



## Clinical trial results:

### An Observational Study Providing 12 Months of Safety Follow-Up from First Exposure to HP802-247 in Subjects Who Participated in Study 802-247-09-032 (EU)

#### Summary

EudraCT number	2013-000949-39
Trial protocol	HU PL DE BE CZ
Global end of trial date	20 November 2015

#### Results information

Result version number	v1 (current)
This version publication date	27 October 2016
First version publication date	27 October 2016

#### Trial information

##### Trial identification

Sponsor protocol code	802-247-09-033
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01970657
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, Smith & Nephew, Inc 3909 Hulen Street Fort Worth, TX 76107 United States, +1 8173023914,
Scientific contact	Jaime Dickerson, PhD VP Global Medical and Clinical Affairs, Smith & Nephew, Inc 3909 Hulen Street Fort Worth, TX 76107 United States, +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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	23 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2015
Global end of trial reached?	Yes
Global end of trial date	20 November 2015
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective of this study was to assess new adverse events and ongoing adverse events not resolved in subjects who were exposed to an Investigational Medicinal Product in the 802-247-09-032 trial (EudraCT number 2012-003286-18)

Protection of trial subjects:

Only subjects that met all the study inclusion criteria and none of the exclusion criteria were to be entered in the study.

All subjects were informed about the study and 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: -

Evidence for comparator: -

Actual start date of recruitment	27 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Poland: 101
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Czech Republic: 38
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Hungary: 41
Worldwide total number of subjects	221
EEA total number of subjects	221

Notes:

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**Subjects enrolled per age group**

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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)	97
From 65 to 84 years	108
85 years and over	16

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled based on participation in the 802-247-09-032 trial (EudraCT number 2012-003286-18), evidenced by randomization in and completion (or discontinuation) of that trial and having received at least one application of test article.

### Pre-assignment

Screening details:

The present study allowed subjects to transition immediately upon exit from the 802-247-09-032 trial (EudraCT number 2012-003286-18).

### 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	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

The group assignment was retained from the 802-247-09-032 trial (EudraCT number 2012-003286-18) and remained blinded to everyone, with the exception of the Sponsor, until the completion of this trial to prevent any bias being introduced into the assessments.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	HP802-247 (in 802-247-09-032 trial)

Arm description:

Patients who received HP802-247 as treatment in the 802-247-09-032 trial (EudraCT number 2012-003286-18)

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:

The product was administered in the 802-247-09-032 trial (EudraCT number 2012-003286-18). 260 µL of HP802-247 containing 0.5x10<sup>6</sup> cells/mL was administered every 14 days and Vehicle on the alternate weeks.

<b>Arm title</b>	Vehicle (in 802-247-09-032 trial)
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Arm description:

Patients who received the Vehicle as treatment in the 802-247-09-032 trial (EudraCT number 2012-003286-18)

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 product was administered in the 802-247-09-032 trial (EudraCT number 2012-003286-18). 260µL of the vehicle formulation (fibrinogen solution and thrombin solution without cells) was administered every 7 days.

<b>Number of subjects in period 1</b>	HP802-247 (in 802-247-09-032 trial)	Vehicle (in 802-247-09-032 trial)
Started	115	106
Completed	98	95
Not completed	17	11
Consent withdrawn by subject	2	3
Adverse events	2	3
Lost to follow-up	7	2
Scheduling error	5	3
Protocol deviation	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	HP802-247 (in 802-247-09-032 trial)
Reporting group description: Patients who received HP802-247 as treatment in the 802-247-09-032 trial (EudraCT number 2012-003286-18)	
Reporting group title	Vehicle (in 802-247-09-032 trial)
Reporting group description: Patients who received the Vehicle as treatment in the 802-247-09-032 trial (EudraCT number 2012-003286-18)	

Reporting group values	HP802-247 (in 802-247-09-032 trial)	Vehicle (in 802-247-09-032 trial)	Total
Number of subjects	115	106	221
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)	55	42	97
From 65-84 years	53	55	108
85 years and over	7	9	16
Age continuous Units: years			
arithmetic mean	64.8	67.7	-
standard deviation	± 13	± 12.8	-
Gender categorical Units: Subjects			
Female	68	56	124
Male	47	50	97

### Subject analysis sets

Subject analysis set title	HP802-247 (in 802-247-09-032 trial) - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All enrolled subjects in the HP802-247 arm who had at least one assessment of ulcer status post-enrollment. The ITT population was the primary dataset for the evaluation of efficacy persistence.	
Subject analysis set title	Vehicle (in 802-247-09-032 trial) - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All enrolled subjects in the Vehicle arm who had at least one assessment of ulcer status post-enrollment. The ITT population was the primary dataset for the evaluation of efficacy persistence.	

<b>Reporting group values</b>	HP802-247 (in 802-247-09-032 trial) - ITT	Vehicle (in 802-247-09-032 trial) - ITT	
Number of subjects	112	105	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	52	42	
From 65-84 years	53	55	
85 years and over	7	8	
Age continuous			
Units: years			
arithmetic mean	65	67.5	
standard deviation	± 13.1	± 12.8	
Gender categorical			
Units: Subjects			
Female	66	56	
Male	46	49	

## End points

### End points reporting groups

Reporting group title	HP802-247 (in 802-247-09-032 trial)
Reporting group description: Patients who received HP802-247 as treatment in the 802-247-09-032 trial (EudraCT number 2012-003286-18)	
Reporting group title	Vehicle (in 802-247-09-032 trial)
Reporting group description: Patients who received the Vehicle as treatment in the 802-247-09-032 trial (EudraCT number 2012-003286-18)	
Subject analysis set title	HP802-247 (in 802-247-09-032 trial) - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All enrolled subjects in the HP802-247 arm who had at least one assessment of ulcer status post-enrollment. The ITT population was the primary dataset for the evaluation of efficacy persistence.	
Subject analysis set title	Vehicle (in 802-247-09-032 trial) - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All enrolled subjects in the Vehicle arm who had at least one assessment of ulcer status post-enrollment. The ITT population was the primary dataset for the evaluation of efficacy persistence.	

### Primary: Proportion of subjects with persistent ulcer closure over the duration of the study for those subjects who had achieved confirmed ulcer closure in the 802-247-09-032 study.

End point title	Proportion of subjects with persistent ulcer closure over the duration of the study for those subjects who had achieved confirmed ulcer closure in the 802-247-09-032 study.
End point description:	
End point type	Primary
End point timeframe: From Week 08 to End of follow-up	

End point values	HP802-247 (in 802-247-09-032 trial) - ITT	Vehicle (in 802-247-09-032 trial) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57 <sup>[1]</sup>	57 <sup>[2]</sup>		
Units: Percentage of Subjects				
number (not applicable)				
Ulcer not closed	12.3	10.5		
Ulcer closed	87.7	89.5		

Notes:

[1] - Only subjects with confirmed closure from the prior study were included in this end point

[2] - Only subjects with confirmed closure from the prior study were included in this end point

### Statistical analyses

<b>Statistical analysis title</b>	Durable Ulcer Closure at End of Follow-Up Visit
Comparison groups	Vehicle (in 802-247-09-032 trial) - ITT v HP802-247 (in 802-247-09-032 trial) - ITT
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [3]
Method	Fisher exact

Notes:

[3] - p-value was based on the Fisher's Exact Test

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The evaluation of safety was conducted from the Enrollment visit (Visit 0) until the End of follow-up visit.

Adverse event reporting additional description:

The evaluation of safety included analysis of new test article-related events, as well as continued follow-up of those adverse events that originated in the 802-247-09-032 trial (EudraCT number 2012-003286-18)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.0
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### Reporting groups

Reporting group title	HP802-247 (in 802-247-09-032 trial)
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Reporting group description:

Subjects enrolled in the current study and who recieved HP802-247 as treatment in the 802-247-09-032 trial (EudraCT number 2012-003286-18)

Reporting group title	Vehicle (in 802-247-09-032 trial)
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Reporting group description:

Subjects enrolled in the current study and who recieved the Vehicle as treatment in the 802-247-09-032 trial (EudraCT number 2012-003286-18)

<b>Serious adverse events</b>	HP802-247 (in 802-247-09-032 trial)	Vehicle (in 802-247-09-032 trial)	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 115 (13.04%)	15 / 106 (14.15%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile cancer			

subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac pacemaker replacement			
subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 115 (0.00%)	2 / 106 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Impaired healing			
subjects affected / exposed	2 / 115 (1.74%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			

subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory, thoracic and mediastinal disorders</b>			
Dyspnoea			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Psychiatric disorders</b>			
Depression			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Injury, poisoning and procedural complications</b>			
Contusion			
subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			

subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Eye disorders</b>			
Keratitis			
subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
Umbilical hernia, obstructive			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hepatobiliary disorders</b>			
Bile duct obstruction			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Skin and subcutaneous tissue disorders</b>			
Eczema nummular			
subjects affected / exposed	1 / 115 (0.87%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 115 (0.87%)	3 / 106 (2.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stasis dermatitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Musculoskeletal and connective tissue disorders</b>			
Osteoarthritis			

subjects affected / exposed	2 / 115 (1.74%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Erysipelas			
subjects affected / exposed	1 / 115 (0.87%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

<b>Non-serious adverse events</b>	HP802-247 (in 802-247-09-032 trial)	Vehicle (in 802-247-09-032 trial)	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	53 / 115 (46.09%)	56 / 106 (52.83%)	
<b>Injury, poisoning and procedural complications</b>			
Excoriation			
subjects affected / exposed	4 / 115 (3.48%)	1 / 106 (0.94%)	
occurrences (all)	4	1	
<b>Vascular disorders</b>			
Hypertension			
subjects affected / exposed	5 / 115 (4.35%)	3 / 106 (2.83%)	
occurrences (all)	6	3	
<b>Skin and subcutaneous tissue disorders</b>			
Dermatitis			
subjects affected / exposed	4 / 115 (3.48%)	3 / 106 (2.83%)	
occurrences (all)	4	4	
Eczema			
subjects affected / exposed	4 / 115 (3.48%)	5 / 106 (4.72%)	
occurrences (all)	4	5	
Pruritus			
subjects affected / exposed	4 / 115 (3.48%)	2 / 106 (1.89%)	
occurrences (all)	4	2	
Skin ulcer			
subjects affected / exposed	25 / 115 (21.74%)	22 / 106 (20.75%)	
occurrences (all)	40	47	
Venous ulcer pain			

subjects affected / exposed occurrences (all)	1 / 115 (0.87%) 1	4 / 106 (3.77%) 4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 115 (3.48%)	1 / 106 (0.94%)	
occurrences (all)	4	1	
Pain in extremity			
subjects affected / exposed	0 / 115 (0.00%)	4 / 106 (3.77%)	
occurrences (all)	0	4	
Infections and infestations			
Infected skin ulcer			
subjects affected / exposed	2 / 115 (1.74%)	5 / 106 (4.72%)	
occurrences (all)	2	6	
Urinary tract infection			
subjects affected / exposed	1 / 115 (0.87%)	5 / 106 (4.72%)	
occurrences (all)	1	5	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2013	The amendment prescribed procedures for the handling of missing and incomplete data.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported