Clinical trial results:
An Interventional, Single Arm, Phase I/IIa Clinical Trial to Investigate the Efficacy and Safety of APZ2 on Wound Healing of Chronic Venous Ulcer (CVU)

Summary

EudraCT number	2015-000399-81
Trial protocol	DE
Global end of trial date	15 January 2019

Results information

Result version number	v1 (current)
This version publication date	26 May 2021
First version publication date	26 May 2021

Trial information

Trial identification

Sponsor protocol code	APZ2-II-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02742844
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	15 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 January 2019
Global end of trial reached?	Yes
Global end of trial date	15 January 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy (by monitoring the wound size reduction of CVUs) and safety (by monitoring adverse events [AEs]) of one dose of the IMP APZ2 topically administered on wounds of patients with CVU.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH 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 500,000 ABCB5+ cells/cm² administered topically on CVU wounds of a maximum size of 50 cm² (in the clinical Phase I/IIa trial) was considered to be safe and to provide benefit to the patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 August 2016
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: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

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)	3
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 13 patients screened at one center, 11 patients were enrolled and 2 patients were screening failures. 9 patients were treated. 6 of whom met all eligibilty criteria and were, thus, included in the full analysis set.

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	Biopsy period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	APZ2

Arm description:

Patients who underwent a skin biopsy in period 1.

Arm type	Biopsy collection & APZ2 production
Investigational medicinal product name	APZ2
Investigational medicinal product code	
Other name	ATP-binding cassette sub-family B member 5 (ABCB5)-positive dermal mesenchymal stem cells
Pharmaceutical forms	Cutaneous suspension
Routes of administration	Topical use

Dosage and administration details:

One dose of APZ2 (500,000 autologous skin-derived ABCB5+ MSCs/50 µL/cm2) was topically administered on the wound surface of patients with CVU. In case of multiple wounds, one wound was selected as the target wound of APZ2 application.

Number of subjects in period 1	APZ2
Started	11
Biopsy (first visit in Biopsy period)	11
Completed	9
Not completed	2
IMP production not successful	2

Period 2

Period 2 title	Treatment and follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	APZ2

Arm description:

Patients treated with APZ2.

Arm type	Experimental
Investigational medicinal product name	APZ2
Investigational medicinal product code	
Other name	ATP-binding cassette sub-family B member 5 (ABCB5)-positive dermal mesenchymal stem cells
Pharmaceutical forms	Cutaneous suspension
Routes of administration	Topical use

Dosage and administration details:

One dose of APZ2 (500,000 autologous skin-derived ABCB5+ MSCs/50 µL/cm2) was topically administered on the wound surface of patients with CVU. In case of multiple wounds, one wound was selected as the target wound of APZ2 application.

Number of subjects in period 2	APZ2
Started	9
IMP administration	9
Completed	6
Not completed	3
Protocol deviation	3

Baseline characteristics

Reporting groups	
Reporting group title	APZ2
Reporting group description:	
Patients who underwent a skin biopsy in period 1.	

Reporting group values	APZ2	Total	
Number of subjects	11	11	
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)	3	3	
From 65-84 years	8	8	
85 years and over	0	0	
Gender categorical Units: Subjects			
male	5	5	
female	6	6	

Subject analysis sets	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients who were enrolled and who were treated with APZ2 cells.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set included all patients of the safety analysis set, who did not violate efficacy exclusion criteria 1 and 2 and had wound size assessments at Baseline and at least at one post-baseline visit.	

Reporting group values	Safety analysis set	Full analysis set	
Number of subjects	9	6	
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)	2	1	
From 65-84 years	7	5	
85 years and over	0	0	
Gender categorical Units: Subjects			
male	3	2	
female	6	4	

End points

End points reporting groups

Reporting group title	APZ2
Reporting group description: Patients who underwent a skin biopsy in period 1.	
Reporting group title	APZ2
Reporting group description: Patients treated with APZ2.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: Patients who were enrolled and who were treated with APZ2 cells.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set included all patients of the safety analysis set, who did not violate efficacy exclusion criteria 1 and 2 and had wound size assessments at Baseline and at least at one post-baseline visit.	

Primary: Percentage of wound size reduction at Week 12 or last available post-baseline measurement

End point title	Percentage of wound size reduction at Week 12 or last available post-baseline measurement[1]
End point description: The percentage of wound size reduction in comparison to the size at the day of APZ2 application was assessed by standardized photography.	
End point type	Primary
End point timeframe: Change from Baseline to Week 12 or last available post-baseline measurement if the Week 12 measurement was missing (last observation carried forward).	

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: No formal hypothesis was statistically tested. All variables were analyzed descriptively.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Target wound size reduction [%]				
median (full range (min-max))	63.38 (32.11 to 100.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of wound size reduction at Weeks 2, 3, 4, 6, 8, 10 and 12 (without LOCF)

End point title	Percentage of wound size reduction at Weeks 2, 3, 4, 6, 8, 10 and 12 (without LOCF)

End point description:

The percentage of wound size reduction was assessed by standardized photography. The assessment of wound size reduction in comparison to the size at the day of APZ2 application started on the day of the first change of wound dressing (in general on Day 3).

End point type	Secondary

End point timeframe:

Weeks 2, 3, 4, 6, 8, 10 and 12 (without last observation carried forward).

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Target wound size reduction [%]				
median (full range (min-max))				
Week 2	23.14 (6.16 to 29.19)			
Week 3	23.01 (9.10 to 64.30)			
Week 4	27.78 (24.16 to 72.54)			
Week 6	65.86 (47.61 to 83.90)			
Week 8	57.14 (37.19 to 93.97)			
Week 10	56.81 (38.37 to 93.17)			
Week 12	63.38 (32.11 to 100.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute wound size reduction at Weeks 2, 3, 4, 6, 8, 10, and 12

End point title	Absolute wound size reduction at Weeks 2, 3, 4, 6, 8, 10, and 12

End point description:

The wound size reduction in comparison to the size at the day of APZ2 application was assessed by standardized photography.

End point type	Secondary

End point timeframe:

Weeks 2, 3, 4, 6, 8, 10, and 12.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Target wound size reduction [cm2]				
median (full range (min-max))				
Week 2	1.94 (0.83 to 4.44)			
Week 3	2.60 (0.90 to 7.45)			
Week 4	2.46 (1.54 to 9.63)			
Week 6	4.89 (2.49 to 10.01)			
Week 8	5.96 (2.49 to 15.95)			
Week 10	5.98 (2.24 to 16.78)			
Week 12	6.24 (2.40 to 13.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving complete wound closure at Weeks 2, 3, 4, 6, 8, 10, 12, and at any time point

End point title	Proportion of patients achieving complete wound closure at Weeks 2, 3, 4, 6, 8, 10, 12, and at any time point

End point description:

Wound closure was defined as 95% to 100% epithelialization of the wound and was assessed by the investigator. The number of patients instead of the proportion is repoprted due to the low number of patients.

End point type	Secondary

End point timeframe:

Weeks 2, 3, 4, 6, 8, 10, 12, and at any time point.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6[2]			
Units: number of patients				
Week 2	0			
Week 3	0			
Week 4	0			
Week 6	0			
Week 8	1			
Week 10	1			
Week 12	1			

Notes:

[2] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first complete wound closure

End point title	Time to first complete wound closure

End point description:

Wound closure was defined as 95% to 100% epithelialization of the wound and was assessed by the investigator.

End point type	Secondary

End point timeframe:

Day 0 to Week 12

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6[3]			
Units: days	53			

Notes:

[3] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first 30% wound closure

End point title	Time to first 30% wound closure

End point description:

The probabilty of achieving 30% wound closure and the median time to 30% reduction along with the 95% confidence interval were calculated with a Kaplan-Meier analysis.

End point type	Secondary

End point timeframe:

Day 0 to Week 12

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Days				
median (confidence interval 95%)	42 (21.0 to 57.0)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

End point type	Secondary

End point timeframe:

Day 0 to Week 12

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: number of patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Epithelialization assessed at Weeks 2, 3, 4, 6, 8, 10, and 12

End point title	Epithelialization assessed at Weeks 2, 3, 4, 6, 8, 10, and 12

End point description:

End point type	Secondary

End point timeframe:

Day 0 to Week 12

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6[4]			
Units: % of wound area				
median (full range (min-max))				
Week 2	15.0 (0 to 35)			
Week 3	27.5 (0 to 60)			
Week 4	35.0 (2 to 70)			
Week 6	65.0 (45 to 85)			
Week 8	55.5 (40 to 95)			
Week 10	56.5 (40 to 95)			
Week 12	62.5 (35 to 100)			

Notes:

[4] - At Weeks 4 and 6 only 5 patients were evaluated.

Statistical analyses

No statistical analyses for this end point

Secondary: Formation of granulation tissue before IMP application (Day 0, Weeks 2, 3, 4, 6, 8, 10, and 12)

End point title	Formation of granulation tissue before IMP application (Day 0, Weeks 2, 3, 4, 6, 8, 10, and 12)
End point description:	
5 patients were analyzed at Weeks 4 and 6.	
End point type	Secondary
End point timeframe:	
Day 0, Weeks 2, 3, 4, 6, 8, 10, and 12.	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: % of wound area				
median (full range (min-max))				
Day 0	75.0 (50 to 100)			
Week 2	75.0 (55 to 95)			
Week 3	62.5 (40 to 100)			
Week 4	65.0 (30 to 98)			
Week 6	35.0 (15 to 55)			
Week 8	42.0 (5 to 60)			
Week 10	42.5 (5 to 60)			
Week 12	35.0 (0 to 65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Wound exudation before IMP application (Day 0, Weeks 2, 3, 4, 6, 8, 10, and 12)

End point title	Wound exudation before IMP application (Day 0, Weeks 2, 3, 4, 6, 8, 10, and 12)

End point description:

The number (%) of patients with low, moderate, and high wound exudation was reported.

End point type	Secondary

End point timeframe:

Day 0 to Week 12

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Patients				
low at Day 0	4			
moderate at Day 0	2			
high at Day 0	0			
low at Week 12	3			
moderate at Week 12	2			
high at Week 12	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Pain assessment as per numerical rating scale (NRS)

End point title	Pain assessment as per numerical rating scale (NRS)

End point description:

The pain perceived was rated on an NRS ranging from 0 (no pain) to 10 (strongest pain perceivable). The median (full range) pain at Baseline was 4.0 (0 - 5).

End point type	Secondary

End point timeframe:

Day 0 to Week 12

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: scale values (change from Baseline)				
median (full range (min-max))				
Day 1 - 3	-1.0 (-4 to 0)			
Day 8	-1.0 (-2 to 0)			
Week 2	-1.0 (-2 to 5)			
Week 3	-1.0 (-2 to 0)			
Week 4	-2.0 (-2 to 0)			
Week 6	-1.0 (-3 to 0)			
Week 8	-0.5 (-3 to 1)			
Week 10	-1.5 (-3 to 0)			
Week 12	-0.5 (-5 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of quality of life (QoL) using the Short Form Health Survey 36 (SF-36) questionnaire

End point title	Assessment of quality of life (QoL) using the Short Form Health Survey 36 (SF-36) questionnaire

End point description:

Quality of life was assessed using the SF-36 questionnaire. Changes from Baseline at Week 12 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: 37.50 (0.0 - 85.0)
Limitations in role activities due to problems in physical health: 12.50 (0.0 - 100.0)
Bodily pain: 41.00 (21.0 - 100.0)
General health: 48.50 (30.0 - 82.0)
Vitality (fatigue and energy): 45.00 (25.0 - 100.0)
Limitations in social functioning due to physical or emotional problems: 75.00 (50.0 - 100.0)
Limitations in usual role due to emotional problems: 66.65 (0.0 - 100.0)
Mental health (depressed or happy): 72.00 (44.0 - 92.0)
Health transition: 2.50 (1.0 - 4.0)

End point type	Secondary

End point timeframe:

Day 0 to Week 12

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6[5]			
Units: Subscale - change from Baseline				
median (full range (min-max))				
Limitations in physical functioning	-5.00 (-31.4 to 90.0)			

Limit. in role act. due to probl. in phys. health	0.00 (-25.0 to 0.0)			
Bodily pain	5.50 (-20.0 to 39.0)			
General health	0.00 (-17.0 to 25.0)			
Vitality (fatigue and energy)	-4.15 (-11.7 to 0.0)			
Limit. in soc. funct. due to phys. or emot. probl.	-12.50 (-50.0 to 12.5)			
Limit. in usual role due to emotional problems	-33.35 (-100.0 to 0.0)			
Mental health (depressed or happy)	-14.00 (-37.0 to 4.0)			
Health transition	-0.50 (-1.0 to 1.0)			

Notes:

[5] - The change from Baseline of "Limitations in physical functioning" was reported for 5 patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of dermatology-specific quality of life based on the Dermatology Life Quality Index (DLQI) questionnaire

End point title	Assessment of dermatology-specific quality of life based on the Dermatology Life Quality Index (DLQI) questionnaire

End point description:

The dermatology-specific QoL was assessed based on the DLQI questionnaire. 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 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 (full range) dermatology-specific quality of life summary score was 3.5 (1 - 7).

End point type	Secondary

End point timeframe:

Day 0 to Week 12

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6[6]			
Units: Summary score (change from Baseline)				
median (full range (min-max))				
Week 4	0.0 (-6 to 9)			
Week 8	2.5 (-1 to 9)			
Week 12	0.5 (-4 to 11)			

Notes:

[6] - Analysis at Week 4 and Week 12 included 4 patients.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs that occurred after the patient provided informed consent until the safety follow-up (Month 12) were reported. AEs were followed up until they were resolved, stabilized, or assessed to be chronic. The final status was obtained at safety follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

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	3 / 9 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiatus hernia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Skin injury			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
General disorders and administration site conditions			

Condition aggravated subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 4 1 / 9 (11.11%) 1		
Gastrointestinal disorders Gastric haemorrhage subjects affected / exposed occurrences (all) Hiatus hernia subjects affected / exposed occurrences (all) Pancreatitis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 2 1 / 9 (11.11%) 1		
Hepatobiliary disorders Cholecystitis subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 2		
Skin and subcutaneous tissue disorders Blister subjects affected / exposed occurrences (all) Decubitus ulcer subjects affected / exposed occurrences (all) Ingrowing nail subjects affected / exposed occurrences (all) Skin irritation subjects affected / exposed occurrences (all) Skin ulcer	 1 / 9 (11.11%) 2 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Soft tissue infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2016	The first patients were enrolled under trial protocol version 3.0. The main changes in the trial protocol Version 3.0 compared to Version 2.0 were: - Inclusion criterion 5 was changed from "Patients suffering from 2 ulcers at the same extremity, as long as these ulcers are separated by a minimum bridge of 1 cm of epithelialized skin" to "Patients suffering from 2 or more ulcers at the same extremity, as long as these ulcers are separated by a minimum bridge of 1 cm of epithelialized skin". - Exclusion criterion 3 was changed from "Diabetes mellitus that has to be evaluated by blood test (Hemoglobin A1c [HbA1c] 6.5 – 7.5%)" to "Diabetes mellitus that has to be evaluated by blood test (Hemoglobin A1c [HbA1c] >7.5%);". - Formation of granulation tissue was to be assessed after debridement instead of before debridement. - Sample size calculation (section 15.1): "To be able to still determine that the product has sufficient activity to warrant more extensive study and development, sample size calculation was performed based on responders using the optimal two stage design" was changed to "To be able to still determine that the product has sufficient activity to warrant more extensive study and development, sample size calculation was performed based on responders using the Minimax two stage design according to R. Simon".
11 November 2016	The main changes in the trial protocol Version 4.0 compared to Version 3.0 were: - Two subchapters “General exclusion criteria” and “Exclusion criteria for efficacy assessments” were included. - The former exclusion criterion 9, i.e. “A wound size enlargement of more than 25% between the wound assessment at the screening visit and the wound assessment at Visit 5” and the exclusion criterion 8, i.e. “A wound size reduction of more than 50% between the wound assessment at the screening visit and wound assessment at Visit 5” were listed as “Exclusion criteria for efficacy assessments”. - Procedures to ensure sufficient IMP supply for patients with wound size enlargement of more than 25% were specified. - The biopsy period was extended from “6 to 12 weeks” to “6 to 20 weeks”. - The general exclusion criterion 8 was included specifying that the wound size must be at least 1.5 cm^2 at Visit 5. - The time window for Visit 7 was extended from “Day 3” to “Day 1 to 3”. - It was clarified that in case of multiple CVU wounds the target wound for IMP administration was to be selected only at Visit 5. - The clinical trial duration was extended. - “Screening” was replaced by “screening period” in the flow chart and the schedule of assessments. - The last protocol version with the change history is provided in Appendix 16.1.1.

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.

No control arm was implemented in this clinical trial, but the trial demonstrated that one dose of topically administered APZ2 on CVUs was overall safe and well tolerated. The trial was prematurely discontinued due to the COVID-19 pandemic.

Notes: