Clinical trial results:
A randomized, controlled, open-label, parallel-group, multi-center study to compare the effect of Intrathecal Baclofen Therapy (ITB Therapy) versus Best Medical Treatment (BMT) on severe spasticity in post-stroke patients after 6 months active treatment

Summary

EudraCT number	2009-011216-38
Trial protocol	AT ES BE DE IT NL GB
Global end of trial date	21 September 2016

Results information

Result version number	v1 (current)
This version publication date	05 November 2017
First version publication date	05 November 2017

Trial information

Trial identification

Sponsor protocol code	1.02.7001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01032239
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medtronic International Trading Sarl
Sponsor organisation address	Route du Molliau 31, Tolochenaz, Switzerland, CH-1131
Public contact	Meghann Loven, Medtronic International Trading Sarl, 1 7635262604, meghann.m.loven@medtronic.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2016
Global end of trial reached?	Yes
Global end of trial date	21 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that Intrathecal Baclofen Therapy (ITB) Therapy, compared to Best Medical Treatment (BMT), has superior efficacy in the treatment of severe spasticity in adult post-stroke patients with generalized spastic hypertonia who have not reached their therapy goal with other treatment interventions assessed by a decrease in the average Ashworth Scale (AS) score in the lower extremities.

Protection of trial subjects:

Following the 6 week post-implant visit, oral antispastic medications may be prescribed as rescue medication for patients enrolled in the ITB Therapy® treatment arm. Investigators may consider using rescue medication when there is a significant deterioration of the clinical picture with an increase in painful spasticity and inability to control symptoms. Rescue medications are not deemed necessary for patients enrolled in the BMT treatment arm as these patients are on oral antispastic medication throughout the study and these medications may be adjusted per clinical practice.

Patients in both arms of the study received physiotherapy for their post-stroke spasticity.

Background therapy:

The purpose of the the study was to compare ITB Therapy with Best Medical Treatment (BMT). Therefore patients in the latter arm received oral antispasmodic medicinal products along with physiotherapy for their post-stroke spasticity whereas patients in the former arm recevied ITB and physiotherapy.

Evidence for comparator:

The Best Medical Treatment comparator arm included conventional oral medication for treating post-stroke spasticity (plus physiotherapy) and therefore was considered to be the appropriate comparator.

Actual start date of recruitment	16 December 2009
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	Netherlands: 2
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Slovenia: 1
Country: Number of subjects enrolled	United States: 25

Worldwide total number of subjects	60
EEA total number of subjects	35

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)	49
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 61 patients were screened for the study of which 60 met the study eligibility criteria and were therefore randomised in to the study.

Period 1

Period 1 title	Run-in phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ITB Therapy

Arm description:

Intrathecal Baclofen therapy (Intrathecal Baclofen + implantable pump)

Intrathecal administration of baclofen via implanted infusion pump together with physiotherapy. During this phase, patients already prescribed oral antispastic medication were allowed to continue their oral medication therapy.

Run in phase: up to 25 days for ITB arm

Arm type	Experimental
Investigational medicinal product name	Intrathecal baclofen
Investigational medicinal product code	
Other name	Lioresal
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intrathecal use

Dosage and administration details:

Commercially available baclofen (Lioresal) was used in the study. The dosage and administration details were therefore in accordance with the authorised Summmary of Product Characteristics for Lioresal.

Arm title	Best Medical Treatment (BMT)

Arm description:

Use one or a combination oral antispastic medication

Patients were prescribed at least one of the following oral antispastic medications: oral baclofen, tizanidine, diazepam (or other benzodiazepines), or dantrolene. Medications and doses could be adjusted in accordance with normal clinical practice. Patients also received physiotherapy according to a protocol that was pre-defined at each center.

Run in phase: up to 21 days for BMT arm

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	ITB Therapy	Best Medical Treatment (BMT)
Started	31	29
Completed	28	26
Not completed	3	3
Consent withdrawn by subject	1	3
Lost to follow-up	2	-

Period 2

Period 2 title	Active trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ITB Therapy

Arm description:

Intrathecal administration of baclofen via implanted infusion pump together with physiotherapy. During this phase, any already prescribed oral antispastic medications were required to be stopped by Week 6.

Period 2 is after implant

Arm type	Experimental
Investigational medicinal product name	Intrathecal baclofen
Investigational medicinal product code	
Other name	Lioresal
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intrathecal use

Dosage and administration details:

Commercially available baclofen (Lioresal) was used in the study. The dosage and administration details were therefore in accordance with the authorised Summmary of Product Characteristics for Lioresal.

Arm title	Best Medical Treatment (BMT)

Arm description:

Patients were prescribed at least one of the following oral antispastic medications: oral baclofen, tizanidine, diazepam (or other benzodiazepines), or dantrolene. Medications and doses could be adjusted in accordance with normal clinical practice. Patients also received physiotherapy according to a protocol that was pre-defined at each center.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	ITB Therapy	Best Medical Treatment (BMT)
Started	28	26
Completed	24	24
Not completed	4	2
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Lost to follow-up	1	2
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	ITB Therapy

Reporting group description:

Intrathecal Baclofen therapy (Intrathecal Baclofen + implantable pump)

Intrathecal administration of baclofen via implanted infusion pump together with physiotherapy. During this phase, patients already prescribed oral antispastic medication were allowed to continue their oral medication therapy.

Run in phase: up to 25 days for ITB arm

Reporting group title	Best Medical Treatment (BMT)

Reporting group description:

Use one or a combination oral antispastic medication

Patients were prescribed at least one of the following oral antispastic medications: oral baclofen, tizanidine, diazepam (or other benzodiazepines), or dantrolene. Medications and doses could be adjusted in accordance with normal clinical practice. Patients also received physiotherapy according to a protocol that was pre-defined at each center.

Run in phase: up to 21 days for BMT arm

Reporting group values	ITB Therapy	Best Medical Treatment (BMT)	Total
Number of subjects	31	29	60
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)	24	25	49
From 65-84 years	7	4	11
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	7	11	18
Male	24	18	42

End points

End points reporting groups

Reporting group title	ITB Therapy

Reporting group description:

Intrathecal Baclofen therapy (Intrathecal Baclofen + implantable pump)

Intrathecal administration of baclofen via implanted infusion pump together with physiotherapy. During this phase, patients already prescribed oral antispastic medication were allowed to continue their oral medication therapy.

Run in phase: up to 25 days for ITB arm

Reporting group title	Best Medical Treatment (BMT)

Reporting group description:

Use one or a combination oral antispastic medication

Patients were prescribed at least one of the following oral antispastic medications: oral baclofen, tizanidine, diazepam (or other benzodiazepines), or dantrolene. Medications and doses could be adjusted in accordance with normal clinical practice. Patients also received physiotherapy according to a protocol that was pre-defined at each center.

Run in phase: up to 21 days for BMT arm

Reporting group title	ITB Therapy

Reporting group description:

Intrathecal administration of baclofen via implanted infusion pump together with physiotherapy. During this phase, any already prescribed oral antispastic medications were required to be stopped by Week 6.

Period 2 is after implant

Reporting group title	Best Medical Treatment (BMT)

Reporting group description:

Patients were prescribed at least one of the following oral antispastic medications: oral baclofen, tizanidine, diazepam (or other benzodiazepines), or dantrolene. Medications and doses could be adjusted in accordance with normal clinical practice. Patients also received physiotherapy according to a protocol that was pre-defined at each center.

Primary: Change in Average Ashworth Scale (AS) in Affected Lower Extremities From Baseline to Month 6

End point title	Change in Average Ashworth Scale (AS) in Affected Lower Extremities From Baseline to Month 6

End point description:

Change in Average Ashworth Scale (AS) in affected lower extremities from baseline to month 6 between ITB and BMT arm.

Change= AS at month 6 - AS at baseline

End point type	Primary

End point timeframe:

Baseline and month 6

End point values	ITB Therapy	Best Medical Treatment (BMT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: 1-5				
arithmetic mean (standard deviation)	-0.99 (± 0.75)	-0.43 (± 0.72)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	ITB Therapy v Best Medical Treatment (BMT)
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Wilcoxon (Mann-Whitney)
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From ITB test (for ITB arm) and randomization (for BMT arm) until month 6 follow-up visit	
Adverse event reporting additional description:	
Safety analyses were performed on a modified ITT (intent to treat) patient set: all patients were analysed as treated; ITB-I included only implanted patients. BMT+ITB-NI included also patients randomized to ITB, but not implanted.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups	
Reporting group title	ITB-I
Reporting group description:	
Patients implanted with intrathecal baclofen pump	
Reporting group title	BMT+ITB-NI
Reporting group description:	
Patients randomized to BMT plus patients randomized to ITB but not implanted (treated with one or a combination oral antispastic medication)	

Serious adverse events	ITB-I	BMT+ITB-NI	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 25 (48.00%)	10 / 35 (28.57%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondroma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device dislocation			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 25 (8.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site effusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (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			
Alcohol poisoning			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Suture related complication			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Diastolic dysfunction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve stenosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (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			
Epilepsy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasticity			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischeamic attack			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Cataract			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Ingrowing nail			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 25 (8.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plantar fasciitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 25 (8.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (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: 0 %

Non-serious adverse events	ITB-I	BMT+ITB-NI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 25 (92.00%)	21 / 35 (60.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 25 (4.00%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Hypertensive crisis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	4 / 25 (16.00%)	3 / 35 (8.57%)	
occurrences (all)	4	3	
Oedema peripheral			
subjects affected / exposed	2 / 25 (8.00%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Implant site pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Adverse drug reaction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	

Asthenia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Chronic fatigue syndrome			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Gait disturbance			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Implant site reaction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Hypersensitivity			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Social circumstances			
Alcohol use			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Postnasal drip			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 25 (12.00%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
Insomnia			
subjects affected / exposed	3 / 25 (12.00%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
Aggression			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Depressed mood			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Listless			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 25 (4.00%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Residual urine volume increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	3 / 25 (12.00%)	3 / 35 (8.57%)	
occurrences (all)	10	4	
Procedural pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Contusion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Head injury			
subjects affected / exposed	1 / 25 (4.00%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Incision site erythema			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Incision site pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Postoperative ileus			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Procedural headache			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Skin laceration			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Muscle spasticity			
subjects affected / exposed	2 / 25 (8.00%)	3 / 35 (8.57%)	
occurrences (all)	2	3	
Headache			
subjects affected / exposed	2 / 25 (8.00%)	1 / 35 (2.86%)	
occurrences (all)	3	1	

Epilepsy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Hemiparesis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Hypotonia			
subjects affected / exposed	3 / 25 (12.00%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Somnolence			
subjects affected / exposed	0 / 25 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	4	
Dizziness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Sedation			
subjects affected / exposed	0 / 25 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Complex regional pain syndrome			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Myoclonus			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	2 / 25 (8.00%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Tinnitus			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Vertigo			

subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Conjunctivitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Eyelid oedema			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 25 (12.00%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
Diarrhoea			
subjects affected / exposed	3 / 25 (12.00%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Faecaloma			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Gastritis			

subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Hypoaesthesia oral			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 25 (4.00%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	2 / 25 (8.00%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Blister			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Ingrowing nail			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 25 (8.00%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Dysuria			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Urinary incontinence			

subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	4 / 25 (16.00%)	1 / 35 (2.86%)	
occurrences (all)	5	1	
Pain in extremity			
subjects affected / exposed	4 / 25 (16.00%)	1 / 35 (2.86%)	
occurrences (all)	4	1	
Arthralgia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Bursitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Neck pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Plantar fasciitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 25 (12.00%)	1 / 35 (2.86%)	
occurrences (all)	4	1	
Upper respiratory tract infection			

subjects affected / exposed	2 / 25 (8.00%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Bronchitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Bronchopneumonia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	1 / 25 (4.00%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Nail infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 25 (4.00%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	0 / 25 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2012	Addition of the Quality Metric SF-12 as a secondary endpoint. Addition of an interim analysis and increase in the duration of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported