Clinical trial results:
Multicentre, randomised, controlled and double-blind clinical trial to evaluate the effectiveness and safety of bemiparin sodium as a treatment for diabetic foot ulcers (ROV-BEM-2006-01)

Summary

EudraCT number	2006-005201-60
Trial protocol	ES
Global end of trial date	23 December 2009

Results information

Result version number	v1 (current)
This version publication date	05 August 2016
First version publication date	05 August 2016

Trial information

Trial identification

Sponsor protocol code	ROV-BEM-2006-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Laboratorios Farmacéuticos ROVI, S.A.
Sponsor organisation address	C/ Julián Camarillo, 35, Madrid, Spain, 28037
Public contact	Medical Department Laboratorios Farmacéuticos Rovi, SA, Laboratorios Farmacéuticos ROVI, S.A. C/ Julián Camarillo, 35 28037 Madrid, +34 912444434,
Scientific contact	Medical Department Laboratorios Farmacéuticos Rovi, SA, Laboratorios Farmacéuticos ROVI, S.A. C/ Julián Camarillo, 35 28037 Madrid, +34 912444434, departamento.medico@rovi.es

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	29 May 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 December 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study the efficacy and safety of bemiparin sodium as a treatment for diabetic foot ulcers

Protection of trial subjects:

In the case of the appearance of an adverse event, the necessary support measures were taken for the recovery and maintenance of the vital signs of the subject within normality. The principal investigator were responsible for assuring the availability of the resources and staff necessary with sufficient experience to face the emergency situations that may occur in the study.

Data protection: All data were handled confidentially according to the applicable law on personal data protection. The subjects were only identified by a number (inclusion and/or randomisation code). It was kept the confidentiality, only the principal investigator and co-workers had access to the personal data of the patients. Authorised agents from the sponsor and/or regulatory authorities and/or Clinical Research Ethics Committees had access to the site records that were relevant for the study, including clinical histories, laboratory reports with results, admission reports or summaries of discharge and other tests directly related to the study for verifying the data and information related to this protocol. In case the access to these medical records required express authorization or different from the informed consent, the investigator obtained directly and in writing this authorization from the patient before entry in the study.

Background therapy:

Diabetic foot ulcer is characterised by a poor outcome, and a third of the cases can experience amputation after 3 years. Appropriate skin microcirculation and an adequate blood supply to the ulcer are critically important for healing the diabetic foot lesion. It has been also seen that in chronic wounds, the concentrations of growth factors such as platelet-derived growth factor and tumour growth factor are reduced. Both are essential for ulcer healing and there are studies describing that heparin can increase their production. Non-enzyme glycation of proteins of the endothelial basal membrane occurring in patients with
diabetes mellitus affects the synthesis of heparin sulphate, a major endogenous activator of antithrombin III, that appears to play an essential role in the maintenance of homeostasis and endothelial function. It must be noted, for its significance in this protocol, that heparin stimulates the synthesiof heparin sulphate in endothelial culture cells and also in studies on the effect of heparin on diabetic angiopathy in animal models, identifying positive changes in the endothelial basal membrane. In humans treated with heparin, an improvement of diabetic retinopathy has been seen, with a reduction in the number of exudates and a reduction of
proteinuria. In the context of diabetic foot ulcer, encouraging results have been also found in patients treated with heparin. Low-molecular weight heparins are known antithrombotics and antiinflammatories that can enhance microcirculation. A clinical trial has already shown that a LMWH (dalteparin) improves the outcome of diabetic foot ulcer in patients with peripheral occlusive arterial disease. A double-blind, placebo-controlled clinical trial has been also performed to evaluate the efficacy of bemiparin (another LMWH) in patients with diabetic foot ulcers. Preliminary results of this study appear to show that bemiparin sodium could have a beneficial effect on the healing of this type of wounds.

Evidence for comparator: -

Actual start date of recruitment	21 March 2007
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	Spain: 47
Country: Number of subjects enrolled	Croatia: 78
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Romania: 126
Country: Number of subjects enrolled	Russian Federation: 48
Country: Number of subjects enrolled	Serbia: 19
Worldwide total number of subjects	329
EEA total number of subjects	262

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)	329
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment of the study was from 21 March 2007 until 1 July 2009. The study was conducted in the following countries: Spain, Croatia, Russia, Romania, Serbia and Polonia.

Pre-assignment

Screening details:

In this period 416 patients, of which 329 were randomized finally being excluded a total of 87 (20.9%) patients (56 patients did not meet the selection criteria, 23 ulcers Neuropathic were not included, and 8 patients withdrew informed consent after inclusion).

Pre-assignment period milestones

Number of subjects started	416[1]
Number of subjects completed	329

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inframalleolar ulcers / no neuropatic ulcers: 23
Reason: Number of subjects	Consent withdrawn by subject: 8
Reason: Number of subjects	Patients did not meet selection criteria: 56

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In this period 416 patients, of which 329 were randomized finally being excluded a total of 87 (20.9%) patients (56 patients did not meet the selection criteria, 23 ulcers Neuropathic were not included, and 8 patients withdrew informed consent after inclusion).

Period 1

Period 1 title	Visit 1 (day-6 to -4) Selection Visit
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

If patients met inclusion criteria and none of the exclusion, they were registered for randomization. With this registry a stratified randomization process was performed for each patient, classificating them into strata based on characteristic criteria. After this process a randomization code is generated which identifies the patient with the corresponding treatment by randomization. Both MCI and placebo were physically the same including dosage in order to maintain double blind of study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sodic Bemiparine

Arm description:

Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution

Arm type	Experimental
Investigational medicinal product name	Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution

Arm title	Placebo
Arm description:	
Placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular and intravenous use
Dosage and administration details:	
Placebo	

Number of subjects in period 1	Sodic Bemiparine	Placebo
Started	164	165
Completed	164	165

Period 2

Period 2 title	Visit 2 (Day 0) Treatment Initiation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Sodic Bemiparine
Arm description:	
Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution	
Arm type	Experimental
Investigational medicinal product name	Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular and intravenous use
Dosage and administration details:	
Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution	
Arm title	Placebo
Arm description:	
Placebo	
Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Placebo

Number of subjects in period 2	Sodic Bemiparine	Placebo
Started	164	165
Completed	164	165

Period 3	
Period 3 title	Visit 3 (4 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms	
Are arms mutually exclusive?	Yes
Arm title	Sodic Bemiparine

Arm description:

Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution

Arm type	Experimental
Investigational medicinal product name	Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Placebo

Number of subjects in period 3	Sodic Bemiparine	Placebo
Started	164	165
Completed	159	158
Not completed	5	7
Consent withdrawn by subject	1	-
Lost to follow-up	2	7
Protocol deviation	2	-

Period 4	
Period 4 title	Visit 4 (8 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms	
Are arms mutually exclusive?	Yes
Arm title	Sodic Bemiparine

Arm description:

Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution

Arm type	Experimental
Investigational medicinal product name	Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Placebo

Number of subjects in period 4	Sodic Bemiparine	Placebo
Started	159	158
Completed	151	148
Not completed	8	10
Consent withdrawn by subject	-	2
Physician decision	-	4
Lost to follow-up	7	2
Protocol deviation	1	2

Period 5

Period 5 title	Visit 5 (12 weeks) End of treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Sodic Bemiparine

Arm description:

Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution

Arm type	Experimental
Investigational medicinal product name	Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Placebo

Number of subjects in period 5	Sodic Bemiparine	Placebo
Started	151	148
Completed	141	143
Not completed	10	5
Consent withdrawn by subject	6	5
Lost to follow-up	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Sodic Bemiparine
Reporting group description:	
Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Reporting group values	Sodic Bemiparine	Placebo	Total
Number of subjects	164	165	329
Age categorical Units: Subjects			
Adults (18-64 years)	164	165	329
Age continuous Units: years			
arithmetic mean	61.5	61	
standard deviation	± 10.9	± 11.1	-
Gender categorical			
The percentage of men and women (71.3% - 28.7% respectively and 77.8% bemiparina - 22.2% placebo), mean age of the patients (61.5 years, 95% CI (59.5, 63.5) bemiparina, 61.0 years (95% CI 59.0, 63.0) placebo) and BMI of patients (27.7 kg / m2 95% CI (26.9, 28.6) bemiparina, 28.5 kg / m2 95% (27.7, 29.4) placebo) show no significant differences between treatment groups in study.			
Units: Subjects			
Female	52	46	98
Male	112	119	231
Ulcer Units: Subjects			
Grade I	51	53	104
Grade II	113	112	225
Antiplatelet treatment Units: Subjects			
Yes	41	38	79
No	123	127	250
Previous ulcers Units: Subjects			
Yes	62	60	122
No	102	105	207
Previous foot ulcers location Units: Subjects			
Righ foot	28	31	59
Left foot	34	29	63

None	102	105	207
Previous ulcers amputations Units: Subjects			
Yes	39	42	81
No	23	18	41
None	102	105	207
Type previous ulcers amputations Units: Subjects			
Majors	7	6	13
Minors	32	36	68
None	125	123	248
Type of diabetes mellitus Units: Subjects			
DM1	22	20	42
DM2	142	145	287
Treatment of diabetes mellitus Units: Subjects			
Yes	156	152	308
No	8	13	21
Retinopathy Units: Subjects			
Yes	66	53	119
No	98	112	210
Nephropathy Units: Subjects			
Yes	37	30	67
No	127	135	262
Neurophathy Units: Subjects			
Yes	111	116	227
No	53	49	102
Peripheral vascular disease Units: Subjects			
Yes	67	65	132
No	97	100	197
Cerebrovascular disease Units: Subjects			
Yes	11	20	31
No	153	145	298
Cardiovascular disease Units: Subjects			
Yes	81	84	165
No	83	81	164
Previous bleeding events Units: Subjects			
Yes	4	2	6
No	160	163	323
Dyslipidemia Units: Subjects			
Yes	58	57	115
No	106	108	214

Obesity Units: Subjects			
Yes	43	44	87
No	121	121	242
Hypertriglyceridemia Units: Subjects			
Yes	43	50	93
No	121	115	236
Hypercholesterolemia Units: Subjects			
Yes	58	59	117
No	106	106	212
Hypertension Units: Subjects			
Yes	110	120	230
No	54	45	99
Actual ulcer location Units: Subjects			
Righ foot	83	75	158
Left foot	81	90	171
Previous hospitalizations for ulcer in study Units: Subjects			
Yes	20	24	44
No	144	141	285
Clinical signs of infection in the ulcer in study Units: Subjects			
Yes	8	12	20
No	156	153	309
T/B Index			
T/B Index			
Units: Subjects			
0,9≥T/B≥0,7	65	66	131
T/B>0,9	99	99	198
Ulcer Area - Current location: Plantar Units: Subjects			
Yes	61	59	120
No	103	106	209
Ulcer Area - Current location: Dorsal Units: Subjects			
Yes	17	17	34
No	147	148	295
Ulcer Area - Current location: Digital Units: Subjects			
Yes	58	74	132
No	106	91	197
Ulcer Area - Current location: Interdigital Units: Subjects			
Yes	7	6	13
No	157	159	316

Ulcer Area - Current location: Heel Units: Subjects			
Yes	30	15	45
No	134	150	284
IMC (Kg/m2)			
IMC (Kg/m2)			
Units: subjects			
arithmetic mean	28.2	28.5	
standard deviation	± 4.8	± 4.6	-
Years of evolution of diabetes mellitus (mead) Units: Years			
arithmetic mean	12.6	12.4	
standard deviation	± 9.5	± 9.7	-
Weeks of evolution of the current ulcer Units: weeks			
arithmetic mean	28.1	22.9	
standard deviation	±	±	-

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Included all randomized patients who had a neuropathic ulcer (with inframalleolar location and index T / B ≥ 0.7) whose area of the ulcer in V2 is equal to or greater than 50 mm2 (using the measurement system VISITRAK wounds) which also had at least one post-randomization assessment of key variables (meet or not inclusion/exclusion) and they had received at least one dose of study medication. In the modified ITT population were not included 49 of the 164 patients included in the group bemiparina (36 patients for ulcer size <0.5 cm2, 8 of them with no features ulcers Neuropathic and supramalleolar or not and five location without at least one post-randomization evaluation of primary endpoint) and 48 of the 165 patients in the placebo group (37 ulcer size <0.5 cm2 5 with no neuropathic and supramalleolar or ulcers and 6 without at least an assessment postrandomization efficacy. Therefore the modified ITT population make up a total of 232 (115 in bemiparine group and 117 in placebo)

Subject analysis set title	Protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

Included all patients who meet all requirements for ITT, the inclusion criteria and no exclusion criteria, which have had a compliance with study medication at least 80%, any prohibited medication had been administered and have not left the study for loss in follow-up during study medication treatment. In the protocol population were not included 36 of the 115 patients included in the group bemiparina (17 patients for poor adherence, 6 being treated with prohibited medication, 4 for failing to meet eligibility criteria and 9 patients older protocol deviations putting on compromise the integrity of the data) and 30 of the 117 patients in the placebo group (20 poor compliance, prohibited medication 3 1 did not meet selection criteria for engaging and 6
in major protocol deviations). Therefore the protocol population composes a total of 166 patients (79 patients in bemiparin group and 87 in placebo group).

Subject analysis set title	Safety population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included those randomized patients who received at least one dose of study medication. From 416 patients recruited were not included 87 patients (56 for failing to meet eligibility criteria, 23 inframaleolares / non-neuropathic ulcers and 8 informed consent withdrawal). So, 329 patients were randomized in which 164 were treated with bemiparin and 165 with placebo. These patients constituted the safety population, because they have received at least one dose of study medication.

Reporting group values	ITT population	Protocol population	Safety population
Number of subjects	232	166	329
Age categorical Units: Subjects			
Adults (18-64 years)	232	166	329
Age continuous Units: years			
arithmetic mean	61.2	61.3	61.8
standard deviation	± 11	±	±
Gender categorical			
The percentage of men and women (71.3% - 28.7% respectively and 77.8% bemiparina - 22.2% placebo), mean age of the patients (61.5 years, 95% CI (59.5, 63.5) bemiparina, 61.0 years (95% CI 59.0, 63.0) placebo) and BMI of patients (27.7 kg / m2 95% CI (26.9, 28.6) bemiparina, 28.5 kg / m2 95% (27.7, 29.4) placebo) show no significant differences between treatment groups in study.			
Units: Subjects			
Female	59	36	98
Male	173	130	231
Ulcer Units: Subjects			
Grade I	69	54	104
Grade II	163	112	225
Antiplatelet treatment Units: Subjects			
Yes	61	42	79
No	171	124	250
Previous ulcers Units: Subjects			
Yes	87	61	122
No	145	105	207
Previous foot ulcers location Units: Subjects			
Righ foot	42	27	59
Left foot	45	34	63
None	185	105	207
Previous ulcers amputations Units: Subjects			
Yes	63	47	81
No	24	14	41
None	145	105	207
Type previous ulcers amputations Units: Subjects			
Majors	8	4	13
Minors	55	43	68
None	169	119	248
Type of diabetes mellitus			

Units: Subjects			
DM1	32	17	42
DM2	200	149	287
Treatment of diabetes mellitus Units: Subjects			
Yes	216	155	308
No	16	11	21
Retinopathy Units: Subjects			
Yes	87	59	119
No	145	107	210
Nephropathy Units: Subjects			
Yes	44	32	67
No	188	134	262
Neurophathy Units: Subjects			
Yes	158	119	227
No	74	47	102
Peripheral vascular disease Units: Subjects			
Yes	87	54	132
No	145	112	197
Cerebrovascular disease Units: Subjects			
Yes	16	11	31
No	216	155	298
Cardiovascular disease Units: Subjects			
Yes	108	82	165
No	124	84	164
Previous bleeding events Units: Subjects			
Yes	4	3	6
No	228	163	323
Dyslipidemia Units: Subjects			
Yes	87	55	115
No	145	111	214
Obesity Units: Subjects			
Yes	52	35	87
No	180	131	242
Hypertriglyceridemia Units: Subjects			
Yes	62	47	93
No	170	119	236
Hypercholesterolemia Units: Subjects			
Yes	80	54	117
No	152	112	212

Hypertension Units: Subjects			
Yes	158	111	230
No	74	55	99
Actual ulcer location Units: Subjects			
Righ foot	116	83	158
Left foot	116	83	171
Previous hospitalizations for ulcer in study Units: Subjects			
Yes	34	27	44
No	198	139	285
Clinical signs of infection in the ulcer in study Units: Subjects			
Yes	16	7	20
No	216	159	309
T/B Index			
T/B Index			
Units: Subjects			
0,9≥T/B≥0,7	52	60	131
T/B>0,9	150	106	198
Ulcer Area - Current location: Plantar Units: Subjects			
Yes	101	80	120
No	131	86	209
Ulcer Area - Current location: Dorsal Units: Subjects			
Yes	21	13	34
No	211	153	295
Ulcer Area - Current location: Digital Units: Subjects			
Yes	81	54	132
No	151	112	197
Ulcer Area - Current location: Interdigital Units: Subjects			
Yes	9	6	13
No	223	160	316
Ulcer Area - Current location: Heel Units: Subjects			
Yes	29	19	45
No	203	147	284
IMC (Kg/m2)			
IMC (Kg/m2)			
Units: subjects			
arithmetic mean	28.1	28.1	28.3
standard deviation	± 4.6	±	±
Years of evolution of diabetes mellitus (mead) Units: Years			

arithmetic mean	12.2	12.1	12.5
standard deviation	± 9.5	±	±
Weeks of evolution of the current ulcer Units: weeks			
arithmetic mean	25.5	25.3	23.6
standard deviation	± 25.6	±	±

End points

End points reporting groups

Reporting group title	Sodic Bemiparine

Reporting group description:

Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Sodic Bemiparine

Reporting group description:

Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Sodic Bemiparine

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Reporting group description:

Placebo

Reporting group title	Sodic Bemiparine

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Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Sodic Bemiparine

Reporting group description:

Sodic Bemiparine 3.500 IU/day, prefilled syringes with 0,2 ml injectable solution

Reporting group title	Placebo

Reporting group description:

Placebo

Subject analysis set title	ITT population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Included all randomized patients who had a neuropathic ulcer (with inframalleolar location and index T / B ≥ 0.7) whose area of the ulcer in V2 is equal to or greater than 50 mm2 (using the measurement system VISITRAK wounds) which also had at least one post-randomization assessment of key variables (meet or not inclusion/exclusion) and they had received at least one dose of study medication. In the modified ITT population were not included 49 of the 164 patients included in the group bemiparina (36 patients for ulcer size <0.5 cm2, 8 of them with no features ulcers Neuropathic and supramalleolar or not and five location without at least one post-randomization evaluation of primary endpoint) and 48 of the 165 patients in the placebo group (37 ulcer size <0.5 cm2 5 with no neuropathic and supramalleolar or ulcers and 6 without at least an assessment postrandomization efficacy. Therefore the modified ITT population make up a total of 232 (115 in bemiparine group and 117 in placebo)

Subject analysis set title	Protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

Included all patients who meet all requirements for ITT, the inclusion criteria and no exclusion criteria, which have had a compliance with study medication at least 80%, any prohibited medication had been administered and have not left the study for loss in follow-up during study medication treatment. In the protocol population were not included 36 of the 115 patients included in the group bemiparina (17 patients for poor adherence, 6 being treated with prohibited medication, 4 for failing to meet eligibility

criteria and 9 patients older protocol deviations putting on compromise the integrity of the data) and 30 of the 117 patients in the placebo group (20 poor compliance, prohibited medication 3 1 did not meet selection criteria for engaging and 6
in major protocol deviations). Therefore the protocol population composes a total of 166 patients (79 patients in bemiparin group and 87 in placebo group).

Subject analysis set title	Safety population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included those randomized patients who received at least one dose of study medication. From 416 patients recruited were not included 87 patients (56 for failing to meet eligibility criteria, 23 inframaleolares / non-neuropathic ulcers and 8 informed consent withdrawal). So, 329 patients were randomized in which 164 were treated with bemiparin and 165 with placebo. These patients constituted the safety population, because they have received at least one dose of study medication.

Primary: Significant improvement or complete healing of the ulcer

End point title	Significant improvement or complete healing of the ulcer

End point description:

Significant improvement defined as >=50% ulcer size reduction or 1 grade reduction on Wagner Scale

End point type	Primary

End point timeframe:

3 months

End point values	Sodic Bemiparine	Placebo	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	164[1]	165[2]	232	
Units: Percentage				
number (not applicable)	66.1	65.8	65.9	

Notes:

[1] - ITT Sodic Bemiparine Results

[2] - ITT Placebo Results

Statistical analyses

Statistical analysis title	ITT - Sodic Beniparine vs Placebo - Chi-Squared
Comparison groups	Sodic Bemiparine v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.965
Method	Chi-squared

Statistical analysis title	PP - Sodic Beniparine vs Placebo - Chi-Squared
Comparison groups	Sodic Bemiparine v Placebo

Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.58
Method	Chi-squared

Secondary: Complete healing of the ulcer at the end of the study

End point title	Complete healing of the ulcer at the end of the study

End point description:

Complete healing of the ulcer at the end of the study

End point type	Secondary

End point timeframe:

3 months

End point values	Sodic Bemiparine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[3]	165[4]		
Units: Percentage				
number (not applicable)	25.2	25.6		

Notes:

[3] - ITT Sodic Beniparine Results

[4] - ITT Placebo Results

Statistical analyses

Statistical analysis title	ITT - Sodic Beniparine vs Placebo - Chi-Squared
Comparison groups	Sodic Bemiparine v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.941
Method	Chi-squared

Statistical analysis title	PP - Sodic Beniparine vs Placebo - Chi-Squared
Comparison groups	Sodic Bemiparine v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.884
Method	Chi-squared

Other pre-specified: Complete healing of the ulcer by Wagner Scale Grade	
End point title	Complete healing of the ulcer by Wagner Scale Grade
End point description: Complete healing of the ulcer by Wagner Scale Grade	
End point type	Other pre-specified
End point timeframe: 3 months	

End point values	Sodic Bemiparine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[5]	165[6]		
Units: Percentage				
number (not applicable)				
Grade I	40	60		
Grade II	55.9	44.1		

Notes:

[5] - ITT Sodic Beniparine Results

[6] - ITT Placebo Results

Statistical analyses

Statistical analysis title	Grade I (Sodic Beniparine vs Placebo)-Chi-Squared
Statistical analysis description: Grade I (Sodic Beniparine vs Placebo)	
Comparison groups	Sodic Bemiparine v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.423
Method	Chi-squared

Statistical analysis title	Grade II (Sodic Beniparine vs Placebo)-Chi-Squared
Statistical analysis description: Grade I (Sodic Beniparine vs Placebo) -Chi-Squared	
Comparison groups	Sodic Bemiparine v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.921
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety information was collected from the 329 randomized patients which received bemiparine or placebo treatment. SAEs were collected during the period of treatment, occurring after administration of treatment to 2 calendar days after completion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Bemiparine Group
Reporting group description: -	
Reporting group title	Placebo group

Reporting group description: -

Serious adverse events	Bemiparine Group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 164 (17.07%)	21 / 165 (12.73%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	1 / 164 (0.61%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrosis ischaemic			
subjects affected / exposed	2 / 164 (1.22%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			

subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular calcification			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Amputation			
subjects affected / exposed	4 / 164 (2.44%)	3 / 165 (1.82%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot amputation			
subjects affected / exposed	3 / 164 (1.83%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodialysis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leg amputation			
subjects affected / exposed	2 / 164 (1.22%)	2 / 165 (1.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toe amputation			

subjects affected / exposed	9 / 164 (5.49%)	9 / 165 (5.45%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
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			
Disease progression			
subjects affected / exposed	1 / 164 (0.61%)	3 / 165 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound secretion			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Personality change due to a general medical condition			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	2 / 164 (1.22%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose abnormal			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular pressure increased			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac hypertrophy			
subjects affected / exposed	2 / 164 (1.22%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 164 (1.22%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 164 (0.61%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
sudden death			

subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 164 (0.00%)	2 / 165 (1.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 164 (1.22%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrogenic anaemia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Melaena			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry gangrene			

subjects affected / exposed	3 / 164 (1.83%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (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	1 / 164 (0.61%)	0 / 165 (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			
Abscess limb			
subjects affected / exposed	2 / 164 (1.22%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 164 (1.83%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	4 / 164 (2.44%)	3 / 165 (1.82%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	6 / 164 (3.66%)	2 / 165 (1.21%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infected skin ulcer			
subjects affected / exposed	3 / 164 (1.83%)	2 / 165 (1.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	4 / 164 (2.44%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	4 / 164 (2.44%)	5 / 165 (3.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Bemiparine Group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 164 (26.83%)	33 / 165 (20.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 164 (1.22%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Concomitant disease aggravated			
subjects affected / exposed	1 / 164 (0.61%)	1 / 165 (0.61%)	
occurrences (all)	1	1	
Injection site haematoma			

subjects affected / exposed	2 / 164 (1.22%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Injection site haemorrhage			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Injection site pruritus			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	2 / 164 (1.22%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 164 (0.61%)	2 / 165 (1.21%)	
occurrences (all)	1	2	
Blood pressure increased			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Poisoning			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	

Road traffic accident			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Skin injury			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Traumatic haematoma			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dementia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 164 (0.61%)	1 / 165 (0.61%)	
occurrences (all)	1	1	
Eosinophilia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Lymphocytosis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Monocytosis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Eye disorders			

Ocular hyperaemia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Oesophagitis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Excoriation			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Hyperkeratosis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Neuropathic ulcer			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Diabetic nephropathy			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Hypercreatininaemia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Diabetic retinopathy			
subjects affected / exposed	2 / 164 (1.22%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			

Arthritis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Fungal infection			
subjects affected / exposed	2 / 164 (1.22%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Infected skin ulcer			
subjects affected / exposed	11 / 164 (6.71%)	8 / 165 (4.85%)	
occurrences (all)	11	8	
Influenza			
subjects affected / exposed	2 / 164 (1.22%)	2 / 165 (1.21%)	
occurrences (all)	2	2	
Lymphangitis			
subjects affected / exposed	0 / 164 (0.00%)	2 / 165 (1.21%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Osteomyelitis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Purulent discharge			
subjects affected / exposed	3 / 164 (1.83%)	0 / 165 (0.00%)	
occurrences (all)	3	0	
Pyelonephritis acute			

subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	1 / 164 (0.61%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Deficiency anaemia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Diabetic foot			
subjects affected / exposed	2 / 164 (1.22%)	3 / 165 (1.82%)	
occurrences (all)	2	3	
Hypercholesterolaemia			
subjects affected / exposed	1 / 164 (0.61%)	3 / 165 (1.82%)	
occurrences (all)	1	3	
Hyperglycaemia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Hyperosmolar state			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	2 / 164 (1.22%)	1 / 165 (0.61%)	
occurrences (all)	2	1	
Hyperuricaemia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2007	Version 2.0 dated 26/01/2007 was the second substantial amendment to protocol. It was authorized on 22/03/2007
02 July 2007	Version 3.0 dated 02/07/2007 was the third substantial amendment to protocol. It was authorized on 07/08/2007
01 July 2008	Version 4.0 dated 01/08/2008 was the 4th substantial amendment to protocol. It was authorized on 19/08/2008
16 July 2008	Version 5.0 dated 16/07/2008 was the 5th substantial amendment to protocol. It was authorized on 04/11/2008
10 March 2009	Version 6.0 dated 10/03/2009 was the 6th substantial amendment to protocolo. It was authorized on 19/05/2009
02 July 2009	Last version (ongoing) is 7.0 dated 02/07/2009 substantial amendment to protocol. It was authorized on 12/09/2009

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported