



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 |
| Scientific contact | Alessandra Calabrese, Medtronic International Trading Sarl, 41 218038160, alessandra.calabrese@medtronic.com |

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 received 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 Summary 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 Summary 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 ischaemic 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 occurrences (all) Chronic fatigue syndrome subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Gait disturbance subjects affected / exposed occurrences (all) Implant site reaction subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) | 0 / 35 (0.00%) | |
| | 1 | 0 | |
| | 1 / 25 (4.00%) | 0 / 35 (0.00%) | |
| | 1 | 0 | |
| | 0 / 25 (0.00%) | 1 / 35 (2.86%) | |
| | 0 | 1 | |
| | 0 / 25 (0.00%) | 1 / 35 (2.86%) | |
| | 0 | 1 | |
| | 1 / 25 (4.00%) | 0 / 35 (0.00%) | |
| | 1 | 0 | |
| | 0 / 25 (0.00%) | 1 / 35 (2.86%) | |
| | 0 | 1 | |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) Hypersensitivity subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) | 0 / 35 (0.00%) | |
| | 1 | 0 | |
| | 0 / 25 (0.00%) | 1 / 35 (2.86%) | |
| | 0 | 1 | |
| Social circumstances Alcohol use subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) | 0 / 35 (0.00%) | |
| | 1 | 0 | |
| Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all) Pelvic pain subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) | 0 / 35 (0.00%) | |
| | 1 | 0 | |
| | 0 / 25 (0.00%) | 1 / 35 (2.86%) | |
| | 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 occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 35 (2.86%) 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 occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 35 (2.86%) 1 | |
| Hypoaesthesia oral subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 35 (0.00%) 0 | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 2 | 0 / 35 (0.00%) 0 | |
| Toothache subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 35 (2.86%) 1 | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 35 (2.86%) 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 35 (0.00%) 0 | |
| Blister subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 35 (0.00%) 0 | |
| Eczema subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 35 (2.86%) 1 | |
| Ingrowing nail subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 35 (0.00%) 0 | |
| Renal and urinary disorders | | | |
| Urinary retention subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 35 (0.00%) 0 | |
| Dysuria subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 35 (2.86%) 1 | |
| Urinary incontinence | | | |

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