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
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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: ɳhealingPGE1≤ ɳhealingPlacebo, with ɳhealing=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 ɑ=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 p1=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: ɳhealingPGE1≤ ɳhealingPlacebo, with ɳhealing=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 p2=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: πampPGE1≥ πampPlacebo, with πamp=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 α=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 p1=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: πampPGE1≥ πampPlacebo, with πamp=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 p2=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 (Alprostadil 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 (Alprostadil 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 (Alprostadil 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 (Alprostadil 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: - 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: - The volume of the isotonic sodium chloride solution used for alprostadil (Prostavasin®) 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: - The rate of subjects with an increase or decrease in the ulcer area of ≥ 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: - 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	Protocol Amendment 6 provided the following definition for Adverse Events (AEs) representing deterioration of PAOD: - 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. 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.
18 June 2009	Protocol Amendment 8 introduced the following changes: - 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: