Document title	**STATISTICAL ANALYSIS PLAN (SAP)** **ATTACHED TO CL2-42909-016 STUDY**
Study 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.**
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Development phase	**IIa**
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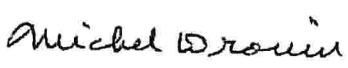
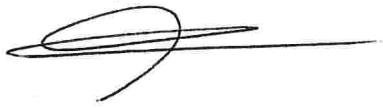
Michel DROUIN Chief Medical Officer Ilkos Therapeutic Inc.		02/03/2020
Lucas ROBY C.T.I. I.R.I.S. – FRANCE	P.O. Marjolaine Fazilleau 	02/03/2020

Follow up of versions

Version	Release date (dd/mm/yyyy)	Key modifications (*)	Impact
1.0	02/03/2020	The linear advance of the wound margin towards the wound center will not be described as a relative change from baseline, as the value at baseline of the linear advance is equal to zero by definition. Only value at each visit will be provided.	No impact
		Additional subgroup : Size of the ulcer at baseline ($\leq$ 20 cm² / > 20 cm²)	No impact
		Randomised set definition: Only patients included will be considered.	2.1 Analysis sets
		MCPMod adjusted on diabetic factor and prognosis criteria on size and age of the ulcer at baseline will be provided as sensitivity analysis	3.4.2.2 Sensitivity analyses
		The primary analysis will be repeated in the FAS with patients from centers where PK results confirm the treatment intake.	3.4.2.2 Sensitivity analyses
		The number, dose and/or duration of analgesic drug for Venous Leg Ulcer (VLU) will not be described. The analgesic description will be done only through the question "Need to take medication for control of the pain associated with VLU?" from the pain questionnaire	3.4.3 Secondary efficacy criteria
		Since ECG are not centralised and heart rate is also measured from the vital signs, heart rate from ECG will not be described	3.6.3.2 Electrocardiogram

(*) Main changes as compared to the statistical analyses planned in the protocol for the first SAP signed version (1.0). Main changes from the previous signed version for the other SAP signed version(s).

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%	:	percentage
AE	:	Adverse Event
ASSE	:	Selection visit
ATC	:	Anatomical Therapeutic Chemical
b.i.d.	:	bis in die (twice a day)
BMI	:	Body Mass Index
BP	:	Blood Pressure
Bpm	:	beats per minute (heart rate unit)
CHMP	:	Committee for Medicinal Products for Human Use
CI	:	Confidence Interval
cm	:	centimetre
CPMP	:	Committee for Proprietary Medicinal Products
CVD	:	Chronic Venous Disease
DBP	:	Diastolic Blood Pressure
e.g.	:	exempla gratia (for example)
EAE	:	Emergent Adverse Event
ECG	:	ElectroCardioGram
e-CRF	:	electronic-Case Report Form
EMA	:	European Medicines Agency
FAS	:	Full Analysis Set
FWER	:	Family Wise Error Rate
g	:	gram
G/L	:	Giga (109) per litre
g/dL	:	Gram per decilitre
h	:	hour
HbA1c	:	Glycated Haemoglobin
HR	:	Heart Rate
i.e.	:	id est
I.R.I.S.:	:	Institut de Recherches Internationales Servier
ICH	:	International Conference on Harmonization
IMP	:	Investigational Medicinal Product
IS	:	Included Set
IU	:	International Unit
IWRS	:	Interactive Web Response System
kg	:	kilogram
L	:	Litre
LLN	:	Lower Limit of Normal laboratory reference range
LLS	:	Lower Limit used to define potentially clinically Significant abnormal values
Max	:	Maximum
MCPMod		Multiple Comparison Procedures and Modeling
MED	:	Minimal Effective Dose
MedDRA	:	Medical Dictionary for Regulatory Activities
mg	:	milligram
min	:	minute
Min	:	Minimum

mL	:	millilitre
mm	:	millimetre
mmHg	:	millimetre of mercury
ms	:	millisecond
NA	:	Not Applicable
NAE	:	Number of Adverse Events
NEAE	:	Number of Emergent Adverse Events
ng	:	nanogram
NPD	:	Number of Protocol Deviations
o.d.	:	omni die (every day)
PCSA	:	Potentially Clinically Significant Abnormal value
PD	:	Pharmacodynamics
PK	:	Pharmacokinetics
po	:	per os (orally)
PPS	:	Per Protocol Set
PT	:	Preferred Term
PV	:	PharmacoVigilance
QTc	:	QT interval corrected for heart rate
RBC	:	Red Blood Cells
RS	:	Randomised Set
RU	:	Reference Ulcer
s	:	second
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SBP	:	Systolic Blood Pressure
SD	:	Standard Deviation
SEAE	:	Serious Emergent Adverse Event
SOC	:	System Organ Class
SS	:	Safety Set
t.i.d.	:	ter in die (three times a day)
TLG	:	Tables, Listings and Graphs
TU	:	Therapeutic Unit
ULN	:	Upper Limit of Normal laboratory reference range
ULS	:	Upper Limit used to define potentially clinically Significant abnormal values
VAS	:	Visual Analog Scale
VLU	:	Venous Leg Ulcer
WHO	:	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) details the planned analyses to be performed, in accordance with the main characteristics of the amended study protocol (version N° 4 dated 05 March 2018).
The templates for Tables, Listings and Graphs (TLG) are described in a separate document.

Of note, this SAP does not cover the pharmacokinetic and metabolism profiling and genomic assessment and non genomic biomarkers data analyses described in the study protocol. These analyses are covered in separate analysis plans.

1.1. Study objectives

The purpose of this study is to investigate if S42909 at any dose has an effect on healing of venous leg ulcer (VLU) (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.

The primary objective 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.

The secondary objectives 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 (PK) of S42909 and its metabolites in patients after repeated administration of S42909.

The additional objectives are:
- To assess any potential PK/Pharmacodynamics (PD) relationship (mainly on improving healing of venous leg ulcers and pain related to venous leg ulcer).
- Genomic assessment of S42909.
- To collect the blood for 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).

1.2. Study design

Study CL2-42909-016 is a Phase IIa, prospective, international, multicentre, randomised, double-blind, placebo-controlled, parallel group (S42909: 100, 200, 400, 800 or 1200 mg per day and placebo), dose-finding study in patients with venous leg ulcers.

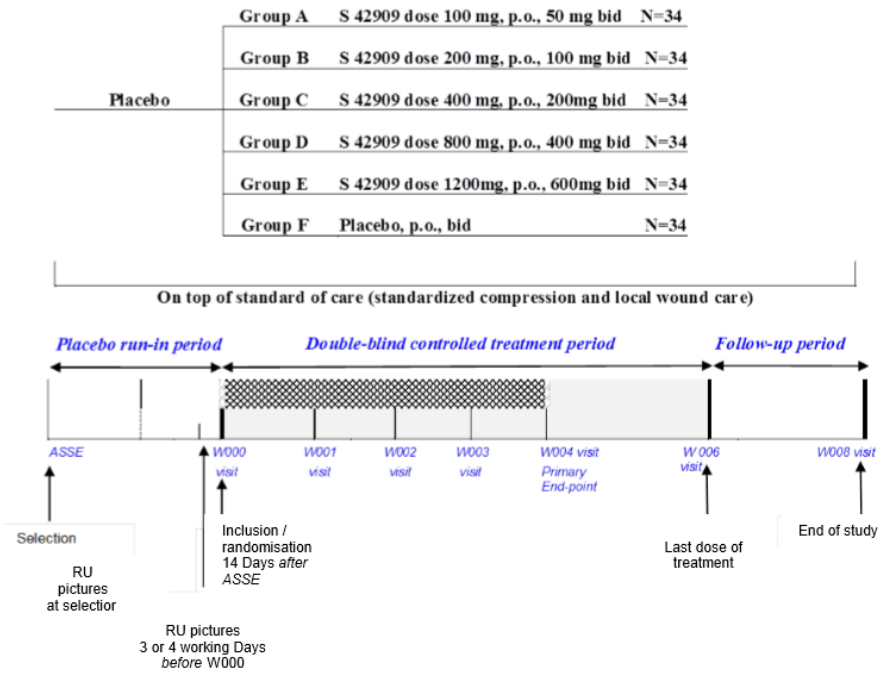
1.2.1. Study plan

The study is divided into the following three periods:

- A placebo run-in period of 14 days (from the selection visit (ASSE) to the inclusion/randomisation visit at week 0 (W000)), in which patients are investigated for documenting the presence of Chronic Venous Disease (CVD) and for assessing the type and the size of the Reference Leg Ulcer.
- A double-blind treatment period of 6 weeks (from visit 0 (W000) to visit 6 (W006)) on top of standard of care (standardized compression and local wound care with sterile saline solution or sterile water and "non-active" dressing):
  At W000:
  - Patients are randomised to one of the following six groups – S42909: 100, 200, 400, 800 or 1200 mg per day - or placebo.
    Note that the treatment (S42909 or Placebo) post randomisation is considered as Investigational Medicinal Product (IMP).
  - For each group, patients are instructed to take 3 tablets orally (per os administration) twice a day at the end of the meals in the morning and in the evening. The appearance and taste of the tablets are the same for all IMPs throughout the study.
  - The first IMP intake takes place the day of the inclusion visit (W000).
- A follow-up period of 2 weeks without treatment (from visit 6 (W006) to visit 8 (W008)). During this period, patients continue to receive the standard of care only.

The study plan is shown in Figure (1.2.1) 1.

Figure (1.2.1) 1 - Study plan



1.2.2. Type of randomisation

The treatment randomisation and allocation are centralised using an Interactive Web Response System (IWRS) procedure. The treatment (S42909: 100, 200, 400, 800 or 1200 mg per day or placebo) is assigned at the inclusion visit (W000) by a 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). The randomisation algorithm is built according to an adaptive randomisation by minimisation.

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.

For the randomisation, the diabetic status is defined by known diabete and/or a fasting blood sugar ≥7 mmol/L and/or elevated HbA1c value between 6.5% and 8% on pre-inclusion laboratory results.

Participants in the optional 24-hour PK analysis are distributed across treatment arms.

1.3. Determination of sample size

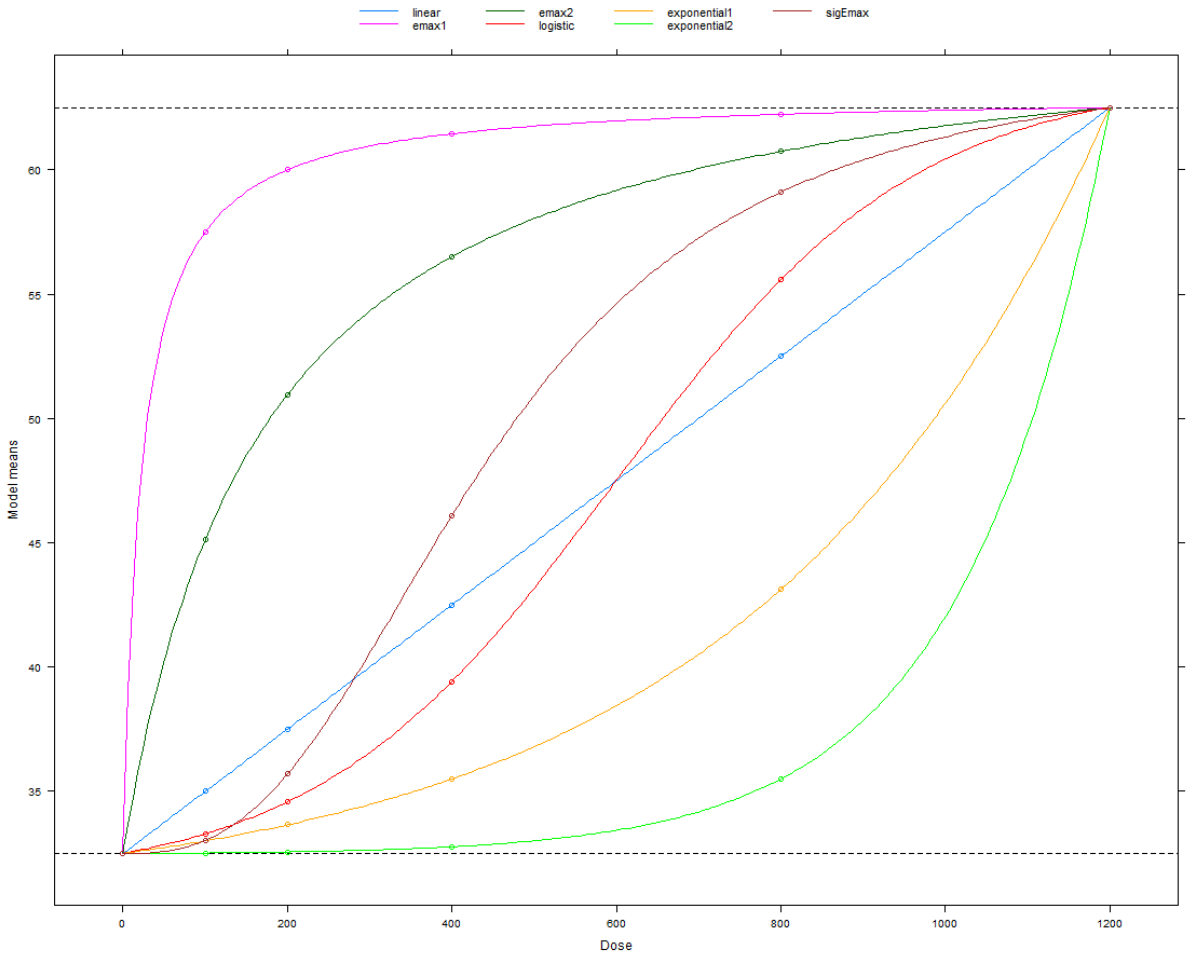
Sample size was estimated with a type one error rate set at 2.5% and using the statistic function “sampsize” described in the publication “MCPMod: An R Package for the Design and Analysis of Dose-Finding Studies” edited by B. Bornkamp, J. Pinheiro and F. Bretz (2009).

Considering:

- A standard deviation of 42%.
- A minimal relative change of Reference ulcer area at 4 weeks (Rmin) of 32.5%.
- A maximal relative change of Reference ulcer area at 4 weeks (Rmax) of 62.5%.
- A maximal efficacy (Rmax – Rmin) of 30%.
- Six doses: 0 (placebo), 100, 200, 400, 800, 1200 mg per day.
- 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%).

Candidate models are presented in Figure (1.3) 1.

Figure (1.3) 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%.

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

Based on that exclusion rate, a total of 204 patients was planned to be included in the study. Due to recruitment difficulties, 121 patients were finally included in the study.

2. ANALYSIS SETS / TREATMENT GROUPS

2.1. Analysis sets

- **Randomised Set (RS):**

All included and randomised patients (*i.e.* all patients to whom a Therapeutic Unit (TU) was randomly assigned using IWRS).

- **Safety set for double blind period (SS):**

All patients having taken at least one dose of IMP.

Note: Patients for whom no information is available about any IMP intake, will be excluded from the Safety Set if they have no post-baseline safety assessment.

- **Full Analysis Set (FAS):**

In accordance with the intention-to-treat principle and Section 5.2.1 of the ICH E9 guideline, all randomised patients who received at least one dose of IMP and who have at least one baseline value and one value of Reference ulcer (RU) area (primary efficacy criterion) at W004.

- **Per Protocol Set (PPS):**

All patients of the Full Analysis Set (FAS) without relevant deviation(s) which could affect the evaluation of the IMP effect on the primary efficacy criterion. The deviations are categorized in three groups, as follows:

* : According to protocol deviation
**: According to medical review
¤ : Derived in datasets

More precisely, the PPS includes all patients of the FAS with:

Before/at inclusion (all Caucasian patients of the FAS) with:

- BMI at ASSE between 18.5 and 45 kg/m^2 inclusive*.
- RU localised in the gaiter area. RU diagnosed or reoccurred for more than 6 weeks and less than 2 years at ASSE*.
- Size of RU ≥ 5 cm^2 and ≤ 100 cm^2 in the picture taken at the selection visit (ASSE) (or ASSE-R), as measured by 3D imaging device*.
- Size of RU ≥ 4.5 cm^2 and ≤ 100 cm^2 at picture taken before inclusion (W000).¤
- Change in RU area < 20% between picture taken at ASSE (or ASSE-R) and the picture taken 3 or 4 days before inclusion (W000) *.
- Ankle Brachial Pressure Index ≥ 0.8 and ≤ 1.3 *.
- Patients with chronic venous disease documented by Duplex Scan (during the selection period, or within 6 months before selection), with a venous reflux in the superficial and/or deep veins and/or a venous obstruction in the deep veins*.
- Required Laboratory values (authorized).
  - Serum albumin ≥20 g/l*.
  - Hb ≥10 g/dL*.
  - HbA1c ≤ 8% (either from a test done within 3 months before selection or during the selection period)*.

Before/at inclusion (all Caucasian patients of the FAS) without:

- Unauthorized diseases**:
  - Presence of malabsorption disease (Crohn's disease), inflammatory bowel disease, Gilbert syndrome, history of chronic diarrhoea.
  - History of lower extremity deep venous thrombosis within the last 3 months.
  - 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 Class III-IV within 6 months prior to the study.
- Unauthorized diseases*:
  - Other non-venous leg ulcers or other associated skin conditions: vasculitis, malignancies, burns, post-surgery, pressure ulcers, diabetic foot, connective tissue disorders such as lupus, systemic sclerosis, cellulitis, ulcers due to sickle-cell disease .
  - 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).

- Unauthorized treatments**:
  - 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.
  - Participants who have been exposed to venoactive drugs within the month prior to the selection.
  - 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.
- 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 **.

During the W000 - W004 period with:

- Blind not broken.
- Received treatment = planned treatment (IWRS).
- Duration of Study Treatment between 26 and 30 days (inclusive).
- Compliance with Study Treatment should be between 80% and 120%.
- Compliance with compression stockings should be ≥ 80%.

During the W000 - W004 period without:

- Unauthorized concomitant treatment**:
  - Topical corticosteroid application on and around the ulcer.
  - Oral corticosteroids.
  - Immunomodulators, immunosuppressants, cytotoxic chemotherapy.
  - Pentoxifylline.
  - 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.
- Oral and parenteral antibiotherapy during the study, except if less than or equal to 7 days.

- Withdrawal criteria:
  - Clinically significant anemia 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. ¤

The size of each analysis set and reasons for exclusion of patients will be described.

Listings of patients with their membership, or not, in each analysis set and of excluded patients with reasons for exclusion will be provided.

Listing of patients randomised but non included patients will be provided.

2.2. Treatment groups

Treatment groups considered for the analyses are S42909 50 mg b.i.d, S42909 100 mg b.i.d, S42909 200 mg b.i.d, S42909 400 mg b.i.d, S42909 600 mg and placebo corresponding to S42909 100 mg per day, S42909 200 mg per day, S42909 400 mg per day, S42909 800 mg per day, S42909 1200 mg per day and placebo.

They correspond to the randomised treatment over the W000-W006 period except for safety analyses for which treatment taken at inclusion visit is considered.

In the unlikely event of a patient has taken an incorrect Therapeutic Unit (TU) at a particular post-W000 visit in the double-blind treatment period, which would result in a switch of treatment group, the patient will be considered in the treatment group corresponding to their TU(s) taken until the switch. Their data recorded from the switch will be kept in the analyses. However, all safety data and IMP administration data of the patients with a switch of treatment group will be listed separately.

3. STATISTICAL METHODS

3.1. General considerations

3.1.1. Descriptive statistics

For **qualitative data**, the number of observed values, the number and the percentage of patients per class will be presented. Unless otherwise specified in the Tables, Listings and Graphs (TLG), no class "Missing" is considered.

For **quantitative data**, the number of observed values, the mean, the standard deviation, the median, the first and third quartiles, the minimum and the maximum will be presented.

For **event**, the following will be presented :
- Number of patients having experienced the event (n).
- Number of events that occurred (for AE analyses only) (NAE).
- Number of patients at risk for the event (N).
- Global incidence rate (%) calculated as the ratio between the number of patients having experienced the event and the number of patients at risk at the beginning of the study.

3.1.2. General definitions

The following definitions will be considered:
- **IMP** is the treatment intake (S42909 or Placebo) post randomisation.
- **Analysable value** will be defined as any non-missing value.
- **Baseline value** will be defined as the last analysable value prior to the first IMP intake (*i.e.* before or the same date as the first IMP intake date).
  Note: In case of patient included and/or randomised but not treated (*i.e.* patients with treatment duration equal to 0): value at baseline is defined as the last analysable value prior or equal to the date of the inclusion visit.
- **Post-baseline value** will be defined as any value recorded at a given timepoint after baseline.
- **Change from baseline** will be defined as the arithmetic difference between a post-baseline value and the baseline value for a given variable at a given time point.
- **Relative change from baseline** will be defined as : 100 * change from baseline / baseline value.

For safety criteria (except for adverse events), the following definitions will be applied:
- A value is considered under treatment if the assessment date is between the first IMP intake date (excluded) over the W000 and W006 period and the last IMP intake date "+ 15 days" (included).

Note: for all definitions concerning value under treatment '+ 15 days' was calculated according to the half-life of the S42909.

- High emergent abnormal value under treatment according to the laboratory reference ranges is defined as value ≤ ULN (Upper Limit of Normal laboratory reference range) or missing at baseline and > ULN under treatment.
- Low emergent abnormal value under treatment according to the laboratory reference ranges is defined as value ≥ LLN (Lower Limit of Normal laboratory reference range) or missing at baseline and < LLN under treatment.

- High emergent abnormal value under treatment according to the cut-offs for PCSA (Potentially Clinically Significant Abnormal value) values is defined as value ≤ ULS (Upper Limit used to define potentially clinically Significant abnormal values) or missing at baseline and > ULS under treatment.
- Low emergent abnormal value under treatment according to the cut-offs for PCSA values is defined as value ≥ LLS (Lower Limit used to define potentially clinically Significant abnormal values) or missing at baseline and < LLS under treatment.

3.2. Disposition and baseline characteristics

Disposition of patients and baseline characteristics will be described by randomised treatment group, to assess their comparability, and overall (treatment groups pooled).

Details concerning definitions on the disposition of patients and baseline characteristics are provided in Appendix 5.2. and provided in the Specifications document.

3.2.1. Disposition of patients

Disposition of patients, including reasons for withdrawal, will be summarized during the study by randomised treatment, overall and by visit, in the RS).

3.2.2. Protocol deviations

Protocol deviations before or at inclusion (W000), as well as after inclusion on W000-W004, W000-W006 and W000-W008 periods, will be described in the RS, by category of important deviations *(based on ICH E3 guideline and ICH E3 Q&A)*.

If necessary a listing of non-included randomised patients will be provided.

3.2.3. Demographic data and other baseline characteristics

Demographic data and other baseline characteristics such as life habits, history of the venous leg ulcers, venous duplex scan results, compression stocking dispensing(at W000 and at each visit), ankle brachial pressure index, baseline value of efficacy criteria (ulcer assements and pain intensity), vital signs and ECG parameters at baseline will be described in the RS.

The main patients' characteristics will also be described in the FAS and the PPS.

The QTcF interval at baseline will be also described in classes (≤ 450,]450; 480],]480; 500] and > 500ms, in accordance with ICH E14 guideline) and the following continuous data will also be described in classes:

Age ([18 ; 64], [65; 84], ≥85 years).

All previous treatments for venous leg ulcers will be described in the RS, by Anatomical Therapeutic Chemical (ATC) code. All medical history other than venous leg ulcers and surgical or medical procedures history, will be described in the RS by primary system organ class (SOC) and preferred term (PT).

For compression stocking, compliance on W000-W004 and W000-W006 period will be also described in classes (< 80, [80; 120], and > 120%).

Details concerning this compliance are provided in Appendix 5.2.

3.3. Treatments of patients

Details concerning definitions on extent of exposure, treatment compliance and concomitant treatments are provided in Appendix 5.2 and provided in the Specifications document.

3.3.1. Global duration, extent of exposure and treatment compliance

Global duration (days), extent of exposure (treatment exposure (days) and treatment duration (days)) and treatment compliance (%) over the W000-W004 and the W000-W006 period will be described in the FAS and the SS.

Treatment compliance (over the W000-W004 and W000-W006 periods) will be also described in classes (< 80, [80; 120], and > 120%).

3.3.2. Concomitant treatments

All concomitant treatments taken at inclusion, during the treatment period (over the W000-W004 and W000-W006 periods) and after the last IMP intake will be described in the RS, by ATC code.

3.4. Efficacy analysis

General definitions are provided in Section 3.1.2. Details concerning efficacy criteria definitions are provided in Appendix 5.2.

3.4.1. Statistical hypotheses

The statistical hypothesis is based on a multi-contrast test.

The hypothesis of the test is:

$$H_0: c'\mu = 0 \quad \text{vs} \quad H_1: c'\mu > 0.$$

Where:

- μ is a vector of mean response.
- c is a vector of contrast.

Due to the use of the MCPMod methodology, the overall Type I error rate across the assumed dose-response relationships will be controlled at a one-sided 2.5% level.

3.4.2. Primary efficacy criterion

Definition: The primary efficacy criterion is defined as 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.

3.4.2.1. Primary analysis

Primary analysis: the MCPMod method (Multiple Comparison Procedures and Modelling) will be applied to the primary efficacy endpoint in the FAS. The MCP-step corresponds to the establishing of a dose-response signal (the dose-response curve is not flat) and the Mod-step to the estimation of the dose-response curve.

The MCPMod method was introduced for developing robust dose-response evaluation strategies in Phase II trials (Bretz, Pinheiro and Branson, 2005). All details of this method are provided in Appendix 5.3.1.

More specifically, let Y_{ij} be the relative change from baseline at W004 for the patient j treated at the dose i of S42909.

We assume that:

$$Y_{ij} = \mu_i + \varepsilon_{ij}$$
$$\varepsilon_{ij} \overset{ind}{\sim} N(0, \sigma^2)$$

Where:

- $\mu_i = f(d_i, \theta)$ is the mean response at dose d_i for the dose response models $f(.)$ parameterized by a vector of parameters θ.
- $i = 1, \ldots, k$ where k is the number of doses.
- $j = 1 \ldots, n_i$ where n_i the number of patients at the dose i.
- ε_{ij} is the error term for patient j within dose group i follows a normal distribution with mean 0 and variance σ^2.

Dose-finding will be performed using the following set of predefined candidate models of $f(.)$ defined by some couples (d*, p*) (dose per day, percentage of efficacy at this 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%).

See Appendix 5.3.1 for more details on each model.

The MCPMod procedure is based on a multi-contrast test. A unique dose-response contrast is associated with each dose-response model. This contrast is defined as the contrast that has the highest power, i.e., the highest probability of rejecting the associated null hypothesis of no effect, under this particular model. The computation of the optimal contrast is explained in Appendix 5.3.1.

The significance of the dose-response trend based on each model-specific contrast will be assessed using the following t statistics:

$$t_m = \frac{\sum_{i=1}^{k} c_{mi} . \overline{Y_i}}{S \sqrt{\sum_{i=1}^{k} \frac{c_{mi}^2}{n_i}}}$$

Where :

- $\overline{Y_i}$ is the empiric mean of the response within dose group d_i.
- m is the number of models.
- n_i is the number of patients within the dose group d_i.

- $S^2 = \sum_{i=1}^{k} \sum_{j=1}^{n_i} \frac{(Y_{ij} - \overline{Y_i})^2}{N-k}$
- c_m is the vector of contrasts with $\sum_{i=1}^{k} c_{mi} = 0$

The dose-response tests identify the set of clinically relevant models. A multiplicity adjustment is taken into account in the MCP-step. The joint distribution of the m test statistics is taken into account to compute an adjusted critical value that defines the threshold for statistical significance.

Under the global null hypothesis of no treatment effect under any model, the test statistics follow a central multivariate t distribution with $N-k$ degrees of freedom and correlation matrix R. More details for matrix R are given in Appendix 5.3.1.

To derive the multiplicity-adjusted critical value, denoted by q, let $T_1; \ldots; T_m$,denote the random variables that have the same joint distribution as $t_1; \ldots; t_m$ under the global null hypothesis. The adjusted critical value q is found from :

$$\Pr(T_{max} > q) = \propto$$

Where α is the pre-specified Family Wise Error Rate (FWER) level equal to 0.025 (one-sided test).

The set of clinically relevant dose-response model corresponds to the models associated with $t_i > q$. The adjusted p-value will be calculated according to the value of q.

Among the set of clinically relevant dose-response models, the best dose-response contrast will be identified as the contrast test with the maximum test statistics.

An estimation of parameters of the best model selected will be provided according to the observed data as well as a plot of this model.
If relevant, modelisation will be done even if no dose-response model is significant.

Multiplicity issues:
The multiplicity issue due to multiple dose-response models is corrected with the computation of an adjusted critical value and adjusted p-values.

Missing data handling: missing data will not be imputed.

Statistical elements:
Finally, the following elements will be provided in summary tables:
- Descriptive statistics and 95% CI of the primary criterion in each arm.
- The best dose-response selected.
- An estimation of parameters of the best model selected.

3.4.2.2. Sensitivity analyses

- The MCPMod method adjusted on diabetes status factor and prognosis criteria on size and age of the ulcer factor will be applied to the primary efficacy endpoint in the FAS.
  Details of the MCPMod approach with covariate-adjusted inferences are provided in Appendix 5.3.2.
- The primary analysis will be repeated in the FAS with patients from centers where PK results confirm the treatment intake.

3.4.2.3. Supplementary analyses

- To meet the secondary objective, the Minimal Effective Dose (MED) will be estimated using the selected model resulting from the primary analysis.

The MED is defined as:

$$MED = \min\left(d: f(d) > f(d_0) + \Delta\,, L(d) > f(d_0)\right)$$

with Δ is the clinically relevant difference, $L(d)$ the lower confidence limit of the predicted mean value $f(d)$ at dose d.

The estimator will be provided considering a hypothesis of a clinically relevant effect as compared to placebo of 6.5%. A confidence interval will be provided by bootstrap method.

- The primary analysis will be repeated in the PPS.
- For RU area, description at each visit and the relative change from baseline to each visit will also be provided in FAS and PPS.
- Description of the relative change from W006 to W008 of the reference ulcer (RU) area, for patients with a non null value at W006, as well as the description of the relative change from W004 to W006, for patients with a non null value at W004, will be described in FAS and PPS.

3.4.3. Secondary efficacy criteria

Definition:

- Reference Ulcer Volume (using a digital 3D imaging device).
- Linear advance of the wound margin towards the wound centre.
- Pain intensity (using a questionnaire including a Visual Analog Scale (VAS)).
- Analgesic drug consumption (patient using analgesic drug for Venous Leg Ulcer (VLU) during the study).

Analyses:

For all secondary efficacy criteria, descriptive statistics at each concerned visit will be performed in the FAS and PPS.

The Reference Ulcer volume, will be described at each visit, on the change from baseline to each visit, as well as the description of the change from W004 to W006 and from W006 to W008.

Linear advance of the wound margin towards the wound centre will be described at each visit.

Pain intensity will be described at each concerned visit (W000, W004 and W006) and on the change from baseline to W004 and W006.

Analgesic drug consumption will be described through the question "Need to take medication for control of the pain associated with VLU?" From the pain questionnaire at each concerned visit (W0, W4 and W6).

3.4.4. Subgroups analysis

In addition, descriptive statistics at each concerned visit of the reference ulcer area, linear advance of the wound margin towards the wound centre and reference ulcer volume will be performed.
Except for the linear advance of the wound margin towards the wound centre, the relative change from baseline (change for volume) will also be described.
These description will be performed in the FAS in the following subgroups:

- Combined prognosis criteria on size and age of the ulcer ($\leq$ 10 cm² and $\leq$ 6 months / > 10 cm² or > 6 months) at baseline.
- Size of the ulcer at baseline ($\leq$ 20 cm² / > 20 cm²).
- Size of the ulcer at baseline ($\leq$ 50 cm² / > 50 cm²).
- Diabetes status (yes/no).

If a subgroup contains less than 20 patients, only listings will be provided for this subgroup.

3.5. Exploratory analysis

Not applicable.

3.6. Safety analysis

All safety analyses will be performed in the SS on the taken IMP treatment, by treatment group over the W000-W006 period.

Only for adverse events, in addition, an analysis will be performed on post treatment intake (i.e after last treatment intake date + 15 days (excluded)).

General definitions are provided in Section 3.1.2. Specific definitions are provided in Appendix 5.2. and provided in the Specifications document.

3.6.1. Adverse events

Definition:

- Treatment Emergent Adverse Events (TEAE) are defined as all adverse events:
  - which occur between the first IMP intake date (included) and the last IMP intake date + 15 days (included)

  or
  - which occur before the first IMP intake date and which worsen (in terms of intensity) or become serious according to the investigator's opinion between the first IMP intake date (included) and the last IMP intake date + 15 days (included).

  Note: + 15 days is calculated according to the half-life of the S42909.

Of note, in case of multiple information of the same event before the first IMP intake date, the information nearest to the first IMP intake date is taken into account.

The seriousness of the adverse event and the relationship with the IMP are based on the investigator's opinion but often also include the sponsor's decision to upgrade the seriousness and/or relation to the IMP (see TLG for details).

Analyses:

The number of events, the number and percentage of patients reporting at least one event, presented by primary system organ class (SOC) and/or preferred term (PT) (depending of the analysis) will be provided for :

- Serious AE over the study period according to the investigator's or sponsor's opinion.
- Treatment emergent AE (TEAE), TEAE leading to IMP withdrawal, TEAE requiring new treatment or increase of ongoing treatment, TEAE requiring surgical or medical procedure, TEAE related to IMP, serious TEAE, severe TEAE, non serious TEAE over the treatment period (EUDRACT), After treatment AE.

TEAE will be described according to the seriousness, the intensity, the relationship with the IMP, the action taken regarding the IMP, the requirement of added therapy and the outcome.

The medical concept of diarrhea, *i.e.* TEAE related to diarrhea, will be analysed through a listing. The MedDRA code list to use is the list n°3741 Diarrhoea medical concept M22.0.

A listing of deaths and ERIN will be provided.

A Listing of AE occurring after the treatment period will also provided.

The following information will be taken into account:

- For the analyses where the intensity of the adverse event is considered, the worst intensity from the day of emergence to the end of the studied period will be taken into account.
- For the analyses where the action taken regarding the IMP is considered, all the actions taken recorded from the day of emergence to the end of the studied period will be taken into account.
- For the analysis of recovered emergent adverse events during the treatment period, an EAE is considered as recovered "during treatment period" if the associated outcome is "recovered" or "recovered with sequelae" and occurs between the first IMP intake date and the last IMP intake date + 15 days (included).

3.6.2. Clinical laboratory evaluation

For all parameters, **the dosing of samples come from local laboratories**. So no quantitative analysis will be performed. In the qualitative analysis, data will be compared to reference ranges provided by these local laboratories.

Definition:

- A laboratory value is considered as analysable if non-missing and not flagged in the ClinTrial database as "not analysable".

Analyses:

For each biochemical and haematological parameter, the following analyses will be performed:

- Number and percentage of patients with at least one high/low emergent abnormal value under treatment, according to the laboratory reference ranges and to the cut-offs for PCSA values.

- Laboratory parameters classified (number and percentage of patients in each class) according to these reference ranges and cut-offs, and using shift tables from baseline to the worst (high and/or low) values under treatment.

Moreover, listings of patients with out-of-range or PCSA analysable values emergent under treatment and of non-analysable values excluded from analyses will be provided.

Urinary parameters will be described in classes (absent, trace, +, ++, +++, ++++) at baseline and at each post-baseline visit under treatment.

3.6.3. Vital signs, clinical examination and other observations related to safety

3.6.3.1. Vital signs and clinical examination

Definition:

The following vital signs and clinical examination will be analysed during the study:

- Weight (kg).
- BMI (kg/m²).
- Sitting Systolic Blood Pressure (SBP) (mmHg).
- Sitting Diastolic Blood Pressure (DBP) (mmHg).
- Sitting heart rate (bpm).

Analysis:

They will be described, in terms of value at baseline, value at each post-baseline visit under treatment as well as in terms of change from baseline to last post-baseline visit under treatment.

3.6.3.2. Electrocardiogram

Definition:

- All non-missing values are considered as analysable.

The following ECG parameters will be analysed:

- Presence of clinically significant ECG abnormalities (yes/no).
- PR interval (msec).
- QT interval (msec).
- RR interval (msec).
- Duration of QRS (msec).
- QTcF - Fridericia's Correction Formula (msec).
- Sinus Rhythm (yes/no).

Emergence of clinically significant ECG during the treatment period:

- When no ECG is judged as clinically significant at baseline and the clinical significance appears between the first IMP intake date (included) and the last IMP intake date + 15 days (included)

Analyses:
ECG parameters will be described, in terms of values at baseline, values at each post-baseline visit under treatment and last post-baseline values under treatment; as well as, for quantitative criteria, in terms of change from baseline to each post-baseline visit under treatment and to last post-baseline visit under treatment and in term of emergence of clinically significant ECG.

Moreover, values at each visit and changes from baseline of QTcF interval will be described in classes, considering thresholds defined in ICH E14 (*i.e.*, ≤ 450,]450; 480],]480; 500] and > 500 msec for values at each visit and ≤ 30,]30; 60] and > 60 msec for changes from baseline to each visit).

3.7. Biomarkers analysis

Not applicable.

4. INTERIM ANALYSIS

Not applicable.

5. APPENDICES

5.1. General analytic definitions

Definitions below correspond to calculation rules for first and last IMP intake dates and other general definitions.

5.1.1. First and last IMP intake dates

For patients having taken at least one dose of IMP over the period between W000 and W006, the dates of first and last IMP intake on the analysis period will be defined as follows:

- The date of the first IMP intake at the first visit performed within the analysis period.
- The date of the last IMP intake at the last visit performed within the analysis period.

Note: Visits with both missing first and last IMP intake dates and with number of returned tablets equal to number of tablets delivered at the previous visit (or with estimated number of tablets taken equal to 0) will not be taken into account.

After selection of the dates of first and last IMP intake as defined above, if these dates are missing or incomplete, substitution rules will be applied to identify baseline value, values under treatment and emergent adverse events.

5.2. Specific analytic definitions and data handling conventions

5.2.1. Disposition and baseline characteristics

Disease duration and reference ulcer duration

The disease duration according to the first leg ulcer (days) is defined as:
Date of selection visit (ASSE) – Date of diagnosis of the first leg ulcer

The reference ulcer duration according to the patient (days):
Date of selection visit (ASSE) – Date of occurence or recurrence of the reference ulcer according to patient

The reference ulcer duration according to the physician (days):
Date of selection visit (ASSE) – Date of diagnosis or recurrence of the reference ulcer by the physician

Reference ulcer duration according to the physician will also be described in classes defined as:
If (disease duration (days)/30.44) ≤ 6 then disease duration in class = '≤ 6 months'.
If (disease duration (days)/30.44) > 6 then disease duration in class = '> 6 months'.

The reference ulcer duration according to the **physician** in classes is used for the **subgroup**.

CEAP classification (Clinical-Etiology-Anatomy-Pathophysiology)

Presence of an obstruction or a reflux in each type of veins (superficial veins and deep veins) will be derived with:

- **Superficial veins** will be defined as:
  Telangiectasies or reticular veins; Great saphenous vein above knee; Great saphenous vein below knee; Small saphenous vein and Nonsaphenous veins.

- **Deep veins** will be defined as :
  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) and Muscular: gastrocnemial, soleal veins, other.
- **Presence of an obstruction** is defined if the classification in (« Obstruction » or « Reflux and obstruction ») is completed.
- **Presence of a reflux** is defined if the classification in (« Reflux» or « Reflux and obstruction ») is completed.

Medical history other than studied disease and surgical or medical procedures history
The existence of a history (Yes/No) is defined from the presence, or not, of a Primary system organ class (SOC) and/or Preferred term (PT).
No specific medical and surgical histories or medical procedures are defined**.**

Previous treatments
The previous treatments are the treatments for venous leg ulcers taken within 6 months before selection, or any previous treatments which could interfere with the IMP or the study assessments in the last 6 weeks before the selection with associated stop date strictly inferior to the first IMP intake date (W000).

Note: In case of patient included and/or randomised but not treated (*i.e.* patients with treatment duration equal to 0), the previous treatment is defined as any treatment with an associated stop date strictly inferior to the date of the inclusion visit.

Only treatment with an Anatomical Therapeutic Chemical (ATC) classification and/or a Preferred name is considered.
No specific previous treatments are defined.

The compliance of compression stocking
The compliance of compression stocking (%) for each period (W000-W004 and W000-W006 periods) is defined as:
(Sum of number of days of stockings wearing / Sum of number of days when stockings had to be worn) x 100 (for the considered period)
with:
- Number of days of stockings wearing = Number of days of stockings wearing.
- Number of days when stockings had to be worn = Last visit date - First visit date, in days (for the considered period)

Note: Compliance is not calculated in case of missing information.

5.2.2. Treatments of patients

Global duration
Global duration (days) is defined as:
Date of the last visit – Date of selection visit + 1

Extent of exposure and treatment compliance

The treatment duration (days) for each period (W000-W004 and W000-W006 periods) is defined as:
Date of the last IMP intake (for the considered period) – Date of the first IMP intake (for the considered period) + 1

Notes:

- For patients with no dose of IMP (for the considered period), the duration is null.
- For patients with missing or incomplete date of first or/and last IMP intake (for the considered period) before substitution, the duration is not calculated.

The treatment exposure (days) for each period (W000-W004 and W000-W006 periods) is defined as:
Treatment duration – Overall duration of interruption
with the overall duration of interruption defined as: Sum of (Date of IMP restarted – Date of last IMP intake before interruption – 1 (*)).
(*) or the number of days of interruption in case of missing or incomplete date of IMP restarted or date of last IMP intake before interruption.

The treatment compliance (%) for each period (W000-W004 and W000-W006 periods) is defined as:
(Sum of number of tablets taken / Sum of number of tablets to be taken) x 100 (for the considered period)
with:

- Number of tablets taken = Estimated number of tablets taken, or if not completed, Number of tablets dispensed - Number of tablets returned (for the considered period).
- Number of tablets to be taken = The formula is different depending on the concerned period because of the following points:

The last tablets to be taken during the W000-W004 period are the 6 tablets (3 in the morning and 3 in the evening) the day before the visit W004, whereas the last tablets to be taken during the W000-W006 period are the 3 tablets in the morning of the visit W006 after the PK predose sampling at the site.
Of note that the visit W003 is the only visit to which patients have to take the 3 tablets in the morning before the visit W003. For the other visits, the patient have to take the 3 tablets in the morning after the PK predosesampling at the site.

- For the W000-W004 period, number of tablets to be taken:
  For withdrawn patients at W003:
  Number of tablets prescribed per day x [Last visit date - First visit date, in days] + Number of tablets prescribed for the morning of the visit W003
  For other patients:
  Number of tablets prescribed per day x [Last visit date - First visit date, in days]
- For the W000-W006 period, number of tablets to be taken :
  For completers or withdrawn patients at W003:
  Number of tablets prescribed per day x [(Last visit date - First visit date), in days] + Number of tablets prescribed the last morning (*i.e.*, 3 tablets)
  For withdrawn patients at other visits than W003:
  Number of tablets prescribed per day x [(Last visit date - First visit date), in days]

Note: Compliance is not calculated in case of missing information.

Concomitant treatments

The existence of a concomitant treatment (Yes/No) is defined from the presence, or not, of an Anatomical Therapeutic Chemical (ATC) classification and/or Preferred name.

The **periods** considered **for the analysis** are:

- **At inclusion** for which treatments with start date ≤ inclusion date and stop date ≥ inclusion date or missing are taken into account.
- **During the treatment period** for each considered period (W000-W004 and W000-W006) for which treatments:
  - with start date ≥ first IMP intake date and < last IMP intake date (for the considered period), or
  - with start date ≤ first IMP intake date and stop date ≥ first IMP intake date or missing

  are taken into account.
- **After the last IMP intake** for which treatments:
  - with start date ≥ last IMP intake, or
  - with start date ≤ last IMP intake date and stop date > last IMP intake date or missing

  are taken into account.

Concomitant treatments could be considered in one or several of the possible analysis periods.

5.2.3. Efficacy analysis

Linear advance of the wound margin

Computation of **linear advance** of the wound margin towards the wound center from baseline:

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

Where ΔA is the difference in the area (A_{visit} - $A_{baseline}$) and p the average of the wound perimeter:

$$(\overline{p} = \frac{p_{visit} + p_{Baseline}}{2})$$

Computation of **linear advance** of the wound margin towards the wound center from previous visit:

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

Where ΔA is the difference in the area ($A_{visit\ v} - A_{visit\ v-1}$) and p the average of the wound perimeter:

$$(\overline{p} = \frac{P_{visit\ v} + P_{visit\ v-1}}{2})$$

Pain intensity

Pain intensity is defined as the Visual Analog Scale (VAS) values.
In case of response "No" to the question "Does the participant feel any pain or discomfort related to his/her leg ulcer?" and the VAS value is missing this value will be imputed to zero.

Diabetic status

For efficacy analysis, a patient with HbA1c ≥ 6.5% or a medical history in the following list : 1689.2 Evidences of diabetes mellitus M220 is considered as diabetic.

5.2.4. Safety analysis

5.2.4.1. Adverse events

Each **medical concept of adverse event coded according to the internal "multiple medical concept" process** is taken into account as a single adverse event in the statistical analysis.
The modalities of the adverse event (onset and end dates, intensity, seriousness, action taken, additional therapy, relationship, outcome...) replicated by default to each medical concept are also taken into account in the statistical analyses.

5.3. Statistical methods details

5.3.1. MCPMod method for primary analysis

The MCPMod method is presented in details in the following paragraph.

Let Y_{ij} be the relative change from baseline at W004 for the patient j treated at the dose i of S42909.

We assume that:

$$Y_{ij} = \mu_i + \varepsilon_{ij}$$

$$\varepsilon_{ij} \overset{ind}{\sim} N(0, \sigma^2)$$

Where:

- $\mu_i = f(d_i, \theta)$ is the mean response at dose d_i for the dose response models $f(.)$ parameterized by a vector of parameters θ.
- $i = 1, \ldots, k$ where k is the number of dose.
- $j = 1 \ldots, n_i$ where n_i the number of patients at the dose i.
- ε_{ij} is the error term for patient j within dose group i. ε_{ij} follows a normal distribution with mean 0 and variance σ^2.

Dose-finding will be performed using a set of candidate models of $f(.)$. The candidate models are set up using the hypothesized dose-response functions as follows:

$$f(d, \theta) = a + bg(d, \theta_0)$$

where $g(.)$ is the standardized form of the dose-response function with θ_0 denoting the vector of initial values of the model parameters or guesstimates that are derived from the expected shape of the dose-response relationship. Further, a is the location parameter, and b is the scale parameter.

Dose response models are defined in the Table (5.3.1) 1.

Table (5.3.1) 1 - Dose-response models

Model	$f(d,\theta)$	$g(d,\theta_0)$
Linear	$E_0 + \delta d$	d
Emax	$E_0 + \frac{E_{max} d}{ED_{50} + d}$	$\frac{d}{ED_{50} + d}$
Sigmoïd Emax	$E_0 + \frac{E_{max} d^h}{ED_{50}^h + d^h}$	$\frac{d^h}{ED_{50}^h + d^h}$
Exponential	$E_0 + E_1(\exp\left(\frac{d}{\delta}\right) - 1)$	$\exp\left(\frac{d}{\delta}\right) - 1$
Logistic	$E_0 + \frac{E_{max}}{(1 + \exp\left(\frac{ED_{50} - d}{\delta}\right))}$	$\frac{1}{(1 + \exp\left(\frac{ED_{50} - d}{\delta}\right))}$

In this study, dose-finding will be performed using the following set of m candidate models of f(.) defined by some couples (d*, p*) (dose, percentage of efficacy at this 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%).

The parameter values for each candidate model corresponding at the set of candidate models are mentionned in the Table (5.3.1) 2.

Table (5.3.1) 2 - Dose-response models parameters

Candidate model	Parameter values (θ)
Linear	E_0 = 32.5, δ = 0.025
Emax 1	E_0 = 32.5, E_{max}= 30.6, ED_{50} = 22.2
Emax 2	E_0 = 32.5, E_{max} = 34.3, ED_{50} = 171.4
Sigmoïd Emax	E_0 = 32.5, E_{max} = 32, ED_{50} = 447.2, h = 2.7
Logistic	E_0 = 31.3, E_{max} = 32.3, ED_{50} = 600, h = 182.1
Exponential 1	E_0 = 32.5, E_1 = 1.95, δ = 428.9
Exponential 2	E_0 = 32.5, E_1 = 0.03, δ = 174.4

Optimal contrasts

The MCPMod procedure is based on a multi-contrast test. A unique dose-response contrast is associated with each dose-response model. This contrast is defined as the contrast that has the highest power, *i.e.*, the highest probability of rejecting the associated null hypothesis of no effect, under this particular model. The standardized version of the model is used and the predicted effects is computed under this standardized model:

$$u_{ij} = g_i(d_j, \theta_0)$$

Where:
- j = 0, … , m, with m the number of candidate model.
- i the dose.

The predicted effects can be computed using the initial values defined in the Table (5.3.1) 1.
The optimal constrast is calculated from the predicted effects by centering and normalizing this vector.
The coefficients of the optimal constrast for each model are defined with the following formula:

$$c_{ij} = \frac{u_{ij} - \frac{1}{m+1}\sum_{l=0}^{m} u_{il}}{\sqrt{\sum_{l=0}^{m}(u_{ij} - \frac{1}{m+1}\sum_{l=0}^{m} u_{il})^2}}, j = 0, \dots, m$$

Where
- j = 0, … , m, with m the number of candidate model
- i the dose

Dose-reponse tests

The significance of the dose-response trend based on each model-specific contrast will be assessed using the following t statistics:

$$t_m = \frac{\sum_{i=1}^{k} c_{mi}.\overline{Y_i}}{S\sqrt{\sum_{i=1}^{k}\frac{c_{mi}^2}{n_i}}}$$

where
- $\overline{Y_i}$ is the empiric mean of the response within dose group d_i.
- m is the number of model.
- n_i is the number of patients within the dose group d_i.
- $S^2 = \sum_{i=1}^{k}\sum_{j=1}^{n_i}\frac{(Y_{ij} - \overline{Y_i})^2}{N-k}$
- c_m is the vector of contrasts with $\sum_{i=1}^{k} c_{mi} = 0$

The dose-response tests identify the set of clinically relevant models. A multiplicity adjustment is taken into account in MCP. The joint distribution of the m test statistics is taken into account to compute an adjusted critical value that defines the threshold for statistical significance.
Under the global null hypothesis of no treatment effect under any model, the test statistics follow a central multivariate t distribution with $N-k$ degrees of freedom and correlation matrix R.

The correlation between the test statistics t_i and t_j is given by:

$$\rho_{ij} = \frac{\sum_{l=0}^{m} c_{il}c_{jl}}{\sqrt{\sum_{l=0}^{m} {c_{il}}^2 \sum_{l=0}^{m} {c_{jl}}^2}}$$

To derive the multiplicity-adjusted critical value, denoted by q, let $T_1; \ldots; T_m$,denote the random variables that have the same joint distribution as $t_1; \ldots; t_m$ under the global null hypothesis. The adjusted critical value q is found from:

$$\Pr(T_{max} > q) = \propto$$

where α is the pre-specified Family Wise Error Rate (FWER) level equal to 0.025 (one-sided test).

The set of clinically relevant dose-response model corresponds to the models associated with $t_i > q$. Adjusted p-value will be calculated according to the value of q.

Among the set of clinically relevant dose-response models, the best dose-response contrast will be identified as the contrast test with the maximum test statistic.

An estimation of parameters of the best model selected will be provided as well as a plot of this model.

5.3.2. MCPMod method with covariate-adjusted inferences

The MCPMod method was originally introduced for developing robust dose-response evaluation strategies in Phase II trials with simple primary analyses, e.g., analyses without covariate adjustment (Bretz, Pinheiro and Branson, 2005). The original method was later extended in multiple directions. Pinheiro et al. (2013) demonstrated how a generalized version of the MCPMod approach can be set up to enable covariate-adjusted inferences in the primary analysis.

The general MCPMod method proposed in Pinheiro et al. (2013) will be applied to the primary endpoint in the FAS. This endpoint is assumed to be normally distributed and will be analyzed using an analysis of covariance (ANCOVA) model adjusted for two stratification factors (combined prognosis criteria and diabetic status).

The general MCPMod method will be applied to the seven pre-defined dose-response models (see definition in Table (5.3.2) 1) with the 6 doses. The models will be denoted by $f_i(d, \beta)$, $i = 1 \ldots,7$, where d is the dose and β is a vector of model parameters, and the doses will be denoted by $d_1, \ldots, d_6$.

The method will be implemented as follows. As the very first step, initial values of the model parameters will be selected for the pre-defined models. The column vector of initial values for the ith model will be denoted by b_i, $i = 1 \ldots,7$. Let μ_i denote the column vector of mean effects computed from the ith model using these initial values of the model parameters, i.e., $\mu_{ij} = f_i(d_j, b_i)$, $i = 1 \ldots,7$, $j = 1 \ldots,6$.

The ANCOVA model without an intercept adjusted for the two stratification factors will be fitted to the data. Let $\hat{\mu}_j$ denote the covariate-adjusted mean effect in the jth dose group, $j = 1 \ldots,6$, and let $\hat{\mu}$ denote the column vector of covariate-adjusted mean effects. Also, let S denote the covariance matrix for these mean effects estimated from the ANCOVA model.

The optimal dose-response contrasts will be found by computing the following set of vectors:

$$c_i = S^{-1}\left(\mu_i - \frac{\mu_i' S^{-1} I}{I' S^{-1} I}\right),$$

where the prime denotes transposition and I is a column vector of 6 ones, i.e., $I' = (1\ 1\ 1\ 1\ 1\ 1)$. After that each vector is normalized, i.e., $c_i = c_i/|c_i|$. The resulting column vector c_i is the optimal dose-response contrast for the ith model, $i = 1 \ldots,7$.

Let C denote the contrast matrix created from the model-specific optimal contrasts and define the matrix D as $D = C'SC$. This matrix is the covariance matrix for the optimal contrasts.
The test statistic for assessing the significance of the optimal contrast based on the ith model is given by

$$t_i = \frac{c_i' \hat{\mu}}{c_i' S c_i}, i = 1 \ldots,7.$$

These test statistics follow a multivariate t distribution with an infinite degrees of freedom and correlation matrix $A^{-1}DA^{-1}$, where $A = \sqrt{\operatorname{diag} D}$, i.e., A is a diagonal matrix constructed by finding the diagonal elements of D and computing the square root.

The set of significant dose-response models is selected by comparing each test statistic to an adjusted critical value q. This critical value is found from the joint distribution of the test statistic under the global null distribution of no dose-response effect for any of the seven pre-defined models. In other words,

$$P(\max(t_1, \ldots, t_7) \geq q) = \alpha,$$

where α is a one-sided Type I error rate ($\alpha = 0.025$).

If the set of significant dose-response models is non-empty, the best dose-response model is chosen as the model corresponding to the most significant test statistic. Let k denote the index of the best dose-response model.

Once the best dose-response model is identified, it is fitted to the covariate-adjusted mean effects using the method of weighted least squares (WLS), i.e., the model is fitted by minimizing the following WLS criterion

$$(\hat{\mu} - f_k(d, \beta))' S^{-1} (\hat{\mu} - f_k(d, \beta))$$

with respect to the vector of model parameters β.

If relevant, modelisation will be done even if no dose-response model is significant.

5.4. Software and programming codes

MCPMod analyses and the MED determination will be performed with the "DoseFinding" package using the R® software. Seed parameter will be set at 1234.

Others statistical analyses will be performed using SAS®/PC Software version 9.2.

6. REFERENCES

Guideline

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