



Clinical trial results:

Multinational, prospective, randomized, double-blind, placebo-controlled, parallel groups study to assess the efficacy and safety of Prostaglandin E1 in subjects with Critical Limb Ischemia (Fontaine Stage IV)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2005-001970-29 |
| Trial protocol | CZ |
| Global end of trial date | 30 July 2013 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 28 June 2016 |
| First version publication date | 27 March 2015 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | SP777 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00596752 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | UCB BIOSCIENCES GmbH |
| Sponsor organisation address | Alfred-Nobel-Straße 10, Monheim, Germany, 40789 |
| Public contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 1515, clinicaltrials@ucb.com |
| Scientific contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 1515, clinicaltrials@ucb.com |
| Sponsor organisation name | UCB BIOSCIENCES GmbH |
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| Scientific contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.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 | 23 October 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 July 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary objective of this study is to show a superior effect of Prostavasin® compared to placebo on the rate of complete healing of ischemic necroses and ulcerations at 12 weeks after the end of treatment as well as on the frequency and height of major amputations in subjects suffering from PAOD Fontaine stage IV at 24 weeks after the end of treatment.

Protection of trial subjects:

Subjects were hospitalized during the 4-week treatment phase. Standard analgesic treatment was provided to all subjects. Antibiotic treatment was provided if necessary.

Background therapy:

All subjects received in-house standard analgesic treatment and daily wound treatment.

Evidence for comparator:

Not applicable

| | |
|---|---------------|
| Actual start date of recruitment | 26 March 2004 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Mexico: 5 |
| Country: Number of subjects enrolled | Poland: 90 |
| Country: Number of subjects enrolled | Russian Federation: 406 |
| Country: Number of subjects enrolled | Ukraine: 335 |
| Worldwide total number of subjects | 840 |
| EEA total number of subjects | 94 |

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) | 323 |
| From 65 to 84 years | 505 |
| 85 years and over | 12 |

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in March 2004 in order to end up with 840 enrolled subjects. The study was conducted using a two-stage group sequential adaptive design with possible sample size adjustment after the planned interim analysis, which was performed after stage 1. After the interim analysis subjects were included in stage 2.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Set (RS). RS consists of all subjects randomized into the study who have completed the study or terminated prematurely.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Alprostadil |

Arm description:

Prostavasin® 40 µg will be infused intravenously twice daily over 2 hours in 50 to 150 ml isotonic sodium chloride solution during a Treatment Phase of 4 weeks.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Alprostadil |
| Investigational medicinal product code | |
| Other name | Prostavasin |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Prostavasin® 40 µg will be infused intravenously twice daily over 2 hours in 50 to 150 ml isotonic sodium chloride solution during a Treatment Phase of 4 weeks.

- Active Substance: Prostaglandin E1
- Concentration: 40 µg b.d.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo will be infused intravenously twice daily over 2 hours in 50 to 150 ml isotonic sodium chloride solution during a Treatment Phase of 4 weeks.

| | |
|--|-----------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo will be infused intravenously twice daily over 2 hours in 50 to 150 ml isotonic sodium chloride solution during a Treatment Phase of 4 weeks.

- Active Substance: Lactose
- Concentration: 40 µg b.d.

| Number of subjects in period 1 | Alprostadil | Placebo |
|--|-------------|---------|
| Started | 415 | 425 |
| Randomized and Treated | 415 | 424 |
| Completed | 289 | 282 |
| Not completed | 126 | 143 |
| Adverse event, serious fatal | 13 | 11 |
| Unsatisfactory Compliance | 9 | 6 |
| Consent withdrawn by subject | 12 | 9 |
| SAE, fatal + SAE, non-fatal | 2 | 2 |
| SAE, fatal + AE, non-serious non-fatal | - | 1 |
| AE, non-serious non-fatal | 3 | 3 |
| Other Reason | 44 | 49 |
| Lost to follow-up | 22 | 38 |
| SAE, non-fatal | 16 | 17 |
| Protocol deviation | 1 | - |
| Lack of efficacy | 4 | 7 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Alprostadil |
|-----------------------|-------------|

Reporting group description:

Prostavasin® 40 µg will be infused intravenously twice daily over 2 hours in 50 to 150 ml isotonic sodium chloride solution during a Treatment Phase of 4 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo will be infused intravenously twice daily over 2 hours in 50 to 150 ml isotonic sodium chloride solution during a Treatment Phase of 4 weeks.

| Reporting group values | Alprostadil | Placebo | Total |
|---|-------------|---------|-------|
| Number of subjects | 415 | 425 | 840 |
| 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) | 153 | 170 | 323 |
| From 65-84 years | 257 | 248 | 505 |
| 85 years and over | 5 | 7 | 12 |
| Age continuous Units: years | | | |
| arithmetic mean | 66.8 | 66.4 | |
| standard deviation | ± 8.5 | ± 9.3 | - |
| Gender categorical Units: Subjects | | | |
| Female | 122 | 119 | 241 |
| Male | 293 | 306 | 599 |
| Weight Units: kilogram(s) | | | |
| arithmetic mean | 75.4 | 76.5 | |
| standard deviation | ± 11.9 | ± 12.6 | - |

End points

End points reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Alprostadil |
|-----------------------|-------------|

Reporting group description:

Prostavasin® 40 µg will be infused intravenously twice daily over 2 hours in 50 to 150 ml isotonic sodium chloride solution during a Treatment Phase of 4 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo will be infused intravenously twice daily over 2 hours in 50 to 150 ml isotonic sodium chloride solution during a Treatment Phase of 4 weeks.

| | |
|----------------------------|---|
| Subject analysis set title | Safety Set (Alprostadil treated subjects) |
|----------------------------|---|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Safety Set includes all randomized subjects who received at least one dose of trial medication. Subjects were analyzed according to the actual treatment received. 4 PBO subjects were treated with Alprostadil, 3 Alprostadil subjects were treated with PBO.1 PBO subject withdrew prior to start of study treatment.

| | |
|----------------------------|---------------------------------------|
| Subject analysis set title | Safety Set (Placebo treated subjects) |
|----------------------------|---------------------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Safety Set includes all randomized subjects who received at least one dose of trial medication. Subjects were analyzed according to the actual treatment received. 4 PBO subjects were treated with Alprostadil, 3 Alprostadil subjects were treated with PBO.1 PBO subject withdrew prior to start of study treatment.

| | |
|----------------------------|--|
| Subject analysis set title | Full Analysis Set (Alprostadil treated subjects) |
|----------------------------|--|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Full Analysis Set (FAS) consists of all randomized subjects who received at least one dose of trial medication and who provide valid data to assess at least one of the primary efficacy endpoints.

| | |
|----------------------------|--|
| Subject analysis set title | Full Analysis Set (Placebo treated subjects) |
|----------------------------|--|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Full Analysis Set (FAS) consists of all randomized subjects who received at least one dose of trial medication and who provide valid data to assess at least one of the primary efficacy endpoints.

Primary: Complete Healing of Ischemic Necroses and Ulcerations at 12 Weeks After the End of Study Drug Treatment

| | |
|-----------------|---|
| End point title | Complete Healing of Ischemic Necroses and Ulcerations at 12 Weeks After the End of Study Drug Treatment |
|-----------------|---|

End point description:

The assessment of ulcer area was collected per lesion with up to 2 lesions per subject (both legs could be affected). In the analysis a subject is only considered completely healed at a time point, if all ischemic lesions are reported as completely healed at that time point.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At 12 weeks after the end of study drug treatment

| End point values | Full Analysis Set (Alprostadil treated subjects) | Full Analysis Set (Placebo treated subjects) | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[1] | 424 ^[2] | | |
| Units: participants | | | | |
| Stage 1 (n=253, n=251) | 49 | 43 | | |
| Stage 2 (n=161, n=173) | 27 | 30 | | |

Notes:

[1] - Full Analysis Set (FAS) with Last Observation Carried Forward (LOCF) in case of missing values.

[2] - Full Analysis Set (FAS) with Last Observation Carried Forward (LOCF) in case of missing values.

Statistical analyses

| Statistical analysis title | Statistical analysis of stage 1 |
|----------------------------|---------------------------------|
|----------------------------|---------------------------------|

Statistical analysis description:

Primary goal was to test the following null hypothesis:

H01: $n_{\text{healingPGE1}} \leq n_{\text{healingPlacebo}}$, with n_{healing} =proportion of subjects with complete ulcer healing. The planned information rate for stage 1 of the two-stage group sequential test design with an overall one-sided comparison-wise $\alpha=0.0125$ for this co-primary endpoint is given by 0.83.

| | |
|---|---|
| Comparison groups | Full Analysis Set (Placebo treated subjects) v Full Analysis Set (Alprostadil treated subjects) |
| Number of subjects included in analysis | 838 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.2587 ^[4] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[3] - The 2 primary endpoints were tested at one-sided 0.0125 each so that the overall type I error rate of 0.025 was controlled in a strong sense.

[4] - For confirmatory hypothesis testing the p-values of the normal approximation test for comparing two rates was used as input for the weighted inverse normal method. The 1-sided boundary p-value for stage 1 is given by $p_1=0.00587$.

| Statistical analysis title | Statistical analysis of stage 1 and 2 combined |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Primary goal was to test the following null hypothesis:

H01: $n_{\text{healingPGE1}} \leq n_{\text{healingPlacebo}}$, with n_{healing} =proportion of subjects with complete ulcer healing.

| | |
|---|---|
| Comparison groups | Full Analysis Set (Alprostadil treated subjects) v Full Analysis Set (Placebo treated subjects) |
| Number of subjects included in analysis | 838 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.3463 ^[6] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[5] - The 2 primary endpoints were tested at one-sided 0.0125 each so that the overall type I error rate of 0.025 was controlled in a strong sense.

[6] - For confirmatory hypothesis testing the p-values of the normal approximation test for comparing two rates was used as input for the weighted inverse normal method. The 1-sided boundary p-value for stage 1 and 2 combined is given by $p_2=0.01085$.

Primary: Occurrence of Major Amputations at 24 Weeks After the End of Study Drug Treatment

| | |
|-----------------|---|
| End point title | Occurrence of Major Amputations at 24 Weeks After the End of Study Drug Treatment |
|-----------------|---|

End point description:

Assessment of amputations was collected per leg affected by a lesion with up to 2 lesions per subject. Amputations were regarded as major if they were performed at the ankle joint level or above. Amputations of toes or part of the foot leaving a stump thereon the subject can walk were regarded as minor. An affected leg is defined as a leg with at least 1 lesion on Study Day -6 to -2 and only amputations of affected legs are considered in the efficacy analysis of amputations. A subject is counted as major/minor amputated, if at least 1 affected leg was major/minor amputated.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At 24 weeks after the end of study drug treatment

| End point values | Full Analysis Set (Alprostadil treated subjects) | Full Analysis Set (Placebo treated subjects) | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[7] | 424 ^[8] | | |
| Units: participants | | | | |
| Stage 1 (n=253, n=251) | 32 | 49 | | |
| Stage 2 (n=161, n=173) | 20 | 13 | | |

Notes:

[7] - Full Analysis Set (FAS) with Last Observation Carried Forward (LOCF) in case of missing values.

[8] - Full Analysis Set (FAS) with Last Observation Carried Forward (LOCF) in case of missing values.

Statistical analyses

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Statistical analysis of stage 1 |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Primary goal was to test the following null hypothesis:

H02: $\pi_{\text{ampPGE1}} \geq \pi_{\text{ampPlacebo}}$, with π_{amp} =proportion of subjects with major amputations.

The planned information rate for stage 1 of the two-stage group sequential test design with an overall one-sided comparison-wise $\alpha=0.0125$ for this co-primary endpoint is given by 0.83.

| | |
|---|---|
| Comparison groups | Full Analysis Set (Alprostadil treated subjects) v Full Analysis Set (Placebo treated subjects) |
| Number of subjects included in analysis | 838 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[9] |
| P-value | = 0.0173 ^[10] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[9] - The 2 primary endpoints were tested at one-sided 0.0125 each so that the overall type I error rate of 0.025 was controlled in a strong sense.

[10] - For confirmatory hypothesis testing the p-values of the normal approximation test for comparing two rates was used as input for the weighted inverse normal method. The 1-sided boundary p-value for stage 1 is given by $p_1=0.00587$.

| | |
|-----------------------------------|--|
| Statistical analysis title | Statistical analysis of stage 1 and 2 combined |
|-----------------------------------|--|

Statistical analysis description:

Primary goal was to test the following null hypothesis:

H02: $\pi_{\text{ampPGE1}} \geq \pi_{\text{ampPlacebo}}$, with π_{amp} =proportion of subjects with major amputations.

| | |
|-------------------|---|
| Comparison groups | Full Analysis Set (Alprostadil treated subjects) v Full Analysis Set (Placebo treated subjects) |
|-------------------|---|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 838 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[11] |
| P-value | = 0.1154 ^[12] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[11] - The 2 primary endpoints were tested at one-sided 0.0125 each so that the overall type I error rate of 0.025 was controlled in a strong sense.

[12] - For confirmatory hypothesis testing the p-values of the normal approximation test for comparing two rates was used as input for the weighted inverse normal method. The 1-sided boundary p-value for stage 1 and 2 combined is given by $p_2=0.01085$.

Secondary: Complete Healing of Ischemic Necroses and Ulcerations at 24 Weeks After the End of Study Drug Treatment

| | |
|-----------------|---|
| End point title | Complete Healing of Ischemic Necroses and Ulcerations at 24 Weeks After the End of Study Drug Treatment |
|-----------------|---|

End point description:

The assessment of ulcer area was collected per lesion with up to 2 lesions per subject (both legs could be affected). In the analysis a subject is only considered completely healed at a time point, if all ischemic lesions are reported as completely healed at that time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 24 weeks after the end of study drug treatment

| End point values | Full Analysis Set (Alprostadi treated subjects) | Full Analysis Set (Placebo treated subjects) | | |
|-----------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 289 ^[13] | 279 ^[14] | | |
| Units: participants | 108 | 103 | | |

Notes:

[13] - Of the 414 subjects in the Full Analysis Set, 289 are included in the analysis of this endpoint.

[14] - Of the 424 subjects in the Full Analysis Set, 279 are included in the analysis of this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Intensity of Rest Pain Induced by Ischemic Lesions at 24 Weeks After the End of Study Drug Treatment

| | |
|-----------------|--|
| End point title | Intensity of Rest Pain Induced by Ischemic Lesions at 24 Weeks After the End of Study Drug Treatment |
|-----------------|--|

End point description:

Visit values of intensity of rest pain from a visual analogue scale, ranging from 0 mm (no pain) to 100 mm (maximum conceivable pain), had to be reported in the case of presence of rest pain only. If the leading question in regard to the presence of rest pain is answered with "No" and no visit value is specified, the visit value will be set to 0 for the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 24 weeks after the end of study drug treatment

| End point values | Full Analysis Set (Alprostadil treated subjects) | Full Analysis Set (Placebo treated subjects) | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 ^[15] | 424 ^[16] | | |
| Units: millimeter(s) | | | | |
| arithmetic mean (standard deviation) | 17.57 (± 25.33) | 16.38 (± 25.08) | | |

Notes:

[15] - Full Analysis Set (FAS) with Last Observation Carried Forward (LOCF) in case of missing values.

[16] - Full Analysis Set (FAS) with Last Observation Carried Forward (LOCF) in case of missing values.

Statistical analyses

No statistical analyses for this end point

Secondary: Increase/Decrease in Ulcer Area of ≥ 50 % at 24 Weeks After the End of Study Drug Treatment

| | |
|-----------------|---|
| End point title | Increase/Decrease in Ulcer Area of ≥ 50 % at 24 Weeks After the End of Study Drug Treatment |
|-----------------|---|

End point description:

In case of two ulcers the worse ulcer status is analyzed. The categories of investigator assessment are: complete healing, decrease by ≥ 50 %, unchanged, increase by ≥ 50 %.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 24 weeks after the end of study drug treatment

| End point values | Full Analysis Set (Alprostadil treated subjects) | Full Analysis Set (Placebo treated subjects) | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 233 ^[17] | 232 ^[18] | | |
| Units: participants | | | | |
| Complete healing | 101 | 98 | | |
| Decrease by ≥ 50 % | 57 | 56 | | |
| Remains unchanged | 45 | 48 | | |
| Increase by ≥ 50 % | 30 | 30 | | |

Notes:

[17] - Of the 414 subjects in the Full Analysis Set, 233 are included in the analysis of this endpoint.

[18] - Of the 424 subjects in the Full Analysis Set, 232 are included in the analysis of this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption and Type of Analgesic Medication During the Course of the

Study (up to 196 Days)

| | |
|---|--|
| End point title | Consumption and Type of Analgesic Medication During the Course of the Study (up to 196 Days) |
| End point description: The number of subjects who used analgesics are summarized for different time points/intervals during the course of the study. | |
| End point type | Secondary |
| End point timeframe: During the course of the study (up to 196 days) | |

| End point values | Full Analysis Set (Alprostadil treated subjects) | Full Analysis Set (Placebo treated subjects) | | |
|---|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 414 | 424 | | |
| Units: participants | | | | |
| Prior to treatment (n=414, n=424) | 300 | 318 | | |
| Concomitant, Study Day 1 (n=414, n=424) | 292 | 314 | | |
| Concomitant, Study Day 2 (n=414, n=424) | 295 | 313 | | |
| Concomitant, Study Day 3 (n=413, n=424) | 295 | 317 | | |
| Concomitant, Study Day 4 (n=412, n=423) | 292 | 316 | | |
| Concomitant, Study Day 5 (n=411, n=423) | 294 | 311 | | |
| Concomitant, Study Day 6 (n=411, n=423) | 290 | 312 | | |
| Concomitant, Study Day 7 (n=409, n=422) | 290 | 306 | | |
| Concomitant, Week 2 (n=409, n=422) | 292 | 308 | | |
| Concomitant, Week 3 (n=399, n=416) | 259 | 284 | | |
| Concomitant, Week 4 (n=393, n=404) | 238 | 257 | | |
| Post treatment, Study Days 29-42 (n=348, n=354) | 170 | 191 | | |
| Post treatment, Study Days 43-56 (n=361, n=370) | 164 | 173 | | |
| Post treatment, Study Days 57-70 (n=361, n=346) | 155 | 155 | | |
| Post treatment, Study Days 71-84 (n=352, n=344) | 146 | 148 | | |
| Post treatment, Study Days 85-98 (n=341, n=339) | 143 | 140 | | |
| Post treatment, Study Days 99-112 (n=321, n=318) | 132 | 127 | | |
| Post treatment, Study Days 113-140 (n=309, n=301) | 122 | 117 | | |
| Post treatment, Study Days 141-168 (n=306, n=304) | 118 | 109 | | |
| Post treatment, Study Days 169-196 (n=272, n=271) | 98 | 90 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic Pressure at Ankle Level at 24 Weeks After the End of Study Drug Treatment

| | |
|-----------------|--|
| End point title | Systolic Pressure at Ankle Level at 24 Weeks After the End of Study Drug Treatment |
|-----------------|--|

End point description:

Systolic pressure at ankle level was measured at the Arteria tibialis posterior and the Arteria dorsalis pedis. Two individual series of measurements of arterial pressures per subject across the assessed visits were selected for the analysis. For the first analysis (worst change analysis) the series of measurements in the one artery which has the worst change from Baseline at the final measurement was used. For the second analysis (worst value analysis) the series of measurements which has the worst final post-Baseline measurement was used. The series relevant for the analyses was selected from the series for the affected leg or legs only. The selection is 1 out of up to 4 series available per subject. Series without Baseline value and series with at least 1 measurement of more than 150 mmHg were excluded from the selection process due to the suspicion of media sclerosis of the lower limb artery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 24 weeks after the end of study drug treatment

| End point values | Full Analysis Set (Alprostadil treated subjects) | Full Analysis Set (Placebo treated subjects) | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 383 ^[19] | 394 ^[20] | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Worst change analysis | 42.83 (± 30.16) | 39.47 (± 28.32) | | |
| Worst value analysis | 39.39 (± 29.92) | 36.45 (± 27.19) | | |

Notes:

[19] - Full Analysis Set (FAS) with Last Observation Carried Forward (LOCF) in case of missing values.

[20] - Full Analysis Set (FAS) with Last Observation Carried Forward (LOCF) in case of missing values.

Statistical analyses

No statistical analyses for this end point

Secondary: Minor Amputations at 24 Weeks After the End of Study Drug Treatment

| | |
|-----------------|---|
| End point title | Minor Amputations at 24 Weeks After the End of Study Drug Treatment |
|-----------------|---|

End point description:

Assessment of amputations was collected per leg affected by a lesion with up to 2 lesions per subject.

Amputations were regarded as major if they were performed at the ankle joint level or above. Amputations of toes or part of the foot leaving a stump thereon the subject can walk were regarded as minor. An affected leg is defined as a leg with at least 1 lesion on Study Day -6 to -2 and only amputations of affected legs are considered in the efficacy analysis of amputations. A subject is counted as major/minor amputated, if at least 1 affected leg was major/minor amputated. The number of subjects with minor amputation prior to or at 24 weeks after the end of study drug treatment is presented below.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| At 24 weeks after the end of study drug treatment | |

| End point values | Full Analysis Set (Alprostadil treated subjects) | Full Analysis Set (Placebo treated subjects) | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 316 ^[21] | 297 ^[22] | | |
| Units: participants | 65 | 40 | | |

Notes:

[21] - Of the 414 subjects in the Full Analysis Set, 316 are included in the analysis of this endpoint.

[22] - Of the 424 subjects in the Full Analysis Set, 297 are included in the analysis of this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Revascularization Procedures at 24 Weeks After the End of Study Drug Treatment

| | |
|-----------------|--|
| End point title | Revascularization Procedures at 24 Weeks After the End of Study Drug Treatment |
|-----------------|--|

End point description:

The number of subjects with revascularization prior to or at 24 weeks after the end of study drug treatment is presented below.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| At 24 weeks after the end of study drug treatment | |

| End point values | Full Analysis Set (Alprostadil treated subjects) | Full Analysis Set (Placebo treated subjects) | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 294 ^[23] | 283 ^[24] | | |
| Units: participants | 6 | 7 | | |

Notes:

[23] - Of the 414 subjects in the Full Analysis Set, 294 are included in the analysis of this endpoint.

[24] - Of the 424 subjects in the Full Analysis Set, 283 are included in the analysis of this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: All-cause Mortality During the Course of the Study (up to 196 Days)

| | |
|-----------------|---|
| End point title | All-cause Mortality During the Course of the Study (up to 196 Days) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During the course of the study (up to 196 days)

| End point values | Safety Set (Alprostadi treated subjects) | Safety Set (Placebo treated subjects) | | |
|-----------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 416 | 423 | | |
| Units: participants | 20 | 15 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cardiovascular Mortality During the Course of the Study (up to 196 Days)

| | |
|-----------------|--|
| End point title | Cardiovascular Mortality During the Course of the Study (up to 196 Days) |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During the course of the study (up to 196 days)

| End point values | Safety Set (Alprostadi treated subjects) | Safety Set (Placebo treated subjects) | | |
|-----------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 416 | 423 | | |
| Units: participants | 11 | 14 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cardiovascular Morbidity During the Course of the Study (up to 196 Days)

| | |
|-----------------|--|
| End point title | Cardiovascular Morbidity During the Course of the Study (up to 196 Days) |
|-----------------|--|

End point description:

Cardiovascular morbidity is presented as number of subjects with myocardial infarction and/or stroke during the course of the study.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During the course of the study (up to 196 days)

| End point values | Safety Set (Alprostadiol treated subjects) | Safety Set (Placebo treated subjects) | | |
|-----------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 416 | 423 | | |
| Units: participants | | | | |
| Myocardial infarctions | 5 | 6 | | |
| Strokes | 3 | 3 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected during the course of the study from Study Day 0 up to Study Day 196.

Adverse event reporting additional description:

Adverse Events refer to the Safety Set. Safety Set consists of all subjects who have completed the study or terminated prematurely and who have received at least 1 dose of study medication.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Alprostadil |
|-----------------------|-------------|

Reporting group description:

Prostavasin® 40 µg will be infused intravenously twice daily over 2 hours in 50 to 150 ml isotonic sodium chloride solution during a Treatment Phase of 4 weeks.

- Active Substance: Prostaglandin E1
- Pharmaceutical Form: solution for infusion
- Concentration: 40 µg b.d.
- Route of Administration: intravenous infusion

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo will be infused intravenously twice daily over 2 hours in 50 to 150 ml isotonic sodium chloride solution during a Treatment Phase of 4 weeks.

- Active Substance: Lactose
- Pharmaceutical Form: solution for infusion
- Concentration: 40 µg b.d.
- Route of Administration: intravenous infusion

| Serious adverse events | Alprostadil | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 87 / 416 (20.91%) | 62 / 423 (14.66%) | |
| number of deaths (all causes) | 20 | 15 | |
| number of deaths resulting from adverse events | 1 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hypopharyngeal cancer stage III | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|-----------------|--|
| Vascular disorders | | | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 11 / 416 (2.64%) | 9 / 423 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extremity necrosis | | | |
| subjects affected / exposed | 10 / 416 (2.40%) | 9 / 423 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrosis ischaemic | | | |
| subjects affected / exposed | 6 / 416 (1.44%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial thrombosis limb | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemia | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis limb | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Ischaemic ulcer | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrosis | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Impaired healing | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 3 / 423 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound necrosis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hydrothorax | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary artery thrombosis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary embolism | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Limb traumatic amputation | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shunt thrombosis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaw fracture | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 3 / 423 (0.71%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 4 / 423 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 4 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 3 / 423 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 2 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute right ventricular failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nodal arrhythmia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 2 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic coma | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular insufficiency | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesenteric artery embolism | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin ulcer | | | |
| subjects affected / exposed | 4 / 416 (0.96%) | 5 / 423 (1.18%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dry gangrene | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin necrosis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Tenosynovitis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Gangrene | | | |
| subjects affected / exposed | 14 / 416 (3.37%) | 11 / 423 (2.60%) | |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 3 / 423 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Infected skin ulcer | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Purulent discharge | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Osteomyelitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lobar pneumonia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Alprostadil | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 61 / 416 (14.66%) | 62 / 423 (14.66%) | |
| Vascular disorders | | | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 40 / 416 (9.62%) | 41 / 423 (9.69%) | |
| occurrences (all) | 41 | 45 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin ulcer | | | |
| subjects affected / exposed | 24 / 416 (5.77%) | 26 / 423 (6.15%) | |
| occurrences (all) | 29 | 28 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 10 February 2004 | Protocol Amendment 1 introduced the following changes: <ul style="list-style-type: none">- The angiography to be performed as a pre-requisite for inclusion was extended to the calf to meet more adequately the requirements for documentation of PAOD. Inclusion Criterion 5 was updated accordingly.- Monitor checks of the data in the electronic case report form (eCRF) were performed twice a week instead of daily for feasibility reasons. |
| 23 April 2004 | Protocol Amendment 2 introduced the following changes: <ul style="list-style-type: none">- The volume of the isotonic sodium chloride solution used for alprostadil (Prostava[®]) 40 µg and Placebo infusion was increased from 50 mL to 150 mL to allow for better control when using drip infusions instead of infusion pumps.- Change in responsibility for the position of Drug Safety Officer.- Reports about immediately reportable adverse events (AEs) were to be transmitted electronically by completion of the appropriate pages in the eCRF instead by facsimile to allow for storage of all study information in a central database located at the CRO. The transmission of information already contained in the eCRF/database became unnecessary. |
| 03 December 2004 | Protocol Amendment 4 introduced the following changes: <ul style="list-style-type: none">- The rate of subjects with an increase or decrease in the ulcer area of $\geq 50\%$ became an additional secondary efficacy criterion. This criterion was added to evaluate treatment effects below the level of complete healing as well as possible increases in ulcer area more exactly.- Picture(s) of the ulcer(s) together with a calibrated ruler were taken to allow assessments of the ulcer area.- Subjects in the position to be primarily revascularized but refusing surgery were allowed to be included in the study.- Subjects with a major amputation on the affected extremity were excluded from the study, as major amputations could have interfered with ulcer healing.- In order to standardize the evaluation of pictures from angiography and skin lesions, a committee of medical experts was appointed to decide in compliance with the Clinical Trial Protocol whether a subject was allowed to be included in the study. |
| 05 July 2006 | Protocol Amendment 5 introduced the following changes: <ul style="list-style-type: none">- Concomitant use of vasoactive medication (eg, naftidrofuryl, pentoxifylline, buflomedil, cilostazol) or other prostaglandins became prohibited during the entire study participation of each subject, as these drugs could have interfered with the study medication.- Subjects had to be withdrawn from the study if treatment with vasoactive medication or other prostaglandins was deemed necessary by the investigator.- Subjects had to be withdrawn from the study if the ulcer(s) under investigation was/were removed by a major amputation.- Results of investigations performed within the last 7 days prior to the first day of the Run-In Phase were allowed to be used as Baseline values if deemed appropriate by the investigator.- Changes in responsibilities for the positions of Head of Medical Experts and Medical Director.- The study was extended to the Czech Republic to increase the recruitment rate.- A new section specifying the reference documents for the sponsor's assessment of expectedness was inserted. This section was later revised as per Protocol Amendment 8. |

| | |
|----------------|---|
| 18 August 2006 | <p>Protocol Amendment 6 provided the following definition for Adverse Events (AEs) representing deterioration of PAOD:</p> <ul style="list-style-type: none"> - AEs representing a deterioration of PAOD such as the increase in lesion area (ulcer/necrosis), number of lesion (ulcer/necrosis) or rest pain induced by ischemic lesions were defined as AEs of disease origin. These AEs were not to be assessed as serious adverse events (SAEs) even if they led to amputation and therefore required inpatient hospitalization, led to prolongation of existing inpatient hospitalization or resulted in persistent or significant disability/incapacity. <p>The investigator had to report the AEs of disease origin within 24 hours to the responsible drug safety unit. The responsible drug safety unit reviewed the events and, in case a specific event did not fulfill the above mentioned criteria for AE of disease origin, the event was reported to the sponsor. The sponsor decided whether the AEs had to be revised into SAEs.</p> |
| 18 June 2009 | <p>Protocol Amendment 8 introduced the following changes:</p> <ul style="list-style-type: none"> - Change in responsibility for the position of the Clinical Lead. - The email-addresses of UCB/Schwarz Pharma Deutschland GmbH personnel changed from XXX@ucb-group.com to XXX@ucb.com. - It was defined that the sponsor's assessment of expectedness of AEs was performed according to the information given in the Company Core Data Sheet for subjects in all countries instead of according to the information given in the international core data sheet/core summary of product characteristics for subjects in Russia, Ukraine, Poland and Czech Republic as well as according to the German "Fachinformation" for subjects in Germany. - According to the recommendation of the independent data monitoring committee (IDMC), the study was continued and the number of subjects to be included in the second stage was increased from 50 subjects per Treatment group to 170 subjects per treatment group. It was added that the IDMC did not raise any objections against the continuation of the study or the increase in the sample size. |

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.

Not applicable

Notes: