



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multinational Clinical Study to Evaluate the Efficacy and Safety of 2.0 mg/kg/week and 2.0 mg/kg/every other week BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome)

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2010-020198-18 |
| Trial protocol | GB NL FR DE PT IT NO DK |
| Global end of trial date | 23 August 2012 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 02 September 2018 |
| First version publication date | 02 September 2018 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | MOR-004 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01275066 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | BioMarin Pharmaceutical Inc. |
| Sponsor organisation address | 105 Digital Drive, Novato, United States, CA 94949 |
| Public contact | Clinical Trials Information, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com |
| Scientific contact | Clinical Trials Information, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000973-PIP01-10 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 23 August 2012 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 August 2012 |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 August 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the ability of 2.0 mg/kg/week BMN 110 and 2.0 mg/kg/qow BMN 110 compared with placebo to enhance endurance in patients with MPS IVA, as measured by an increase in the number of meters walked in the 6MW test from baseline to Week 24.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki including amendments in force up to and including the time the study was conducted. The study was conducted in compliance with the International Conference on Harmonization E6 Guideline for Good Clinical Practice, and is compliant with the European Union Clinical Trial Directive 2001/20/EC. The study was also conducted in compliance with the United States Food and Drug Administration regulations in 21 Code of Federal Regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 February 2011 |
| 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 | Argentina: 2 |
| Country: Number of subjects enrolled | Brazil: 21 |
| Country: Number of subjects enrolled | Canada: 14 |
| Country: Number of subjects enrolled | Colombia: 6 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | France: 20 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Italy: 10 |
| Country: Number of subjects enrolled | Japan: 6 |
| Country: Number of subjects enrolled | Netherlands: 6 |
| Country: Number of subjects enrolled | Portugal: 3 |
| Country: Number of subjects enrolled | Qatar: 2 |
| Country: Number of subjects enrolled | Saudi Arabia: 7 |
| Country: Number of subjects enrolled | Taiwan: 5 |
| Country: Number of subjects enrolled | United Kingdom: 23 |
| Country: Number of subjects enrolled | United States: 33 |
| Country: Number of subjects enrolled | Korea, Republic of: 7 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 176 |
| EEA total number of subjects | 73 |

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) | 93 |
| Adolescents (12-17 years) | 47 |
| Adults (18-64 years) | 36 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 33 study centers in 17 countries.

Pre-assignment

Screening details:

Total of 204 patients screened, 177 randomized and 175 subjects completed the study. One subject was excluded before treatment due to unconfirmed diagnosis of Mucopolysaccharidosis IVA (MPS IVA).

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Intravenous infusion of placebo solution at a volume equivalent to that needed for 2.0 mg/kg dose of BMN 110 administered over a period of approximately 4 hours once a week.

| | |
|--|-----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Intravenous infusion of placebo solution at a volume equivalent to that needed for 2.0 mg/kg dose of BMN 110 administered over a period of approximately 4 hours once a week.

| | |
|------------------|----------------------|
| Arm title | BMN110 2.0 mg/kg/Qow |
|------------------|----------------------|

Arm description:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours every other week and infusions of placebo on alternating weeks.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | BMN 110 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours every other week and infusions of placebo on alternating weeks.

| | |
|------------------|-----------------------|
| Arm title | BMN110 2.0 mg/kg/Week |
|------------------|-----------------------|

Arm description:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours once a week.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-----------------|
| Investigational medicinal product name | BMN 110 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours once a week.

| Number of subjects in period 1 | Placebo | BMN110 2.0 mg/kg/Qow | BMN110 2.0 mg/kg/Week |
|---------------------------------------|---------|----------------------|-----------------------|
| Started | 59 | 59 | 58 |
| Completed | 59 | 59 | 57 |
| Not completed | 0 | 0 | 1 |
| Consent withdrawn by subject | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Intravenous infusion of placebo solution at a volume equivalent to that needed for 2.0 mg/kg dose of BMN 110 administered over a period of approximately 4 hours once a week.

| | |
|-----------------------|----------------------|
| Reporting group title | BMN110 2.0 mg/kg/Qow |
|-----------------------|----------------------|

Reporting group description:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours every other week and infusions of placebo on alternating weeks.

| | |
|-----------------------|-----------------------|
| Reporting group title | BMN110 2.0 mg/kg/Week |
|-----------------------|-----------------------|

Reporting group description:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours once a week.

| Reporting group values | Placebo | BMN110 2.0 mg/kg/Qow | BMN110 2.0 mg/kg/Week |
|------------------------------------|---------|----------------------|-----------------------|
| Number of subjects | 59 | 59 | 58 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Age continuous Units: years arithmetic mean standard deviation | 15.0 ± 11.30 | 15.3 ± 10.79 | 13.1 ± 8.10 |
| Gender categorical Units: Subjects | | | |
| Female | 32 | 25 | 32 |
| Male | 27 | 34 | 26 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 13 | 16 | 9 |
| Not Hispanic or Latino | 46 | 43 | 49 |
| Race Units: Subjects | | | |
| Asian | 11 | 15 | 14 |
| Black or African American | 0 | 2 | 2 |
| White | 44 | 35 | 36 |
| Other | 4 | 7 | 6 |
| Walk Category Units: Subjects | | | |
| ≤ 200m | 23 | 24 | 23 |
| > 200m | 36 | 35 | 35 |
| Normalized Urine Keratan Sulfate | | | |
| Baseline Units: ug/mg arithmetic mean standard deviation | 26.1 ± 15.43 | 28.6 ± 21.17 | 26.9 ± 14.11 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 176 | | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 89 | | |
| Male | 87 | | |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 38 | | |
| Not Hispanic or Latino | 138 | | |
| Race Units: Subjects | | | |
| Asian | 40 | | |
| Black or African American | 4 | | |
| White | 115 | | |
| Other | 17 | | |
| Walk Category Units: Subjects | | | |
| <= 200m | 70 | | |
| > 200m | 106 | | |
| Normalized Urine Keratan Sulfate | | | |
| Baseline | | | |
| Units: ug/mg arithmetic mean standard deviation | - | | |

End points

End points reporting groups

| | |
|---|-----------------------|
| Reporting group title | Placebo |
| Reporting group description: Intravenous infusion of placebo solution at a volume equivalent to that needed for 2.0 mg/kg dose of BMN 110 administered over a period of approximately 4 hours once a week. | |
| Reporting group title | BMN110 2.0 mg/kg/Qow |
| Reporting group description: Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours every other week and infusions of placebo on alternating weeks. | |
| Reporting group title | BMN110 2.0 mg/kg/Week |
| Reporting group description: Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours once a week. | |

Primary: Change From Baseline in Endurance as Measured by the 6-minute Walk Test

| | |
|---|---|
| End point title | Change From Baseline in Endurance as Measured by the 6-minute Walk Test |
| End point description: Intention to treat (ITT) population consist of all subjects who were randomized to study treatment and received at least one dose of study drug. Two missing outcomes at Week 24 were imputed using method of multiple imputation. | |
| End point type | Primary |
| End point timeframe: Baseline to Week 24 | |

| End point values | Placebo | BMN110 2.0 mg/kg/Qow | BMN110 2.0 mg/kg/Week | |
|--------------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 59 | 59 | 58 | |
| Units: Meters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 211.9 (± 69.88) | 205.7 (± 81.19) | 203.9 (± 76.32) | |
| Week 24 | 225.4 (± 83.22) | 219.9 (± 87.60) | 240.0 (± 86.61) | |
| Change from Baseline to Week 24 | 13.5 (± 50.63) | 14.2 (± 40.82) | 36.0 (± 58.11) | |

Statistical analyses

| | |
|----------------------------|----------------------------------|
| Statistical analysis title | Placebo vs BMN110 2.0 mg/kg/Week |
| Comparison groups | Placebo v BMN110 2.0 mg/kg/Week |

| | |
|---|---------------|
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0174 |
| Method | ANCOVA |

| | |
|---|---------------------------------|
| Statistical analysis title | Placebo vs BMN110 2.0 mg/kg/Qow |
| Comparison groups | Placebo v BMN110 2.0 mg/kg/Qow |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9542 |
| Method | ANCOVA |

Secondary: Change From Baseline in Endurance as Measured by the 3-minute Stair Climb Test

| | |
|---|--|
| End point title | Change From Baseline in Endurance as Measured by the 3-minute Stair Climb Test |
| End point description: ITT population. | |
| End point type | Secondary |
| End point timeframe: Baseline to Week 24 | |

| End point values | Placebo | BMN110 2.0 mg/kg/Qow | BMN110 2.0 mg/kg/Week | |
|--------------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 59 | 59 | 58 | |
| Units: Stairs/minute | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 30.0 (± 14.05) | 27.1 (± 15.8) | 29.6 (± 16.44) | |
| Week 24 | 33.6 (± 18.36) | 30.4 (± 17.77) | 34.3 (± 18.7) | |
| Change from Baseline to Week 24 | 3.6 (± 8.51) | 3.2 (± 10.29) | 4.7 (± 7.99) | |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Placebo vs BMN110 2.0 mg/kg/Week |
| Comparison groups | Placebo v BMN110 2.0 mg/kg/Week |

| | |
|---|---------------|
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4935 |
| Method | ANCOVA |

| | |
|---|---------------------------------|
| Statistical analysis title | Placebo vs BMN110 2.0 mg/kg/Qow |
| Comparison groups | BMN110 2.0 mg/kg/Qow v Placebo |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7783 |
| Method | ANCOVA |

Secondary: Percent Change From Baseline in Normalized Urine Keratan Sulfate

| | |
|-----------------|--|
| End point title | Percent Change From Baseline in Normalized Urine Keratan Sulfate |
|-----------------|--|

End point description:

ITT population. Normalized urine keratan sulfate is calculated as urine keratan sulfate divided by urine creatinine.

Nine missing outcomes at Week 24 were imputed using method of multiple imputation.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 24

| End point values | Placebo | BMN110 2.0 mg/kg/Qow | BMN110 2.0 mg/kg/Week | |
|--------------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 59 | 59 | 58 | |
| Units: ug/mg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Percent Change From Baseline | -3.6 (± 27.41) | -35.3 (± 20.74) | -43.7 (± 22.29) | |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Placebo vs BMN110 2.0 mg/kg/Week |
| Comparison groups | Placebo v BMN110 2.0 mg/kg/Week |

| | |
|---|---------------|
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |

| | |
|---|---------------------------------|
| Statistical analysis title | Placebo vs BMN110 2.0 mg/kg/Qow |
| Comparison groups | Placebo v BMN110 2.0 mg/kg/Qow |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 24

Adverse event reporting additional description:

Safety Population: Consisted of all subjects who received any study drug (either BMN 110 or placebo).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|----------------------|
| Reporting group title | BMN110 2.0 mg/kg/Qow |
|-----------------------|----------------------|

Reporting group description: -

| | |
|-----------------------|-----------------------|
| Reporting group title | BMN110 2.0 mg/kg/Week |
|-----------------------|-----------------------|

Reporting group description: -

| Serious adverse events | Placebo | BMN110 2.0 mg/kg/Qow | BMN110 2.0 mg/kg/Week |
|--|----------------|----------------------|-----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 4 / 59 (6.78%) | 9 / 58 (15.52%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Surgical and medical procedures | | | |
| Suture removal | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 59 (1.69%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cervical cord compression | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 59 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Infusion site pain | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 59 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 59 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 59 (1.69%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 59 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 59 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 59 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 59 (1.69%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 59 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 59 (1.69%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 59 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 59 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Placebo | BMN110 2.0 mg/kg/Qow | BMN110 2.0 mg/kg/Week |
|---|------------------|-------------------------|--------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 57 / 59 (96.61%) | 59 / 59 (100.00%) | 56 / 58 (96.55%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 4 / 59 (6.78%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 6 | 3 |
| Hypertension | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | 4 / 59 (6.78%) | 3 / 58 (5.17%) |
| occurrences (all) | 13 | 18 | 6 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 2 / 59 (3.39%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 3 | 3 |
| Flushing | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 59 (1.69%) | 5 / 58 (8.62%) |
| occurrences (all) | 0 | 1 | 7 |
| Poor venous access | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | 1 / 59 (1.69%) | 3 / 58 (5.17%) |
| occurrences (all) | 8 | 1 | 4 |
| General disorders and administration site conditions | | | |

| | | | |
|--|------------------|------------------|------------------|
| Pyrexia | | | |
| subjects affected / exposed | 17 / 59 (28.81%) | 22 / 59 (37.29%) | 25 / 58 (43.10%) |
| occurrences (all) | 29 | 35 | 47 |
| Fatigue | | | |
| subjects affected / exposed | 15 / 59 (25.42%) | 8 / 59 (13.56%) | 9 / 58 (15.52%) |
| occurrences (all) | 24 | 10 | 17 |
| Chills | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 6 / 59 (10.17%) | 6 / 58 (10.34%) |
| occurrences (all) | 1 | 7 | 7 |
| Infusion site extravasation | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 4 / 59 (6.78%) | 2 / 58 (3.45%) |
| occurrences (all) | 2 | 4 | 2 |
| Infusion site pain | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 4 / 59 (6.78%) | 4 / 58 (6.90%) |
| occurrences (all) | 0 | 7 | 4 |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 4 / 59 (6.78%) | 1 / 58 (1.72%) |
| occurrences (all) | 2 | 6 | 1 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 59 (5.08%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 3 | 1 |
| Puncture site pain | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 3 / 59 (5.08%) | 1 / 58 (1.72%) |
| occurrences (all) | 2 | 3 | 1 |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 2 / 59 (3.39%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 2 | 4 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 59 (1.69%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 1 | 3 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 4 / 59 (6.78%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 7 | 3 |
| Reproductive system and breast disorders | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| Dysmenorrhoea subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 2 | 3 / 59 (5.08%) 3 | 1 / 58 (1.72%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 7 / 59 (11.86%) 8 | 9 / 59 (15.25%) 12 | 12 / 58 (20.69%) 14 |
| Cough subjects affected / exposed occurrences (all) | 21 / 59 (35.59%) 28 | 17 / 59 (28.81%) 29 | 16 / 58 (27.59%) 20 |
| Dyspnoea subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 4 | 6 / 59 (10.17%) 8 | 7 / 58 (12.07%) 12 |
| Nasal congestion subjects affected / exposed occurrences (all) | 5 / 59 (8.47%) 8 | 5 / 59 (8.47%) 7 | 5 / 58 (8.62%) 7 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 4 / 59 (6.78%) 6 | 4 / 59 (6.78%) 9 | 5 / 58 (8.62%) 5 |
| Asthma subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 3 / 59 (5.08%) 3 | 1 / 58 (1.72%) 1 |
| Epistaxis subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 5 | 2 / 59 (3.39%) 2 | 3 / 58 (5.17%) 3 |
| Tonsillar hypertrophy subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 3 | 0 / 59 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Throat irritation subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 0 / 59 (0.00%) 0 | 3 / 58 (5.17%) 4 |
| Psychiatric disorders | | | |
| Agitation subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 2 / 59 (3.39%) 2 | 3 / 58 (5.17%) 3 |
| Investigations | | | |

| | | | |
|--|-----------------------|----------------------|-----------------------|
| Oxygen saturation decreased subjects affected / exposed occurrences (all) | 6 / 59 (10.17%) 19 | 7 / 59 (11.86%) 8 | 6 / 58 (10.34%) 10 |
| Blood pressure diastolic increased subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 5 | 3 / 59 (5.08%) 4 | 2 / 58 (3.45%) 2 |
| Blood pressure systolic increased subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 5 | 3 / 59 (5.08%) 16 | 1 / 58 (1.72%) 1 |
| Body temperature increased subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 10 | 2 / 59 (3.39%) 2 | 4 / 58 (6.90%) 24 |
| Respiratory rate increased subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 3 | 1 / 59 (1.69%) 1 | 1 / 58 (1.72%) 1 |
| Injury, poisoning and procedural complications | | | |
| Fall subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 4 / 59 (6.78%) 5 | 0 / 58 (0.00%) 0 |
| Head injury subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 3 / 59 (5.08%) 3 | 2 / 58 (3.45%) 2 |
| Ligament sprain subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 3 | 0 / 59 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Cardiac disorders | | | |
| Tricuspid valve incompetence subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 3 | 7 / 59 (11.86%) 7 | 4 / 58 (6.90%) 4 |
| Mitral valve incompetence subjects affected / exposed occurrences (all) | 4 / 59 (6.78%) 4 | 3 / 59 (5.08%) 3 | 3 / 58 (5.17%) 3 |
| Tachycardia subjects affected / exposed occurrences (all) | 6 / 59 (10.17%) 7 | 2 / 59 (3.39%) 6 | 3 / 58 (5.17%) 8 |
| Pulmonary valve incompetence | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 2 | 1 / 59 (1.69%) 1 | 3 / 58 (5.17%) 3 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 21 / 59 (35.59%) | 24 / 59 (40.68%) | 24 / 58 (41.38%) |
| occurrences (all) | 38 | 52 | 69 |
| Dizziness | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 4 / 59 (6.78%) | 7 / 58 (12.07%) |
| occurrences (all) | 3 | 6 | 10 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 59 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 6 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 59 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 3 |
| Hyperreflexia | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 1 / 59 (1.69%) | 0 / 58 (0.00%) |
| occurrences (all) | 6 | 3 | 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 5 / 59 (8.47%) | 8 / 59 (13.56%) | 3 / 58 (5.17%) |
| occurrences (all) | 6 | 11 | 3 |
| Eye disorders | | | |
| Corneal opacity | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 59 (0.00%) | 5 / 58 (8.62%) |
| occurrences (all) | 1 | 0 | 5 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 21 / 59 (35.59%) | 21 / 59 (35.59%) | 26 / 58 (44.83%) |
| occurrences (all) | 42 | 44 | 61 |
| Nausea | | | |
| subjects affected / exposed | 12 / 59 (20.34%) | 14 / 59 (23.73%) | 18 / 58 (31.03%) |
| occurrences (all) | 13 | 22 | 37 |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 59 (11.86%) | 12 / 59 (20.34%) | 12 / 58 (20.69%) |
| occurrences (all) | 8 | 14 | 14 |
| Abdominal pain | | | |

| | | | |
|---|-----------------|------------------|------------------|
| subjects affected / exposed | 5 / 59 (8.47%) | 8 / 59 (13.56%) | 14 / 58 (24.14%) |
| occurrences (all) | 5 | 14 | 23 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 59 (8.47%) | 4 / 59 (6.78%) | 9 / 58 (15.52%) |
| occurrences (all) | 6 | 4 | 22 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 3 / 59 (5.08%) | 2 / 58 (3.45%) |
| occurrences (all) | 1 | 4 | 4 |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | 1 / 59 (1.69%) | 1 / 58 (1.72%) |
| occurrences (all) | 4 | 1 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 1 / 59 (1.69%) | 0 / 58 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 5 / 59 (8.47%) | 6 / 59 (10.17%) | 6 / 58 (10.34%) |
| occurrences (all) | 6 | 7 | 9 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 4 / 59 (6.78%) | 4 / 58 (6.90%) |
| occurrences (all) | 0 | 5 | 6 |
| Petechiae | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 59 (5.08%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 3 / 59 (5.08%) | 4 / 58 (6.90%) |
| occurrences (all) | 2 | 5 | 4 |
| Eczema | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 1 / 59 (1.69%) | 1 / 58 (1.72%) |
| occurrences (all) | 3 | 1 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 9 / 59 (15.25%) | 14 / 59 (23.73%) | 9 / 58 (15.52%) |
| occurrences (all) | 13 | 24 | 16 |
| Back pain | | | |

| | | | |
|-----------------------------------|---|------------------|------------------|
| subjects affected / exposed | 6 / 59 (10.17%) | 10 / 59 (16.95%) | 7 / 58 (12.07%) |
| occurrences (all) | 7 | 17 | 10 |
| Arthralgia | | | |
| subjects affected / exposed | 17 / 59 (28.81%) | 9 / 59 (15.25%) | 10 / 58 (17.24%) |
| occurrences (all) | 27 | 14 | 14 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 3 / 59 (5.08%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 59 (5.08%) | 5 / 58 (8.62%) |
| occurrences (all) | 0 | 5 | 6 |
| Osteopenia | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 3 / 59 (5.08%) | 0 / 58 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 2 / 59 (3.39%) | 3 / 58 (5.17%) |
| occurrences (all) | 4 | 2 | 4 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 59 (1.69%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 1 | 4 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 59 (15.25%) | 12 / 59 (20.34%) | 10 / 58 (17.24%) |
| occurrences (all) | 12 | 13 | 11 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 59 (15.25%) | 10 / 59 (16.95%) | 10 / 58 (17.24%) |
| occurrences (all) | 14 | 13 | 15 |
| Gastroenteritis | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | 8 / 59 (13.56%) | 7 / 58 (12.07%) |
| occurrences (all) | 4 | 10 | 8 |
| Viral infection | Additional description: Safety population | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 6 / 59 (10.17%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 6 | 3 |
| Influenza | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 5 / 59 (8.47%) | 2 / 58 (3.45%) |
| occurrences (all) | 4 | 5 | 3 |

| | | | |
|---|-----------------|----------------|-----------------|
| Otitis media | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | 5 / 59 (8.47%) | 9 / 58 (15.52%) |
| occurrences (all) | 4 | 6 | 10 |
| Rhinitis | | | |
| subjects affected / exposed | 6 / 59 (10.17%) | 4 / 59 (6.78%) | 5 / 58 (8.62%) |
| occurrences (all) | 8 | 8 | 8 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 4 / 59 (6.78%) | 2 / 58 (3.45%) |
| occurrences (all) | 5 | 5 | 4 |
| Pharyngitis | | | |
| subjects affected / exposed | 7 / 59 (11.86%) | 3 / 59 (5.08%) | 4 / 58 (6.90%) |
| occurrences (all) | 7 | 3 | 4 |
| Ear infection | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 2 / 59 (3.39%) | 5 / 58 (8.62%) |
| occurrences (all) | 1 | 2 | 5 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 04 October 2010 | <ul style="list-style-type: none">•Study design modified to include a third treatment arm(2.0mg/kg/every other week)•Total number of patients increased from 120(60 patients per treatment arm) to 162•Number of study centers increased from approximately 20 to approximately 40•Randomization stratification factors were revised. Stratification by age group(5-11,12-18&≥19yrs old)was added. Randomization will be stratified by screening 6MW test categories(≤200m&>200m)& age group•PK sample size revised from 60(30 per treatment arm) to 54(18 per treatment arm)•PK time point at 180 min after start of infusion deleted & a new PK time point at 180 min post infusion added•PK assessment at Week 1 deleted.PK assessment for Week 23 moved to Week 22•Immunogenicity testing deleted at Week 1&23•Definition of infusion associated reaction(IAR) modified to include more thorough description of potential symptoms & to be inclusive of all reactions occurring after onset of infusion/within 1day following end of infusion regardless of investigator's assessment of whether or not event was related to study drug administration•Immunogenicity testing in event of a severe IAR/IAR requiring cessation of infusion revised to include C4. CH50 deleted from testing•Allergic Reaction Review Board(ARRB) added to review severe/serious infusion associated reactions•Thyroid panel moved from Baseline to Screening•Schedule for 6MW test & 3MSC test revised from every 6 wks to every 12 wks•Cervical spine & lumbar spine radiographs deleted from Week 24&Early Termination Visit(ETV)•Audiometry examinations added to Baseline & Week 24 assessments for selected sites. Change in hearing assessments will be evaluated as a tertiary objective•Echocardiogram assessments will include evaluation for presence/absence of valve stenosis/regurgitation & clinical significance at Screening & Week 24•Corneal clouding examinations added as part of physical examination at Screening, Week 12&Week 24 assessments |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported