Clinical trial results:
An interventional, multicenter, single arm, phase I/IIa clinical trial to investigate the efficacy and safety of allo-APZ2-DFU on wound healing of diabetic neuropathic ulcer (DFU)

Summary

EudraCT number	2017-000234-57
Trial protocol	DE
Global end of trial date	29 June 2020

Results information

Result version number	v1 (current)
This version publication date	01 July 2021
First version publication date	01 July 2021

Trial information

Trial identification

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

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, RHEACELL GmbH & Co. KG, +49 6221718330, office@rheacell.com
Scientific contact	Information Office, RHEACELL GmbH & Co. KG, 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	29 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 June 2020
Global end of trial reached?	Yes
Global end of trial date	29 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy (by monitoring the wound surface area reduction of diabetic foot ulcers [DFUs]) and safety (by monitoring adverse events [AEs]) of 2 doses of the investigational medicinal product (IMP) allo-APZ2-DFU topically administered to the wound matrix of patients with DFU.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) Good Clinical Practice (GCP, CPMP/ICH/135/95). All national and local regulatory requirements were followed. The investigator ensured that the patient was fully informed about the objectives, procedures, potential risks, any discomforts, and expected benefits of the trial.
Based on the available data, a starting dose of 2x10^6 allogeneic skin-derived ATP-binding cassette sub-family B member 5 (ABCB5)-positive cells/cm², if administered topically on DFU wounds (1 to 50 cm²), was considered to be safe (196-fold safety margin) and expected to be beneficial for patients with DFU.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 August 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	Germany: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	13
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 63 patients screened at 8 centers, 40 patients were screening failures; 23 patients met the eligibility criteria, were treated with allo-APZ2-DFU, and were included in the safety analysis set (SAF).

Pre-assignment

Screening details:

Patients who met all inclusion and none of the exclusion criteria were eligible to participate in the trial.

Period 1

Period 1 title	Treatment and follow-up (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	allo-APZ2-DFU

Arm description:

Patients treated with the IMP, allo-APZ2-DFU

Arm type	Experimental
Investigational medicinal product name	allo-APZ2-DFU
Investigational medicinal product code	
Other name	ABCB5-positive mesenchymal stem cells
Pharmaceutical forms	Cutaneous suspension
Routes of administration	Topical use

Dosage and administration details:

Up to 2 topical applications of 2x10^6 cells/cm², applied in 200 µL Human Serum Albumin/Ringer-Lactate/Glucose solution with a syringe on the wound surface of patients with DFU and optionally covered with fibrin gel after 15-30 minutes.

Number of subjects in period 1	allo-APZ2-DFU
Started	23
Completed	22
Not completed	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment and follow-up
Reporting group description:	
Patients treated with allo-APZ2-DFU	

Reporting group values	Treatment and follow-up	Total	
Number of subjects	23	23	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	13	13	
From 65-84 years	10	10	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	3	3	
Male	20	20	

End points

End points reporting groups

Reporting group title	allo-APZ2-DFU
Reporting group description: Patients treated with the IMP, allo-APZ2-DFU	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: The SAF included all patients who were treated with allo-APZ2-DFU at least once.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set (FAS) included all patients of the SAF with wound surface area assessments at Day 0 (Baseline) and at least one post-baseline visit.	
Subject analysis set title	Modified full analysis set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The modified FAS (mFAS) included all patients of the FAS except for 3 patients with major protocol deviations affecting efficacy assessments.	

Primary: Percentage of wound surface area reduction at Week 12

End point title	Percentage of wound surface area reduction at Week 12[1]
End point description: The wound surface area was assessed using digital photographs and digital planimetry software.	
End point type	Primary
End point timeframe: From Baseline to Week 12	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: In a posthoc analysis the precent reduction in wound surface area was evaluated with a Wilcoxon signed rank test. H0 tested was median = 0. The 2-sided p was <0.0001 in both the FAS and mFAS.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	20		
Units: Percentage				
median (full range (min-max))	59.00 (-56.0 to 100.0)	63.50 (-56.0 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of wound surface area reduction at Weeks 2, 4, 6, 8 and 12 (without last observation carried forward [LOCF])

End point title	Percentage of wound surface area reduction at Weeks 2, 4, 6, 8 and 12 (without last observation carried forward [LOCF])

End point description:

The wound surface area was assessed using digital photographs and digital planimetry software.

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[2]	20[3]		
Units: Percentage				
median (full range (min-max))				
Week 2	30.85 (-24.1 to 83.1)	30.85 (-24.1 to 83.1)		
Week 4	44.10 (-315.3 to 99.8)	47.55 (-315.3 to 99.8)		
Week 6	28.90 (-98.5 to 100.0)	42.05 (-98.5 to 100.0)		
Week 8	48.25 (-123.2 to 100.0)	52.70 (-123.2 to 100.0)		
Week 12	59.00 (-56.0 to 100.0)	63.50 (-56.0 to 100.0)		

Notes:

[2] - At some visits, less than 23 patients were investigated.

[3] - At some visits, less than 20 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of visible wound surface area reduction at Weeks 2, 4, 6, 8 and 12 (without LOCF)

End point title	Percentage of visible wound surface area reduction at Weeks 2, 4, 6, 8 and 12 (without LOCF)

End point description:

The wound surface area was assessed using digital photographs and digital planimetry software.

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[4]	20[5]		
Units: Percentage				
median (full range (min-max))				
Week 2	30.85 (-1.6 to 83.1)	30.85 (0.2 to 83.1)		
Week 4	44.10 (-105.5 to 99.8)	47.55 (-105.5 to 99.8)		

Week 6	28.90 (-98.5 to 100.0)	42.05 (-98.5 to 100.0)		
Week 8	48.25 (-123.2 to 100.0)	52.70 (-123.2 to 100.0)		
Week 12	58.35 (-56.0 to 100.0)	60.40 (-56.0 to 100.0)		

Notes:

[4] - At some visits, less than 23 patients were investigated.

[5] - At some visits, less than 20 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute target wound surface area reduction at Weeks 2, 4, 6, 8 and 12 (without LOCF)

End point title	Absolute target wound surface area reduction at Weeks 2, 4, 6, 8 and 12 (without LOCF)

End point description:

The wound surface area was assessed using digital photographs and digital planimetry software.
At Baseline, the median size of the wound was 2.58 cm² (range: 1.03 - 15.20) in the FAS and 3.08 cm² (range: 1.13 - 15.20) in the mFAS.

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[6]	20[7]		
Units: cm²				
median (full range (min-max))				
Week 2	1.07 (-0.50 to 4.08)	1.18 (-0.50 to 4.08)		
Week 4	1.13 (-6.58 to 5.16)	1.56 (-6.58 to 5.16)		
Week 6	1.09 (-1.49 to 4.39)	1.40 (-1.49 to 4.39)		
Week 8	1.76 (-1.75 to 6.92)	1.99 (-1.75 to 6.92)		
Week 12	1.71 (-3.62 to 7.83)	2.00 (-3.62 to 7.83)		

Notes:

[6] - At some visits, less than 23 patients were investigated.

[7] - At some visits, less than 20 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to first complete target wound closure

End point title	Median time to first complete target wound closure

End point description:

The wound surface area was assessed using digital photographs and digital planimetry software. Complete wound closure was defined as 95% to 100% epithelialization of the wound.

End point type	Secondary

End point timeframe:

From Baseline to Week 12.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	20		
Units: Days	89	89		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving complete target wound closure at Weeks 2, 4, 6, 8 and 12, and at any timepoint

End point title	Number of patients achieving complete target wound closure at Weeks 2, 4, 6, 8 and 12, and at any timepoint

End point description:

The wound surface area was assessed using digital photographs and digital planimetry software. Complete wound closure was defined as 95% to 100% epithelialization of the wound.

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[8]	20[9]		
Units: Patients				
Week 2	0	0		
Week 4	1	1		
Week 6	2	2		
Week 6.1	0	0		
Week 8	1	1		
Week 12	6	6		
Any time up to Week 12	6	6		

Notes:

[8] - At some visits, less than 23 patients were investigated.

[9] - At some visits, less than 20 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first 30% reduction of target wound surface area

End point title	Time to first 30% reduction of target wound surface area

End point description:

The wound surface area was assessed using digital photographs and digital planimetry software.

End point type	Secondary

End point timeframe:

From Baseline to Week 12.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	20		
Units: Days				
median (confidence interval 95%)	27 (14 to 30)	22 (14 to 30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving at least 30% reduction of target wound surface area at Weeks 2, 4, 6, 8 and 12, and at any timepoint

End point title	Number of patients achieving at least 30% reduction of target wound surface area at Weeks 2, 4, 6, 8 and 12, and at any timepoint

End point description:

The wound surface area was assessed using digital photographs and digital planimetry software.

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[10]	20[11]		
Units: Patients				
Week 2	11	10		
Week 4	13	13		
Week 6	9	9		
Week 8	15	14		
Week 12	17	17		
Any time up to Week 12	19	18		

Notes:

[10] - At some visits, less than 23 patients were investigated.

[11] - At some visits, less than 20 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients whose target wound reopened after wound closure within the 12-week efficacy follow-up

End point title	Number of patients whose target wound reopened after wound closure within the 12-week efficacy follow-up

End point description:

The wound surface area was assessed using digital photographs and digital planimetry software. Complete wound closure was defined as 95% to 100% epithelialization of the wound.

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	20		
Units: Patients	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of target wound exudation at Day 0 and Week 6.1 prior to IMP application, and at Week 12

End point title	Assessment of target wound exudation at Day 0 and Week 6.1 prior to IMP application, and at Week 12

End point description:

Wound exudation was classified by the investigator using the following scores:
High: small amounts of fluid or free fluids are visible when the dressing is removed; dressing is extensively marked or wet.
Moderate: Small amounts of fluid are visible when dressing is removed; wound bed may appear glossy; primary dressing may be lightly marked.
Low: Wound bed is dry; there is no visible moisture; primary dressing is unmarked; dressing may be adherent to wound.
Wound exudation was assessed at all visits, representative results for 3 visits are reported below.

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[12]	20[13]		
Units: Patients				
Low at Day 0	10	7		
Moderate at Day 0	11	11		
High at Day 0	2	2		
Low at Week 6.1	8	6		
Moderate at Week 6.1	7	6		
High at Week 6.1	1	1		
Low at Week 12	12	10		
Moderate at Week 12	10	9		
High at Week 12	1	1		

Notes:

[12] - At Week 6.1, 16 patients were investigated.

[13] - At Week 6.1, 13 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of target wound epithelialization at Day 0 and Week 6.1 prior to IMP application, and at Week 12

End point title	Assessment of target wound epithelialization at Day 0 and Week 6.1 prior to IMP application, and at Week 12

End point description:

Epithelialization (in % of wound area) was assessed by the investigator based on image analysis and is shown here for 3 selected visits.

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[14]	20[15]		
Units: Percentage of patients				
median (full range (min-max))				
Day 0	0.0 (0 to 10)	0.0 (0 to 10)		
Week 6.1	0.0 (0 to 100)	0.0 (0 to 90)		
Week 12	50.0 (0 to 100)	58.5 (0 to 100)		

Notes:

[14] - At Week 6.1, 9 patients were analyzed.

[15] - At Week 6.1, 6 patients were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of target wound formation of granulation tissue at Day 0 and Week 6.1 prior to IMP application, and at Week 12

End point title	Assessment of target wound formation of granulation tissue at Day 0 and Week 6.1 prior to IMP application, and at Week 12

End point description:

Formation of granulation tissue was assessed by the investigator based on image analysis and is shown here for 3 seleted visits.

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[16]	20[17]		
Units: Percentage of granulation tissue				
median (full range (min-max))				
Day 0	100.0 (0 to 100)	100.0 (0 to 100)		
Week 6.1	80.0 (0 to 100)	77.5 (0 to 100)		
Week 12	41.0 (0 to 100)	35.0 (0 to 100)		

Notes:

[16] - At Week 6.1, 9 patients were investigated.

[17] - At Week 6.1, 6 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to amputation at target leg until Week 12

End point title	Time to amputation at target leg until Week 12

End point description:

An amputation at the target leg until Week 12 was reported in only one patient.

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	20		
Units: Patients				
Day 42	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain assessment as per numerical rating scale (NRS) at Day 0, Week 6.1, and Week 12

End point title	Pain assessment as per numerical rating scale (NRS) at Day 0, Week 6.1, and Week 12

End point description:

Pain was assessed by the patient using an NRS ranging between no pain (0) and worst imaginable pain (10) and is shown here for 3 seleted visits.

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	23[18]			
Units: pain score				
median (full range (min-max))				
Day 0	1.0 (0 to 9)			
Week 6.1	0.0 (-1 to 3)			
Week 12	0.0 (-1 to 7)			

Notes:

[18] - At Week 6.1, 16 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of life (QoL) as assessed with the short form 36 (SF-36) questionnaire at Week 12

End point title	Change from Baseline in Quality of life (QoL) as assessed with the short form 36 (SF-36) questionnaire at Week 12

End point description:

Quality of life was assessed using the short form 36 (SF-36) questionnaire. Changes from Baseline in the scores of 9 subscales were measured. A higher score corresponds to a more positive health status.
Median (full range) values at Baseline were:
Limitations in physical functioning: 50.00 (5.0 - 100.0)
Limitations in role activities due to problems in physical health: 25.00 (0.0 - 100.0)
Limitations in usual role due to emotional problems: 100.00 (0.0 - 100.0)
Limitations in social functioning due to physical or emotional problems: 87.50 (0.0 - 100.0)
Mental health (depressed or happy): 76.00 (0.0 - 100.0)
Bodily pain: 74.00 (12.0 - 100.0)
Vitality (fatigue and energy): 55.00 (0.0 - 85.0)

General health: 55.00 (10.0 - 92.0)
Health transition: 3.00 (2.0 - 5.0)

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Score (change from Baseline)				
median (full range (min-max))				
Limitations in physical functioning	0.00 (-20.0 to 80.0)			
Limit. in role act. due to probl. in phys. health	0.00 (-75.0 to 100.0)			
Limit. in usual role due to emotional probl.	0.00 (-100.0 to 100.0)			
Limit. in soc. funct. due to phys. or emot. probl.	0.00 (-37.5 to 50.0)			
Mental health (depressed or happy)	0.00 (-24.0 to 52.0)			
Bodily pain	0.00 (-40.0 to 62.0)			
Vitality (fatigue and energy)	0.00 (-30.0 to 50.0)			
General health	0.00 (-27.0 to 40.0)			
Health transition	0.00 (-4.0 to 2.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Dermatology-specific QoL as assessed with the Dermatology Life Quality Index (DLQI) questionnaire at Weeks 4 and 12

End point title	Change from Baseline in Dermatology-specific QoL as assessed with the Dermatology Life Quality Index (DLQI) questionnaire at Weeks 4 and 12

End point description:

The DLQI consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work, school, personal relationships, and treatment. Each question is answered by a tick box: 'not at all', 'a little', 'a lot', or 'very much'. Each question is scored from 0 to 3 and the scores are summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment). All questions relate to the previous week.
At Baseline, the median DLQI summary score was 6.0 (range: 0 - 28).

End point type	Secondary

End point timeframe:

As indicated in the end point title.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Score (change from Baseline)				
median (full range (min-max))				
Week 4 Week 12	0.0 (-14 to 5) -1.0 (-17 to 11)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs were reported from the application of allo-APZ2-DFU (Day 0) until the end of the safety follow-up (Month 12).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Safety analysis set

Reporting group description: -

Serious adverse events	Safety analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 23 (43.48%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Sciatica			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected skin ulcer			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Safety analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)		
Injury, poisoning and procedural complications			
Ligament sprain			

subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 3		
Skin and subcutaneous tissue disorders Blister subjects affected / exposed occurrences (all) Decubitus ulcer subjects affected / exposed occurrences (all) Skin ulcer subjects affected / exposed occurrences (all)	 6 / 23 (26.09%) 10 1 / 23 (4.35%) 3 4 / 23 (17.39%) 5		
Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all)	 1 / 23 (4.35%) 3		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	 3 / 23 (13.04%) 3		
Infections and infestations Wound infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Localised infection subjects affected / exposed occurrences (all) Infected skin ulcer subjects affected / exposed occurrences (all)	 2 / 23 (8.70%) 4 4 / 23 (17.39%) 4 3 / 23 (13.04%) 5 4 / 23 (17.39%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2017	o Inclusion criterion 3: 'If the ABI is >1.3, an additional doppler ultrasonography must be performed to exclude a PAOD masked by media sclerosis' was added o Wound debridement can also be carried out at Visit 1 o Definition of "best standard of care management" of the diabetic foot ulcer was added o New Inclusion Criterion 4 added: At Screening Visit (Visit 1) the target ulcer should exist for at least six weeks without complete wound healing despite receiving standard of care treatment as described in the study protocol, and the wound surface area should be between 1 and 50 cm² measured by using a scaled measuring sensor in combination with digital image analysis o New Inclusion Criterion 6 added: Patients suffering from two or more ulcers at the same extremity, as long as these ulcers are separated by a minimum bridge of 1 cm of healthy tissue o New Exclusion Criterion 8 added: Ulcers due to non-diabetic etiology.
17 August 2017	o Change of Inclusion Criterion 4: 'At Screening visit (Visit 1) the target ulcer should exist for at least six weeks without complete wound healing despite receiving standard of care treatment as described in the study protocol, and the wound surface area should be between 1 and 50 cm² measured by using a scaled measuring sensor in combination with digital image analysis' was changed to 'At Screening Visit 1 and 2 the wound surface area should be between 1 and 50 cm² measured by using a scaled measuring sensor in combination with digital image analysis' o Change of Exclusion Criterion 2: presence of osteomyelitis was changed to clinical signs of active osteomyelitis in the last three months o Change of Exclusion Criterion 14: 'History of tumour disease or active tumour disease, systemic or local neoplasia or suspicion of any carcinomas or malignant tumour' was changed to 'Any malignancy within the past 5 years, excluding successfully treated carcinoma in situ, basal cell carcinoma or squamous cell carcinoma of the skin without evidence of metastases' o Secondary efficacy endpoint 'Percentage of invisible and visible wound surface area reduction at Weeks 2, 4, 8 and 12 (without LOCF)' was added o Secondary efficacy endpoint 'Absolute invisible and visible wound surface area reduction at Weeks 2, 4, 8 and 12 (without LOCF)' was added o Secondary efficacy endpoints: assessments of QoL using the SF-36 questionnaire and of dermatology-specific QoL based on the DLQI were additionally to be done at Visit 3 o Visit 1 was moved from 1-7 days before Visit 2 to at least 6 weeks before Visit 2 o Wound debridement can also be carried out at Visit 3.
09 April 2018	o Change of Inclusion Criterion 8: allowed BMI was extended from a range between 20 and 40 kg/m² to a range of 20 and 45 kg/m² o Clarified that Tisseel application after IMP application is optional and should occur 15-30 minutes after IMP application o Specified that determination of the wound surface will be done at Visit 1 and Visit 2 (instead of only Visit 2) o Appendix 1, wound surface area calculation was updated.

28 May 2018	o A second IMP application was introduced (adding Visit 10, Week 6.1), including 1 additional visit before and 2 additional visits after the 2nd IMP application (Visit 9, Visit 11 and Visit 12 to be performed at Week 6, Week 6.2, and Week 6.3, respectively). Visit 9 was added to measure the wound size 1 to 3 days before the 2nd IMP application to calculate the required cell amount. All treatments and procedures related to the IMP application were to be repeated at Visit 10 (physical examination and vital signs, and optional wound debridement). The risk/benefit assessment was adapted for the inclusion of a 2nd IMP application. o Due to the inclusion of 4 new visits for the 2nd IMP application, new time points, i.e. Week 6, Week 6.1, Week 6.2, and Week 6.3, were added to the following secondary efficacy endpoints: − Percentage wound surface area reduction (Week 6 only) − Percentage of invisible and visible wound surface area reduction (Week 6 only) − Absolute wound surface area reduction (Week 6 only) − Absolute invisible and visible wound surface area reduction (Week 6 only) − Assessment of wound infection − Proportion of patients achieving 30% and complete wound closure (Week 6 only) − Wound exudation, epithelialization and formation of granulation tissue (Week 6 and Week 6.1), and − Pain assessment as per NRS. o Primary efficacy endpoint: Week 6 was added as an LOCF measurement in case of a missing wound surface area measurement at Week 12. o Safety endpoints: Week 6.1 was added to analyze data obtained by physical examination and the assessment of vital signs. o For Inclusion Criterion 4 clarified that the required wound surface area between 1 and 50 cm^2 applies for the target ulcer. o Inclusion Criterion 6 wording changes.
07 March 2019	o In Inclusion Criterion 2 the following: '…..The HbA1c value at Visit 1 should not vary more than 1.5% (absolute range) compared to a HbA1c value that was previously measured 1 to 3 months before visit 1' changed to '….The HbA1c value at Visit 1 should not vary more than 1.5% (absolute range) compared to a HbA1c value that was previously measured 1 to 6 months before visit 1.' o In Inclusion Criterion 3 the following: '…..The presence of diabetic neuropathic ulcers "malum perforans" not involving subcutis (Grade I according to Wagner) at plantar side of the foot diagnosed by ABI ≥0.8, without claudication, or TcPO2 >40 mmHg…' changed to '….The presence of diabetic neuropathic ulcers "malum perforans" (Grade I and II according to Wagner) at plantar side of the foot diagnosed by ABI ≥0.7, without claudication, or TcPO2 >40 mmHg.' o Exclusion Criterion 1 clarified that acute Charot foot is meant.
12 December 2019	o The procedure to transfer wound photographs to the sponsor added. o New SOP references added.
27 April 2020	o Specified that due to the COVID-19 pandemic and the already reached target of responders, it was planned to complete the trial on 30-Jun-2020. References to the respective trial stop were added and adjusted. o The possibility to treat non-target wounds was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial was completed on 29-June-2020 (last patient last visit) due to the coronavirus disease-2019 (COVID-19) pandemic and the efficacy of allo-APZ2-DFU as specified in a protocol amendment.

Notes: