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

Summary

EudraCT number	2017-000233-31
Trial protocol	DE
Global end of trial date	30 June 2020

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

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

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03257098
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	30 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2020
Global end of trial reached?	Yes
Global end of trial date	30 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this clinical trial was to investigate the efficacy (by monitoring the wound size reduction of chronic venous ulcers [CVUs]) and safety (by monitoring adverse events [AEs]) of two doses of allo-APZ2-CVU topically administered on wounds of patients with CVU.

Protection of trial subjects:

The clinical trial was conducted in accordance with the Declaration of Helsinki in its current revision and the International Conference on Harmonisation (ICH) Guideline for 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.
The COVID-19 pandemic did impact the conduct of the trial (e.g. delay of follow-up visits and examinations, delay of data entry/cleaning activities, change/delay of monitoring activities).
The situation in this clinical trial was continuously monitored to ensure the safety of patients and to reduce the delays in collection and verification of data. The sponsor was informed and updated with short interval reports on critical issues in the trial, and on measures taken to control them. Investigators received a sponsor statement on handling patient visits and were informed about recruitment stop.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 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: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	6
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 58 patients enrolled and screened at 9 centers, 27 patients were screening failures, and 31 patients were treated.

Pre-assignment

Screening details:

Patients who met each of the 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-CVU

Arm description:

Patients treated with the investigational medicinal product (IMP), allo-APZ2-II-CVU.

Arm type	Experimental
Investigational medicinal product name	allo-APZ2-CVU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous suspension
Routes of administration	Topical use

Dosage and administration details:

One (for patients enrolled under protocol Version 2.0) or 2 (for patients enrolled under protocol Version 3.0 or higher) topical applications of 1x10^6 cells/cm² of allo-APZ2-CVU cells were applied on the surface of the target ulcer with a syringe. Non-target wounds were treated as per standard of care.

Number of subjects in period 1	allo-APZ2-CVU
Started	31
Completed	31

Baseline characteristics

Reporting groups

Reporting group title	Treatment and follow-up

Reporting group description:

Patients were treated with 1x10^6 skin-derived ABCB5-positive mesenchymal stem cells/cm², which were topically applied under local anesthesia on the wound surface of a target CVU.

Reporting group values	Treatment and follow-up	Total	
Number of subjects	31	31	
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)	6	6	
From 65-84 years	25	25	
85 years and over	0	0	
Age continuous Units: years			
median	75.0		
full range (min-max)	36 to 82	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	16	16	

Subject analysis sets

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients who signed the informed consent form and who received allo-APZ2-CVU at least once.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Patients included in the safety analysis set who had a wound size assessment at Baseline (Visit 3, Day 0) and on at least one post-baseline visit.

Subject analysis set title	Modified full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients of the full analysis set except for patients with major protocol deviations affecting efficacy assessments. The modified full analysis set was used as sensitivity analysis
set for efficacy analyses concerning wound assessments and contained all except 4 patients belonging to the full analysis set.

Reporting group values	Safety analysis set	Full analysis set	Modified full analysis set
Number of subjects	31	31	27
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	6	5
From 65-84 years	25	25	22
85 years and over	0	0	0
Age continuous Units: years			
median	75.0	75.0	75.0
full range (min-max)	36 to 82	36 to 82	36 to 82
Gender categorical Units: Subjects			
Female	15	15	14
Male	16	16	13

End points

End points reporting groups

Reporting group title	allo-APZ2-CVU
Reporting group description:	
Patients treated with the investigational medicinal product (IMP), allo-APZ2-II-CVU.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients who signed the informed consent form and who received allo-APZ2-CVU at least once.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients included in the safety analysis set who had a wound size assessment at Baseline (Visit 3, Day 0) and on at least one post-baseline visit.	
Subject analysis set title	Modified full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients of the full analysis set except for patients with major protocol deviations affecting efficacy assessments. The modified full analysis set was used as sensitivity analysis set for efficacy analyses concerning wound assessments and contained all except 4 patients belonging to the full analysis set.	

Primary: Percentage of wound size reduction at Week 12, or last available post-baseline measurement if the Week 12 measurement was missing (last observation carried forward [LOCF])

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

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 statistical analyses were done in this phase I/II trial.

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[2]	27[3]		
Units: Target wound size reduction [%]				
median (full range (min-max))	75.60 (-278.9 to 100.0)	78.40 (-27.4 to 100.0)		

Notes:

[2] - At some visits, less than 31 patients were investigated.

[3] - At some visits, less than 27 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of wound size reduction at Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10 and 12 (without LOCF)

End point title	Percentage of wound size reduction at Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10 and 12 (without LOCF)

End point description:

End point type	Secondary

End point timeframe:

From Baseline to Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10 and 12

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[4]	27[5]		
Units: Target wound size reduction [%]				
median (full range (min-max))				
Week 2	28.70 (-8.6 to 75.9)	28.70 (-8.6 to 75.9)		
Week 3	39.50 (-10.8 to 100.0)	39.65 (-10.8 to 100.0)		
Week 4	47.20 (-61.0 to 100.0)	49.90 (-11.0 to 100.0)		
Week 6	53.25 (-147.5 to 100.0)	59.00 (-12.8 to 100.0)		
Week 6.1	36.95 (-187.9 to 95.1)	42.80 (-23.0 to 95.1)		
Week 6.2	36.75 (-64.2 to 90.4)	41.50 (-13.2 to 90.4)		
Week 8	58.30 (-136.0 to 100.0)	58.70 (-24.5 to 100.0)		
Week 10	68.70 (-84.3 to 100.0)	69.60 (-23.4 to 100.0)		
Week 12	76.85 (-278.9 to 100.0)	78.40 (-27.4 to 100.0)		

Notes:

[4] - At some visits, less than 31 patients were investigated.

[5] - At some visits, less than 27 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute wound size reduction at Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, and 12

End point title	Absolute wound size reduction at Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, and 12

End point description:

End point type	Secondary

End point timeframe:

From Baseline to Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, and 12

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[6]	27[7]		
Units: Wound size reduction [cm²]				
median (full range (min-max))				
Week 2	1.18 (-3.38 to 15.06)	1.18 (-3.38 to 15.06)		
Week 3	1.89 (-4.25 to 15.93)	1.90 (-4.25 to 15.93)		
Week 4	2.39 (-4.31 to 16.94)	2.39 (-4.31 to 16.94)		
Week 6	2.08 (-8.12 to 19.95)	2.11 (-5.03 to 19.95)		
Week 6.1	2.51 (-10.34 to 20.21)	2.52 (-2.20 to 20.21)		
Week 6.2	2.72 (-3.53 to 23.38)	2.77 (-2.75 to 23.38)		
Week 8	2.91 (-9.62 to 19.55)	2.94 (-9.62 to 19.55)		
Week 10	3.19 (-9.19 to 19.87)	3.37 (-9.19 to 19.87)		
Week 12	2.69 (-62.79 to 21.74)	3.16 (-10.76 to 21.74)		

Notes:

[6] - At some visits, less than 31 patients were investigated.

[7] - At some visits, less than 27 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving complete wound closure at Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, 12, and at any time point

End point title	Number of patients achieving complete wound closure at Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, 12, and at any time point

End point description:

Complete wound closure was defined as 95% to 100% epithelialization of the wound.

End point type	Secondary

End point timeframe:

From Baseline to Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, 12, and at any time point

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[8]	27[9]		
Units: Number of patients				
Day 1-3	0	0		
Day 8	0	0		

Week 2	0	0		
Week 3	1	1		
Week 4	1	1		
Week 6	2	2		
Week 6.1	1	1		
Week 6.2	0	0		
Week 8	3	3		
Week 10	3	3		
Week 12	6	6		
Any time up to Week 12	7	7		

Notes:

[8] - At some visits, less than 31 patients were investigated.

[9] - At some visits, less than 27 patients were investigated.

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:

Complete wound closure was defined as 95% to 100% epithelialization of the wound. Not all patients had a complete wound closure during the trial, thus, it was not possible to calculate the median time to wound closure. Instead, a Kaplan-Meier analysis was done to calculate product-limit survival estimates for the time to wound closure.

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	31[10]	27[11]		
Units: days to ≥50% probability of closure				
number (confidence interval 95%)	91.0 (85.00 to 91.00)	91.0 (85.00 to 91.00)		

Notes:

[10] - At some visits, less than 31 patients were analyzed.

[11] - At some visits, less than 27 patients were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving an at least 30% wound size reduction at Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, 12, and at any time point

End point title	Number of patients achieving an at least 30% wound size reduction at Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, 12, and at any time point

End point description:

End point type	Secondary

End point timeframe:

From Baseline to Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, 12, and at any time point

End point values	Full analysis set	Modified full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31[12]	27[13]		
Units: Patients				
Day 1-3	2	2		
Day 8	7	7		
Week 2	14	13		
Week 3	20	18		
Week 4	20	19		
Week 6	21	19		
Week 6.1	12	11		
Week 6.2	15	14		
Week 8	21	20		
Week 10	20	19		
Week 12/end of treatment	21	21		
Week 12	21	21		
Week 12 (LOCF)	21	21		
Any time up to Week 12	26	24		

Notes:

[12] - At some visits, less than 31 patients were investigated.

[13] - At some visits, less than 27 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first 30% wound size reduction

End point title	Time to first 30% wound size reduction

End point description:

The time (days) from Baseline until a probabilty of at least 50% for a wound size reduction of at least 30% was calculated.

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	31	27		
Units: days to ≥50% probability				
number (confidence interval 95%)	21.0 (12.00 to 27.00)	15.0 (9.00 to 27.00)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number 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:

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	31	27		
Units: Patients	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Epithelialization at Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, and 12

End point title	Epithelialization at Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, and 12

End point description:

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	31[14]	27[15]		
Units: % of wound area				
median (full range (min-max))				
Day 0	0.0 (0 to 30)	0.0 (0 to 30)		
Day 1 - 3	0.0 (0 to 60)	1.0 (0 to 60)		
Day 8	10.0 (0 to 50)	10.0 (0 to 50)		
Week 2	20.0 (0 to 80)	20.0 (0 to 80)		
Week 3	20.0 (0 to 100)	20.0 (0 to 100)		
Week 4	30.0 (0 to 100)	30.0 (0 to 100)		
Week 6	40.0 (0 to 100)	40.0 (0 to 100)		
Week 6.1	30.5 (0 to 95)	30.0 (0 to 95)		
Week 6.2	40.0 (0 to 88)	40.0 (0 to 88)		
Week 8	40.0 (0 to 100)	40.0 (0 to 100)		
Week 10	42.5 (0 to 100)	56.0 (0 to 100)		
Week 12	40.0 (0 to 100)	45.0 (0 to 100)		

Notes:

[14] - At some visits, less than 31 patients were investigated.

[15] - At some visits, less than 27 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Formation of granulation tissue before IMP applications (Visit 3, Visit 10) and at each follow-up visit (Days 1-3 and 8, Weeks 2, 3, 4, 6, 6.2, 8, 10, and 12)

End point title	Formation of granulation tissue before IMP applications (Visit 3, Visit 10) and at each follow-up visit (Days 1-3 and 8, Weeks 2, 3, 4, 6, 6.2, 8, 10, and 12)

End point description:

End point type	Secondary

End point timeframe:

From Day 0 (before allo-APZ2-CVU application) 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	31[16]	27[17]		
Units: % of wound area				
median (full range (min-max))				
Day 0	70.0 (0 to 100)	65.0 (0 to 100)		
Day 1 - 3	65.0 (0 to 100)	60.0 (0 to 100)		
Day 8	50.0 (0 to 95)	50.0 (0 to 95)		
Week 2	50.0 (5 to 95)	50.0 (5 to 95)		
Week 3	50.0 (0 to 80)	50.0 (0 to 80)		
Week 4	50.0 (0 to 95)	50.0 (0 to 95)		
Week 6	50.0 (0 to 95)	50.0 (0 to 95)		

Week 6.1	60.0 (5 to 100)	60.0 (5 to 100)		
Week 6.2	53.0 (10 to 100)	50.0 (10 to 100)		
Week 8	50.0 (0 to 95)	50.0 (0 to 95)		
Week 10	30.0 (0 to 95)	25.0 (0 to 95)		
Week 12	30.0 (0 to 95)	22.0 (0 to 95)		

Notes:

[16] - At some visits, less than 31 patients were investigated.

[17] - At some visits, less than 27 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Further wound healing parameters: formation of wound exudation before IMP applications (Visit 3, Visit 10) and at each follow-up visit (Days 1-3 and 8, Weeks 2, 3, 4, 6, 6.2, 8, 10, and 12)

End point title	Further wound healing parameters: formation of wound exudation before IMP applications (Visit 3, Visit 10) and at each follow-up visit (Days 1-3 and 8, Weeks 2, 3, 4, 6, 6.2, 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:

From Day 0 (before allo-APZ2-CVU application) 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	31[18]	27[19]		
Units: Patients				
low at Day 0	14	11		
moderate at Day 0	15	14		
high at Day 0	2	2		
low at Week 6.1	14	11		
moderate at Week 6.1	8	8		
high at Week 6.1	0	0		
low at Week 12	18	16		
moderate at Week 12	10	10		
high at Week 12	1	0		

Notes:

[18] - At Weekt 6.1, 22 patients and at Week 12, 30 patients (including 1 with missing data) were analyzed.

[19] - At Weekt 6.1, 19 patients were analyzed; Week 12 includes 1 patient with missing data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in pain assessment as per numerical rating scale (NRS) at Days 1-3 and 8, Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, and 12

End point title	Change from Baseline in pain assessment as per numerical rating scale (NRS) at Days 1-3 and 8, Weeks 2, 3, 4, 6, 6.1, 6.2, 8, 10, and 12

End point description:

The pain perceived was rated on an NRS ranging from score 0 (no pain) to score 10 (strongest pain perceivable).
The median (full range) pain score at Baseline was 3.0 (0 - 9).

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	31[20]			
Units: score (change from Baseline)				
median (full range (min-max))				
Day 1 - 3	0.0 (-3 to 6)			
Day 8	0.0 (-3 to 6)			
Week 2	1.0 (-3 to 9)			
Week 3	1.0 (-2 to 9)			
Week 4	1.9 (-4 to 8)			
Week 6	1.0 (-3 to 9)			
Week 6.1	1.0 (-2 to 9)			
Week 6.2	1.0 (-2 to 9)			
Week 8	1.0 (-4 to 9)			
Week 10	1.0 (-6 to 9)			
Week 12	0.5 (-4 to 9)			

Notes:

[20] - At some visits, less than 31 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in assessment of Quality of Life (QoL) using the short form 36 (SF-36) questionnaire at Week 12/end of treatment

End point title	Change from Baseline in assessment of Quality of Life (QoL) using the short form 36 (SF-36) questionnaire at Week 12/end of treatment

End point description:

Quality of life was assessed using the short form 36 (SF-36) questionnaire. Changes from Baseline at Week 12/end of treatment 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: 45.00 (0.0 - 100.0)
Limitations in role activities due to problems in physical health: 25.00 (0.0 - 100.0)
Bodily pain: 51.00 (0.0 - 100.0)
General health: 52.0 (25.0 - 95.0)
Vitality (fatigue and energy): 45.00 (15.0 - 100.0)
Limitations in social functioning due to physical or emotional problems: 75.00 (25.0; 100.0)
Limitations in usual role due to emotional problems: 100.00 (0.0; 100.0)
Mental health (depressed or happy): 64.0 (36.0; 100.0)
Health transition: 3.00 (1.0 - 5.0)

End point type	Secondary

End point timeframe:

Day 0 to Week 12/end of treatment

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	31[21]			
Units: subscore (change from Baseline)				
median (full range (min-max))				
Limitations in physical functioning	2.50 (-30.0 to 35.0)			
Limit. in role act. due to probl. in phys. health	0.00 (-100.0 to 100.0)			
Bodily pain	0.00 (-31.0 to 51.0)			
General health	0.00 (-25.0 to 37.0)			
Vitality (fatigue and energy)	0.00 (-50.0 to 30.0)			
Limit. in soc. funct. due to phys. or emot. probl.	0.00 (-37.5 to 62.5)			
Limit. in usual role due to emot. probl.	0.00 (-100.0 to 100.0)			
Mental health (depressed or happy)	-4.00 (-40.0 to 28.0)			
Health transition	0.00 (-2.0 to 2.0)			

Notes:

[21] - At some visits, less than 31 patients were investigated.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in dermatology-specific quality of life based on the Dermatology Life Quality Index (DLQI) questionnaire at Weeks 4, 8 and 12 (summary score)

End point title	Change from Baseline in dermatology-specific quality of life based on the Dermatology Life Quality Index (DLQI) questionnaire at Weeks 4, 8 and 12 (summary score)

End point description:

At Baseline, the median (full range) dermatology-specific quality of life summary score was 9.5 (0 - 23).

End point type	Secondary

End point timeframe:

From Day 0 (Baseline) to Week 12

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	31[22]			
Units: Score (change from Baseline)				
median (full range (min-max))				
Week 4	-1.0 (-20 to 3)			
Week 8	-1.0 (-15 to 4)			
Week 12	-3.0 (-15 to 10)			

Notes:

[22] - At some visits, less than 31 patients were analyzed.

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 first allo-APZ2-CVU application (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	Treated patients

Reporting group description:

All patients who were treated with allo-APZ2-CVU at least once.

Serious adverse events	Treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 31 (22.58%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Malaise	Additional description: The event recovered with sequelae.		
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Skin ulcer	Additional description: One event resolved without sequelae, one event resolved with sequelae.		

subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal amyloidosis	Additional description: The event recovered with sequelae.		
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Foot deformity	Additional description: The event recovered with sequelae.		
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis	Additional description: The event recovered without sequelae.		
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection	Additional description: The event recovered without sequelae.		
subjects affected / exposed	1 / 31 (3.23%)		
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	Treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 31 (87.10%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
Limb injury subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
Skin pressure mark subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
Traumatic haematoma subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
Peripheral arterial occlusive disease subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
Cardiac disorders Cardiac failure subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
General disorders and administration site conditions Condition aggravated subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3		
Oedema peripheral subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Application site erosion subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
Malaise subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		

Immune system disorders			
Amyloidosis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	2		
Dermatitis allergic			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Dermatitis contact			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	5		
Dermatitis psoriasiform			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Eczema			

subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Hyperkeratosis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Intertrigo			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Mechanical urticaria			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Skin ulcer			
subjects affected / exposed	11 / 31 (35.48%)		
occurrences (all)	15		
Stasis dermatitis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Venous ulcer pain			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	7		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Osteoarthritis			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Wound infection			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Erysipelas			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Superinfection bacterial			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Wound infection bacterial			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2018	Main changes from protocol version 1.0 (03-Feb-2017) to 2.0 (21-Mar-2018) included: - Inclusion criterion #1 was changed from "Male or female patients aged 45 to 85 years" to "Male or female patients aged 35 to 85 years" - Inclusion criterion #6 was changed from "Body mass index (BMI) between 20 and 40 kg/m²" to "Body mass index (BMI) between 20 and 45 kg/m²" - Wound dressing treatment changed from "For further wound dressing Mepilex® or Biatain® plaster must be used until Week 12" to "For further wound dressing Mepilex® or Biatain® or Cutimed® Sorbact® plaster must be used until Week 12".
18 May 2018	Main changes from protocol version 2.0 (21-Mar-2018) to 3.0 (18-May-2018) included: - A second IMP application after 6 weeks, at Visit (V)10 - Section 9.4: Due to the inclusion of two new visits (Visit 10 and Visit 11) that were required for the second IMP application, Week 6.1 and Week 6.2 were supplemented as secondary efficacy endpoints for determining: o Percentage and absolute wound size reduction, o Proportion of patients achieving 30% wound closure, o Epithelialization, formation of granulation tissue and wound exudation, o Pain assessment, o Secondary safety endpoints for determining physical examination and vital signs at Week 6.1 and Week 12.
27 April 2020	Main changes from protocol version 3.0 (18-May-2018) to 4.0 (27-Apr-2020) included: - Due to the COVID-19 pandemic and the already reached target of responders (at least 14 of 18 patients with 30% wound size reduction), the trial was completed on 30-Jun-2020 - The possibility to treat non-target wounds was removed (Section 13.1).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported