24 hours at the W004 visit instead of the 4 PK samples.

At each visit general compliance with standardized compression will be checked and size of the stockings will be adjusted, if needed. The participant should be explained that the standardized compression stockings should be worn everyday and used according to the recommendations given by the investigator.

- If complete healing of the reference ulcer is observed during the study conduct but other ulcers are still open, the participant will keep the same standardized compression until complete healing of all ulcers is observed or until the end of the study and will continue to take IMP treatment until W006 visit.
- If complete healing of all ulcers (including the reference ulcer) is observed, the participant will keep the same standardized compression until the end of the study or be switched to a compression for leg ulcer recurrence prevention (> 18 mmHg) if the participant refuses (this type of compression will not be provided to the sites). The participant will continue to take the study drug until W006.

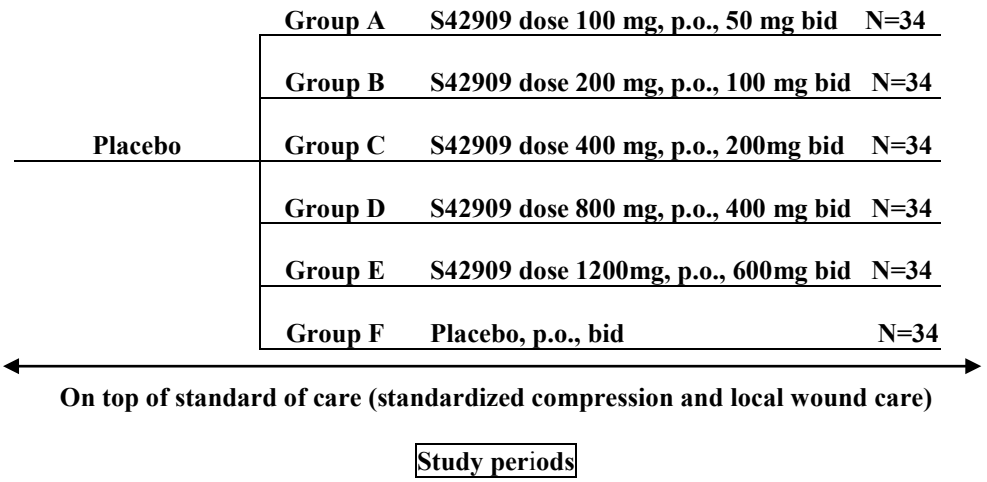
The end-of-study visit is scheduled to take place at W008 or, in case of prematurely withdrawn participants as soon as possible, after stopping the use of standardized compression, or after the last IMP intake. In case of premature withdrawal, the next expected visit will be performed. If the next expected visit is W003, biochemistry and haematology should be added to the assessments to be performed during this visit.

An electronic case report form (e-CRF) will be used for data capture during the study.

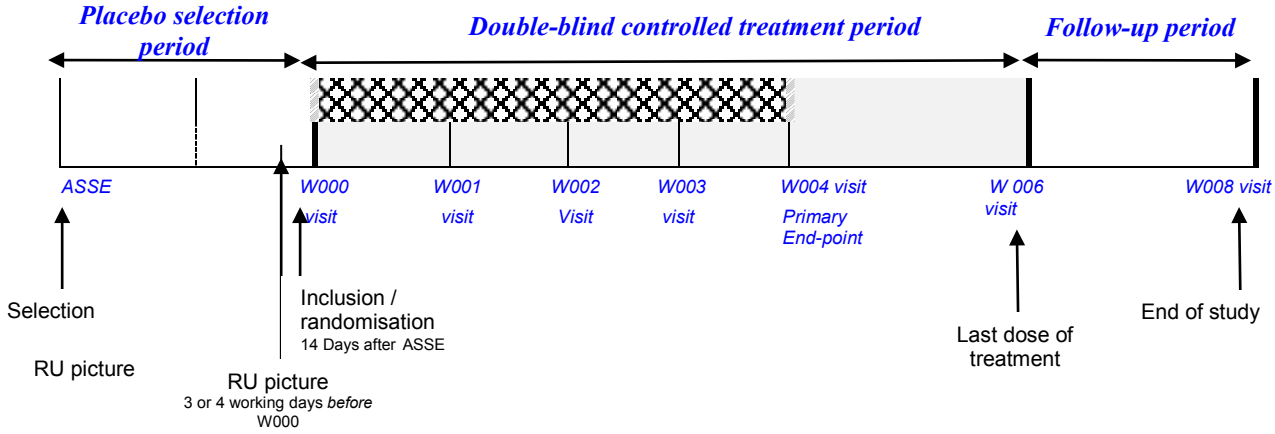
The study plan is shown in Figure (4.2.1) 1.

Figure (4.2.1) 1 - Study plan

- Treatment periods-



Study periods



4.2.2. Investigation schedule

Table (4.2.2) 1 describes the measurement of efficacy and safety assessed during the study.

Table (4.2.2) 1 - Investigation schedule

	Selection	**Inclusion**	**Treatment period**					**End of Study**
	ASSE	W000	W001	W002	W003	W004	W006	W008
Visits Time windows	D –14	D0 ±2 days	D0 +7 days ±2 days	D0 +14 days ±2 days	D0 +21 days ±2 days	D0 +28 days ±2 days	D0 +42 days ±4 days	D0 +56 days ±4 days
Informed consent	X							
Selection / non-selection criteria	X							
Inclusion / non-inclusion criteria		X						
Previous treatment	X							
Medical / surgical history	X	X(1)						
Concomitant treatments	X	X	X	X	X	X	X	X
CEAP classification	X							
CVD imaging (duplex ultrasonography (2)	X							
ABPI measurement (Doppler ultrasound)	X							
IWRS connexion (3)	X	X		X		X		
Treatments								
Treatment dispensing	X	X		X		X		
Local wound care	X	X	X	X	X	X	X	X
Standardized compression education	X	X						
Standardized compression dispensing	X							
Leg measurements	X	X(4)	X(4)	X(4)	X(4)	X(4)	X(4)	
Treatment Compliance		X	X	X	X	X	X	
Compliance stocking wearing (diary)		X	X	X	X	X	X	X
Efficacy measurements								
3D Picture	X (5)	X (6)	X	X	X	X	X	X
Reference Ulcer area measurement (investigator)	X							
Reference Ulcer area measurement (central)	X (5)	X (6)	X	X	X	X	X	X
Reference Ulcer features Validation (Independent expert)	X	X (7)						
Pain assessment by VAS (8)		X				X	X	
Analgesic drug – consumption		X				X	X	
Clinical assessment of RU	X	X (9)	X	X	X	X	X	X
Safety measurements								
Adverse events	X (10)	X (10)	X	X	X	X	X	X
β-HCG (women with childbearing potential) (11)	Prescription(16)	Results(16)				X		X
FSH (menopausal women)	Prescription(16)	Results(16)						
Physical examination	X	X	X	X	X	X	X	X
Vital signs (HR, SBP, DBP, body temperature)	X	X	X	X	X	X	X	X
Body weight	X	X		X			X	X
Height (for BMI calculation)	X							
ECG 6 or 12-lead (12)	Prescription(16)	Results(16)	X	X	X	X	X	X
Biochemistry and haematology (13)	Prescription(16)	Results(16)	X	X		X	X	X
INR(17)	Prescription(16)	Results(16)	X	X	X	X	X	X
Standard urinalysis (dipstick)	Prescription(16)	Results(16)				X	X	X
Other assessments								
Blood sampling for PK (14)		X	X	X		X	X	
Blood sampling for genomic		X (15)						
Blood sampling for non genomic biomarkers (biorepository)		X (15)				X (15)		

(1) events occurring before the first intake of the test drug and not associated with a procedure scheduled in the study protocol (duplex, blood sampling, etc.), a withdrawal of treatment related to the conditions of the protocol, a product other than the IMP, taken as part of the protocol will be recorded in the medical history (see section 8.3.2.6 Recording methods).
(2) if no duplex ultrasonography available within 6 months prior to selection and or/ insufficient data to fill in the e-CRF and /or suspicious of acute Venous Thrombosis (at ASSE or during the selection period).
(3)IWRS connections to obtain patient number (ASSE), randomisation of patient & allocation of TU (W000), reallocation of TUs (W002; W004) and in case of premature withdrawal (withdrawal visit).
(4) check that the size allocated at selection is still applicable according to the leg measurements. If the size has changed, adequate compression stockings size will be supplied.
(5) To be done and uploaded to central review on the day of ASSE visit to receive the central RU area measurement within 3 working days.
(6) To be done and uploaded to central review 3 or 4 working days prior to W000 visit at the latest to receive the central RU area measurement before W000. Additionally, patients found to be eligible for randomisation will have a baseline 3D picture of the RU (W-000B) on the day of W000, taken after randomisation and after wound bed preparation and before the 1st dose of IMP is administered.
(7) in case of doubt on venous aetiology of the RU after the double check of the picture taken at ASSE.
(8) Pain assessment should be performed at the beginning of the visit, before RU clinical assessment and care of the RU.
(9) The RU clinical assessment will be performed when the participant comes for the picture 3 or 4 working days before W000.
(10) Events occurring between the signing of the consent form and the inclusion visit (inclusion visit included) and associated with a procedure scheduled in the study protocol (Doppler, duplex ultrasonography, blood sampling, etc.), or a withdrawal of treatment related to the conditions of the protocol, or a product other than the IMP taken as part of the protocol will be recorded on an Adverse Event form (see section 8.3.2.6 Recording methods).
(11) Depending on the local regulation, pregnancy tests can be repeated throughout the treatment period.
(12) ECG must be done before blood sampling.
(13) In fasting condition for 10 hours.
(14) Four PK samples will be taken at W000, W004 and W006 visits and one predose PK sample will be taken at W001, W002 visits in all participants. The participants who agreed to participate in the optional PK analysis in participating centres will have 9 PK samples collected over 12 hours at W000 visit and 13 PK samples collected over 24 hours at W004 visit instead of the 4 PK samples and will be assigned to a dose group by the IWRS.
(15) Before the IMP intake and after specific consent collected for these optional samplings.
(16) β-HCG, FSH, biochemistry, HbA1c (if a result from previous 3 months is not available), haematology, urinalysis and ECG prescribed at ASSE visit: they should be collected within the 5 calendar days prior to W000 visit, with the results available to be checked at W000 visit (at the latest) before randomisation.
(17) INR to be followed at each visit (or more often if judged necessary by the investigator) if patient is under anticoagulant therapy with warfarin or phenprocoumon.

The maximum total volume of blood collected per participant during the study will be around 304 ml for the mandatory study and around 410 ml in case of optional pharmacokinetic analysis, genomic and non genomic biomarkers sampling.

Table (4.2.2) 2 - Pharmacokinetic Investigation Schedule

Time relative to the first administration on the visit day	Pre-dose	0h	1h	2h	3h	End of visit (2)	4h	5h	6h	8h	12h (4)	13h	14h	15h	24h
IMP intake at the end of the meal		X									X				
PK Blood sampling for all participants: W000, W004, W006 (3)	X(1)		X		X	X									
PK Blood sampling for all participants: W001, W002	X(1)														
PK Blood sampling over 12-hours for participants having agreed to this optional PK analysis: W000	X(1)		X	X	X	NA	X	X	X	X	X(1)				
PK Blood sampling over 24-hours for participants having agreed to this optional PK analysis: W004	X(1)		X	X	X	NA	X	X	X	X	X(1)	X(5)	X(5)	X(5)	X (1),(5)

(1) PK sampling before meal and IMP administration.
(2) Blood sampling will be performed in all patients at the end of the study visit, just before leaving or at T4h if possible.
(3) Except at W000 and W004 for patients participating to the optional PK blood sampling over 12 hours and 24 hours respectively.
(4) Could be adjusted to a maximum of 2 hours before, to accommodate a more convenient dinner time.
(5) PK sampling schedule for H13, H14, H15 and H24 is relative to the evening IMP administration (respectively 1, 2, 3 and 12h after evening IMP administration).
NA: Not Applicable

For further practical details, methods of measurement are provided in sections 7, 8 and 9.

4.3. Measures to minimise bias

The following measures are taken to avoid or minimise bias:

- This is a double-blind study.
- All treatments will be identical to protect the blinding for the participants and the investigators.
    - All tablets of S42909 or its placebo will be identical in form and appearance
    - Packaging and labelling of all treatment groups will be identical
    - The number of tablets will be identical for all groups
- Participants will be distributed within each group of treatment equally by a centralised, dynamic, balanced with 1:1:1:1:1:1 ratio, stratified randomisation according to the country, a combined prognosis criteria for venous ulcer healing, and diabetic status.
- Participants in the optional PK analysis will be distributed across treatment arms

The combined prognosis criteria (size and age of ulcer) are:
A : ≤ 10 cm² and ≤ 6 months
B : > 10 cm² or > 6 months

- At the inclusion visit, a centralized randomisation using the IWRS will randomly assign the participants to one of the six treatment groups. The randomisation algorithm will be built by CRO IWRS according to an adaptive randomisation by minimisation.
- The pictures of the ulcers will be performed by the same 3D imaging device in all centres. The investigators (or designee) will be trained in the use of the device.
- The area, perimeter and volume measurements of the reference venous leg ulcer will be performed centrally by a CRO following the same measurement methodology for all patients during the entire study. CRO experts in charge of the central reading will be all trained on that methodology. The use of the 3D imaging device and software standardize the reference ulcer measurement methodology.

4.4. Study products and blinding systems

4.4.1. Products administered

- **Study drug:**

During the selection period (from ASSE to W000), the participant will receive placebo selection oral treatment.

During the double-blind treatment period (from W000 to W006), the participant will be treated with one of the 5 oral doses of S42909 or placebo.

At W006, the participants will stop the IMP treatment until the end of the follow-up period (W008). The standardized compression with the local wound care applied during the study will be continued.

The tablets of placebo and S42909 (dosages 50 and 200 mg) will have identical appearance.

The regimen will be 3 tablets twice a day taken at the end of the meals (3 tablets taken in the morning and 3 tablets in the evening) with a glass of water (250 ml). 3 tablets twice a day are necessary to reach each of the 5 doses used in the study and keep the blind for all participants.

On the day of the study visit, the participant will not take his/her morning study drug treatment before the study visit to ensure that pharmacokinetic samples are taken before next dose. He/she will take the study drug during the visit after pre-dose PK sampling and at the end of the breakfast.

Table (4.4.1) 1 provides a description of the IMP(s).

Table (4.4.1) 1 - Description of the IMPs

	50 mg S42909	200 mg S42909	Placebo
Pharmaceutical form	Film-coated tablet	Film-coated tablet	Film-coated tablet
Unit dosage	50 mg of S42909-1	200 mg of S42909-1	-
Appearance, colour	Oblong, red	Oblong, red	Oblong, red
Composition*	Lactose monohydrate		Lactose monohydrate

** only excipients to have a recognized action*

Table (4.4.1) 2 provides a description of the packaging of the IMP(s).

Table (4.4.1) 2 - Description of packaging for Selection and IMP treatment period

Number of units of the pharmaceutical form per primary packaging	18 tablets per blister (6 rows of 3 tablets)
Number of primary packaging per secondary packaging	6 blisters per sachet
Number of secondary packaging per participant and per treatment period	**Selection period** 1 kit (i.e. small box) with 1 sachet per participant **Double-blind controlled period** W000-W002: 1 kit (i.e. small box) with 1 sachet per participant W002-W004: 1 kit (i.e. small box) with 1 sachet per participant W004-W006: 1 kit (i.e. small box) with 1 sachet per participant

The labelling of packages complies with the regulatory requirements of each country involved in the study, as well as the recommendations in appendix 13 of the European Guide to Good Manufacturing Practice (http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf) and with US recommendations (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm).

- **Standardized compression and local wound care:**

Standardized compression (compression stockings) will be provided to all participants according to the leg measurement chart and will be applied throughout the study (from ASSE to W008). The participants will be trained by their investigator to the use of the stockings.

The compression stocking kit provided consists of two understockings and one overstocking. The materials of the compression understocking are polyamide, elastane, and cotton, and the materials of the compression overstocking are polyamide, elastodiene, and cotton. The understocking is first applied on the leg up to the knee over the dressings protecting the ulcer and has to be worn 24/7. The overstocking is then applied over the understocking during the day and must be removed during the night.

The stockings have to be worn for one day and then be washed to recover the initial compression properties. That is why two understockings and one overstocking will be provided to each participant.
The cleansing of the wound should only be done with sterile saline solution or sterile water. No antiseptic solution (e.g. Prontosan® –betaine/polyhexanide, Chlorexidine) is allowed during the study conduct (from ASSE to W008).
The debridement should only be mechanical (except wet-to-dry gauze dressings): only Stiefel curette and spoon are allowed. Local anaesthetics are allowed for the debridement. Autolytic, enzymatic, absorptive dressings, surgical and shaved debridement are not allowed.
The primary dressings usually used at the site and adequate for the ulcer will be applied taking into account that "active" dressings are not allowed during the study (e.g. silver dressings, NOSF -nano-OligoSaccharide Factor- dressings, ibuprofen dressings) and that the dressing to be applied are: hydrogel for dry wounds, hydrocellular foam dressing for normal or exudative wounds and alginate dressing for very exudative wounds, or bleeding wound or fibrinous wound.

4.4.2. Treatment management

- **IMP management**:

Manufacturing, packaging, labelling and dispatching of the IMP to the sites will be the responsibility of Les Laboratoires Servier Industrie - Clinical Supply Unit (CSU) (905 Route de Saran, 45520 Gidy, France).

The investigator and/or the person assigned by him and/or the pharmacist of the healthcare institution are responsible for the treatment management (receipt, storage, dispensing, accountability).

IMPs will be stored at controlled temperature according to the specifications given by the labelling of the therapeutic units in a dry and secure room with restricted access, under the investigator's or designated person responsibility.

IMP management will be verified on a regular basis by the study monitor.

At reception of IMPs, the responsible person must return as soon as possible the acknowledgment of receipt, duly completed and signed to the address given on the document and contact IWRS to acknowledge therapeutic units receipt as the system will ensure the stock accountability and automatic restock. All defects or damaged IMP must be declared to IWRS by the dedicated functions.

The investigator/pharmacist is responsible for the IMP temperature monitoring on a daily basis with the recording of Min-Max temperature every working day and the documentation in a temperature log sheet.

In case of temperature deviations the investigator/pharmacist should immediately:

- Block the concerned IMPs in IWRS and place them in quarantine,
- Alert the monitor or the local project manager if the monitor is absent, forward him/her all required information and follow the instructions received.

Furthermore the investigator/pharmacist must put in place an adequate action plan once the first temperature deviation occurs in order to avoid recurrence.

The IMP boxes will be allocated by strictly following the instructions included in IWRS manual and IWRS connections will be performed at ASSE, W000, W002, W004 visits (for the description of dispensing methods, refer to section 6.2 (Treatment dispensing).
The investigator and/or the pharmacist of the healthcare institution should only use the treatment provided for the participants involved in the study. The participants must return all unused study drugs to the site.

The investigator and/or the pharmacist of the medical institution and/or a designated person from their study team must complete in real time all documents provided by the sponsor concerning treatment management

- IMP receipt, allocation and dispensing to the participants and study drugs returned by the participants will be completed in a therapeutic unit tracking form or equivalent form in the centre. Therapeutic unit tracking form (or equivalent form in the centre) is the source document to be completed.
- IMP dispensing and return will also be recorded in the e-CRF.

The detachable portion of the label on the IMP box must be affixed on a treatment label collection form by the investigator or the pharmacist when the IMP box is given to the participant**.**

The investigator will notify the monitor of all complaints set out by a participant within 24 hours (change of taste, appearance…).

Remaining IMPs at site will be collected by the study monitor and returned to a storage or destruction site. A tracking form for the recovery and destruction of the IMPs must be completed and attached to the remaining IMPs sent for destruction.

In the event of anticipated return of IMPs to the sponsor (batch recall), the sponsor will prepare an information letter intended for the investigator and/or pharmacist of the medical institution. This letter will be sent to each study centre by the person locally responsible for the study. On receipt of the letter, the investigator and/or the pharmacist will identify the participants in possession of the IMP at the moment the incident becomes known, by using, among other tools, the therapeutic unit tracking form, and will contact them immediately.

- Standardized compression management
Stockings receipt, allocation and dispensing to the participants will be managed by the investigator (or a delegated person).

4.4.3. Management of blinding systems

The blind for any study participant should only be broken by the investigator or authorised person if it is absolutely necessary to ascertain the type of treatment given.

The circumstances under which the blind may be broken are:

- When the knowledge of the treatment allocation will influence the participant management. For example, after overdose of study treatment, or
- When the outcome of a life-threatening medical emergency depends on knowing which treatment the participant has received.

In the cases where the study treatment blind needs to be broken by the investigators for an imperative justified medical reason, a centralised decoding system integrated to IWRS is adopted for the study. No sealed envelopes will be used.

The centralised decoding procedure will be performed by the investigators or an authorised person by contacting the IWRS. The system will be available 24 hours a day, 7 days a week. The procedure to be followed is detailed in the IWRS manual. If IWRS is not available, the helpdesk of the IWRS will be contacted by phone to solve connection issues to allow the unblinding with the IWRS system. Additionally, decoding will be possible by calling the Servier Emergency Phone Number (+33 1 55 72 60 00) available 24 hours a day, 7 days a week.

4.5. Discontinuation of the study

4.5.1. Premature discontinuation of the study

The study can be prematurely discontinued if significant safety concerns are detected at any time during the study, if new scientific knowledge emerges or if other conditions arise which would place the subjects at undue risk if they were to continue in the study.

After having informed the investigator//coordinator, the sponsor or the investigator/ coordinator or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or the Competent Authorities may terminate the study before its scheduled term. Two copies of the written confirmation will be dated and signed by the coordinators. The IRB/IECs and Competent Authorities will be informed according to local regulations.

4.5.2. Discontinuation of the study in the event of objective reached

Not applicable

4.6. Source data

ECG printouts, e-copy of the 3D pictures and central RU measurement reports, the duplex ultrasonography report, the questionnaire for ulcer clinical assessment, the pain assessment with VAS, the participant diary will be considered as source document.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1. Selection criteria

5.1.1. Demographic characteristics

1. Caucasian (defined for this study as having 2 Caucasian parents), men or women :
   - A pregnancy test (β-HCG analysis) will be required for women of child-bearing potential. Menopausal women will be confirmed by an FSH > 30U/L

76. Age ≥ 18 years old.

77. 18.5 kg/m2 ≤ BMI ≤ 45.0 kg/m2 (= Weight (kg) / height² (m²)).

5.1.2. Medical and therapeutic criteria

4. Patients with chronic venous disease documented by imaging (duplex ultrasonography – See Appendix 2) to detect a venous disorder in both the sub- and extra-fascial venous

systems. The examination performed within 6 months before selection can be used for documentation in the e-CRF. If data of the report don't permit to complete the e-CRF and in case of suspicion of acute venous thrombosis, a duplex ultrasonography must be performed before inclusion (during the selection period and before inclusion (W000)).

78. Patients with at least one active venous leg ulcer localised in the gaiter area (CEAP C6) diagnosed or reoccurred for more than 6 weeks and less than 2 years at selection and 3 cm away from other ulcers (See Appendix 3 - Ulcer definition and Appendix 4 - CEAP classification). Patients with bilateral ulcerations or multiple ulcerations on one or both legs are eligible for selection.
6. Size of Reference Ulcer (defined as the largest ulcer in size that is fitting the area selection criteria) should be ≥ 5 cm2 and ≤ 100 cm2 (measured by transparent sheet and confirmed with the digital 3D imaging device).
7. Ankle Brachial Pressure Index ≥ 0.8 and ≤ 1.3 measured by Doppler ultrasound (See Appendix 5).
8. Ulcer not circumferential.
9. Ankle circumference between 19 and 32 cm and circumference below the knee between 28 and 49 cm to be in the range of the compression measurement chart.
10. Participant able to swallow the tablets, put on and remove the compression stockings.
11. Participant able to read and complete the diary.
12. Participant vasectomized or willing to avoid sperm donation for the duration of first dosing to 3 months after the last dose taken.
13. Participant willing to use highly effective contraceptive measures adequate to prevent the participant or the participant's partner from becoming pregnant (i.e. not menopausal, non-hysterectomised, non-surgically sterilised women) throughout the study and for 3 months after completion of study treatment. Highly effective methods of birth control refer to those which result in a low failure rate (i.e. less than 1% per year), when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), some intra uterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant). The investigator must inform the participants about the risks of not using an effective method of birth control during the course of the study.
    - Non menopausal woman means that the time since last menstrual period is < 1 year, in a woman of appropriate age.
    - Surgically sterilised is defined as having had a bilateral tubal ligation, hysterectomy or bilateral oophorectomy.

5.1.3. Informed consent

14. Obtained as described in section 13.3 of the protocol.

5.2. Non-selection criteria

5.2.1. General criteria

15. Unlikely or unwilling to be compliant to standardized compression recommendation, study medication and visits, previous records of poor compliance to compression stockings.

16. Known pregnancy, breastfeeding.
79. Participation in a clinical study involving another study drug, a compression bandage or local care treatment (i.e. dressings) if less than 6 weeks from the end of participation in the previous study or from receiving the last treatment of the previous study. Participation in another clinical study is not allowed during the participation in this study.
80. Participant already randomised in the study
19. Subject is either an immediate family member of a participating investigator, study coordinator, employee of investigator or is a member of the staff conducting the study (in order to avoid any assessment bias).
20. History of excessive consumption of drugs or alcohol abuse (>30 units/week for men and >25 units/week for women) or participant at risk of acute alcohol poisoning. 1 unit of alcohol is defined as half a pint (280 ml) of beer or cider, 1 glass (125 ml) of wine, 1 glass (70 ml) of sherry or port, a single shot (25 ml) of gin, brandy or rum, 2 glasses (250 ml) of low alcohol wine, 3 half pints (840 ml) of low alcohol beer.

5.2.2. Medical and therapeutic criteria

Concerning leg ulcer:

21. Ulcer bed with black necrotic tissue.
22. Infected ulcer that requires local or systemic antibiotherapy (See Appendix 6 – Ulcer Infection).
23. Ulcer of more than 2 cm in depth or ulcers involving or exposing underlying structures (tendon, ligament or bone).
24. Recent history of lower extremity deep venous thrombosis within the last 3 months.
25. Other non-venous leg ulcers or other associated skin conditions such as: vasculitis, malignancies, burns, post-surgery, pressure ulcers, diabetic foot, connective tissue disorders such as lupus, systemic sclerosis, cellulitis, ulcers due to sickle-cell disease.
26. Asymptomatic and symptomatic peripheral occlusive arterial disease with an ABPI < 0.8 or > 1.3 in the affected leg.
27. Planned surgery and venous procedures (including vein stripping, foam sclerotherapy or any endovenous procedure) on the leg with the Reference venous leg ulcer during the study period.
28. Concomitant disease (within the past 3 months before selection) that could significantly affect the healing process during the study.
29. Known participants with inappropriate nutritional status (serum albumin <20 g/l).
30. Participants unable to walk or with severe ankle dysfunction (ankylose) leading to muscle pump alteration.
31. Any clinically relevant abnormality detected during the physical examination performed at the selection visit.
81. Inadequately controlled type 1 and type 2 diabetes, treated or not treated, with an HbA1c > 8% either from the result of a test done within the 3 months before selection or from a result discovered at the laboratory test done within the 5 calendar days prior to the W000 visit.
33. Known severe renal impairment (estimated GFR <30 ml/min) at ASSE visit, calculated with MDRD formula (See Appendix 7).
34. Known acute or chronic hepatic disease.

35. Known major cardiovascular events (acute coronary syndrome including unstable angina and myocardial infarction, stroke) within 6 months prior to the study or congestive heart failure New York Heart Association (NYHA) Class III-IV within 6 months prior to the study (See Appendix 8 – Heart failure classification).
36. Participant with pacemaker or clinically significant arrhythmia.
37. Presence of malignancy or recurrence of cancer within the past 5 years (except for basal cell carcinoma treated by local excision).
38. Presence of malabsorption disease (Crohn's disease), inflammatory bowel disease, Gilbert syndrome, history of chronic diarrhoea,
39. History of clinically significant psychiatric disease or any affective disorders likely to preclude participation in the study.
40. History of epilepsy, organic brain disease.
41. Any chronic or acutely infectious disease up to 2 weeks prior to selection.
42. Blood donation or frequent blood sampling up to 90 days prior to screening for the study.
43. History of severe allergies or multiple adverse drug reactions.
44. Haematology and biochemistry with clinically significant abnormalities and that could in the opinion of investigator preclude study participation.
45. Clinically significant anaemia (i.e. Hb <10 g/dL).
46. Known carriers of HbS antigen or anti HCV or anti-HIV antibodies.
47. Clinically significant co-morbidities that may interfere with the study (morbid obesity, significant chronic oedema from other origin than chronic venous disease: renal failure or decompensated cardiac insufficiency (stage 3 or 4 NYHA classification) or hepatic failure or persistent lymphoedema…).
48. Criterion deleted

Concerning contra-indications to the treatment

49. History of hypersensitivity reaction due to intolerance or allergy to any of study medication excipients and material of compression stockings.
50. Contra-indication to lower limb compression with an applied pressure of approximately 45 mmHg
51. Contra-indication to the compression stocking wearing other than the ones previously listed, including but not limited to: oozing skin disease, blue phlebitis (Phlegmasia coerulea dolens) and septic phlebitis, sensitivity disorder in extremities and neuropathy disorder, primary chronic polyarthritis.
52. Grossly oedematous leg (ankle perimeter > 32 cm unable to fit with stockings sizes) or participants with abnormal shape of leg that does not allow proper compression therapy according to compression stockings recommendations.

Concerning concomitant medications

53. Participants who are undergoing treatments known to affect healing within the month prior to selection: pentoxifylline, immunosuppressive drugs, immunomodulators, cytotoxic chemotherapy or oral corticosteroids.
54. Topical corticosteroids application on and around the ulcer within 15 days prior to selection.
55. Acetylsalicylic acid treatment started within the last 6 weeks prior to the selection or during the study. Acetylsalicylic acid is allowed if started more than 6 weeks before the

selection and remaining stable until the end of the study (i.e.: acetylsalicylic acid at antiaggregant dose ≤ 350 mg daily).

56. Participants treated with drugs known to be BCRP substrates such as methotrexate, mitoxantrone, irinotecan, imatinib, lapatinib, topotecan, rosuvastatin, sulfasalazin.
57. Participants who have been exposed to venoactive drugs within the month prior to the selection.
82. Participants treated with oral anticoagulant treatments known to be BCRP substrates such as acenocoumarol, fluindione, apixaban, rivaroxaban.
59. Participants on oral or parenteral antibiotherapy. Long-term, low dose prophylactic antibiotherapy started at least one month prior to the selection is however acceptable if there is no change in the treatment during the study.
60. NSAIDs on long-term chronic treatment within the last month, except if taken less than one week within the last month.
61. History of major abdominal surgery which in the investigator's opinion could interfere with the absorption, metabolism of the drug (e.g. gastro-intestinal resection, intestinal anastomosis or shunt).

5.3. Inclusion criteria

83. Still eligible as per requirement of Selection/Non-selection criteria (except for RU area at inclusion which should be ≥ 4.5 cm^2 and ≤ 100 cm^2).
84. Presence of venous disease characterized by imaging methods (duplex ultrasonography) to detect a venous disorder of both sub- and extra-fascial venous systems and to rule out a venous thrombosis. The disorder may be a combination of different manifestations such as venous reflux, venous dilation, thickening of venous wall, etc. The results of the examinations should be available for the inclusion visit.
64. No clinically significant change in ulcer healing process confirmed by central reading (size and clinical features if applicable).

5.4. Exclusion criteria

65. Tablet compliance < 80% or > 120 % during the placebo selection period.
66. Compliance with the standardized compression regimen < 80% during the placebo selection period.
67. Clinically significant change in the reference ulcer examination between selection and inclusion showing unstable evolution or complications (i.e. by infection, erosion) of the healing process.
68. Clinically significant change in ulcer healing process showing a change in reference ulcer area of more than 20% between selection and inclusion assessed by the central reviewer.
69. Laboratory results or examinations performed to confirm the diagnosis not available.
85. Clinically significant abnormalities in laboratory tests (haematology, biochemistry) sampled within the 5 calendar days prior to W000 visit, with results available at W000 visit (at the latest) before randomisation:
    - Serum albumin <20 g/l
    - eGFR <30 ml/min calculated with MDRD formula (see Appendix 7)
    - AST or ALT > 3ULN (Upper Limit of normal laboratory range)
    - GGT > 3 ULN
    - Total bilirubin > 2 ULN

- Clinically significant anaemia (i.e. Hb <10 g/dL)
- HbA1c > 8% in an available result from the previous 3 months in a known diabetic patient or discovered between selection and inclusion (HbA1c > 8% in the laboratory test done within the 5 calendar days prior to the W000 visit).
  Note: If a patient is discovered with hyperglycaemia (fasting blood sugar ≥7 mmol/L) and/or with an elevated HbA1c ≥ 6.5% but ≤ 8% between selection and inclusion, the patient can be included in the study and will be stratified as a diabetic.

71. Positive pregnancy test performed within the 5 calendar days prior to W000 visit, or results not available.
72. Any adverse event that might compromise the participant's safety in the study or any study evaluation.
73. Any new concomitant medication or surgical procedures that could interfere with the study.
74. Not willing to respect the drug or alcohol abuse criteria for the duration of the study.
75. Clinically significant abnormalities, or marked prolongation of QT/QTc interval in ECG performed within the 5 calendar days prior to W000 visit (QTcF interval >450 ms, confirmed by a repeated ECG, with measurements validated by a cardiologist)

To be eligible for participation in the study, participants will be required to meet all inclusion criteria and should not meet any of the exclusion criteria. Participants will be then included in the double-blind period of the study and randomised to a treatment group.

5.5. Additional information recorded at the selection/inclusion visit

If not already present at the selection visit, the participant will be scheduled for a full set of investigations including imaging and functional diagnostic tests to document the pre-existence of venous disease (duplex ultrasonography …). The results not available at the selection visit need to be available and reviewed before the inclusion visit. The ethnic origin of participants will also be collected to confirm that participants are Caucasian.

5.6. Participant withdrawal

5.6.1. Withdrawal criteria

Information to be collected during the last visit of these participants is given in section 5.6.2. These follow-up modalities are used to ensure the efficacy and safety evaluation of all participants who received the IMP.

The reasons for premature discontinuation of IMP are:

- Adverse events or any condition that would jeopardise participants' safety and is incompatible with continuation of the IMP according to the judgement of the investigator. These include:
  - **ALT or AST increase > 3 times the ULN value**, after 2 consecutive tests performed 7 days apart.
  - **Total bilirubin increase > 2 times the ULN value**, after 2 consecutive tests performed 7 days apart**.**
  - **CPK increase > 5 times the ULN value,** after 2 consecutive tests performed 7 days apart.

- **Clinically significant anaemia** defined by an haemoglobin level < 10g/dL and a decrease ≥ 1.5 g/dL in men and ≥ 1 g/dL in women compared to previous value.
- **QTcF > 500 ms**, or **QTcF > 480 ms with increase in QTcF > 60 ms as compared with QTcF at selection period**, confirmed by a repeated ECG, with measurements validated by a cardiologist.
- Clinically significant adverse event related to the cardiovascular system for which, in the judgement of the investigator, continuation of the IMP could constitute a risk for the safety of the participant.
- **Severe uncontrolled diarrhoea with risk of dehydration.**
- **Major deviation to the protocol or any medical condition incompatible with continuation of the IMP treatment** (including pregnancy) **or preventing the analysis of the primary endpoint** (e.g. non-compliance with standardized compression regimen or with protocol requirements or study-related procedures).
- Any medical event requiring administration of an unauthorised concomitant treatment (see section 6.3).
- **Non-medical reason** (e.g. withdrawal of participant's consent), which should be carefully documented.
- **Lost to follow-up** (see section 5.6.3).

5.6.2. Procedure

- The investigator must record in the medical file and in the electronic case report form, the reason and the time for the premature discontinuation of treatment / for the withdrawal from the study, the main assessment criteria, and the medical follow-up data.
- If there are several reasons, the investigator must indicate the main reason. An end-of-study visit should always be suggested to the participant and when it should be scheduled (at the same time as the date of discontinuation of treatment, at the theoretical end-of-study date…).
- In the case of premature withdrawal from the study due to an adverse event (event requiring immediate notification or not), the investigator must make every effort to collect the information related to the outcome of the event. If necessary, the information will be collected afterwards (see section 8.3.2.4). This information is recorded in that part of the electronic case report form which concerns adverse events. If the investigator cannot collect the information from a visit, he must collect it from the physician ensuring the follow-up of the participant.
- If the study is stopped / IMP is discontinued as a result of an event requiring immediate notification, the procedure described in section 8.3.1.5 is to be implemented.
- Treatment discontinuation or withdrawal from the study is to be documented by completing the appropriate page in the e-CRF. The investigator or a designated person must connect to the IWRS to perform the withdrawal visit in case of treatment discontinuation or withdrawal of the participant from the study.

The dispositions to be taken after the IMP discontinuation are described in section 6.5.

5.6.3. Lost to follow-up

When the investigator has no news of the participant, he/she must make every effort to contact him/her or a person around him/her (phone calls, letters including registered ones…etc.), to establish the reason for the discontinuation of the IMP and to suggest the participant comes to an end-of-study visit. If all these attempts to contact the participant fail,

the investigator can then declare the participant "lost to follow-up". The investigator should document all these attempts in the corresponding medical file.

6. TREATMENT OF PARTICIPANTS

6.1. IMPs administered

There are three periods in the study

- Placebo selection period of 14 days ± 2 days:

During this period, the participants will take orally 3 placebo tablets twice a day at the end of the meals with a glass of water (250 ml): 3 placebo tablets in the morning at the end of the breakfast and 3 placebo tablets in the evening at the end of the dinner.

In addition, all participants will be provided with standardized compression (compression stockings) adapted to their leg size. The adequate size of the stockings will be chosen according to leg measurements and the leg measurement chart. If applicable, the participant will discontinue his/her usual compression treatment.

The stockings kit consists of two understockings and one overstocking. The understocking is applied on the leg up to the knee over the dressings protecting the ulcer. The overstocking is applied over the understocking. The participant has to wear both during the day and must remove the overstocking during the night, keeping the understocking which has to be worn 24/7 over the dressings protecting the ulcer. The stockings have to be worn one day and then washed to recover the initial compression properties. Two understockings and one overstocking with the same size will be provided to the participants. So, the participants will be able to wear one understocking over the night while the used overstocking and the other understocking are washed and dried overnight to be used the following day. The investigator may dispense additional compression stocking kits (of the same size) to the patients if needed to maintain daily compliance with compression therapy.

The participant has to complete a diary on the days he/she is wearing the compression stockings.

- Randomised double-blind active treatment period of 42 days ± 4 days, from W000 to W006:

At W000, after verification of the participant's inclusion criteria and compliance with selection treatment and compression, the participant will be randomly assigned to one of the six treatment arms.

During this period, the participants will take orally 3 tablets twice a day at the end of the meals with a glass of water (250 ml or 8 ounces): 3 tablets in the morning at the end of breakfast and 3 tablets in the evening at the end of dinner of S42909 (a total of 100, 200, 400, 800 or 1200 mg daily) or placebo. Tablets of 0, 50 and 200 mg of strength of S42909 will be used to reach each dose. The packaging will ensure that the 3 tablets to be taken by the participant for each intake will be on one line. This will be clearly explained in the participant's diary.

The measurements of the leg will be done at each visit and the stockings size will be confirmed or changed according to these measurements.

On the day of visits W000, W001, W002, W004 and W006, the participant will omit the morning IMP intake and will come to the study visit under fasting condition (10 hours). The participant will take the assigned IMP treatment with a glass of water (250 ml or 8 ounces) during the study visit after the predose PK sampling and at the end of breakfast.

- Follow-up period of 14 days ± 4 days, from W006 (at D0 + 42 days ± 4 days) to W008:

On the day of the W006 visit, the participant will omit the morning IMP intake and will come to the study visit under fasting condition (10 hours). The participant will take the morning IMP intake during the study visit at the end of the breakfast with a glass of water (250 ml or 8 ounces), will the stop taking the IMP treatment and give the TU box back to the investigator.

During this period, participants will continue with standardized compression therapy and the local wound care up to end of study visit (W008).

After the end-of-study visit, the investigator will decide on continuation of leg ulcer treatment according to the centre's standard of care.

6.2. IMPs dispensing

Therapeutic unit (TU) will be identified by a 6-digit number for identification, tracking and stock management purposes.

The randomisation and allocation of the therapeutic unit numbers to each participant will be managed centrally by the CRO responsible for the IWRS. All procedures will be detailed in the IWRS manual.

IMP treatment will be dispensed by the investigator or the pharmacist or a designated person, according to the local organisation, as follows:

- At the selection visit (ASSE): 14-days placebo selection period.

The investigator will connect to IWRS at the selection visit to register the participant, create a participant's number and register the selection. Then, the system will allocate a selection kit number. The box corresponding to the kit number will be dispensed to the participant.

Moreover, the participants will be provided with 1 stocking kit (containing 2 understockings and 1 overstocking) of the adequate size. The adequate size of the stockings will be chosen according to leg measurements and the leg measurement chart.

- At the inclusion visit (W000):

After verification of the participant's inclusion criteria and compliance with selection treatment and compression, the investigator will connect to the IWRS. The system will allocate to the participant the therapeutic unit (TU) number corresponding to the treatment group randomised (placebo or S42909 100, 200, 400, 800 or 1200 mg). The TU box corresponding to the TU number will be given to the participant and will correspond to 2 weeks of treatment. As the participant must omit the morning IMP intake before the study

visit, he/she will take the new treatment assigned during the study visit after predose PK sampling and at the end of breakfast.

The measurements of the participant's leg will be checked and if the stocking size has changed, 1 new stocking kit will be provided to the participant according to the leg measurement chart.

- At the W001 visit:

The participant will come to the visit and bring back the TU box allocated at W000. He/she will take the treatment at the centre on the day of this visit after predose PK sampling and at the end of breakfast. The drug accountability of the remaining tablets will be performed only if the participant withdraws from the study at this visit.
The participant will continue until W002 with the same TU box. IWRS will not be contacted at W001 visit.
As the participant must omit the morning IMP intake before the study visit, he/she will take the IMP treatment during the study visit after predose PK sampling and at the end of breakfast.

The measurements of the participant's leg will be checked and if the stocking size has changed, 1 new stocking kit will be provided to the participant according to the leg measurement chart.

- At the W002 visit:

The TU box allocated at W000 visit will be retrieved from the participant and the drug accountability of the remaining tablets will be performed.
At the end of the visit, IWRS will be contacted and a new TU number will be allocated. The box corresponding to the TU number will be given to the participant and will correspond to 2 weeks of treatment. As the participant must omit the morning IMP intake before the study visit, he/she will take the treatment from the new TU box assigned during the study visit, after predose PK sampling and at the end of breakfast.

The measurements of the participant's leg will be checked and if the stocking size has changed, 1 new stocking kit will be provided to the participant according to the leg measurement chart.

- At the W003 visit:

The participant will come to the visit with the TU box allocated at W002. The drug accountability of the remaining tablets will be performed only if the participant withdraws from the study at this visit.
The participant will continue until W004 with the same TU box. IWRS will not be contacted at W003 visit.

The measurements of the participant's leg will be checked and if the stocking size has changed, 1 new stocking kit will be provided to the participant according to the leg measurement chart.

- At the W004 visit:

The TU box allocated at W002 visit will be retrieved from the participant and the drug accountability of the remaining tablets will be performed.

At the end of the visit, IWRS will be contacted and a new TU number will be allocated. The box corresponding to the TU number will be given to the participant and will correspond to 2 weeks of treatment.
As the participant must omit the morning IMP intake before the study visit, he/she will take the treatment from the new TU box assigned during the study visit, after predose PK sampling and at the end of breakfast.

The measurements of the participant's leg will be checked and if the stocking size has changed, 1 new stocking kit will be provided to the participant according to the leg measurement chart.

- At the W006 visit:

The TU box allocated at W004 visit will be retrieved from the participant and the drug accountability of the remaining tablets will be performed.
The IMP treatment will be stopped at this visit with the morning dose taken after PK predose at site and the participant will enter the follow-up period where he/she will continue wearing the compression stockings until the end of the study. The measurements of the participant's leg will be checked at this visit and if the stocking size has changed, 1 new stocking kit will be provided to the participant according to the leg measurement chart.

For each participant, the IMP will only be dispensed during the study. At the last visit of the study, the investigator will propose a treatment adapted to the nature of the clinical state of the participant.

6.3. Previous and concomitant treatments

The previous treatments will be recorded within the 6 months prior to the selection for treatment involved in the studied disease and within the 6 weeks prior to the selection for other treatments.
The following treatments will be forbidden because they are known to interact significantly with wound healing or may interact with the IMP treatment:

- Topical corticosteroid application on and around the ulcer within 15 days prior to selection and during the study
- Oral corticosteroids within the month prior to selection and during the study
- Immunomodulators, immunosuppressants, cytotoxic chemotherapy within the month prior to selection and during the study
- Pentoxifylline within the month prior to selection and during the study
- Acetylsalicylic acid treatment started within the last 6 weeks prior to the selection or during the study. Acetylsalicylic acid is allowed at antiaggregant dose and at long term ≤ 350 mg daily (coronary disease).
- Drugs known to be BCRP substrates during the study such as methotrexate, mitoxantrone,irinotecan, imatinib, lapatinib, topotecan, rosuvastatin, sulfasalazin.
- Oral anticoagulant treatments known to be BCRP substrates such as acenocoumarol, fluindione, apixaban, rivaroxaban. Anticoagulant if prescribed during the study.
- Venoactive drugs within the month prior to selection and during the study
- Participants on oral or parenteral antibiotherapy. Long-term, low dose prophylactic antibiotherapy started at least one month before the selection is however acceptable if there is no change in the treatment during the study.
- Local antibiotherapy on the surface of RU, during the study.

- Oral and parenteral antibiotherapy during the study, except if less than or equal to 7 days.
- NSAIDs on long-term chronic treatment within one month prior to the selection, except if taken less than one week within the last month. NSAIDs are not allowed during the study except if taken once and not longer than 3 consecutive days.

6.4. IMP compliance

The dates of the first and last therapeutic unit intake, any treatment interruption if any, will be recorded in the e-CRF.

The number of tablets dispensed and the number of tablets returned by the participant are to be counted by the investigator or a designated person from his/her team and recorded in the electronic case report form. If the participant does not bring back his TU box and diary, the number of tablets taken and number of days when stockings have been applied will be estimated by the investigator by questioning the participant. If the information becomes available at a next visit, the data should be corrected.

The compliance will be assessed at W000, W002, W004 and W006 as therapeutic unit boxes are allocated for 2 weeks of treatment.

The compliance will be calculated on the basis of the ratio between the number of tablets actually taken (and number of days for stockings) and the theoretical number of tablets (or days) required by the number of treatment days.

If the compliance is unsatisfactory during the study (e.g. less than 80% or higher than 120%), the participant should be questioned to identify the reason for this and the study objectives should be reminded. Particular importance should be given to possible occurrence of adverse event.

The investigator should particularly assess the compliance of treatment and stockings at W000 visit to check the related non-inclusion criteria.

The compliance of stockings should also be assessed at each visit. Each participant must record the days he/she is wearing the stockings in a diary provided by the investigator and this number of days will be recorded in the e-CRF. If the compliance of stockings is less than 80%, the participant must be retrained and motivated.

6.5. Arrangements after the discontinuation of the IMP

After the discontinuation of the IMP, the participant will have access to appropriate medical care by his physician.

The treatment chosen after the end of the study or study withdrawal will be prescribed by his/her physician according to the centre standard of care. The study drug is not licensed and will not be available outside of the scope of the study**.**

7. ASSESSMENT OF EFFICACY

7.1. Efficacy measurements

Efficacy measurements performed during the study are indicated in Table (4.2.2) 1.

- Reference Ulcer area

At the selection visit (ASSE), the eligibility will be determined on the Reference Ulcer (RU) area based on the measurements performed by the investigator. This measurement will also be done centrally on the 3D picture taken by the investigator (or a delegated person) at the selection visit (ASSE). The latest will determine the final eligibility in case of discrepancy between the investigator and the central measurement.

For the inclusion visit (W000), the RU area measurement will be performed centrally on a 3D picture taken 3 (or 4) working days before W000 visit. Additionally, patients found to be eligible for randomisation will have a 3D picture of the RU on the day of W000, after randomisation, for baseline measurements.
At W001, W002, W003, W004, W006 and W008, the RU area measurement will be performed centrally on a 3D picture of RU taken and uploaded by the investigator (or a delegated person) during the study visits.

- Reference Ulcer perimeter

The perimeter will be measured centrally at each study visit (ASSE, W000, W001, W002, W003, W004, W006 and W008) on the 3D picture of RU performed and uploaded by the investigator (or a delegated person). The perimeter measured will be used to calculate the linear advance of the wound margin towards the wound centre.

- Reference Ulcer volume

The volume will be measured centrally at each study visit (ASSE, W000, W001, W002, W003, W004, W006 and W008) on the 3D picture of RU performed and uploaded by the investigator (or a delegated person).

- Pain assessment

The pain related to the leg ulcer will be assessed at W000, W004 and W006 visits using a questionnaire which includes a VAS scale (See Appendix 9: Questionnaire for pain assessment).

- Analgesic drug consumption

Analgesic drug consumption related to the leg ulcer will be assessed at W000, W004 and W006 with the help of the concomitant treatment form. This assessment will be done in term of daily dose and duration.

- Clinical assessment

A clinical assessment of the RU will be performed at ASSE, W000, W001, W002, W003, W004, W006 and W008 visits by the investigator (See Appendix 10 - Clinical Assessment of Leg Ulcer).

7.2. Methods and measurement times

- Reference Ulcer area, volume and perimeter measurements:

The 3D pictures of RU will be taken and uploaded to a secured website at each visit after wound cleansing by the investigator (or a delegated person) (except at the selection visit with two pictures: one before cleansing and debridement and another one after cleansing and debridement).

The RU area will be measured by the investigator at selection by tracing the RU outlines using a transparent sheet after wound cleansing and debridement. In addition, two 3D pictures will be taken and uploaded by the investigator (or a delegated person) at the ASSE visit for the central measurement by the CRO for the efficacy analysis. The CRO will send the two pictures to the independent expert with an alert system. The central measurement of RU area will be sent back to the investigator and if the central measurement is not fitting the selection criteria, the participant will be withdrawn before inclusion.

Three (or four) working days before inclusion visit (W000), the participants will come to the site for a RU picture. The investigator (or a delegated person) will upload the image on a secured website on the same day. The CRO in charge of the central reading will receive the picture, perform RU area measurement, and send it back to the investigator within the three following working days and before the inclusion visit.

The CRO will also send to the investigator the central RU area measured on the picture taken 3 (or 4) working days before W000 and the calculation of the change between ASSE and W000 area measurements.

At selection, an independent expert will check the feature of RU. The expert will give an opinion on the RU by reviewing the clinical aspect of RU on the 3D pictures. The expert will confirm the selection or not if RU clinical pictures are consistent with a venous aetiology or give a recommendation for study continuation. If a doubt exists on the venous aetiology of the RU, another expert will give a second opinion on the picture. If the doubt of the venous origin of the RU persists, the expert in charge of the review of the picture at selection will review the picture taken at inclusion. If the doubt still persists at the review of the picture taken at inclusion, the patient will not be included.

At the inclusion visit (W000), these measurements will be used by the investigator to check if the RU area was in the range of inclusion criteria and if the change in the RU area between ASSE and W000 is less or equal to 20% for inclusion.

Area Change $_{W0\text{-}ASSE}$= │Reference Ulcer Area W000 – Reference Ulcer Area ASSE│ / RU Area ASSE. (Reference Ulcer Area ASSE is the one after cleansing and debridement).

Patients found to be eligible for randomisation will also have a 3D picture of the RU on the day of W000 (taken after randomisation) that will be uploaded by the investigator (or a delegated person) on the secured website to send these pictures to the central reviewer.

At W001, W002, W003, W004, W006 and W008, the investigator (or a delegated person) will upload the 3D pictures of RU on the secured website to send these pictures to the central reviewer.

In addition to the RU area measurement, the CRO in charge of the central measurement will perform volume and perimeter measurements at each visit on the 3D picture. These measures will be used for the efficacy criteria.

- Pain assessment

The questionnaire with the VAS will be provided by I.R.I.S and completed at the beginning of W000, W004 and W006 visits, before RU clinical assessment and local care of the RU. The participant will draw a vertical line on the scale to reflect his perception on the intensity of the pain since the last visit. The investigator will measure the exact distance from 0 to the line

drawn by the participant and report the corresponding measurement in millimetres in the e-CRF together with documenting the answers to all the questions.

- Reference Ulcer clinical assessment

The form for RU clinical assessment will be completed after the pain assessment and will be reported in the e-CRF at each study visit: ASSE, W000, W001, W002, W003, W004, W006 and W008.

- Analgesic drug consumption:

Analgesic intake follow-up related to VLU: will be evaluated and reported in the e-CRF at W000, W004 and W006 visits and will be addressed to patient using analgesic drug linked to VLU.

8. SAFETY MEASUREMENTS

8.1. Safety measurements

Safety measurements performed during the study are indicated in Table (4.2.2) 1.

- Recording of any adverse event occurring during the study using the collection methods detailed in section 8.3.
- Physical examination, body weight measurement, vital signs, 6 or 12-lead electrocardiogram (ECG), standard urinalysis and laboratory assessments.

8.2. Methods and measurement times

- Physical examination

Physical examination will be a clinical exam carried out by the investigator at all visits in order to assess participant's condition before deciding to keep the participant in the study. The abnormalities of the physical examination will be reported and evaluated by the physician as clinically significant or not. Any clinically significant changes during the study should be recorded as an adverse event.

- Weight

The participant's weight will be determined at selection (ASSE), inclusion (W000), W002, W006 and W008. It should be measured under the same conditions (i.e. same scale, empty bladder, before breakfast, being only lightly dressed).

The participant's height will be measured at the selection visit for participant's BMI calculation.

- Vital signs

Blood pressure and heart rate will be measured at all visits, they should always be measured under the same conditions for each participant during the study (one measure after 10 minutes in the sitting position). Body temperature will be recorded at all visits for on-site safety.

- Standard electrocardiogram

A standard electrocardiogram ECG (6 or 12-lead) will be performed within the 5 calendar days prior to W000 visit, with results available at W000 visit (at the latest) before randomisation, to check that there are no clinically significant abnormalities. If the investigator does not have the expertise to read ECG tracings and/or in case of abnormalities, the ECG should be verified by a cardiologist prior to the inclusion of the participant in the

study. The ECG will be performed after 15 minutes at rest with the participant in supine position. It will be recorded at speed 50 mm/s with 2 cm/mV amplification and with at least 3 QRS complexes by lead.

The 6 or 12-lead ECG will be repeated at all subsequent visits. If the investigator does not have the expertise to read ECG tracings and/or in case of abnormalities, the ECGs should be verified by a cardiologist. Any clinically significant abnormality discovered must be recorded as an adverse event in the e-CRF. The following parameters are to be recorded: rhythm, heart rate, PR interval, QRS duration, QTc duration and RR interval [QTc calculated using Fridericia formula ($QTcF = QT / \sqrt[3]{RR}$)]

In order to avoid the possible artefacts in the ECG interpretation (e.g. hysteresis effect in which an increase in HR is followed more slowly by an adaptation of QT duration and consequently lead to an alteration of QT-RR relationship), it is recommended to follow the below recommendations:

- To allow the subject to be reclining at rest for at least 15 minutes prior to ECG acquisition and in this time no emotional stimulation of the subject is allowed (TV, vital sign acquisition, blood sampling) as they might have an impact on heart rate.
- To perform blood sampling after the ECG recording when the same time points are needed for blood sampling and ECG acquisition.

- Laboratory assessments

Local laboratories will be responsible for analysing the biochemistry and haematology samples, FSH, β-HCG. The laboratory will send a laboratory report to the investigator who will be responsible for the clinical assessment of the results and data entry in the e-CRF. Any clinically significant abnormal laboratory value should be recorded as an adverse event in the e-CRF. The investigator should follow up all clinically relevant changes until recovery.

- Biochemistry (within the 5 calendar days prior to W000 with results available at W000 at the latest, W001, W002, W004, W006 and W008 visits): AST (SGOT), ALT (SGPT), CPK, alkaline phosphatase, GGT, total bilirubin, total protein, albumin, Calcium, Urea, Creatinine, CRP, glucose, Na, K and Cl. The analyses will be done under fasting condition (10 hours). Within the 5 calendar days prior to W000 with results available at W000 at the latest, a test for HbA1c must be done for all patients except known diabetics with a result ≤ 8% obtained in the 3 months before the selection visit.
- Fasting Lipids (within the 5 calendar days prior to W000 with results available at W000 at the latest, W001, W002, W004, W006 and W008 visits): Triglycerides, HDL, LDL, and total cholesterol. The analysis will be done under fasting condition (10 hours).
- Haematology (within the 5 calendar days prior to W000 with results available at W000 at the latest, W001, W002, W004, W006 and W008 visits): haemoglobin, haematocrit, red blood cells, MCV, MCH, MCHC, platelets, white blood cells, lymphocytes, monocytes, eosinophils, basophils and neutrophils (white blood cells, lymphocytes, monocytes, eosinophils, basophils and neutrophils must be assayed in absolute value and entered in the e-CRF in this unit). For patients under warfarin or phenprocoumon, International Normalized Ratio (INR) will be performed at each visit (including W003) or more often if judged necessary by the investigator.

- Standard urinalysis will be performed using a dipstick, within the 5 calendar days prior to W000 with results available at W000 at the latest, W004, W006 and W008 visits by the investigator or a delegated person. Urinalysis: pH, proteins, blood, leucocytes, bilirubin, ketones bodies, nitrites and glucose.
- A blood sampling will be performed for β-HCG or FSH analysis (within the 5 calendar days prior to W000 visit, with results available at W000 visit at the latest) to diagnose pregnancy and menopause respectively. β-HCG tests will be repeated at W004 and W008 visits for women of child-bearing potential. Depending on the local regulation, pregnancy tests can be additionally repeated throughout the treatment period (urinary tests which is not to be entered into e-CRF).

8.3. Adverse events

All adverse events and other situations relevant to the safety of the participants must be followed up and fully and precisely documented in order to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial.

The same procedure applies whether the participant receives the test drug or a comparison product (placebo, S42909).

8.3.1. Definitions

8.3.1.1. Adverse events

An adverse event is defined as any untoward medical occurrence in a subject participating in a clinical study, whether or not there is a causal relationship with the IMP and/or experimental procedures, occurring or detected from the date the participant signs the information and consent form, irrespective of the period of the study (periods without administration of the IMP (e.g. selection period) are also concerned).

An adverse event can therefore be:
- any unfavourable and unintended sign, including an abnormal finding from an additional examination (lab tests, X-rays, ECG, etc.) which is deemed clinically relevant by the investigator,
- any symptom or disease,
- any worsening during the study of a symptom or a disease already present when the participant entered the study (increase in frequency and/or intensity), including the studied pathology,

and detected during a study visit or at an additional examination or occurred since the previous study visit (including relevant event reported in participant's diary or safety evaluation scale).

Of note:
- Any **hospitalisation for social reasons, educational purpose** (e.g. learning of arterial hypertension management by the participant) or routine check-up, and the hospitalization for PK sampling purposes at W004 (participants having signed the consent form for the optional PK analysis) should not be considered as an adverse event and should not be reported in the e-CRF.
- The following procedures, whether planned before the study or not, whether leading to a hospitalisation or not, should be reported in the specific page **"Procedures not subsequent to an adverse event"** of the e-CRF:

- therapeutic procedures related to a non-aggravated medical history (e.g. cataract extraction not due to an aggravation of the cataract during the study, haemodialysis sessions related to a renal insufficiency not aggravated during the study),
- prophylactic procedures (e.g. sterilisation, wisdom teeth removal),
- comfort procedures (e.g. cosmetic surgery),
- control procedures of a pre-existing condition without aggravation (e.g. colonoscopy to control the remission of colon cancer).
- any hospitalisation to perform the duplex ultrasonography examination

- In the framework of this protocol, local adverse reactions at ulcer site such as pruritus, erythema, pain, discomfort, bleeding, etc., are reactions that are expected to occur in normal conditions during the healing process and investigators should use their clinical judgement to discern whether a specific event is falling into this category or not. Expected local adverse reactions should not be reported as adverse events.

8.3.1.2. Serious adverse events

Any adverse event that at, any dose:
- results in death,
- is life-threatening(1),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- is medically significant(2),
- results in persistent or significant disability/incapacity(3),
- is a congenital anomaly/birth defect(4).

(1) Life-threatening in this context refers to an event in which the participant 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 was more severe.

(2) Any event that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardise the participant or might require intervention to prevent one of these outcomes (for example: oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalisation, or development of drug dependence or drug abuse). The investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to the sponsor.

(3) Disability/incapacity in this context refers to any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

(4) Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

8.3.1.3. Adverse events of special interest

Not applicable.

8.3.1.4. Overdose

This refers to any intake of a quantity of IMP which is above the maximum dose recommended in the study protocol, independently of the occurrence of any adverse event.

The quantity should be considered per administration or cumulatively regarding the maximum dose recommended in the study protocol. For instance, as the study protocol requires two daily administrations, one intake of the planned two daily intakes at the same time should be considered as overdose.

8.3.1.5. Events requiring an immediate notification (ERIN)

An event must be **notified immediately** (i.e. **within 24 hours**) to the sponsor if it is:
- a serious adverse event,
- an overdose of the IMP even if asymptomatic,
- any intake of the IMP by a person around the participant,
- a pregnancy.

8.3.2. Responsibilities of the investigator

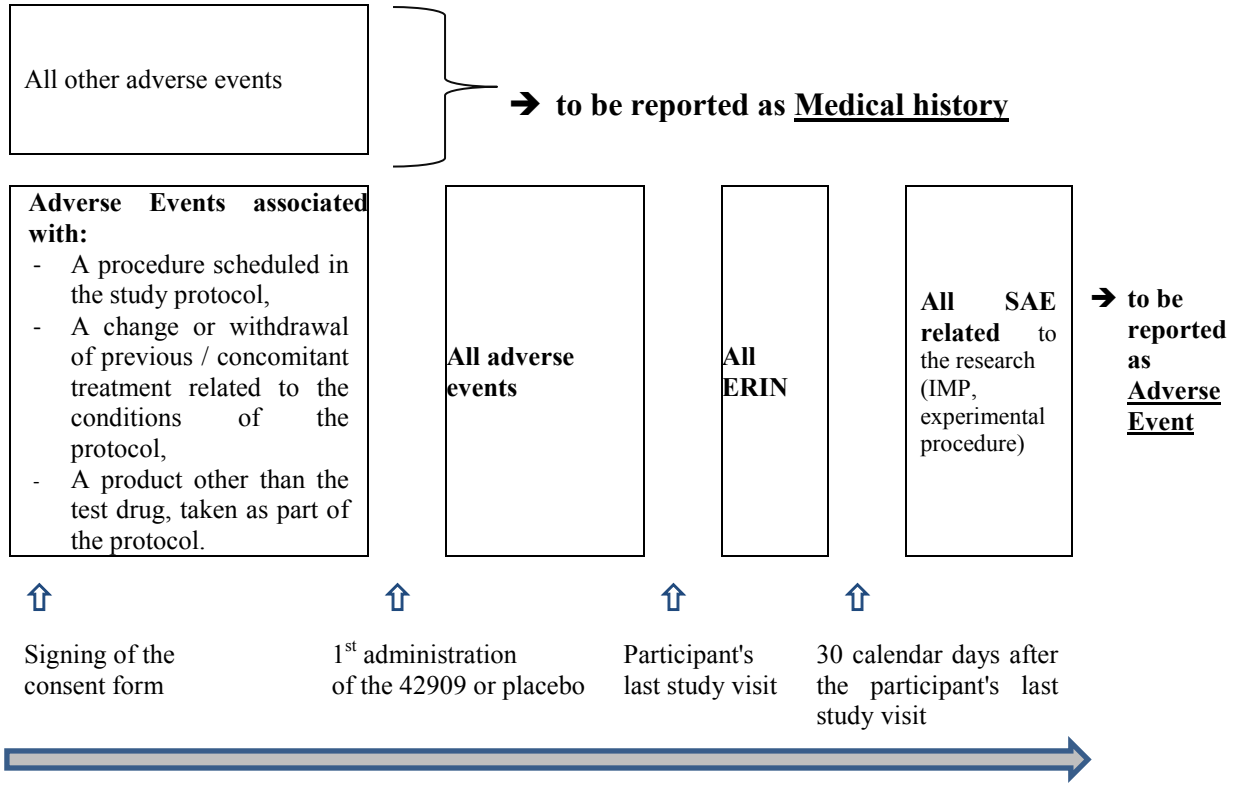
For any adverse event and special situation mentioned above the investigator must:
- **Note in the participant's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the participant or a third person, …) and any other relevant information which he/she has learned of the event,
- **Report the event to the sponsor** using the AE form (in case of ERIN, the reporting should be done immediately),
- Evaluate the seriousness, intensity and causality,
- **Document** the event with additional useful information,
- Ensure the **follow-up** of the event,
- **Fulfil his/her regulatory obligations** to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.

8.3.2.1. Time frame for AE reporting

Any event meeting the above mentioned definitions (see section 8.3.1) must be reported to the sponsor on an adverse event form if it occurred:
- before the first intake of the test drug, **for event associated with any procedure/condition required by the study protocol**: procedure (duplex ultrasonography, ECG, etc.), change or withdrawal of previous/concomitant treatment relating to the conditions of the protocol.
- at any time after the first intake of the **test drug** up to the participant's last study visit for all events,
- after the participant's last study visit:
  - up to 30 calendar days after the participant's last study visit for all ERIN, regardless of the supposed role of the research (IMP, or experimental procedure).
  - irrespective of the time of onset after the end of the study in case of serious adverse event related to the research (IMP, or experimental procedure).

Of note, events occurring between the signature of the informed consent and the first administration of the test drug for which the investigator does not consider an association with

any procedure/condition required by the study protocol must be reported as medical history in the dedicated form of the e-CRF.



8.3.2.2. Evaluation of seriousness, intensity and causality

It is important that the investigator gives his/her own opinion regarding the **seriousness**, the **intensity** of the event as well as the **cause-effect relationship** between an adverse event and the IMP. This evaluation must be assessed by the investigator and reported in the AE form.

The Seriousness should be evaluated according to international guidances (see definition section 8.3.1.2, in accordance with ICH Topic E2A and Directive 2001/20/EC of the European Parliament and of The Council of 4 April and (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf).

The Intensity should be evaluated according to the following rule:

- mild: signs or symptoms, easily tolerated, relieved with symptomatic treatment,
- moderate: enough discomfort to cause interference with usual activity, only partially relieved with symptomatic treatment,
- severe: incapacity in some regular activities, not easily relieved with symptomatic treatment.

The causal relationship to the IMP must be assessed when reporting the AE in the AE form. Only cases ticked "related" by the investigator or judged by the sponsor as having a reasonable suspected causal relationship to the test drug (AE linked to the mechanism of action of the test drug…) will be considered as suspected Adverse Drug Reaction. In general, the expression reasonable causal relationship means to convey that there is evidence or arguments to suggest a causal relationship.

8.3.2.3. Documentation of the event

The investigator must ensure that all events are well documented. In particular for ERIN, he/she should provide the sponsor, as they become available, with anonymized copies of the documents which provide additional useful information, such as hospital admission reports, reports of further consultations, laboratory test reports, reports of other examinations aiding diagnosis *(*where possible, the results from pre-test drug assessments should be appended for comparison with the results obtained under test drug), or the autopsy report, if autopsy is performed.

8.3.2.4. Follow-up of adverse events

The investigator must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution if deemed necessary.

Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported must be written up in a new complete evaluation of the event documented on the "Adverse event" page previously created for the event in the e-CRF.

If the adverse event has not resolved at the participant's final visit in the study, the participant must be followed up suitably and any information on the outcome of the event will be noted on the « Adverse Event » page previously created for the event in the e-CRF.

If the follow-up of the participant is not done by the investigator him/herself (hospitalisation, followed by a specialist or the participant's general practitioner, etc.), the investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of the participant.

8.3.2.5. Special situations (pregnancy, overdoses, intake of IMP by a person around the participant)

Pregnancy

If a female participant in the study becomes pregnant, the investigator must:

- stop immediately the IMP,
- report it on an « Adverse Event » page as well as on the specific paper pregnancy form to be notified immediately (ERIN),
- contribute to the follow-up of this pregnancy and provide the sponsor with information concerning this follow-up
- If the partner of a participant becomes pregnant during the course of the study or within 3 months after completion of study treatment, the pregnancy should not be reported in the e-CRF. The investigator should **immediately** contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

Overdose of IMP

- In case of overdose, the investigator should report it on an "Adverse Event" page to be notified immediately (ERIN).
- Overdose should be followed-up to ensure that the information is as complete as possible with regards to:

- dose details (number of units, duration,…) and, if multiple overdose, details regarding other medicinal products or substance ,
- context of occurrence, i.e. intentional (suicide attempt, other reason) or accidental (error in prescription, administration, dispensing, dosage),
- related signs and symptoms ("No related adverse events" to be reported otherwise),
- outcome.

Intake of IMP by a person around the participant.

This event should not be reported in the e-CRF. The investigator should immediately contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

8.3.2.6. Recording Methods in the e-CRF

Adverse events must be documented on the « Adverse Event » page of the e-CRF.

In case of chronic disease:
- if the disease is known when the participant enters in the study, only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an adverse event,
- if the disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the « Adverse Event » page previously created for the event which will clearly describe the diagnosis.

In case of gastrointestinal events (such as diarrhoea, loose stools, nausea, flatulence, vomiting, dyspepsia, abdominal pain, etc.):
- the investigator will specify, in the "description" area of the AE e-CRF form, the circumstances of occurrence, localisation, duration and frequency of the event.

8.3.2.7. Procedure for an event requiring an immediate notification

In case of an event requiring an immediate notification, the investigator must:
- **Immediately** after being informed of this event, **fill in** the **participant's medical file** as well as the **« Adverse Event » page** of the e-CRF according to the general instructions available in the e-CRF, without waiting for the results of the clinical outcome or of additional investigations. When data will be submitted into Inform, an e-mail will be immediately and automatically sent to the sponsor.
- Provide the sponsor (person designated in the contact details provided in the investigator's study file), as they become available, with anonymized copies of the documents which provide additional useful information,
- Fulfil his/her regulatory obligations to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.

If an adverse event initially judged as non-serious worsens and becomes serious (ERIN), this must be reported **immediately** on an "Adverse event" page of the e-CRF.

In case the e-CRF is unavailable when the investigator was informed of the ERIN, he/she should:
- **Immediately** fill in a paper "Adverse event" page:
  - For a serious event on a paper entitled "Adverse event – Initial information" page,

- For an event initially judged as non-serious on a paper entitled "Adverse event – Initial information" page, and the worsening leading to seriousness on a paper "Adverse event – Additional information" page,
- Immediately send the pages by fax or e-mail to the person(s) designated in the contact details provided in the investigator's study file. Should a Serious Adverse Event or any other reportable event need to be reported outside of the working hours, a phone call will be needed in addition to the expected written information transmitted by fax or by e-mail. The contact information to be used are the following:
  - For European sites: dial the European international prefix followed by 33.1.55.72.60.00
  - For a Canadian site: dial the ICTR phone number listed in your investigator's study file.
  - For a site in USA: contact the Ilkos medical monitor listed in your investigator's study file.
  - In any case, the investigator can contact the central 24-hour phone line in France: 33.1.55.72.60.00
- As soon as the e-CRF becomes available, the investigator should enter these data in the « Adverse Event » page of the e-CRF.

8.3.3. Responsibilities of the sponsor

In accordance with international guidances, the assessment of the seriousness and the causality of adverse events are usually made by the investigator but falls also under sponsor's duties, who is responsible for ensuring that all suspected unexpected serious adverse reactions are reported to Competent Authorities and Ethics Committees.

The sponsor will review the seriousness of the adverse events and the causality of the serious adverse events, whether reported by the investigator or upgraded by the sponsor. The causality and the seriousness may be upgraded (but never downgraded). Anonymized copies of documents providing useful information such as reports of further consultations, laboratory tests reports, reports of other examination aiding diagnosis may be asked for the event assessment. If the assessments of the investigator and the sponsor are different, both will be reported in the clinical study report.

Independently of the regulatory obligations of the investigator, the sponsor must report the pharmacovigilance data to the appropriate Authorities and to all the investigators involved, according to the requirements stated in ICH Good Clinical Practice guidelines and local regulations.

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

9.1. Measurement of drug concentration

The concentrations of S42909 and its metabolites (S45015, S45236 and S55113) in plasma will be analysed according to validated methods by a central CRO (Algorithme Pharma). Procedures will be described in separate bio-analytical protocols established by (Algorithme Pharma).

9.1.1. Collection of blood samples

- Blood samples (6 ml) will be collected into lithium-heparinised tubes according to the tubes provided, each sample being intended for the assay of the parent drug and metabolites.
  - **In participants participating in the mandatory PK analysis only**, a total of 4 venous blood samples will be collected on the day of W000, W004, W006 study visits and one predose venous blood sample will be collected on the day of W001 and W002 study visits (see Table (4.2.2) 2 - Pharmacokinetic Investigation schedule):
    - At W000, W004, W006 visits: prior to breakfast and first study drug intake at the end of the breakfast, which will be considered as T0, then 1h, 3h after drug intake and just before the participant leaves the site at the end of the study visit.
    - At W001, W002 visits: prior to breakfast and first study drug intake at the end of the breakfast.
  - **In participants participating in the mandatory and optional PK analyses** (see Table (4.2.2) 2 - Pharmacokinetic Investigation schedule):
    - a total of 9 venous blood samples will be collected on the day of W000 visit, instead of the 4 blood samples listed above: prior to the breakfast and the first IMP intake at the end of the breakfast (T0) and 1h, 2h, 3h, 4h, 5h, 6h, 8h, 12h after first IMP intake. The 12h timepoint, which will be just prior to the dinner and the IMP intake at the end of the meal, can be adjusted to a maximum of 2 hours earlier to accommodate a more convenient dinner time.
    - at W001, W002 visits: prior to breakfast and first study drug intake at the end of the breakfast, which will be considered as T0.
    - a total of 13 venous blood samples will be collected on the day of W004 visit, instead of 4 blood samples listed above: prior to the breakfast and the first IMP intake at the end of the breakfast (T0) and 1h, 2h, 3h, 4h, 5h, 6h, 8h, 12h, after first IMP intake. The 12h timepoint, which will be just prior to the dinner and the IMP intake at the end of the meal, can be adjusted to a maximum of 2 hours earlier to accommodate a more convenient dinner time. PK sampling schedule for 13h, 14h, 15h and 24h is relative to the evening IMP administration (respectively 1, 2, 3 and 12h after evening IMP administration).
    - at W006 visit: prior to breakfast and first study drug intake at the end of the breakfast, which will be considered as T0, then 1h, 3h after drug intake and just before the participant leaves the site at the end of the study visit.
    - participants having signed the consent form for the optional PK analysis will stay during 12 hours at W000 and be hospitalized one day and one night at W004 visits.

Note: Participation in the CL2-42909-016 study does not imply a mandatory or systematic participation in the optional investigations. All voluntary participants will have to sign a specific informed consent form. The consent given for this analysis can be withdrawn at any moment without compromising the participation in the overall clinical study investigations. In addition, in case of consent withdrawal, related samples will be destroyed on a case by cases basis.

On the day of PK samples, well-balanced meals will be taken by the participants, equivalent to 600 Kcal for breakfast and 900-1100 Kcal for lunch and dinner with no more than 25% of

fat. The participants must consume all contents of their meals on these days. Examples of standard breakfast and lunch/dinner are provided in Appendix 11.

- Plasma samples handling:

Blood samples will be centrifuged according to the laboratory manual instructions.

- After centrifugation, 4 aliquots of at least 0.5ml of clean plasma will be transferred into 4 cryovials tubes intended to assay the parent drug (S42909) and its metabolites (S45015, S45236 and S55113). Real time of sampling must be noted on the relevant page of the e-CRF.

Tubes will be clearly labelled with indelible ink, with labels provided with the tubes and stating for example:

- Protocol number (CL2-42909-016), Participant number, Treatment number, site number
- Visit, date of the sampling, time (e.g. W000, T12h).

9.1.2. Storage and shipment of samples

The plasma tubes will be immediately frozen at approximately –20 or -80°C (-4 or -112°F) and kept at this temperature until shipment.
On a mutually agreed date and according to the instructions written in the laboratory manual, two aliquots of each plasma sample will be sent by special carrier to the logistical platform in an isolated box containing dry ice for storage. Samples will be accompanied with a list of contents.
The shipments will be organised by the logistical platfrom.
The logistical platform will be in charge of the shipment of the aliquots to the assay centre.
The remaining two aliquots (safeguard samples) will be sent later on request of the logistical platform.

9.2. Assessment of non genomic biomarkers relating to healing (biorepository)

9.2.1. Collection of blood samples

Non genomic biomarkers will be measured in plasma and serum (in ante brachial vein). Blood samples will be collected in both EDTA and SST tubes for plasma and serum aliquot preparation at W000 before first administration of treatment and at W004, in participants having given their written informed consent for these optional samplings (See investigational schedule (Table (4.2.2) 1).

9.2.2. Optional assessment

Participation in the CL2-42909-016 study does not imply a mandatory or systematic participation in the optional investigations. All voluntary participants will have to sign a specific informed consent form. The consent given to this analysis can be withdrawn at any moment without compromising the participation in the overall clinical study investigations. In addition, in case of consent withdrawal, related samples will be destroyed before any optional analysis is completed.

Non genomic biomarkers related to venous leg ulcer healing should be measured to establish a potential correlation between the presence or absence from body fluids and healing success. The non genomic biomarkers related to the underlying chronic venous disease, the response to S42909 treatment may also be analysed.

A biorepository will be establish to hold plasma and serum samples collected from the participants having given their written informed consent for these optional samplings, until the candidate non genomic biomarkers will be selected for analysis.

For genomic assessment, see 9.3.Optional assessment-genomics.

9.2.2.1. Sampling and storage

The management of the samples (centrifugation, aliquoting) and the storage before shipment will be done according to the instructions written in the laboratory manual.

The aliquots will be frozen at approximately –80°C (-112°F) and kept at this temperature until shipment.

On a mutually agreed date and according to the instructions written in the laboratory manual, the plasma and serum samples will be sent to the logistical platform in an isolated box containing dry ice for storage according to the instructions written in the laboratory manual.

The logistical platform will store the samples during the study and will organise the shipment to the biorepository for long term storage.

The samples will be stored for a maximum 25 years, after the end of the study or earlier if requested, and according to local regulations.

Samples not stored in the biorepository will be destroyed after analysis or after completion of the analytical report, and at the latest before the end of the study.

9.2.2.2. Labelling and transfer

- Labelling:

Labelling must allow unique sample and participant identification. Information will be detailed in the Logistic platform specifications

- Transfer:

The deep frozen samples will be transported by special delivery in dry ice to the biorepository or to the responsible laboratory.

9.2.2.3. Non genomic biomarkers assessment

Not applicable

9.2.2.4. Transfer of analytical results

Not applicable.

9.3. Optional assessment - genomic

The pharmacokinetics and pharmacodynamics of many medicinal products is prone to assess between subjects' variability, which is caused by several factors such as sex, age, weight, renal and hepatic functions, and genomics factors. In recent years, a rapid development in our

understanding of the influence of genomes between subjects' differences in drug action has occurred.

Determination of genes influencing the response to a treatment could allow the identification of participants having a better response to a given treatment or participants with higher susceptibility to develop adverse events related to a treatment. Identification of these genes could help provide the most suitable therapy to each participant.

An optional genotyping analysis will be performed. The objective is mostly to develop the knowledge of the impact of genomic on the ADME parameters and on the pharmacodynamics of the test drug.

Sequencing of the human genome, identification of informative genomic biomarkers such as single nucleotide polymorphisms (SNP) and development of new technologies such as DNA arrays have facilitated the study of the genome in a large scale. The use of these technologies facilitates the study of genomics biomarkers associated with the susceptibility to have a disease or to respond to a treatment and accelerates the implementation of pharmacogenomics studies in drug development. On the other hand, Regulatory Agencies nowadays encourage development of genomic studies in order to advance the understanding of relationships between genotypes and responses to drugs.

In order to improve the knowledge of S42909 in human (pharmacokinetics and pharmacodynamics), to better understand the mechanism of response to treatment and to determine factors related to the response, a genotyping analysis will be performed to try to:

- identify genes implicated in the S42909 drug absorption, distribution, metabolism and excretion and evaluate associations between polymorphisms of relevant genes and pharmacokinetics of S42909 and the response to treatment.
- identify genes implicated in the pharmacological target, subgroups of participants with genetic susceptibility to develop non-healing venous leg ulcer or to identify novel genes that may play a critical role in the treatment response.

These polymorphisms could be further used as biomarkers of the type of response to treatment.

Candidate genes for genomic studies are those implicated in drug absorption and disposition (e.g. pharmacokinetics) and drug effects (e.g. pharmacodynamics, drug efficacy and adverse effects).

The samples will not be used for any investigations not specified in this protocol or for the elaboration of a DNA bank.

There will be no communication of individual results neither to the investigator nor to the participant.

Note: Participation in the CL2-42909-016 study does not imply a mandatory or systematic participation in the optional investigations. All voluntary participants will have to sign a specific informed consent form. The consent given to this analysis can be withdrawn at any moment without compromising the participation in the overall clinical study investigations. In addition, in case of consent withdrawal, related samples will be destroyed before any optional analysis is completed.

9.3.1. Collection of blood samples

A blood sample will be collected in an EDTA aliquot for DNA isolation in participants having given their written informed consent for this optional analysis. The samples collection will be performed at the inclusion visit before first administration of treatment (W000) as indicated in the investigational schedule (Table (4.2.2) 1) in participants having given their written informed consent form for this optional sampling information.

9.3.2. Sampling and storage

The management of the blood samples and the storage before shipment (if applicable) will be done according to the instructions written in the laboratory manual. The aliquots will be frozen at approximately –80°C (-112°F) and kept at this temperature until shipment.
The blood samples will be first sent to the logistical platform in an isolated box containing dry ice for storage according to the instructions written in the laboratory manual.

The logistical platform will store the samples during the study and will organise the shipment to the laboratory responsible for the DNA extraction and genomic analysis in an isolated box containing dry ice. The shipment for analysis will be organised at the end of the study with the agreement of the sponsor.

After completion of the analysis, remaining aliquots will be sent to the biorepository for long term storage.

The samples will be stored for a maximum of 25 years, after the end of the study or earlier if requested and according to local regulations.

9.3.3. Labelling

Labelling must allow unique sample and participant identification. Information will be detailed in the Logistic platform specifications.

9.3.4. Assay

Genomic biomarkers will be analysed using a Fluidigm Technology platform. Following first analysis the samples containing extracted DNA will be stored for a period of up to 25 years after the end of the study or earlier if requested and could be used for subsequent analyses. All samples will be destroyed after a maximum period of 25 years after the end of the study, or on the simple demand of the participant to the investigator.
Genomic markers will be determined and analysed based on the clinical pharmacokinetic data obtained. The genotyping test will be performed on genes thought to be involved in the absorption, distribution, metabolism and excretion of S42909. After the first analysis, the remaining quantity of the samples will be stored in order to provide the opportunity to investigate unknown polymorphic sites related to the pharmacokinetics and pharmacodynamics of S42909, not identified yet at the time of the first analysis.

10. STATISTICS

10.1. Statistical analysis

A Statistical Analysis Plan will be written after finalising the protocol and definitively completed before breaking the blind. These specifications will detail the implementation of all the planned statistical analyses in accordance with the principal features stated in the protocol.

10.1.1. Evaluation criteria

Efficacy criteria

- Main criterion:
  - Reference Ulcer area expressed as a relative change from baseline to W004 (%):
  - Main analytical approach: Detection of an overall dose-response effect using the MCP-Mod Method (for more details see § 10.1.4, Statistical Methodology).
  - Secondary analytical approach: Determination of dose window for the Minimal Effective Dose (MED) using the MCP-Mod Method (for more details see §10.1.4 Statistical Methodology).

- Secondary criteria
  - Linear advance of the wound margin towards the wound center:

$$\bar{d} = \frac{\Delta A}{\bar{p}}$$

Where ΔA is the difference in the area ($A_{Visit} - A_{Baseline}$) and $\bar{p}$ is the average of the wound perimeter ($\bar{p} = \frac{p_{visit} + p_{Baseline}}{2}$)

  - Reference Ulcer Volume
  - Pain intensity
  - Analgesic drug consumption

Safety criteria

- Adverse events
- Blood biochemistry, haematology, and urinalysis
- Physical examination and vital signs
- 6 or 12-lead electrocardiogram (ECG)

Biomarker criteria

- Plasma biomarkers
- Genomic criteria

The complete list of biomarkers will be subsequently determined.

10.1.2. Statistical elements

The type one error of the statistical analyses will be set at 2.5 % in a one tailed situation.
The following descriptive statistics will be provided depending on the nature of variables:
Quantitative variable: number of observed values, mean and standard deviation, minimum and maximum, median, and if necessary first and third quartiles.
Qualitative or ordinal variable: number and percentage of patients per class.

10.1.3. Analysis sets

Randomised Set (RS)
This set will correspond to all randomised patients.

Safety set for double blind period (SS)
This set will correspond to patients who received at least one dose of study treatment.

Full Analysis Set (FAS)
This set will correspond to randomised patients who received at least one dose of study treatment and who have at least one baseline value and one value of reference ulcer area at W004.

Per Protocol Set (PPS)
This set will correspond to patients of the Full Analysis Set without relevant deviation(s) which could affect the evaluation of the primary efficacy criterion.
Based on the actual deviations, the criteria for exclusion of patients from the different data sets will be specified and updated if necessary before breaking the blind.

10.1.4. Statistical methodology

Study Outcome

Study outcome analyses will be carried out on the RS.
Characteristics of patients including demography, prognostic factors, baseline values of assessment criteria will be described by dose and overall.
Treatment duration, global treatment compliance, status of patients and reason for withdrawal, protocol deviations, concomitant treatments will be described by dose and overall.
Main characteristics of patients will also be described for the SS, the FAS and the PPS.

Efficacy

Efficacy analyses will be carried out on the FAS and the PPS.

- Primary criterion: Reference Ulcer area

Main analysis: Detection of an overall dose-response effect

The objective of the main analysis will be to detect the existence of a dose-response relationship according to the reference ulcer area reduction expressed as the relative change from baseline to W004 (%) and using the MCP-Mod Method ((EMA/CHMP/SAWP/757052/2013, 2014); (Bretz, 2005)).

The doses 0 mg (placebo), 100 mg, 200 mg, 400 mg, 800 mg and 1200 mg will be assessed in the study and the following set of 7 candidate models: $\mathcal{M}$ = (Linear, Emax (2), Sigmoïd Emax, Logistic, Exponential (2)) considered for the main analysis.

The models will be defined as follows with some pairs (d*, p*) where d* is a dose and p* is the maximal percentage of efficacy related to the concerned dose:

- Linear
- Emax1 (200 mg, 90%)
- Emax2 (400 mg, 70%)
- Sigmoïd Emax (200 mg, 10%) and (1000 mg, 90%)
- Logistic (200 mg, 10%) and (1000 mg, 90%)
- Exponential1 (400 mg, 10%)
- Exponential2 (800 mg, 10%)

A test of contrast will be performed on each model to detect the existence of dose response relationship (“proof of concept”) with control of the Family Wise Error Rate (FWER) at a

pre-specified level α. If at least one model is statistically significant, the "best" fit model will be selected.

The "best" fit model will be chosen by the minimum p-value (the one with the strongest statistical test and greater than an appropriate critical value q).

Secondary analyses:

- Determination of dose window for the Minimal Effective Dose (MED)

Using the selected model resulting from the main analysis, a dose window of the Minimal Effective Dose (MED) will be estimated, considering an hypothesis of a clinically relevant effect as compared to placebo of 6.5%.

The parameters of the selected model in the main analysis will be re-assessed and, if the model converges, it will be used to estimate the MED. If the model doesn't converge, the second "best" fit model will be used.

- Description

The relative change from baseline of the reference ulcer area will also be described at each visit.

- Secondary criteria
  - Linear advance of the wound margin towards the wound centre

Description at each visit will be provided.

  - Reference Ulcer Volume

Descriptive statistics at each visit will be performed.

  - Pain intensity

Descriptive statistics at each visit will be carried out.

  - Analgesic drug consumption

Descriptive statistics at each visit will be carried out.

In addition, relative change of the reference ulcer area, linear advance of the wound margin towards the wound centre and reference ulcer volume will be described at each visit in the following subgroups:

- Combined prognosis criteria on size and age of the ulcer (≤ 10 cm² and ≤ 6 months / > 10 cm² or > 6 months)
- Size of the ulcer at baseline (≤ 50 cm² / > 50 cm²)
- Diabetes status (yes/no).

Exploratory data analyses will be conducted as applicable.

Safety

Safety analyses will be carried out on the Safety Set by group over the W0-W6 period.

  - Adverse events

Number of adverse events, number and percentage of patients reporting at least one adverse event will be described by System Organ Class (SOC) and Preferred Term. The same analysis will be performed for emergent adverse events and serious adverse events.

Emergent adverse events will be also described in accordance to the intensity, outcome, relationship to the study treatments, and adverse events leading to the study drug withdrawal.

- Clinical laboratory evaluation

Laboratory parameters will be described using value at the visit, last value under treatment and change from baseline to last value under treatment.

Moreover, biochemistry, haematology and urinary parameters will be classified according to the laboratory reference ranges and alert values for the potentially clinically significant abnormal values, and shift tables from baseline to worst event will be presented.

- Physical Examination and vital signs

Physical examination and vital signs will be described using value at the visit, last post-baseline value and change between baseline and last post-baseline value.

- 6 or 12-lead electrocardiogram (ECG)

ECG parameters and ECG abnormalities will be described at each visit.

Biomarkers

The association between healing and plasma biomarkers could be investigated with prognostic approaches e.g. regression models, Receiver Operating Characteristic (ROC) curve.

In order to study the association between genomic criteria and efficacy or safety of S42909, exploratory analyses using single-marker and multi-marker approaches could be used.

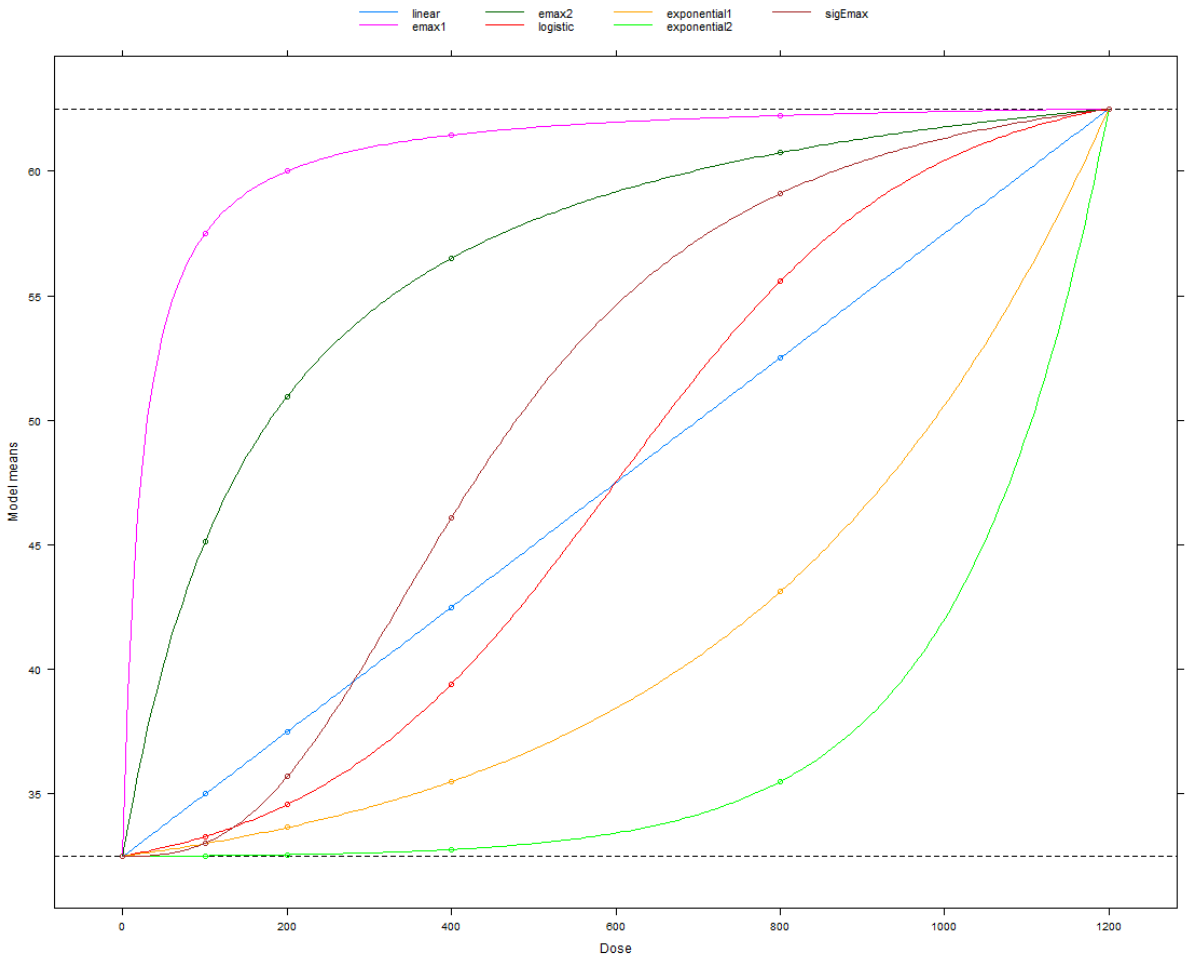
10.2. Determination of sample size

Sample size was estimated with a type one error rate set at 2.5% and using the statistic function "*sampsize*" described in the publication "*MCP-Mod* : *An R Package for the Design and Analysis of Dose-Finding Studies*" edited by B. Bornkamp, J. Pinheiro and F. Bretz (2009).

Considering:

- a standard deviation of 42%,
- a minimal relative change of Reference ulcer area at one month (Rmin) of 32.5%,
- a maximal relative change of Reference ulcer area at one month (Rmax) of 62.5%,
- a maximal efficacy (Rmax – Rmin) of 30%,
- six doses: 0 (placebo), 100, 200, 400, 800, 1200 mg,
- seven candidate models defined by some couples (d*, p*) (dose, maximal percentage of efficacy):
    - Linear
    - Emax1 (200 mg, 90%)
    - Emax2 (400 mg, 70%)
    - Sigmoïd Emax (200 mg, 10%) and (1000 mg, 90%)
    - Logistic (200 mg, 10%) and (1000 mg, 90%)
    - Exponential1 (400 mg, 10%)
    - Exponential2 (800 mg, 10%),

Figure (10.2) 1 - Dose-response models



- function "*min*" of Bretz package (power of each model is greater or equal to the nominal power to detect a signal of dose-response relationship),

27 evaluable participants per group guarantee a nominal power of at least 80% to detect a signal of dose-response relationship (proof-of-concept).

After 1000 data simulations based on above hypotheses, with a true dose-response relationship supposed to be a logistic model (defined by the couples (200 mg, 10%) and (1000 mg, 90%)) and 27 participants by dose, the empiric power to detect a signal of dose-response relationship (main objective) is about 90%.

In this case, for the secondary objective, the empiric power to determine the Minimal Effective Dose with a clinically relevant difference of 6.5% of healing rate at one month (as compared to placebo) is about 87.5%.

Other simulated data with a true dose-response relationship supposed to be an Emax model or an Exponential model lead to an empiric power to detect a signal of dose-response relationship (proof-of-concept) of about 80% and to an empiric power to determine the Minimal Effective Dose with a clinically relevant difference of 6.5% of healing rate at one month (as compared to placebo) of at least 70% for an Emax model, at least 65% for an Exponential model.

Taking into account an exclusion rate from the Randomised Set estimated at 20%, about 34 participants per treatment group will have to be included.

11. DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

The investigator will allow the monitors, the persons responsible for the audit, the representatives of the IRB/IEC, and of the Competent Authorities to have direct access to source data / documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study monitoring

12.1.1. Before the study

The investigator will allow the monitor to visit the site and facilities where the study will take place in order to ensure compliance with the protocol requirements.

Training sessions may be organised for the investigators and/or designated persons.

12.1.2. During the study

The investigator will allow the monitor to:
- inspect the site, the facilities and the material used for the study,
- meet all members of his/her team involved in the study,
- consult the documents relevant to the study,
- have access to the electronic case report forms (i.e. access to an analogic phone line or his/her computer),
- check that the electronic case report forms have been filled out correctly,
- directly access source documents for comparison of data therein with the data in the electronic case report form,
- verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The study monitoring will be carried out at regular intervals, depending on the recruitment rate and / or the investigation schedule, and scheduled between the investigator and/or designated persons and monitor.

All information dealt with during these visits will be treated as strictly confidential.

12.2. Computerised medical file

If computerised medical files are used, and if the computer system allows, no change made in the medical files by the investigator should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information (i.e. audit trail). The investigator will save data at regular intervals.

The investigator must guarantee the integrity of the study data in the medical files by implementing security measures to prevent unauthorised access to the data and to the computer system.

If the computerised medical files are considered as not validated by the sponsor, the investigator undertakes:
- at the start of the study, to print the medical files of all participants allowing a reliable verification of the study criteria (e.g. medical history/previous treatments/ characteristics of the studied disease documented within the period of time defined by the study protocol),
- during the study, to print in real time each data entry and each data change.

The investigator will personally sign, date and give the number of pages on the first or last page of each print-out. At each visit by the monitor, the investigator will provide all the print-outs of the medical files of the participants. The monitor will personally sign and date the first (or last) page then initial all pages in each paper print-out.

If the computer system allows the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the medical files of the participants and the records of the changes made. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

If the computerised medical files are considered as validated by the sponsor, the investigator undertakes to give access to the monitor to the computerised medical files of all participants. If the monitor cannot access to the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the records of the changes made to the medical files of the participants. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

The investigator undertakes to keep:
- all medical file print-outs signed and dated by him/her and by the monitor when the computer system is considered as not validated by the sponsor,
- if the computer system used allows changes to be made, the print-outs of the audit trail when the computer system is considered as not validated by the sponsor or when the monitor cannot access to the audit trail in the computer system,
- all original source-documents (originals of specific examinations, informed consent forms, therapeutic unit tracking form, etc.).

12.3. Audit - Inspection

The investigator should be informed that an audit may be carried out during or after the end of the study.

The investigator should be informed that the Competent Authorities may also carry out an inspection in the facilities of the sponsor and/or the study centre(s). The sponsor will inform the investigators concerned immediately upon notification of a pending study centres inspection. Likewise, the investigator will inform the sponsor of any pending inspection.

The investigator must allow the representatives of the Competent Authorities and persons responsible for the audit:

- to inspect the site, facilities and material used for the study,
- to meet all members of his/her team involved in the study,
- to have direct access to study data and source documents,
- to consult all of the documents relevant to the study.

If the computerised medical file is considered as not validated, the investigator undertakes to provide all the source-documents and the print-outs of the medical files of the participants and, if the computer system used allows, the record of the changes made during the study.

If the computerised medical file is considered as validated, the investigator undertakes to:

- give access to the representatives of the Competent Authorities and persons responsible for the audit to the computerised medical files of all participants,
- provide the print-outs of the changes made during the study, if the tracking of the changes made to the medical files cannot be accessed in the computer.

13. ETHICS

13.1. Institutional Review Board(s)/Independent Ethics Committee(s)

The study protocol, the "Participant information and consent form" document, the list of investigators document, the insurance documents will be submitted to IRB(s)/IEC(s) by the investigator(s) or the national coordinator(s) or the sponsor in accordance with local regulations.

The study will not start in a centre before written approval by corresponding IRB/IEC(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved has been obtained.

13.2. Study conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 (see Appendix 1).

13.3. Participant information and informed consent

In any case, the participant (and/or his/her legal representative, when required) must be informed that he/she is entitled to be informed about the outcome of the study by the investigator.

The investigator or a person designated by him/her is to collect written consent from each participant before his/her participation in the study. Prior to this, the investigator or his/her delegate must inform each participant of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the IMPs, underlying that the participation of the participant is entirely voluntary and he/she can withdraw from the study at any time without affecting standard of care he/she receives.

The participant will be provided with two information and consent forms in clear, simple language: one for the study including the optional PK analysis and one for the optional samples for pharmacogenomic and non genomic biomarkers analysis.

For each information and consent form, two original information and consent forms must be completed, dated and signed personally by the participant and by the person responsible for collecting the informed consent.

If the participant is unable to read, an impartial witness should be present during the entire informed consent discussion. The participant must give consent orally and, if capable of doing so, complete, sign and personally date the information and consent form. The witness must then complete, sign and date the form together with the person responsible for collecting the informed consent.

The participant will be given one signed original information and consent form, the second original will be kept by the investigator.

A copy of the information and consent form in the language(s) of the country is given in the "Participant information and consent form" document attached to the protocol.

13.4. Modification of the information and consent form

Any change to the information and consent form constitutes an amendment to this document and must be submitted for approval to the IRB/IEC(s), and if applicable to the Competent Authorities.

A copy of the new version of the information and consent form in the language(s) of the country will be given in the amendment to the "Participant Information and consent form".

Such amendments may only be implemented after written approval of the IRB/IEC has been obtained and compliance with the local regulatory requirements, with the exception of an amendment required to eliminate an immediate risk to study participants.

Each participant affected by the amendment or an independent witness must complete, date and sign two originals of the new version of the information and consent form together with the person who conducted the informed consent discussion. He/she will receive one signed original amendment to the information and consent form.

14. DATA HANDLING AND RECORD KEEPING

14.1. Study data

An electronic data capture system is going to be used for this study. An electronic case report form (e-CRF) is designed to record the data required by the protocol and collected by the investigator.

The e-CRF will be produced by I.R.I.S. in compliance with its specifications. The investigator or a designated person from his/her team will be trained for the use of the e-CRF by the sponsor.

Data entry at the investigator's site will be performed by the investigator or by the designated person from his/her team after completion of the participant's Medical File.

Upon entry, data will be transmitted via the Internet from the study centre to the study database.

The investigator or the designated person from his/her team agrees to complete the e-CRF, at each participant visit, and all other documents provided by the sponsor (e.g. documents relating to the IMP management…).
Data recorded directly in the e-CRF and considered as source data (see section 4.6) must be collected immediately in the e-CRF. The other e-CRF forms must be completed within 5 days after patient's visits.

All corrections of data in the e-CRF must be made by the investigator or by the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded using the audit trail feature of Inform software, including date, reason for modification and identification of the person who has made the change.

In order to ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the investigator's sites, the sponsor or third parties.
Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed within 5 days after query issue.

Data can be frozen during the study after their validation. However the investigator has the possibility to modify data if deemed necessary via a request to the sponsor.

After the last visit of the participant, the investigator or co-investigator must attest the authenticity of the data collected in the e-CRF by entering his/her user name and password.

After the data base lock, the investigator will receive a CD-ROM containing participant data of his/her centre for the study file.

14.2. Data management

Data are collected via an e-CRF and stored in a secured database.

For data collected on the e-CRF, the Data & Clinical Logistics of I.R.I.S. is responsible for data processing including data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. An electronic data clarification form is sent to the investigator who is required to respond to the query and make any necessary changes to the data.

For data transferred from the logistical platform, central reading centre of the RU measurements, the Data & Clinical Logistics of I.R.I.S. is responsible for data transfer: centralised laboratory, central reading centre of RU measurements provide electronic transfer of computerised data to the Clinical Data Division of I.R.I.S. Data are transferred according to a transfer protocol issued by the I.R.I.S. data manager.

The Medical Data Department of I.R.I.S. is responsible for data coding including:
- medical / surgical history, adverse events and procedures using MedDRA
- medications using WHO-DD.

The coding process is described in a specification manual.

When data validation is achieved, a blind review of the data is performed according to the sponsor standard operating procedure. When the database has been declared to be complete and accurate, it will be locked and the IMP codes will be unblinded and made available for data analysis.

14.3. Archiving

The investigator will keep all information relevant to the study for at least 15 years after the end of the study, or more if specified by local regulations.

At the end of the study, the investigator will be provided with a copy of each participant's data on a CD-ROM support. These data include all data and comments reported in the e-CRF, the history of all queries and signatures and the full audit trail reports.

15. INSURANCE

I.R.I.S., or any parent company of SERVIER GROUP in charge of the management of clinical trials, is insured under the liability insurance program subscribed by ILKOS THERAPEUTIC INC to cover its liability as sponsor of clinical trials on a worldwide basis.

Where an indemnification system and/or a mandatory policy are in place, I.R.I.S. or any parent company of SERVIER GROUP will be insured under a local and specific policy in strict accordance with any applicable law.

All relevant insurance documentation is included in the file submitted to any authorities' where approval is required.

16. OWNERSHIP OF THE RESULTS - PUBLICATION POLICY

ILKOS THERAPEUTIC INC, acting as the study sponsor, assumes full responsibility relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit.

As the study is a multicentre one, the first publication must be performed only with data collected from several centres and analysed under the responsibility of the Pole of Expertise Methodology and Data Valorisation of I.R.I.S. The investigator commits himself not to publishing or communicating data collected in only one centre or part of the centres before the publication of the complete results of the study, unless prior written agreement from the other investigators and ILKOS THERAPEUTIC INC has been provided.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before

submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Any project of publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end, shall be submitted to the sponsor at least 30 days for a publication and 15 days for an abstract before the forecasted date of communication and/or submission for a publication. The sponsor shall make comments on the project within 15 days for a publication and 7 days for an abstract, of receipt of the project. The investigator, who submitted the project, shall take the sponsor's comments into due consideration. In any case, should the investigator who submitted the project decide not to modify the project according to the sponsor's comments, it shall provide the sponsor with the grounds of its decision in writing.

However, in the case where the sponsor is in the process of filing a patent application on the results of the study, the sponsor will be able to delay its authorisation for publication or communication of the results of the study until the date of international registration of the patent.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the sponsor and the investigator

17.1.1. Persons to inform

In accordance with local regulations, the investigator and/or the sponsor will inform, the Director of the medical institution, the pharmacist involved in the study and the Director of the analysis laboratory.

With the agreement of the participant, the investigator will inform the participant’s general practitioner about his/her patient’s participation in a clinical study.

17.1.2. Substantial protocol amendment and amended protocol

If the protocol must be altered after it has been signed, the modification or substantial amendment must be discussed and approved by the international study coordinator and the sponsor.

The substantial protocol amendment must be drafted in accordance with the sponsor standard operating procedure and an amended protocol must be signed by both parties. Both documents must be kept with the initial protocol.

All substantial amendments and corresponding amended protocols must be sent by the investigator(s) or the coordinator(s) or the sponsor, in accordance with local regulations, to the IRB/IEC that examined the initial protocol. They can only be implemented after a favourable opinion of the IRB/IEC has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, with the exception of a measure required to eliminate an immediate risk to the study participants.

When the submission is performed by the investigator or the coordinator, the latter must transmit a copy of IRB/IEC's new written opinion to the sponsor, immediately upon receipt.

Furthermore, the substantial amendment and amended protocol are to be submitted to the Competent Authorities in accordance with local regulations.

17.1.3. Final study report

The study report will be drafted by the report writing department in compliance with I.R.I.S. standard operating procedure.

The sponsor's representative and the international study coordinator must mutually agree on the final version. One copy of the final report, must be dated and signed by the international study coordinator and the sponsor.

17.2. Concerning the sponsor

The sponsor undertakes to:
- supply the investigator with adequate and sufficient information concerning the IMP administered during the study to enable him/her to carry out the study,
- supply the investigator with the Investigator's Brochure if the test drug is not marketed,
- obtain any authorisation to perform the study and/or import licence for the IMP administered that may be required by the local authorities before the beginning of the study,
- provide the international study coordinator annually, or at another frequency defined by the local regulations, with a document describing study progress which is to be sent to the IRB/IEC(s).

17.3. Concerning the investigator

17.3.1. Confidentiality - Use of information

All documents and information given to the investigator by the sponsor with respect to S42909 and study CL2-42909-016 are strictly confidential.
The investigator expressly agrees that data on his/her professional and clinical experience is collected by the sponsor on paper and computer, and stored for its sole use relating to its activities as the sponsor of clinical trials, in accordance with GCP.
He/she has a right to access, modify, and delete his/her own personal data by applying to the sponsor.

The investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the sponsor.

The clinical study protocol given to the investigator may be used by him/her or his/her colleagues to obtain the informed consent of study participants. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorisation of the sponsor.

The investigator must not disclose any information without the prior written consent from the sponsor, except to the representatives of the Competent Authorities, and only at their request. In the latter case, the investigator commits himself to informing the sponsor prior to disclosure of information to these authorities.

A participant screening log and a full identification and enrolment list of each participant will be completed and kept by the investigator who should agree to provide access on site to the auditor and/or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

The participant screening log must be completed from the moment the investigator checks that a participant could potentially take part in the study (by assessment of participant medical history during a visit or by examination of the medical file).

17.3.2. Organisation of the centre

Every person to whom the investigator delegates under his/her responsibility a part of the follow-up of the study (co-investigator, nurse, etc.) and any other person involved in the study for this centre (cardiologist, pharmacist, etc.) must figure be listed in the "Organisation of centre" document.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the centre.

17.3.3. Documentation supplied to the sponsor

The investigator undertakes before the study begins:

- to provide his/her dated and signed English Curriculum Vitae (CV) (maximum 2 pages) or to complete in English the CV form provided by the sponsor and to send it to the sponsor, together with that of his/her co-investigator(s),
- to provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the parameters measured,
- to provide any other document required by local regulation (e.g. Food & Drug Administration 1572 form),
- to send a copy of the IRB/IEC's opinion with details of its composition and the qualifications of its constituent members.

The CVs of other members of the team involved in the study (if possible in English) will be collected during the course of the study (at least members involved in the participant' medical follow-up/study related process decision and persons involved in the measurement of main assessment criteria).

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19. APPENDICES

Appendix 1: Word Medical Association Declaration of Helsinki

Appendix 1: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: Duplex ultrasonography

Both legs will be fully investigated (Coleridge Smith, 2006).

Venous Duplex ultrasonography

Venous obstruction will be assessed using the duplex ultrasonography performed with a superficial probe (7 to 13 Megahertz or MHz), on a participant in supine position, to explore the veins listed below (obstruction list). Vein compression, retrograde flow in deep and superficial veins using compression of the calf muscles, echography B mode, pulsed wave and colour Doppler will be used.
For venous valve incompetence, the participant will be examined in standing position. Reflux will be search on the veins listed below with compression of the calf or valsalva manoeuvre for veins above knee, and with compression on the foot for veins below knee. Reflux will be considered if retrograde flow lasted > 0.5 second for superficial veins, anterior and posterior tibial veins, peroneal veins, perforator veins, and if retrograde flow lasted > 1 second for common femoral vein, femoral vein, and popliteal vein.

Please, tick the appropriate boxes:		**Right/Left leg**	
		Not present	**Present**
Reflux	Great Saphenous Vein above knee	(0) ☐	(1) ☐
	Great Saphenous Vein below knee	(0) ☐	(1) ☐
	Small Saphenous Vein	(0) ☐	(1) ☐
	Non saphenous superficial veins	(0) ☐	(1) ☐
	Gastrocnenial, soleal veins	(0) ☐	(1) ☐
	Tibial anterior vein	(0) ☐	(1) ☐
	Tibial posterior vein	(0) ☐	(1) ☐
	Peroneal vein	(0) ☐	(1) ☐
	Popliteal vein	(0) ☐	(1) ☐
	Femoral vein	(0) ☐	(1) ☐
	Common femoral vein	(0) ☐	(1) ☐

Please, tick the appropriate boxes:		**Right/Left leg**	
		Not present	**Present**
Obstruction	Great Saphenous Vein above knee	(0) ☐	(1) ☐
	Great Saphenous Vein below knee	(0) ☐	(1) ☐
	Small saphenous vein	(0) ☐	(1) ☐
	Non saphenous superficial veins	(0) ☐	(1) ☐
	Gastrocnenial, soleal veins	(0) ☐	(1) ☐
	Tibial anterior vein	(0) ☐	(1) ☐
	Tibial posterior vein	(0) ☐	(1) ☐
	Peroneal vein	(0) ☐	(1) ☐
	Popliteal vein	(0) ☐	(1) ☐
	Femoral vein	(0) ☐	(1) ☐
	Deep femoral vein	(0) ☐	(1) ☐
	Common femoral vein	(0) ☐	(1) ☐
	Pelvic veins*	(0) ☐	(1) ☐
	Internal iliac vein*	(0) ☐	(1) ☐
	External iliac vein*	(0) ☐	(1) ☐
	Common iliac vein*	(0) ☐	(1) ☐
	Inferior vena cava*	(0) ☐	(1) ☐

**If probe for this assessment is available (e.g. convex probe from 3.5 to 5MHz)*

Arterial Duplex ultrasonography

Duplex ultrasonography of the artery system will also be performed in the leg affected by the reference ulcer in order to check for arteriopathy from iliac to tibial arteries.

Please, tick the appropriate boxes:		Leg affected by the reference ulcer		
		Methods**		
		Method 1 (Planimetry)	**or Method 2 (Velocity)**	**and/or Method 3 (Flow type / Waveform)**
Arteriopathy	Common iliac artery*	% stenosis ☐	☐ cm/s	Flow type (0-5) ☐
	Internal iliac artery*	% stenosis ☐	☐ cm/s	Flow type (0-5) ☐
	External iliac artery*	% stenosis ☐	☐ cm/s	Flow type (0-5) ☐
	Common femoral artery	% stenosis ☐	☐ cm/s	Flow type (0-5) ☐
	Internal femoral artery	% stenosis ☐	☐ cm/s	Flow type (0-5) ☐
	External femoral artery	% stenosis ☐	☐ cm/s	Flow type (0-5) ☐
	Popliteal artery	% stenosis ☐	☐ cm/s	Flow type (0-5) ☐
	Tibial anterior artery	% stenosis ☐	☐ cm/s	Flow type (0-5) ☐
	Tibial posterior artery	% stenosis ☐	☐ cm/s	Flow type (0-5) ☐
	Peroneal artery	% stenosis ☐	☐ cm/s	Flow type (0-5) ☐
	Dorsal pedal artery	% stenosis ☐	☐ cm/s	Flow type (0-5) ☐

**If probe for this assessment is available (e.g. convex probe from 3.5 to 5MHz)*
**** For either Method 1 (planimetry) or Method 2 (velocity measurement) or Method 3 (flow type), please fill in all boxes under the heading of that method for which results are available. If results by Methods 2 and 3 are available, please fill them both.**

For information: flow type (waveform) of the arterial curve
0 = no flow; 1 = trickle flow; 2 = dampened monophasic; 3 = monophasic; 4 = biphasic; 5 = triphasic

Appendix 3: Venous Leg Ulcer

A leg ulcer is defined as a non-healing ulcer that fails to heal after a period of 6 weeks.
A venous leg ulcer will be defined as full-thickness defect of skin, most frequently in ankle region, that fails to heal spontaneously and is sustained by documented CVD. Typical localization for venous ulcers: the gaiter area – from just below the ankle or malleolus up to, but not including the knee flexural crease.

For the study purposes the largest existing venous leg ulcer fitting the selection criteria in a participant becomes the Reference Ulcer (RU). All selection/inclusion criteria referring to ulcer characteristics take into account RU.

Appendix 4: Revised CEAP Classification

The CEAP classification (Clinical-Etiology-Anatomy-Pathophysiology) was adopted Worldwide to facilitate meaningful communication about CVD and serve as a basis for more scientific analysis of management alternatives.

Clinical classification
C0: no visible or palpable signs of venous disease
C1: telangiectasies or reticular veins
C2: varicose veins
C3: edema
C4a: pigmentation or eczema
C4b: lipodermatosclerosis or atrophie blanche
C5: healed venous ulcer
C6: active venous ulcer

Even if the patient will be C6, other classification from C1 to C5 will have to be defined (e.g. a patient could be C1, C3 and C6).
Each clinical class is further characterized by a subscript for the presence of symptoms (s, symptomatic) or absence of symptoms (a, asymptomatic), for example, C2a or C5s.
Symptoms include heaviness, pain, aching, tightness, skin irritation, muscle cramps, and other complaints attributable to venous dysfunction.

Etiologic classification
Ec: congenital
Ep: primary
Es: secondary (postthrombotic)
En: no venous cause identified
(Only Ep, Es and En will have to be defined)

Anatomic classification
As: superficial veins
Ap: perforator veins
Ad: deep veins
An: no venous location identified
(Only As, Ad and An will have to be defined)

Pathophysiologic classification (basic)
Pr: reflux
Po: obstruction
Pr,o: reflux and obstruction
Pn: no venous pathophysiology identifiable

Advanced CEAP: Same as basic CEAP, with addition that any of 18 named venous segments can be used as locators for venous pathology
Superficial veins (will have to be defined)
- Telangiectasies or reticular veins
- Great saphenous vein above knee
- Great saphenous vein below knee
- Small saphenous vein
- Nonsaphenous veins

Deep veins (will have to be defined)
- Inferior vena cava
- Common iliac vein
- Internal iliac vein
- External iliac vein
- Pelvic: gonadal, broad ligament veins, other
- Common femoral vein
- Deep femoral vein
- Femoral vein
- Popliteal vein
- Crural: anterior tibial, posterior tibial, peroneal veins (all paired)
- Muscular: gastrocnemial, soleal veins, other

Perforating veins: (will not have to be defined)
- Thigh
- Calf

Appendix 5: Ankle Brachial Pressure Index

Continuous wave Doppler (CWD) is used to perform the assessment of the Ankle Brachial Pressure Index (ABPI) with a probe of 8 MHz (5 MHz for obese patient). The main objective is to determine resting ankle systolic pressure and resting brachial systolic pressure (as an approximation of central pressure).
Systolic blood pressure will be measured after 10 minutes of rest on both arms in sitting or supine position and on each foot on the following 2 locations: posterior tibial, and anterior tibial. Each measurement will be performed twice and tables will have to be completed in a specific form (see Appendix 12).
If CWD is not available, the following procedure will be performed with the Duplex Ultra Sonography with a superficial probe (7 to 13 MHz).

Explain the procedure and reassure the patient and ensure that he/she is lying flat and is comfortable, relaxed and rested with no pressure on the proximal vessels.

1. Measure the brachial systolic blood pressure:
    - Place an appropriately sized cuff around the upper arm
    - Locate the brachial pulse (humeral artery) and apply ultrasound contact gel
    - Angle the Doppler probe and move the probe to obtain the best signal
    - Inflate the cuff until the signal is abolished then deflate the cuff slowly and record the pressure at which the signal returns being careful not to move the probe from the line of the artery (in case of duplex ultrasonography: signal returns must be associated to the systolic curve on the screen)
    - Repeat the procedure for the other arm
    - Use the highest of the two values to calculate the ABPI
2. Measure the ankle systolic pressure:
    - Place an appropriately sized cuff around the ankle immediately above the malleoli having first protected any ulcer that may be present by dressing and cling film
    - Examine the foot, locating the **anterior tibial pulse** and apply contact gel (Figure 3)

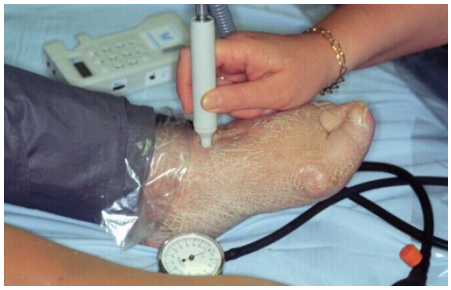


Figure 3 -

    - Continue as for the brachial pressure, recording this pressure in the same way

Repeat this for the **posterior tibial** (Figure 4)

Figure 4 - The posterior tibial artery lies just behind the medial malleolus. Reflux can frequently be heard in the adjacent veins and this can help to locate the artery

3. ABPI calculation
    - Use the highest reading obtained to calculate the ABPI for that leg (each arterial signal must be present: posterior tibial, anterior tibial, if not, occlusion must be excluded by duplex scan)
    - Repeat for the other leg
    - Calculate the ABPI for each leg using the formula below:

$$ABPI_l = \frac{P_l}{P_a}$$

$ABPI_l$ = ABPI for a leg

P_l = Highest pressure obtained from the ankle vessels for that leg

P_a = Highest brachial pressure of the two arms

Causes of error in ABPI calculations

Too small cuff size at the ankle: overestimate of the ABPI.

Repeatedly inflating and deflating: inaccurate pressure reading.

Inappropriate cuff position, as the pressure recorded is the pressure at the level of the cuff and not the pressure at the site of the Doppler probe.

Bad probe: normally 8MHz when assessing superficial blood vessels (best combination of depth of tissue penetration and focus). Obese patient or oedematous legs: 5MHz probe.

Bad position of the probe: ideally 45 degrees to the skin surface with contact gel in case of CWD.

Participants will be eligible for the study if ABPI measured as above is found to be above or equal to 0.8 and below or equal to 1.3

Appendix 6: Ulcer Infection

Chronic wounds are almost always contaminated with micro-organisms and in small numbers they do not necessarily delay healing. Where infection occurs it is most commonly caused by bacteria. The criteria used to describe bacterial loading have been loosely defined by EWMA as follows:

- Contamination is the presence of bacteria with no multiplication
- Colonisation describes multiplication of bacteria with no host response
- Infection is said to be present when there is invasion of healthy tissue with a host response

Assessment of ulcer infection will be made by clinical means taking into account traditional inflammatory signs: redness, swelling, hyperthermia, pain and limited function. Additionally the following parameters should be also considered:

- Increased exudate: substantial increase in the amount of exudate, possibly with increased viscosity, change in colour, offensive odour.
- Friable granulation tissue
- Slough
- Changed odour
- Changed pain
- Stagnation in the healing process
- Serological markers of systemic infection, e.g. leucocytosis, increased CRP

For the purpose of the study, ulcer infection will be graded in 4 different grades taking into account the extent of inflammatory signs:
Grade 1: no signs or symptoms of infection
Grade 2: in subcutaneous tissue only
Grade 3: extensive erythema, infection of deeper tissue
Grade 4: systemic inflammatory response indicating severe infection

Participants with infection of Grades 2-3-4 will undergo medical management at the investigator's discretion including antibiotherapy, except local antibiotherapy on the surface of RU. Should the antibiotics be required for *more than 7 days* during the same month to control the infection the participant will be withdraw from the study.

Appendix 7: Renal Failure Classification

The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) defines chronic kidney disease as either kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 for 3 or more months. Whatever the underlying etiology, the destruction of renal mass with irreversible sclerosis and loss of nephrons leads to a progressive decline in GFR. The different stages of chronic kidney disease form a continuum in time.

In 2002, K/DOQI published its classification of the stages of chronic kidney disease, as follows:

- Stage 1: Kidney damage with normal or increased GFR (>90 ml/min/1.73 m^2)
- Stage 2: Mild reduction in GFR (60-89 ml/min/1.73 m^2)
- Stage 3: Moderate reduction in GFR (30-59 ml/min/1.73 m^2)
- Stage 4: Severe reduction in GFR (15-29 ml/min/1.73 m^2)
- Stage 5: Kidney failure (GFR < 15 ml/min/1.73 m^2 or dialysis)

Estimation of eGFR

Estimation of eGFR will be done using the Modification of Diet in Renal Disease (MDRD) formula

For creatinine in **mg/dL:**

- Female patients
  eGFR= [186 x Serum creatinine $^{-1.154}$ x (Age) $^{-0.203}$] x 0.742 x 0.95
- Male patients
  eGFR= [186 x (Serum creatinine) $^{-1.154}$ x (Age) $^{-0.203}$] x 0.95

For creatinine in **µmol/L:**

- Female patients
  eGFR= [186 x (Serum creatinine x 0.0113)$^{-1.154}$ x (Age) $^{-0.203}$] x 0.742 x 0.95
- Male patients
  eGFR= [186 x (Serum creatinine x 0.0113)$^{-1.154}$ x (Age) $^{-0.203}$] x 0.95

The laboratory will automatically calculate estimated eGFR according to the above formulas. Participants having eGFR < 30 ml/min/1.73 m^2 or participants requiring dialysis are not eligible for participating in the study.

Appendix 8: Heart Failure Classification

Participant's cardiac function should be assessed prior inclusion. In case of heart failure the New York Heart Association (NYHA) functional classification system will be used. This system relates symptoms to everyday activities and the participant's quality of life.

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased .

Patients with heart failure class III and IV are not eligible to participate in the study.

Appendix 9: Questionnaire for Pain Assessment

Please ask the participant the following questions before cleansing and debridement and tick with an X (☒) the response(s) that is/are the most appropriate based on your impression One or several boxe(s) can be checked as appropriate, according to the participant's response:

1. Do you feel any pain or discomfort (aching, heaviness, fatigue, soreness, burning) related to your leg ulcer?

☐ No
☐ Yes If Yes, how would you characterize the intensity of pain or discomfort since your last visit on the following scale (from 0 being no pain to 10 being the worst possible pain)?

Please ask the participant to draw a vertical line on the horizontal axis in accordance with the intensity of his pain since his/her last visit.

---

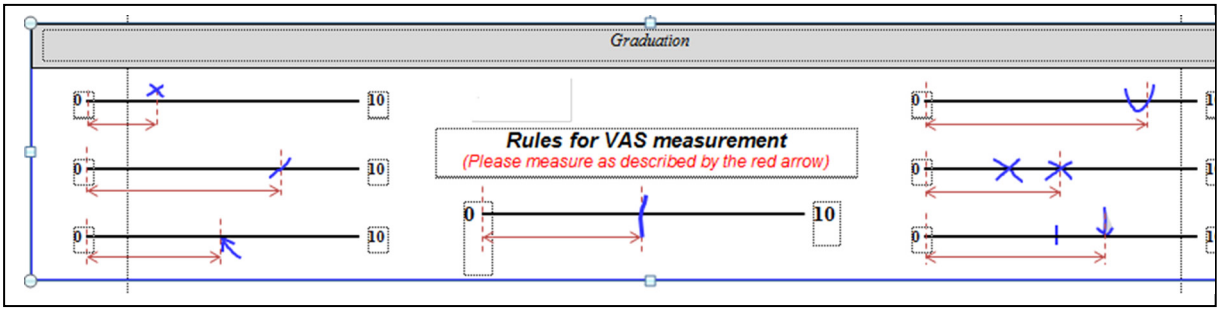
0 **10** ***I__I__I. I__I cm**

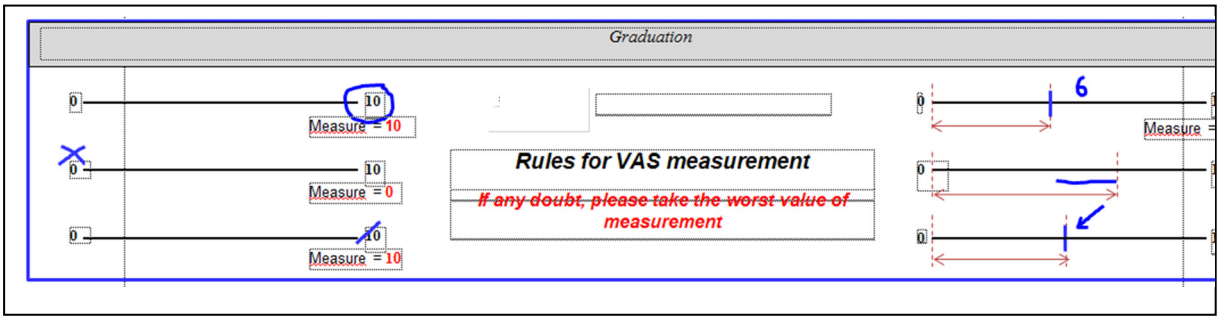
(*Filled in by the investigator)

No pain **Extreme pain**

---

*In case the VAS is not properly completed, please follow the rules defined on the ruler given at the beginning of the study.





2. How would you characterize your pain or discomfort in relation with your daily activities?

   ☐ None
   ☐ Occasional pain or discomfort that does not restrict regular daily activities
   ☐ Daily pain or discomfort that interferes with, but does not prevent, regular daily activities
   ☐ Daily pain or discomfort that limits most regular daily activities

(None = 0)
(Mild = 1)

(Moderate = 2)

(Severe = 3)
*(*For the investigator use)*

3. Is the pain continuous/constant?

   ☐ No
   ☐ Yes

4. Is the pain mostly related with:

   ☐ Dressing change
   ☐ Debridement
   ☐ Other procedure,

   Please specify which procedure(s) (for example, wearing compression stockings, etc…):

   _____
   _____
   _____

5. Is the pain or discomfort more predominant during specific periods of the day:

   ☐ Night
   ☐ Morning
   ☐ Afternoon
   ☐ Evening
   ☐ Same intensity along the whole day

6. Do you need to take medication for control of the pain associated to VLU ?

   ☐ No
   ☐ Yes

   If yes, please specify (analgesic drug consumption):

   - *drug name:* _____
   - *daily dose and number of intakes :*

     _____

   _____

_____

Appendix 10: Clinical Assessment of Leg Ulcer

Chronic venous reference ulcer examination	
Localisation of the ulcer	(At baseline only)
Ulcer imaging	Picture taken Y/N
Observation of new ulceration	Y/N (Except at ASSE)
Complete healing	Y/N (Except at ASSE)
Wound bed % cover	Granulation tissue ☐ Absent ☐ Low (<10%) ☐ Moderate (10 – 50%) ☐ High (>50%)
	Fibrotic tissue ☐ Absent ☐ Low (<10%) ☐ Moderate (10 – 50%) ☐ High (>50%)
	Sclerotic tissue ☐ Absent ☐ Low (<10%) ☐ Moderate (10 – 50%) ☐ High (>50%)
Exudate	High, Moderate or Low
	Increasing of exudate level since last visit Y/N (Except at ASSE)
	Colour of the exudate (Serous, Haemoserous or Purulent)
	Odour Y/N
Surrounding skin appearance	Macerated Eczema Erythema Other (specify)
Signs of infection	Infection suspected (requiring systemic antibiotherapy): Y/N
	If Yes, Action taken
Ulcer treatment	Wound cleansing Y/N
	Debridement performed Y/N (Specify the method)
	Is the patient compliant to compression Y/N
	Local wound dressing: Hydrogel, Hydrocellular Foam, Alginate or Other (specify)

Appendix 11: Examples of Standard Meals

- Example of breakfast (around 600 Kcal):
  - 1 individual packet of cereal (28 grams or one ounce)
  - 2 slices of wholemeal bread
  - 2 slices of butter or low fat spread
  - 28 g Jam (or one ounce)
  - 250 ml semi skimmed milk
  - 240 ml Orange juice
- Example of lunch/dinner (around 1000 Kcal, well balanced with no more than 25% fat):
  - 100 g (or 3.5 ounces) beef or lamb or 160 g (or 5.6 ounces) of chicken / 250 g (or 8.8 ounces) of hake filet/ cooked with a small piece of butter
  - 100 g steamed potatoes / mashed potatoes / rice cooked
  - 100 g carrots
  - 100 g green beans
  - 100 g white bread
  - 1 nature yoghurt + 1 apple or 25 g (0.88 ounces) of gruyere
  - 250 ml of orangina or coca-cola or orange juice

Appendix 12: Ankle Brachial Pressure Index Form

Ankle Brachial Pressure Index (ABPI)

Inclusion criteria: 0.8 ≤ ABPI ≤ 1.3

Systolic blood pressure will be measured after 10 minutes of rest **on both arms** in sitting postion or supine position and **on each foot on the following 2 locations**: posterior tibial, and anterior tibial, following the procedure detailed in Appendix 5 'Ankle Brachial Pressure Index' of the study protocol.

Each measurement will be **performed twice** and completed in the following tables.

Brachial systolic blood pressure

	Measure 1 (mmHg)	Measure 2 (mmHg)
Right arm Systolic blood pressure		
Left arm Systolic blood pressure		

Ankle systolic blood pressure

	Location	Measure 1 (mmHg)	Measure 2 (mmHg)
Right ankle Systolic blood pressure	Posterior Tibial		
	Anterior Tibial		
Left ankle Systolic blood pressure	Posterior Tibial		
	Anterior Tibial		

Calculation of ABPI (Automatic calculation in eCRF)

$$\textbf{ABPI} = \frac{\text{Ankle systolic pressure (\textbf{Highest} pressure of the ankle vessels for a leg)}}{\text{Brachial systolic pressure (\textbf{Highest} brachial pressure of the two arms)}}$$