



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 eligibility 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 reported 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 probability 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

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) | 3 / 9 (33.33%) 4 | | |
| Influenza like illness subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | | |
| Gastrointestinal disorders | | | |
| Gastric haemorrhage subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | | |
| Hiatus hernia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | | |
| Pancreatitis subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 2 | | |
| Vomiting subjects affected / exposed occurrences (all) | 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) | 1 / 9 (11.11%) 2 | | |
| Decubitus ulcer subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | | |
| Ingrowing nail subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | | |
| Skin irritation subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | | |
| Skin ulcer | | | |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 08 June 2016 | <p>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:</p> <ul style="list-style-type: none">- 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 | <p>The main changes in the trial protocol Version 4.0 compared to Version 3.0 were:</p> <ul style="list-style-type: none">- 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 cm² 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: