Clinical trial results:
A Phase 3 Randomized Safety and Efficacy Trial of HP802-247 in the Treatment of Chronic Venous Leg Ulcers (EU)

Summary

EudraCT number	2012-003286-18
Trial protocol	HU PL DE BE CZ
Global end of trial date	27 November 2014

Results information

Result version number	v1 (current)
This version publication date	06 March 2016
First version publication date	06 March 2016

Trial information

Trial identification

Sponsor protocol code	802-247-09-032

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01853384
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Smith & Nephew, Inc.
Sponsor organisation address	3909 Hulen Street, Fort Worth, Texas, United States, 76107
Public contact	Jaime Dickerson, PhD VP Global Medical and Clinical Affairs 3909 Hulen St Fort Worth, TX 76107 , Smith & Nephew, Inc., +1 8173023914,
Scientific contact	Jaime Dickerson, PhD VP Global Medical and Clinical Affairs 3909 Hulen St Fort Worth, TX 76107 , Smith & Nephew, Inc., +1 8173023914,

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	09 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 November 2014
Global end of trial reached?	Yes
Global end of trial date	27 November 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Compare HP802-247 plus compression therapy against Control (Vehicle) plus compression therapy for the proportion of subjects with complete wound closure of venous leg ulcers over the 12-week treatment period from baseline.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. The rationale of the study, procedural details, and investigational goals were explained to each patient, along with potential risks and benefits. Each patient was assured of his/her right to withdraw from the study at any time. Prior to the initiation of any study procedures all subjects were provided the opportunity to ask questions. Subjects, or their legal representatives, read, signed, and dated the IEC-approved consent form before taking part in any study activity.

Background therapy:

Four-layer compression therapy was used across all arms in the trial

Evidence for comparator:

-

Actual start date of recruitment	10 January 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 108
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czech Republic: 38
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Hungary: 52
Worldwide total number of subjects	252
EEA total number of subjects	252

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)	103
From 65 to 84 years	130
85 years and over	19

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A 2-weeks Screening and Run-in period was employed. Eligibility criteria were reviewed and qualified subjects providing informed consent began Screening Run-in Visit 1. Subjects were screened again for eligibility at the end of the Run-in period (Run-in Visit 3) against an additional set of exclusion criteria.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Blinding implementation details:

An IWRS was used for randomization. The IWRS used computer generated random sequences which took into account stratification by wound area and wound duration.

Arms

Are arms mutually exclusive?	Yes
Arm title	HP802-247

Arm description:

Treatment group who received HP802-247 formulation

Arm type	Experimental
Investigational medicinal product name	HP802-247
Investigational medicinal product code	HP802-247
Other name	
Pharmaceutical forms	Cutaneous spray
Routes of administration	Topical use

Dosage and administration details:

HP802-247 formulation consists of two separate components, a fibrinogen solution and a cell suspension. A single dose is created when combined on the wound surface. 260 µL (130 µL, one spray, of each solution) containing 0.5x106 cells/mL is administered every 14 days and Vehicle on alternate weeks.

Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous spray
Routes of administration	Topical use

Dosage and administration details:

The vehicle formulation (260 µL (130 µL, one spray, of each solution) containing fibrinogen solution and thrombin solution without cells) is administered every 14 days, on the alternate weeks.

Arm title	Vehicle

Arm description:

Treatment group who received vehicle formulation only

Arm type	Control

Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous spray
Routes of administration	Topical use

Dosage and administration details:

The vehicle formulation (260 µL (130 µL, one spray, of each solution) containing fibrinogen solution and thrombin solution without cells) is administered every 7 days

Number of subjects in period 1	HP802-247	Vehicle
Started	131	121
Completed	69	75
Not completed	62	46
Consent withdrawn by subject	5	3
Other	3	3
Sponsor's request - Early Termination	47	34
Adverse Events	6	5
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	HP802-247
Reporting group description:	
Treatment group who received HP802-247 formulation	
Reporting group title	Vehicle
Reporting group description:	
Treatment group who received vehicle formulation only	

Reporting group values	HP802-247	Vehicle	Total
Number of subjects	131	121	252
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)	58	45	103
From 65-84 years	65	65	130
85 years and over	8	11	19
Age continuous Units: years			
arithmetic mean	65.6	68.1	
standard deviation	± 13.1	± 12.7	-
Gender categorical Units: Subjects			
Female	76	63	139
Male	55	58	113

End points

End points reporting groups	
Reporting group title	HP802-247
Reporting group description:	
Treatment group who received HP802-247 formulation	
Reporting group title	Vehicle
Reporting group description:	
Treatment group who received vehicle formulation only	

Primary: The average proportion (%) of wounds closed from baseline to completion of the 12-week treatment period	
End point title	The average proportion (%) of wounds closed from baseline to completion of the 12-week treatment period
End point description:	
End point type	Primary
End point timeframe:	
From Baseline to week 12	

End point values	HP802-247	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	121		
Units: percentage of wound				
number (not applicable)				
Wound closed	46.6	50.4		
Wound not closed	53.4	49.6		

Statistical analyses

Statistical analysis title	Average proportion of closed wounds
Statistical analysis description:	
Compare the Treatment Groups for the Average Proportion of Subjects With complete Wound Closure over the 12-week Treatment Period from Baseline	
Comparison groups	HP802-247 v Vehicle
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5348
Method	Cochran-Mantel-Haenszel

Secondary: Time in days to complete wound closure from baseline over the 12 double-blind treatment weeks

End point title	Time in days to complete wound closure from baseline over the 12 double-blind treatment weeks

End point description:

End point type	Secondary

End point timeframe:

From Baseline to wound closure

End point values	HP802-247	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	121		
Units: days				
arithmetic mean (standard deviation)	50.3 (± 27.6)	52.6 (± 27.4)		

Statistical analyses

Statistical analysis title	Efficacy Comparison, based on Median Time (days)

Statistical analysis description:

Compare the Efficacy of the treatment groups in achieving complete wound closure, based on median time (days) to closure over the 12-week treatment period from baseline

Comparison groups	HP802-247 v Vehicle
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.9456
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.988
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.692
upper limit	1.41

Notes:

[1] - Cox Regression Model

Statistical analysis title	Efficacy Comparison, based on Median Time (days)

Statistical analysis description:

Compare the efficacy of the treatment groups in achieving complete wound closure, based on median time (days) to closure over the 12-week treatment period from baseline

Comparison groups	HP802-247 v Vehicle

Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	> 0.5
Method	Logrank

Notes:

[2] - Kaplan-Meier Survival

Secondary: Proportion of Subjects with Complete Ulcer Closure at Each of the 12 Treatment Weeks from Baseline

End point title	Proportion of Subjects with Complete Ulcer Closure at Each of the 12 Treatment Weeks from Baseline

End point description:

End point type	Secondary

End point timeframe:

From Baseline to each of the 12 Treatment Weeks

End point values	HP802-247	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	121		
Units: Percentage of Closure				
number (not applicable)				
Baseline	0	0		
Treatment Week 01	2.3	3.3		
Treatment Week 02	8.4	7.4		
Treatment Week 03	13.7	18.2		
Treatment Week 04	22.1	25.6		
Treatment Week 05	26.7	33.9		
Treatment Week 06	29.8	38		
Treatment Week 07	32.8	39.7		
Treatment Week 08	37.4	39.7		
Treatment Week 09	38.9	43.8		
Treatment Week 10	40.5	46.3		
Treatment Week 11	41.2	47.9		
Treatment Week 12	48.1	53.7		

Statistical analyses

Statistical analysis title	Comparison of Wound closure at each week

Statistical analysis description:

Compare the treatment groups for the proportion of subjects with wound closure at each of the 12-week treatment period from baseline

Comparison groups	HP802-247 v Vehicle

Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3722 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - Week 1: p=0.6194
Week 2: p=0.7930
Week 3: P=0.3362
Week 4: p= 0.5263
Week 5: p=0.1997
Week 6: P=0.1617
Week 7: p=0.2611
Week 8: p=0.7232
Week 9: P=0.4405
Week 10: p=0.3516
Week 11: p=0.2821
Week 12: P=0.3722

Secondary: Pain associated with target wound at each of the 12 double blind treatment weeks

End point title	Pain associated with target wound at each of the 12 double blind treatment weeks

End point description:

End point type	Secondary

End point timeframe:

From baseline to each of the 12 double blind treatment weeks

End point values	HP802-247	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	121		
Units: Mean Change (in mm) in VAS Pain Score				
number (not applicable)				
Baseline	29.4	26.3		
Treatment Week 01	-8.6	-7.5		
Treatment week 02	-10.4	-11		
Treatment week 03	-14	-10.7		
Treatment week 04	-14.3	-12.1		
Treatment week 05	-17.2	-13.6		
Treatment week 06	-17.8	-15.4		
Treatment week 07	-18.5	-17.5		
Treatment week 08	-20	-17.1		
Treatment week 09	-19.7	-17.9		
Treatment week 10	-18.9	-18.4		
Treatment week 11	-19.4	-19.7		
Treatment week 12	-20	-20.1		

Statistical analyses

Statistical analysis title	Pain associated with target wound

Statistical analysis description:

Pain associated with the target wound at each of the 12 double blind treatment weeks, based on a VAS (Range 0-100mm; , 0 denoting no pain and 100mm the maximum pain)

Comparison groups	HP802-247 v Vehicle
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9733 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.958
upper limit	4.095

Notes:

[4] - Week 1: p=0.5909
Week 2: p=0.8234
Week 3: P=0.1556
Week 4: p=0.3487
Week 5: p=0.1064
Week 6: p= 0.2888
Week 7: p=0.6095
Week 8: P=0.1566
Week 9: p=0.4216
Week 10: p= 0.8166
Week 11: p= 0.9114
Week 12: P=0.9733

Secondary: Pain associated with target leg at each of the 12 double blind treatment weeks

End point title	Pain associated with target leg at each of the 12 double blind treatment weeks

End point description:

End point type	Secondary

End point timeframe:

From Baseline to each of the 12 double blind treatment weeks

End point values	HP802-247	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	121		
Units: Mean Change (in mm) in VAS Pain Score				
number (not applicable)				
Baseline	24.18	22.35		
Treatment week 01	-4.1	-4.9		
Treatment week 02	-2.2	-1.3		
Treatment week 03	-9.2	-5.3		

Treatment week 04	-10.1	-8.8		
Treatment week 05	-9.7	-8.6		
Treatment week 06	-12.2	-9.1		
Treatment week 07	-13.1	-8.9		
Treatment week 08	-14.2	-9		
Treatment week 09	-10.1	-6.3		
Treatment week 10	-12.7	-11.1		
Treatment week 11	-12.9	-11.8		
Treatment week 12	-14.3	-12.2		

Statistical analyses

Statistical analysis title	Pain with Target Leg

Statistical analysis description:

Pain associated with the target leg at each of the 12 double blind treatment weeks, base on a VAS (range 0-100mm; 0 denoting no pain and 100mm the maximum pain)

Comparison groups	HP802-247 v Vehicle
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3369 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.218
upper limit	2.137

Notes:

[5] - Week 1: p= 0.7439
Week 2: p=0.6992
Week 3: P=0.0867
Week 4: p=0.5739
Week 5: p=0.6497
Week 6: p=0.1427
Week 7: p=0.0682
Week 8: P=0.0161
Week 9: p=0.0973
Week 10: p=0.4661
Week 11: p=0.6010
Week 12: P=0.3369

Secondary: Proportion of subjects with durable wound healing over the 3 months following complete wound closure

End point title	Proportion of subjects with durable wound healing over the 3 months following complete wound closure

End point description:

End point type	Secondary

End point timeframe:

at 3 months after complete wound healing

End point values	HP802-247	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Number of subjects				
number (not applicable)				
Wound remained closed	51	47		
Wound re-opened	6	10		

Statistical analyses

Statistical analysis title	Durable wound healing over 3months after closure
Statistical analysis description:	
Proportion of subjects with durable wound healing over the 3 months following complete wound closure	
Comparison groups	HP802-247 v Vehicle
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3258
Method	Cochran-Mantel-Haenszel

Other pre-specified: Response to the SPVU-5D, a condition specific preference-based measure of health-related quality of life for use in the assessment of the impact of venous ulceration

End point title	Response to the SPVU-5D, a condition specific preference-based measure of health-related quality of life for use in the assessment of the impact of venous ulceration
End point description:	
End point type	Other pre-specified
End point timeframe:	
From Baseline to End of treatment	

End point values	HP802-247	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	121		
Units: Change in SPVU-5D Score				
least squares mean (standard error)				
Baseline Score	9.34 (± 2.74)	8.69 (± 2.38)		
Change from Baseline at Visit 12	-1.28 (± 0.2)	-1.04 (± 0.21)		

Statistical analyses

Statistical analysis title	Quality of Life comparison
Statistical analysis description:	
Compare the quality of life between the treatments groups using change in the Sheffield Preference - based Venous Ulcer questionnaire (SPVU-5D) from baseline to the end of treatment	
Comparison groups	HP802-247 v Vehicle
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2532
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.672
upper limit	0.178

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The evaluation of safety was conducted on all subjects randomized into the study and who received at least one dose of study drug and was assessed from the Screening/run-in period throughout the study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	HP802-247
Reporting group description: -	
Reporting group title	Vehicle

Reporting group description: -

Serious adverse events	HP802-247	Vehicle	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 131 (3.82%)	12 / 121 (9.92%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lung			
subjects affected / exposed	1 / 131 (0.76%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vulval cancer			
subjects affected / exposed	1 / 131 (0.76%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 131 (0.76%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			

subjects affected / exposed	1 / 131 (0.76%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 131 (0.00%)	2 / 121 (1.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Traumatic haematoma			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia			
subjects affected / exposed	1 / 131 (0.76%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 131 (0.76%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
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			
Oedema peripheral			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pemphigoid			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 131 (0.76%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stasis dermatitis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			

subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 131 (0.76%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound sepsis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 121 (0.83%)	
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: 3 %

Non-serious adverse events	HP802-247	Vehicle	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 131 (45.80%)	64 / 121 (52.89%)	
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	10 / 131 (7.63%)	6 / 121 (4.96%)	
occurrences (all)	12	6	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 131 (3.82%)	7 / 121 (5.79%)	
occurrences (all)	8	8	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	2 / 131 (1.53%)	4 / 121 (3.31%)	
occurrences (all)	7	4	
General disorders and administration site conditions			

General disorders and administration site conditions			
subjects affected / exposed	3 / 131 (2.29%)	9 / 121 (7.44%)	
occurrences (all)	3	11	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	5 / 131 (3.82%)	6 / 121 (4.96%)	
occurrences (all)	9	8	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	4 / 131 (3.05%)	1 / 121 (0.83%)	
occurrences (all)	6	2	
Erythema			
subjects affected / exposed	4 / 131 (3.05%)	5 / 121 (4.13%)	
occurrences (all)	4	6	
Skin maceration			
subjects affected / exposed	2 / 131 (1.53%)	7 / 121 (5.79%)	
occurrences (all)	3	13	
Skin ulcer			
subjects affected / exposed	17 / 131 (12.98%)	20 / 121 (16.53%)	
occurrences (all)	34	37	
Venous ulcer pain			
subjects affected / exposed	6 / 131 (4.58%)	3 / 121 (2.48%)	
occurrences (all)	6	3	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	5 / 131 (3.82%)	12 / 121 (9.92%)	
occurrences (all)	6	15	
Infections and infestations			
Infected skin ulcer			
subjects affected / exposed	7 / 131 (5.34%)	5 / 121 (4.13%)	
occurrences (all)	9	7	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	2 / 131 (1.53%)	4 / 121 (3.31%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported