



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 1×10^6 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 1×10^6 skin-derived ABCB5-positive mesenchymal stem cells/cm ² , 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 [cm ²] | | | | |
| 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 $\geq 50\%$ 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 probability 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 Week 6.1, 22 patients and at Week 12, 30 patients (including 1 with missing data) were analyzed.

[19] - At Week 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 | | | |

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

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

| | | | |
|---|------------------|--|--|
| 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 occurrences (all) | 1 / 31 (3.23%) 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: <ul style="list-style-type: none">- 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: <ul style="list-style-type: none">- 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:<ul style="list-style-type: none">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: <ul style="list-style-type: none">- 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