Clinical trial results:
A RANDOMISED, PLACEBO-CONTROLLED, DOUBLE-BLIND, INTERVENTIONAL, MULTICENTER, PHASE I/IIA CLINICAL TRIAL TO INVESTIGATE THE EFFICACY AND SAFETY OF ALLO-APZ2-PAOD FOR THE TREATMENT OF PERIPHERAL ARTERIAL OCCLUSIVE DISEASE (PAOD)

Summary

EudraCT number	2017-000235-14
Trial protocol	DE GB CZ AT PL
Global end of trial date	15 May 2020

Results information

Result version number	v1 (current)
This version publication date	30 July 2021
First version publication date	30 July 2021

Trial information

Trial identification

Sponsor protocol code	allo-APZ2-PAOD-II-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03339973
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	RHEACELL GmbH & Co. KG
Sponsor organisation address	Im Neuenheimer Feld 517, Heidelberg, Germany, 69120
Public contact	Information Office, RHEACELL GmbH & Co. KG, +49 6221718330, office@rheacell.com
Scientific contact	Information Office, RHEACELL GmbH & Co. KG, +49 6221718330, office@rheacell.com

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	31 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of this clinical trial is to investigate the efficacy (by monitoring the wound size reduction of PAOD-related clinically relevant ulcers) and safety (by monitoring adverse events) of one dose of allo-APZ2-PAOD administered intramuscularly into an affected lower leg of subjects with PAOD.

Protection of trial subjects:

Optional wound debridement and clearance of necrotic tissue at relevant ulcers was performed and the subject was treated with local anesthetic cream (e.g., Lidocain/Prilocain) if necessary, before the investigational product (IMP) was injected. Local anesthetics intravenously or strong analgesics, e.g., Piritramide (Dipidolor®) were to be given at subject's request or in case of severe pain. After application of the IMP (last injection), the subject was requested to stay in the hospital for 2 hours. If strong analgesics were used, safety monitoring may be extended at the discretion of the investigator.
The first 3 subjects were treated at least 2 weeks apart. The Medical Monitor continuously reviewed the safety data and requested assistance from the Independent Data Monitoring Committee (IDMC) as needed. In addition, safety data were reviewed monthly by the IDMC, and a recommendation was made to the sponsor and investigator as to whether administration to patients could be continued or the trial should be discontinued. After 10 subjects completed Week 2, the treatment was temporarily interrupted for a safety analysis by the IDMC. Because of premature termination of the trial due to insufficient patient recruitment, the planned second safety analysis by the IDMC was not performed after 30 subjects completed Week 2.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Germany: 19
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	5
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female subjects aged 45 to 85 years (to 75 years only in Czech Republic) with PAOD (Rutherford category 5) in at least one lower extremity were recruited in 9 centers in Germany and 1 center each in the Czech Republic and Austria. The first subject signed the informed consent form on 05-Mar-2018 and the last subject on 10-Mar-2020.

Pre-assignment

Screening details:

24 subjects signed the informed consent. 10 subjects were screening failures and not treated with IMP. 7 subjects each were randomized to allo-APZ2-PAOD treatment (7.5 x 10E6 cells per injection site) or to placebo treatment. 2 subjects randomized to allo-APZ2-PAOD were not treated because of an AE or an other reason of premature discontinuation.

Period 1

Period 1 title	12-week follow-up
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	allo-APZ2-PAOD

Arm description:

Subjects received 1 dose of allo-APZ2-PAOD per injection site (N=20-30) intramuscularly into the lower leg along the vessel axes at Day 0 and were followed up for efficacy for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	allo-APZ2-PAOD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received 1 dose of allo-APZ2-PAOD per injection site intramuscularly into the lower leg. allo-APZ2-PAOD contains 7.5 x 10E6 allogeneic skin-derived ABCB5-positive mesenchymal stem cells isolated from skin tissue of healthy donors in 750 µL Human Serum Albumin/Ringer-Lactate/Glucose solution. The used cell amount depended on the number of injection sites (N=20-30), which depended on length of the lower leg. Injection sites were to be started about 6-9 cm below the popliteal space. 3 injections were placed in 1 row horizontally along the vessel axes of the posterior tibial artery, anterior tibial artery and fibular artery. Next horizontal row was 3 cm distal to the last one. In the distal last third of the lower leg only 2 injections were placed in 1 row, 1 on the inner and 1 on the outer leg side, with a row distances of 3 cm. Optional wound debridement and clearance of necrotic tissue at relevant ulcers was performed and the subject was treated with local anesthetic before.

Arm title	Placebo

Arm description:

Subjects received 1 dose of placebo per injection site (N=20-30) intramuscularly into the lower leg along the vessel axes at Day 0 and were followed up for efficacy for 12 weeks.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received 1 dose of placebo (750 µL Human Serum Albumin/Ringer-Lactate/Glucose solution) per injection site intramuscularly into the lower leg. The number of injection sites (N=20-30) depended on the length of the lower leg. Injection sites were to be started about 6-9 cm below the popliteal space. 3 injections were placed in 1 row horizontally along the vessel axes of the posterior tibial artery, anterior tibial artery and fibular artery. Next horizontal row was 3 cm distal to the last one. In the distal last third of the lower leg only 2 injections were placed in 1 row, 1 on the inner and 1 on the outer leg side, with a row distances of 3 cm. Optional wound debridement and clearance of necrotic tissue at relevant ulcers was performed and the subject was treated with local anesthetic before.

Number of subjects in period 1[1]	allo-APZ2-PAOD	Placebo
Started	5	7
Completed	5	7

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Twenty-four patients signed the informed consent. Ten patients were defined as screening failures and not treated with IMP. Two patients were randomized to allo-APZ2-PAOD but not treated: 1 patient had an AE and 1 patient discontinued the trial before treatment by other reason. Twelve patients were included in the full- and the safety-anlysis set for final analysis after early clinical trial termination.

Period 2

Period 2 title	12-month safety follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	allo-APZ2-PAOD

Arm description:

Subjects received 1 dose of allo-APZ2-PAOD per injection site (N=20-30) intramuscularly into the lower leg along the vessel axes at Day 0 and were followed up for safety for 12 months.

Arm type	Experimental
Investigational medicinal product name	allo-APZ2-PAOD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received 1 dose of allo-APZ2-PAOD per injection site intramuscularly into the lower leg. allo-APZ2-PAOD contains 7.5 x 10E6 allogeneic skin-derived ABCB5-positive mesenchymal stem cells isolated from skin tissue of healthy donors in 750 µL Human Serum Albumin/Ringer-Lactate/Glucose solution. The used cell amount depended on the number of injection sites (N=20-30), which depended on length of the lower leg. Injection sites were to be started about 6-9 cm below the popliteal space. 3

injections were placed in 1 row horizontally along the vessel axes of the posterior tibial artery, anterior tibial artery and fibular artery. Next horizontal row was 3 cm distal to the last one. In the distal last third of the lower leg only 2 injections were placed in 1 row, 1 on the inner and 1 on the outer leg side, with a row distances of 3 cm. Optional wound debridement and clearance of necrotic tissue at relevant ulcers was performed and the subject was treated with local anesthetic before.

Arm title	Placebo

Arm description:

Subjects received 1 dose of placebo per injection site (N=20-30) intramuscularly into the lower leg along the vessel axes at Day 0 and were followed up for safety for 12 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received 1 dose of placebo (750 µL Human Serum Albumin/Ringer-Lactate/Glucose solution) per injection site intramuscularly into the lower leg. The number of injection sites (N=20-30) depended on the length of the lower leg. Injection sites were to be started about 6-9 cm below the popliteal space. 3 injections were placed in 1 row horizontally along the vessel axes of the posterior tibial artery, anterior tibial artery and fibular artery. Next horizontal row was 3 cm distal to the last one. In the distal last third of the lower leg only 2 injections were placed in 1 row, 1 on the inner and 1 on the outer leg side, with a row distances of 3 cm. Optional wound debridement and clearance of necrotic tissue at relevant ulcers was performed and the subject was treated with local anesthetic before.

Number of subjects in period 2	allo-APZ2-PAOD	Placebo
Started	5	7
Completed	2	4
Not completed	3	3
Adverse event, serious fatal	1	1
Early trial termination by sponsor	2	2

Baseline characteristics

Reporting groups	
Reporting group title	allo-APZ2-PAOD
Reporting group description:	
Subjects received 1 dose of allo-APZ2-PAOD per injection site (N=20-30) intramuscularly into the lower leg along the vessel axes at Day 0 and were followed up for efficacy for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 1 dose of placebo per injection site (N=20-30) intramuscularly into the lower leg along the vessel axes at Day 0 and were followed up for efficacy for 12 weeks.	

Reporting group values	allo-APZ2-PAOD	Placebo	Total
Number of subjects	5	7	12
Age categorical Units: Subjects			
Adults (45-85 years)	5	7	12
Age continuous Units: years			
median	63	74	
full range (min-max)	55 to 76	66 to 80	-
Gender categorical Units: Subjects			
Female	0	2	2
Male	5	5	10

End points

End points reporting groups

Reporting group title	allo-APZ2-PAOD
Reporting group description:	
Subjects received 1 dose of allo-APZ2-PAOD per injection site (N=20-30) intramuscularly into the lower leg along the vessel axes at Day 0 and were followed up for efficacy for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 1 dose of placebo per injection site (N=20-30) intramuscularly into the lower leg along the vessel axes at Day 0 and were followed up for efficacy for 12 weeks.	
Reporting group title	allo-APZ2-PAOD
Reporting group description:	
Subjects received 1 dose of allo-APZ2-PAOD per injection site (N=20-30) intramuscularly into the lower leg along the vessel axes at Day 0 and were followed up for safety for 12 months.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 1 dose of placebo per injection site (N=20-30) intramuscularly into the lower leg along the vessel axes at Day 0 and were followed up for safety for 12 months.	

Primary: Percent change in total wound size from Baseline at Week 12

End point title	Percent change in total wound size from Baseline at Week 12
End point description:	
The primary efficacy endpoint was the percent change from Baseline to Week 12 in total wound size of the target leg. The total wound size of the target leg was calculated as sum of the wound sizes of all relevant ulcers of the target leg. The last observation carried forward (LOCF) approach was applied for 1 patient in the allo-APZ2-PAOD group. The measurement at Week 12 was missing, therefore the last available post-baseline measurement (in this case the value at Week 2) was used for the primary endpoint analysis.	
End point type	Primary
End point timeframe:	
From Baseline (Day 0, pre-dose) until the end of 12-week follow-up (Week 12).	

End point values	allo-APZ2-PAOD	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[1]	7[2]		
Units: Percentage				
median (full range (min-max))				
All	-38.40 (-82.5 to 141.6)	-49.80 (-100.0 to 59.9)		
Diabetics	-3.65 (-49.7 to 141.6)	-46.55 (-88.5 to 59.9)		
Non-diabetics	-82.5 (-82.5 to -82.5)	-49.80 (-100.0 to 13.4)		

Notes:

[1] - Diabetics are N=4 and non-diabetics are N=1.

[2] - Diabetis are N=4 and non-diabetics are N=3.

Statistical analyses

Statistical analysis title	Change in total wound size from Baseline (t-test)

Statistical analysis description:

The 95% confidence interval for the mean change of total wound size from Baseline (pre-dose) at Week 12 was calculated. LOCF for missing data was applied.
The primary efficacy endpoint was analyzed with a t-test with treatment as independent variable. The significance level was 0.05 (2-sided). Stratification by diabetes was not possible because the diabetic stratum sizes were too small (e.g., less than 3 subjects within the stratum). The data were previously tested for normal distribution.

Comparison groups	allo-APZ2-PAOD v Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.4036
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	37.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.99
upper limit	132.57
Variability estimate	Standard deviation
Dispersion value	73.03

Notes:

[3] - The primary efficacy variable was subjected to confirmatory statistical analysis in a two-stage group sequential study design.
The primary null hypothesis to be tested was
H0: μallo-APZ2-PAOD = μPlacebo vs
H1: μallo-APZ2-PAOD ≠ μPlacebo
where μ is the mean percent change from Baseline to Week 12 in total wound size of the target leg.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From administration of the IMP until the end of 12-month follow-up (Month 12).

Adverse event reporting additional description:

In 4 subjects (2 per treatment group), adverse event reporting ended before Month 12 due to early trial termination by the Sponsor.
Two subjects died (1 per treatment group) before Month 12.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.01

Reporting groups

Reporting group title	allo-APZ2-PAOD

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	allo-APZ2-PAOD	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	5 / 7 (71.43%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract stoma complication			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Dry gangrene			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Extremity necrosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Tremor			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Joint destruction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gangrene			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 5 (0.00%)	3 / 7 (42.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	allo-APZ2-PAOD	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	6 / 7 (85.71%)	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Ureteric injury			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Vascular injury			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	
occurrences (all)	1	3	
Vascular disorders			
Dry gangrene			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Extremity necrosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Dysaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Muscle contractions involuntary			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Condition aggravated			

subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	
occurrences (all)	1	2	
Impaired healing			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Injection site haematoma			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal wall haematoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	3	
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	0 / 5 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	3	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

Pain in extremity			
subjects affected / exposed	2 / 5 (40.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Infected skin ulcer			
subjects affected / exposed	0 / 5 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	4	
Influenza			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Localised infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Wound infection staphylococcal			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2018	Protocol v5.0 with the following changes to v4.0: - Inclusion criterion 3 was specified in more detail; inclusion criterion 4 was changed (maximum wound size of 20 cm² instead of 10 cm²), wording of inclusion criterion 9 was changed (from "Patients with hypertension, if they are treated…" to "If patients are hypertensive, they have to be treated…") - Exclusion criterion 6 was changed (from "…with bone exposure" to "…with exposure of destructive bone lesion"), exclusion criterion 7 was split into 2 criteria and specifying details were added; the numbering of subsequent exclusion criteria was changed accordingly - The option to use intravenous injections of strong analgesics upon subject request and longer safety observation time in case of strong analgesics use at the discretion of the investigator was added - The use of vitamin K and direct oral anticoagulants as concomitant medications was specified in more detail - The visit window for screening was changed (from "14 days to 7 days before treatment" to "21 days to 7 days before treatment").
19 April 2018	Protocol v6.0 with the following changes to v5.0: - Exclusion criterion 6 was rephrased (from "… with ulcers with exposure of destructive bone lesions" to "…with osteomyelitis at ulceration").
27 August 2018	Protocol v7.0 with the following changes to v6.0: - The trial was changed from a national (Germany) to an international trial with additional sites in the United Kingdom, Austria, Czech Republic, and Poland - Inclusion criterion 3 was changed to allow angiography results not older than 6 months (formerly 3 months) - The safety observation time after IMP injection was specified to be at least 2 hours; accordingly, vital signs were to be assessed the earliest 2 hours after the IMP administration - Unblinding via randomization envelopes was changed to unblinding via the electronic case report form system.

07 February 2019	Protocol v8.0 with the following changes to v7.0: - The specification that no minimal number of subjects with diabetes or without diabetes was added - Inclusion criterion 7 was changed (from "No evidence of change of wound size of more than 25% for at least 6 weeks before screening" to "No evidence of wound healing after standard of care treatment for at least 1 week before screening") - Exclusion criterion 1, the origin of skin lesions was rephrased (from "mixed anterior-venous" to "leading venous") - Exclusion criterion 9 was changed to include subjects with surgical/interventional reconstruction more than 1 week before screening or with not successful revascularization - Exclusion criterion 10 was changed to include subjects with major amputations of lower extremities within 12 months before screening - Exclusion criterion 22 was changed to allow previous use of glucocorticoid-medication above the cushing threshold dose. Medications that might influence wound healing, hyperbaric oxygen therapy, spinal cord stimulation and sympathectomy, as well as vasoactive substances other than the test drug, haemodilution or rheological therapy were not allowed from screening until Week 12 - Octenisept for wound care was only to be used in subjects without a history of allergic reactions to the product - The visit window for screening was changed (from "21 days to 7 days before treatment" to "21 days to 2 days before treatment") - The examination of injection sites was added for Visits 2-9 - Relationship assessment of adverse events to the procedure was added - Suspected unexpected serious adverse reaction reporting was expanded from German legislation to include applicable European and other applicable national regulatory requirements.
05 April 2019	In Czech Republic, subjects were studied on protocol version CZE 3.0, dated 05-Apr-2019, which corresponds to Version 8.0, dated 07-Feb-2019, except that only subjects aged 45 to 75 years were to be included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 March 2020	Subject recruitment was interrupted due to the COVID-19 pandemic. The sponsor of the trial decided to terminate the clinical trial early due to insufficient subject recruitment, which was not only due to the COVID-19 pandemic. The clinical trial termination was submitted to responsible ethics committees and authorities on 15-May-2020.	-

Notes:

Limitations and caveats

None reported