Clinical trial results:
Dose-response relationship study of S42909 on leg ulcer healing after oral repeated administration in patients with active venous leg ulcer. A 10-week randomized, double-blind, placebo-controlled, prospective, international, multicentre, phase IIa study.

Summary

EudraCT number	2016-004143-36
Trial protocol	AT DK CZ SK ES PL IT
Global end of trial date	20 January 2020

Results information

Result version number	v1 (current)
This version publication date	10 September 2020
First version publication date	10 September 2020

Trial information

Trial identification

Sponsor protocol code	CL2-42909-016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03077165
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ilkos Therapeutic Inc.
Sponsor organisation address	500 boulevard Cartier Ouest Bureau 131, Laval, Québec, Canada, H7V 5B7
Public contact	M. DROUIN, Ilkos Therapeutic Inc., +1 450-680-3381 X2913,
Scientific contact	M. DROUIN, Ilkos Therapeutic Inc., +1 450-680-3381 X2913,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2020
Global end of trial reached?	Yes
Global end of trial date	20 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 26
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Argentina: 11
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Czech Republic: 26
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Poland: 2
Worldwide total number of subjects	121
EEA total number of subjects	87

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	57
From 65 to 84 years	61
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Caucasian men or women, age ≥18 years old, 18.5 kg/m2 ≤ BMI≤ 45.0 kg/m2, with CVD documented by imaging to explore a venous disorder in both sub- and extra-fascial venous systems. At least one active venous leg ulcer localised in the gaiter area (CEAP C6) for more than 6 weeks and less than 2 years. Size of the reference ulcer ≥ 5 cm2 and ≤ 100 cm2

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	S42909 50 mg b.i.d

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S42909
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

During W000-W006 period, the participants were to take orally 3 tablets twice a day at the end of the meals: 3 tablets in the morning at the end of breakfast and 3 tablets in the evening at the end of dinner. Tablets of 0 and 50 mg of strength of S42909 were used to reach the daily dose of S42909 100 mg.

Arm title	S42909 100 mg b.i.d

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S42909
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

During W000-W006 period, the participants were to take orally 3 tablets twice a day at the end of the meals: 3 tablets in the morning at the end of breakfast and 3 tablets in the evening at the end of dinner. Tablets of 0 and 50 mg of strength of S42909 were used to reach the daily dose of S42909 200 mg.

Arm title	S42909 200 mg b.i.d

Arm description: -

Arm type	Experimental

Investigational medicinal product name	S42909
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

During W000-W006 period, the participants were to take orally 3 tablets twice a day at the end of the meals: 3 tablets in the morning at the end of breakfast and 3 tablets in the evening at the end of dinner. Tablets of 0 and 200 mg of strength of S42909 were used to reach the daily dose of S42909 400 mg.

Arm title	S42909 400 mg b.i.d

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S42909
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

During W000-W006 period, the participants were to take orally 3 tablets twice a day at the end of the meals: 3 tablets in the morning at the end of breakfast and 3 tablets in the evening at the end of dinner. Tablets of 0 and 200 mg of strength of S42909 were used to reach the daily dose of S42909 800 mg.

Arm title	S42909 600 mg b.i.d

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S42909
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

During W000-W006 period, the participants were to take orally 3 tablets twice a day at the end of the meals: 3 tablets in the morning at the end of breakfast and 3 tablets in the evening at the end of dinner. Tablets of 200 mg of strength of S42909 were used to reach the daily dose of S42909 1200 mg.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

During W000-W006 period, the participants were to take orally 3 tablets of placebo twice a day at the end of the meals: 3 tablets in the morning at the end of breakfast and 3 tablets in the evening at the end of the dinner.

Number of subjects in period 1	S42909 50 mg b.i.d	S42909 100 mg b.i.d	S42909 200 mg b.i.d
Started	21	22	20
Completed	20	22	20
Not completed	1	0	0
Adverse event, non-fatal	1	-	-
Non-medical reason	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	S42909 400 mg b.i.d	S42909 600 mg b.i.d	Placebo
Started	19	19	20
Completed	19	16	20
Not completed	0	3	0
Adverse event, non-fatal	-	1	-
Non-medical reason	-	1	-
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	S42909 50 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 100 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 200 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 400 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 600 mg b.i.d
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	S42909 50 mg b.i.d	S42909 100 mg b.i.d	S42909 200 mg b.i.d
Number of subjects	21	22	20
Age categorical Units: Subjects			
Adults (18-64 years)	9	12	12
From 65-84 years	12	9	7
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	63.6	60.8	64.0
standard deviation	± 11.8	± 13.1	± 11.2
Gender categorical Units: Subjects			
Female	10	9	10
Male	11	13	10

Reporting group values	S42909 400 mg b.i.d	S42909 600 mg b.i.d	Placebo
Number of subjects	19	19	20
Age categorical Units: Subjects			
Adults (18-64 years)	4	9	11
From 65-84 years	15	9	9
85 years and over	0	1	0
Age continuous Units: years			
arithmetic mean	71.5	62.1	62.1
standard deviation	± 11.4	± 14.5	± 14.7
Gender categorical Units: Subjects			
Female	13	14	10
Male	6	5	10

Reporting group values	Total		
Number of subjects	121		
Age categorical Units: Subjects			
Adults (18-64 years)	57		
From 65-84 years	61		
85 years and over	3		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	66		
Male	55		

End points

End points reporting groups

Reporting group title	S42909 50 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 100 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 200 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 400 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 600 mg b.i.d
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

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 had at least one baseline value and one value of Reference ulcer (RU) area (primary efficacy criterion) at W004

Primary: Relative reduction of RU area after 4 weeks

End point title	Relative reduction of RU area after 4 weeks

End point description:

The primary efficacy endpoint was defined as the relative reduction of reference ulcer (RU) area after 4 weeks of treatment on top of standard of care compared with the baseline RU area assessed during study visits using a digital 3D imaging device.

End point type	Primary

End point timeframe:

RU area was assessed at ASSE, W000, W001, W002, W003, W004, W006 and W008 visits (The primary efficacy endpoint was the relative reduction of RU area after 4 weeks of treatment).

End point values	S42909 50 mg b.i.d	S42909 100 mg b.i.d	S42909 200 mg b.i.d	S42909 400 mg b.i.d
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	22	20	19
Units: cm2				
arithmetic mean (standard deviation)	-52.85 (± 37.79)	-46.42 (± 33.30)	-31.07 (± 38.73)	-43.33 (± 28.37)

End point values	S42909 600 mg b.i.d	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: cm2				

arithmetic mean (standard deviation)	-41.10 (± 33.99)	-41.23 (± 43.71)		

Statistical analyses

Statistical analysis title	MCP-Mod - Test statistics

Statistical analysis description:

The MCP-Mod method was applied to the primary efficacy endpoint in the FAS. The MCP-Mod method includes the MCP-step, which corresponds to the establishment of a dose-response signal, and the Mod-step that estimates the dose-response curve. Of note, the MCP-step procedure was based on a multi-contrast test. The best dose-response was to be identified as the contrast test with the maximum test statistics among the set of relevant dose-response models (i.e. models with adjusted p-value < 0.025).

Comparison groups	Placebo v S42909 600 mg b.i.d v S42909 400 mg b.i.d v S42909 200 mg b.i.d v S42909 100 mg b.i.d v S42909 50 mg b.i.d
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.025
Method	MCP-Mod approach
Parameter estimate	dose response model

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events which occurred or worsened or became serious according to the investigator, or upgraded by the Sponsor, from the date the participant signed the information and consent form, irrespective of the period of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	S42909 50 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 100 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 200 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 400 mg b.i.d
Reporting group description: -	
Reporting group title	S42909 600 mg b.i.d
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	S42909 50 mg b.i.d	S42909 100 mg b.i.d	S42909 200 mg b.i.d
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 21 (9.52%)	0 / 22 (0.00%)	1 / 20 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	S42909 400 mg b.i.d	S42909 600 mg b.i.d	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4.5 %

Non-serious adverse events	S42909 50 mg b.i.d	S42909 100 mg b.i.d	S42909 200 mg b.i.d
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 21 (19.05%)	6 / 22 (27.27%)	8 / 20 (40.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon adenoma			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Pallor			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Increased bronchial secretion			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Blood glucose increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			

subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
International normalised ratio decreased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 21 (4.76%)	1 / 22 (4.55%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Contusion			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Incorrect product administration duration			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Overdose			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin laceration			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			

subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Food poisoning			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pseudopolyposis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			

Blister			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Drug eruption			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	2 / 21 (9.52%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pruritus generalised			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Psoriasis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Rash papular			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			
subjects affected / exposed	2 / 21 (9.52%)	0 / 22 (0.00%)	2 / 20 (10.00%)
occurrences (all)	3	0	4
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Ureterolithiasis			

subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Conjunctivitis bacterial			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Infected skin ulcer			
subjects affected / exposed	0 / 21 (0.00%)	2 / 22 (9.09%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Nasopharyngitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection staphylococcal			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Hyperkalaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	S42909 400 mg b.i.d	S42909 600 mg b.i.d	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 19 (31.58%)	8 / 19 (42.11%)	6 / 20 (30.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon adenoma			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Pallor			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0

Increased bronchial secretion			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Blood glucose increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
International normalised ratio decreased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Contusion			

subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Incorrect product administration duration			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Overdose			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	3 / 20 (15.00%)
occurrences (all)	0	0	4
Somnolence			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			

Tinnitus			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	2 / 19 (10.53%)	3 / 19 (15.79%)	0 / 20 (0.00%)
occurrences (all)	3	4	0
Food poisoning			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Pseudopolyposis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Drug eruption			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Pruritus generalised			

subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Psoriasis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Skin ulcer			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ureterolithiasis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis bacterial			

subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Infected skin ulcer			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Nasopharyngitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Urinary tract infection staphylococcal			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2017	Amendment 1: It was set up, mainly in order to adapt selection/inclusion criteria to new medical data, to clarify wording relative to selection/inclusion criteria, to add withdrawal criteria, to specify items regarding standard of care, and to adjust the investigation schedule during the selection period.
29 June 2017	Amendement 2: was 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. Protocol Appendix 2 was 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.
29 June 2017	Amendment 3: was implemented to integrate prior amendments Nos.°1 and 2 (for European countries where amendment No. 1 had not yet been submitted for regulatory and ethic review at the time of issuance of amendment No. 2).
05 March 2018	Amendment 4: was 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 RU on the day of the inclusion visit after randomisation, and to broaden the study population notably to diabetic patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported