



## Clinical trial results:

### A Phase 2, Open-Label, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Intracerebroventricular BMN 190 in Pediatric Patients < 18 years of age with CLN2 Disease

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-000891-85 |
| Trial protocol           | GB IT          |
| Global end of trial date | 20 April 2022  |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 14 March 2023 |
| First version publication date | 14 March 2023 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | 190-203 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02678689 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | BioMarin Pharmaceutical Inc.   |
| Sponsor organisation address | 105 Digital Drive, Novato, CA, United States, 94949                                    |
| Public contact               | Clinical Trials Information, BioMarin Pharmaceutical Inc. ,<br>clinicaltrials@bmrn.com |
| Scientific contact           | Clinical Trials Information, BioMarin Pharmaceutical Inc. ,<br>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-001362-PIP01-12 |
| 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                       | 20 April 2022 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 20 April 2022 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 20 April 2022 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of this study include the following:

- evaluate safety and tolerability of BMN 190 administered via intracerebroventricular (ICV) device
- evaluate treatment effectiveness as a delay in progression of motor-language (ML) score on the Hamburg CLN2 clinical rating scale
- assess immunogenicity of BMN 190 in CSF and serum

Protection of trial subjects:

This clinical study was designed, conducted, recorded, and reported in compliance with the following:

- Clinical Trial Directive 2001/20/EC and GCP Directive 2005/28/EC
- Other national and local regulations, as applicable
- International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (ICH E6) (Committee for Proprietary Medicinal Products (CPMP) guideline CPMP/ICH/135/95)
- The ethical principles established by the Declaration of Helsinki
- US Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 22 January 2016 |
| Long term follow-up planned                               | Yes             |
| Long term follow-up rationale                             | Safety          |
| Long term follow-up duration                              | 6 Months        |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Germany: 9        |
| Country: Number of subjects enrolled | Italy: 1          |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | United States: 3  |
| Worldwide total number of subjects   | 14                |
| EEA total number of subjects         | 10                |

Notes:

| <b>Subjects enrolled per age group</b>    |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 5 |
| Children (2-11 years)                     | 9 |
| Adolescents (12-17 years)                 | 0 |
| Adults (18-64 years)                      | 0 |
| From 65 to 84 years                       | 0 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This was a multi-center study conducted by four principal investigators at four study centers in four countries (Germany, Italy, United Kingdom and United States).

### Pre-assignment

Screening details:

A total of 14 participants were enrolled and treated in Study.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | BMN190-203 (overall period) |
| Is this the baseline period? | Yes                         |
| Allocation method            | Not applicable              |
| Blinding used                | Not blinded                 |

### Arms

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | BMN 190-203 |
|------------------|-------------|

Arm description:

All subjects were administered BMN 190 by continuous Intracerebroventricular (ICV) infusion at the rate of 2.5 mL/hour for approximately 1.3 to 4 hours every 14 (+/-3) days.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | BMN 190  |
| Investigational medicinal product code |  |
| Other name                             | recombinant human tripeptidyl peptidase-1 (rhTPP1), cerliponase alfa |
| Pharmaceutical forms                   | Solution for infusion  |
| Routes of administration               | Intracerebroventricular use  |

Dosage and administration details:

BMN 190 was administered by continuous Intracerebroventricular (ICV) infusion at the rate of 2.5 mL/hour for approximately 4 hours every 14 (+-3) days, according to the participant's age: Birth to < 6 months: 100 mg, 6 months to < 1 year: 150 mg, 1 year to < 2 years: 200 mg (first four doses), 300 mg (subsequent doses) >=2 years: 300 mg.

|                                       |             |
|---------------------------------------|-------------|
| <b>Number of subjects in period 1</b> | BMN 190-203 |
| Started                               | 14          |
| Completed                             | 13          |
| Not completed                         | 1           |
| Parent/Guardian choice                | 1           |

## Baseline characteristics

### Reporting groups

|   |            |
|---|------------|
| Reporting group title                                       | BMN190-203 |
| Reporting group description:                                |            |
| Subjects received BMN 190 every 14 days for up to Week 144. |            |

| Reporting group values  | BMN190-203 | Total |  |
|---|------------|-------|--|
| Number of subjects  | 14         | 14    |  |
| Age categorical   |            |       |  |
| The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190- 203 study. |            |       |  |
| Units: Subjects   |            |       |  |
| < 2   | 5          | 5     |  |
| >= 2  | 9          | 9     |  |
| Gender categorical  |            |       |  |
| The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study.  |            |       |  |
| Units: Subjects   |            |       |  |
| Female  | 8          | 8     |  |
| Male  | 6          | 6     |  |
| Race  |            |       |  |
| The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study.  |            |       |  |
| Units: Subjects   |            |       |  |
| White   | 14         | 14    |  |
| Ethnicity   |            |       |  |
| The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study   |            |       |  |
| Units: Subjects   |            |       |  |
| Hispanic or Latino  | 2          | 2     |  |
| Not Hispanic or Latino  | 12         | 12    |  |
| Age Category  |            |       |  |
| The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190- 203 study. |            |       |  |
| Units: Subjects   |            |       |  |
| < 3   | 8          | 8     |  |
| >=3   | 6          | 6     |  |
| Age at Enrollment, years  |            |       |  |
| The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190 203 study.  |            |       |  |
| Units: Years  |            |       |  |
| arithmetic mean   | 3.0        |       |  |
| standard deviation  | ± 1.46     | -     |  |
| Age at Baseline, years  |            |       |  |
| Units: Years  |            |       |  |
| arithmetic mean   | 3.1        |       |  |
| standard deviation  | ± 1.45     | -     |  |
| CLN2 motor-language (ML) score at Baseline  |            |       |  |

|  |               |   |  |
|--|---------------|---|--|
| The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study. |               |   |  |
| Units: score on scale<br>arithmetic mean<br>standard deviation   | 4.6<br>± 1.69 | - |  |
| CLN2 motor scale score at Baseline   |               |   |  |
| The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study. |               |   |  |
| Units: Score on a scale<br>arithmetic mean<br>standard deviation   | 2.3<br>± 0.83 | - |  |
| CLN2 language scale score at Baseline  |               |   |  |
| The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study. |               |   |  |
| Units: Score on a scale<br>arithmetic mean<br>standard deviation   | 2.4<br>± 0.93 | - |  |

## End points

### End points reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | BMN 190-203             |
| Reporting group description:<br>All subjects were administered BMN 190 by continuous Intracerebroventricular (ICV) infusion at the rate of 2.5 mL/hour for approximately 1.3 to 4 hours every 14 (+/-3) days.   |                         |
| Subject analysis set title  | Matched ITT BMN 190-203 |
| Subject analysis set type   | Intention-to-treat      |
| Subject analysis set description:<br>Two participants in the 190-203 ITT population (N = 14) were excluded from the 190-203 ITT analysis with matching (N = 12) who did not match with any 190-901 participants on the matching criteria.<br>The matching criteria at baseline were: <ul style="list-style-type: none"><li>• Equal ML score</li><li>• Age within 3 months</li><li>• Genome: equal number of common alleles (c.622CT, c.509.1GC)</li></ul> |                         |

### Primary: Motor Language (ML) Scale: Rate of Decline in the 0 to 6-point ML score.

|   |   |
|---|---|
| End point title   | Motor Language (ML) Scale: Rate of Decline in the 0 to 6-point ML score. <sup>[1]</sup> |
| End point description:<br>The rate of decline in the 0 to 6-point ML score, and the primary analysis was based on up to 3-1 matching of Study 190-901 evaluable participants with Study 190-203 ITT participants.<br>Rate of decline = $(-1) \times (48 \times 7) \times (\text{Ending score} - \text{Starting score}) / (\text{Ending date} - \text{Starting date})$<br><br>ML score decline is measured by motor and language domains on the CLN2 rating scale (which ranges from 0 to 6, with 0 representing no function and 3 representing normal function in each of the two domains).<br><br>There was a statistically significant attenuation of the rate of decline on the ML scale for the matched 190-203 ITT participants when compared with the rate of decline in untreated 190- 901 evaluable participants, as demonstrated by a mean difference between groups (901-203) of 1.15 points (SE 0.174); 95% CI, 0.80, 1.50 points; $p < 0.0001$ . These results show a significant treatment benefit for participants treated with BMN 190 compared with matched natural history participants. |   |
| End point type  | Primary   |
| End point timeframe:<br>Baseline to Week 48.  |   |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was conducted against a population from a natural history study 190-901 Evaluable Population. Due to system limitations, the comparator population cannot be displayed in this format.

| End point values                     | Matched ITT<br>BMN 190-203 |  |  |  |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type                   | Subject analysis set       |  |  |  |
| Number of subjects analysed          | 12                         |  |  |  |
| Units: Points per 48 weeks           |                            |  |  |  |
| arithmetic mean (standard deviation) | 0.15 ( $\pm$ 0.243)        |  |  |  |

### Statistical analyses

No statistical analyses for this end point

**Primary: Time to Unreversed 2-Point Decline or Score of 0 in ML Score**

|                 |   |
|-----------------|---|
| End point title | Time to Unreversed 2-Point Decline or Score of 0 in ML Score <sup>[2]</sup> |
|-----------------|---|

End point description:

An unreversed 2-point decline is any decline of 2 points or more that had not reversed to a 1-point decline (or better) at the last recorded observation. An unreversed score of 0 is a decline to 0 that had not increased to a score > 0 at last recorded observation.

ML score decline is measured by motor and language domains on the CLN2 rating scale (which ranges from 0 to 6, with 0 representing no function and 3 representing normal function in each of the two domains).

Time to unreversed 2-point decline or score of 0 in ML score by last assessment relative to baseline, was analyzed using Kaplan-Meier methods and the Cox proportional hazards model. A Cox proportional hazards model of time to unreversed 2-point decline or score of 0 in ML score demonstrated a statistically significant difference in matched 190-203 ITT participants as compared to matched 190-901 evaluable participants (hazard ratio, 0.091; 95% CI, 0.021 to 0.393;  $p < 0.0001$ ).

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline to Week 49, Week 97, and Week 145.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was conducted against a population from a natural history study 190-901 Evaluable Population. Due to system limitations, the comparator population cannot be displayed in this format.

| End point values                                  | Matched ITT<br>BMN 190-203 |  |  |  |
|---|----------------------------|--|--|--|
| Subject group type                                | Subject analysis set       |  |  |  |
| Number of subjects analysed                       | 12                         |  |  |  |
| Units: Probability of decline                     |                            |  |  |  |
| number (confidence interval 95%)                  |                            |  |  |  |
| Probability of decline: Week 49 (No. at risk=12)  | 0.0 (0.00 to 0.00)         |  |  |  |
| Probability of decline: Week 97 (No. at risk=11)  | 0.083 (0.01 to 0.46)       |  |  |  |
| Probability of decline: Week 145 (No. at risk=10) | 0.167 (0.04 to 0.52)       |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage Change from Baseline to Last Assessment: Volume of cerebrospinal fluid**

|                 |   |
|-----------------|---|
| End point title | Percentage Change from Baseline to Last Assessment: Volume of cerebrospinal fluid |
|-----------------|---|

End point description:

Intent-to-treat (ITT) population.

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

End point timeframe:

Baseline to Last Assessment



|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | BMN 190-203     |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 13              |  |  |  |
| Units: Percentage                    |                 |  |  |  |
| arithmetic mean (standard deviation) | 0.7 (± 13.18)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change from Baseline to Last Assessment: Volume of Total Cortical Gray Matter

|   |  |
|---|--|
| End point title   | Percentage Change from Baseline to Last Assessment: Volume of Total Cortical Gray Matter |
| End point description:<br>Intent-to-treat (ITT) population. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline to Last Assessment         |  |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | BMN 190-203     |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 13              |  |  |  |
| Units: Percentage                    |                 |  |  |  |
| arithmetic mean (standard deviation) | -10.3 (± 13.86) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change from Baseline to Last Assessment: Volume of Total White Matter

|   |  |
|---|--|
| End point title                                     | Percentage Change from Baseline to Last Assessment: Volume of Total White Matter |
| End point description:                              |  |
| End point type                                      | Secondary  |
| End point timeframe:<br>Baseline to Last Assessment |  |

|                                      |                    |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| <b>End point values</b>              | BMN 190-203        |  |  |  |
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 13                 |  |  |  |
| Units: Percentage                    |                    |  |  |  |
| arithmetic mean (standard deviation) | 5.4 ( $\pm$ 20.86) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline to Last Assessment: Whole Brain Apparent Diffusion Coefficient Value

|                 |   |
|-----------------|---|
| End point title | Change from Baseline to Last Assessment: Whole Brain Apparent Diffusion Coefficient Value |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline to Last Assessment

|                                      |                    |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| <b>End point values</b>              | BMN 190-203        |  |  |  |
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 13                 |  |  |  |
| Units: mm <sup>2</sup> /s            |                    |  |  |  |
| arithmetic mean (standard deviation) | -2.5 ( $\pm$ 4.60) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Disease Manifestation

|                 |                               |
|-----------------|-------------------------------|
| End point title | Time to Disease Manifestation |
|-----------------|-------------------------------|

End point description:

Time of disease manifestation is defined as time of the first of the two measurements demonstrating the deficit. Time to disease manifestation was assessed for pre-symptomatic participants, defined as having MLVS=12. MLVS is the combined score of motor, language, vision, seizure subscales on the CLN2 disease rating scale. Within each domain, a score from 0 to 3 is assigned and overall scores are calculated by summing the four domain scores for a final rating of 0 (severely impaired) to 12 (normal).

Subsequent disease manifestation is defined as post-baseline consecutive measurements of M, L, V, or S scores <3, measured at least 22 days apart.

Median (95% CI) time to disease manifestation was 67(34, 94) wks in history participants vs median not reached in 190-203 participants.

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

End point timeframe:

Baseline to Week 49, Week 97, and Week 145.

| End point values                                 | Matched ITT<br>BMN 190-203 |  |  |  |
|--|----------------------------|--|--|--|
| Subject group type                               | Subject analysis set       |  |  |  |
| Number of subjects analysed                      | 12                         |  |  |  |
| Units: Probability of decline                    |                            |  |  |  |
| number (confidence interval 95%)                 |                            |  |  |  |
| Probability of decline: Week 49 (No. at risk=6)  | 0.143 (0.02 to 0.67)       |  |  |  |
| Probability of decline: Week 97 (No. at risk=5)  | 0.286 (0.08 to 0.74)       |  |  |  |
| Probability of decline: Week 145 (No. at risk=4) | 0.429 (0.16 to 0.83)       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up-to Safety Follow-Up (6 months after last dose).Respiratory syncytial virus infection.

Adverse event reporting additional description:

Atrioventricular block 2nd degree assessed as non-serious by inv. later upgraded to SAE by BioMarin in safety database based on medical sig. Inv. assessed AE as not related to BMN190;however,due to absence of alternative etiological factors & strong temporal relationship,BioMarin conservatively assessed AE to be possibly related to BMN190 as SUSAR.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | BMN 190-203 |
|-----------------------|-------------|

Reporting group description:

Safety population : All enrolled participants (N = 14) had an ICV reservoir implanted and were included in the Safety Population.

One AE of atrioventricular block was considered as non-serious event per clinical database and excluded form SAE.

| Serious adverse events                            | BMN 190-203      |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events |                  |  |  |
| subjects affected / exposed                       | 12 / 14 (85.71%) |  |  |
| number of deaths (all causes)                     | 0                |  |  |
| number of deaths resulting from adverse events    | 0                |  |  |
| Investigations                                    |                  |  |  |
| Propionibacteriu m test positive                  |                  |  |  |
| subjects affected / exposed                       | 1 / 14 (7.14%)   |  |  |
| occurrences causally related to treatment / all   | 1 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Injury, poisoning and procedural complications    |                  |  |  |
| Periorbital haematoma                             |                  |  |  |
| subjects affected / exposed                       | 1 / 14 (7.14%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Nervous system disorders                          |                  |  |  |
| Pleocytosis                                       |                  |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 1 / 14 (7.14%)  |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Status epilepticus                                   |                 |  |  |
| subjects affected / exposed                          | 1 / 14 (7.14%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Complication of device insertion                     |                 |  |  |
| subjects affected / exposed                          | 1 / 14 (7.14%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Medical device site haematoma                        |                 |  |  |
| subjects affected / exposed                          | 1 / 14 (7.14%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Medical device site irritation                       |                 |  |  |
| subjects affected / exposed                          | 1 / 14 (7.14%)  |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Pyrexia  |                 |  |  |
| subjects affected / exposed                          | 4 / 14 (28.57%) |  |  |
| occurrences causally related to treatment / all      | 1 / 7           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Immune system disorders                              |                 |  |  |
| Anaphylactic reaction                                |                 |  |  |
| subjects affected / exposed                          | 1 / 14 (7.14%)  |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hypersensitivity                                     |                 |  |  |
| subjects affected / exposed                          | 2 / 14 (14.29%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |

|  |   |  |  |
|--|---|--|--|
| Ear and labyrinth disorders<br>Deafness unilateral<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                       | <br><br>1 / 14 (7.14%)<br>0 / 1<br>0 / 0  |  |  |
| Gastrointestinal disorders<br>Dental caries<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                              | <br><br>1 / 14 (7.14%)<br>0 / 2<br>0 / 0  |  |  |
| Dysphagia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | <br><br>1 / 14 (7.14%)<br>0 / 1<br>0 / 0  |  |  |
| Gastrointestinal fistula<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | <br><br>1 / 14 (7.14%)<br>0 / 1<br>0 / 0  |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Adenoidal hypertrophy<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | <br><br>2 / 14 (14.29%)<br>0 / 2<br>0 / 0 |  |  |
| Hypoxia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | <br><br>1 / 14 (7.14%)<br>0 / 1<br>0 / 0  |  |  |
| Infections and infestations<br>Coronavirus infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                     | <br><br>1 / 14 (7.14%)<br>0 / 1<br>0 / 0  |  |  |
| Escherichia urinary tract infection  |   |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 14 (7.14%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infection                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 14 (7.14%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Influenza                                       |                 |  |  |  |
| subjects affected / exposed                     | 2 / 14 (14.29%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Mycoplasma infection                            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 14 (7.14%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 14 (7.14%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pyelonephritis                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 14 (7.14%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Rhinitis  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 14 (7.14%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Rhinovirus infection                            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 14 (7.14%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Upper respiratory tract infection               |                 |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 14 (7.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Viral infection                                 |                |  |  |
| subjects affected / exposed                     | 1 / 14 (7.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Product issues                                  |                |  |  |
| Device leakage                                  |                |  |  |
| subjects affected / exposed                     | 1 / 14 (7.14%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

|   |                   |  |  |
|---|-------------------|--|--|
| <b>Non-serious adverse events</b>                     | BMN 190-203       |  |  |
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 14 / 14 (100.00%) |  |  |
| Vascular disorders                                    |                   |  |  |
| Haematoma   |                   |  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Hypertension  |                   |  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Pyrexia   |                   |  |  |
| subjects affected / exposed                           | 12 / 14 (85.71%)  |  |  |
| occurrences (all)                                     | 62                |  |  |
| Asthenia  |                   |  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Chills  |                   |  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |



|   |                       |  |  |
|---|-----------------------|--|--|
| Complication of device insertion<br>subjects affected / exposed<br>occurrences (all)            | 1 / 14 (7.14%)<br>1   |  |  |
| Gait disturbance<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 14 (7.14%)<br>2   |  |  |
| Malaise<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 14 (7.14%)<br>1   |  |  |
| Medical device site haematoma<br>subjects affected / exposed<br>occurrences (all)               | 1 / 14 (7.14%)<br>1   |  |  |
| Medical device site irritation<br>subjects affected / exposed<br>occurrences (all)              | 1 / 14 (7.14%)<br>1   |  |  |
| Medical device site swelling<br>subjects affected / exposed<br>occurrences (all)                | 1 / 14 (7.14%)<br>1   |  |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1   |  |  |
| Immune system disorders<br>Hypersensitivity<br>subjects affected / exposed<br>occurrences (all) | 4 / 14 (28.57%)<br>20 |  |  |
| Anaphylactic reaction<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 14 (7.14%)<br>1   |  |  |
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 14 (7.14%)<br>1   |  |  |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 14 (7.14%)<br>1   |  |  |
| Reproductive system and breast disorders  |                       |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Vaginal discharge<br>subjects affected / exposed<br>occurrences (all)     | 1 / 14 (7.14%)<br>1  |  |  |
| Respiratory, thoracic and mediastinal disorders                           |                      |  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                 | 4 / 14 (28.57%)<br>9 |  |  |
| Adenoidal hypertrophy<br>subjects affected / exposed<br>occurrences (all) | 2 / 14 (14.29%)<br>2 |  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)             | 2 / 14 (14.29%)<br>8 |  |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)      | 2 / 14 (14.29%)<br>4 |  |  |
| Hypoxia<br>subjects affected / exposed<br>occurrences (all)               | 1 / 14 (7.14%)<br>1  |  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)    | 1 / 14 (7.14%)<br>1  |  |  |
| Respiratory disorder<br>subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1  |  |  |
| Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all)     | 1 / 14 (7.14%)<br>1  |  |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)           | 1 / 14 (7.14%)<br>1  |  |  |
| Stridor<br>subjects affected / exposed<br>occurrences (all)               | 1 / 14 (7.14%)<br>1  |  |  |
| Psychiatric disorders   |                      |  |  |

|  |   |  |  |
|--|---|--|--|
| <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>2 / 14 (14.29%)</p> <p>2</p>   |  |  |
| <p>Sleep disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>2 / 14 (14.29%)</p> <p>2</p>   |  |  |
| <p>Attention deficit/hyperactivity disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 14 (7.14%)</p> <p>1</p>  |  |  |
| <p>Irritability</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 14 (7.14%)</p> <p>1</p>  |  |  |
| <p>Product issues</p> <p>Device leakage</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Needle issue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Device breakage</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Device malfunction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 14 (21.43%)</p> <p>4</p> <p>2 / 14 (14.29%)</p> <p>3</p> <p>1 / 14 (7.14%)</p> <p>1</p> <p>1 / 14 (7.14%)</p> <p>1</p> |  |  |
| <p>Investigations</p> <p>Viral test positive</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Body temperature increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CSF red blood cell count positive</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Electrocardiogram abnormal</p>                | <p>2 / 14 (14.29%)</p> <p>2</p> <p>1 / 14 (7.14%)</p> <p>4</p> <p>1 / 14 (7.14%)</p> <p>1</p>                                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Electroencephalogram abnormal                  |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Hepatic enzyme increased                       |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 2               |  |  |
| Human rhinovirus test positive                 |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Propionibacterium test positive                |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Respiratory syncytial virus test               |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Respirovirus test positive                     |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Injury, poisoning and procedural complications |                 |  |  |
| Contusion                                      |                 |  |  |
| subjects affected / exposed                    | 4 / 14 (28.57%) |  |  |
| occurrences (all)                              | 8               |  |  |
| Medication monitoring error                    |                 |  |  |
| subjects affected / exposed                    | 4 / 14 (28.57%) |  |  |
| occurrences (all)                              | 4               |  |  |
| Foreign body                                   |                 |  |  |
| subjects affected / exposed                    | 2 / 14 (14.29%) |  |  |
| occurrences (all)                              | 3               |  |  |
| Skin abrasion                                  |                 |  |  |
| subjects affected / exposed                    | 2 / 14 (14.29%) |  |  |
| occurrences (all)                              | 3               |  |  |
| Eyelid contusion                               |                 |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                | 1 / 14 (7.14%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Fall                                       |                |  |  |
| subjects affected / exposed                | 1 / 14 (7.14%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Foot fracture                              |                |  |  |
| subjects affected / exposed                | 1 / 14 (7.14%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Head injury                                |                |  |  |
| subjects affected / exposed                | 1 / 14 (7.14%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Laceration                                 |                |  |  |
| subjects affected / exposed                | 1 / 14 (7.14%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Periorbital haematoma                      |                |  |  |
| subjects affected / exposed                | 1 / 14 (7.14%) |  |  |
| occurrences (all)                          | 2              |  |  |
| Periorbital haemorrhage                    |                |  |  |
| subjects affected / exposed                | 1 / 14 (7.14%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Procedural pain                            |                |  |  |
| subjects affected / exposed                | 1 / 14 (7.14%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Congenital, familial and genetic disorders |                |  |  |
| Bicuspid aortic valve                      |                |  |  |
| subjects affected / exposed                | 1 / 14 (7.14%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Talipes                                    |                |  |  |
| subjects affected / exposed                | 1 / 14 (7.14%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Cardiac disorders                          |                |  |  |
| Atrioventricular block second degree       |                |  |  |
| subjects affected / exposed                | 1 / 14 (7.14%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Nervous system disorders                   |                |  |  |

|                                  |                 |  |  |
|----------------------------------|-----------------|--|--|
| Extensor plantar response        |                 |  |  |
| subjects affected / exposed      | 7 / 14 (50.00%) |  |  |
| occurrences (all)                | 7               |  |  |
| Generalised tonic-clonic seizure |                 |  |  |
| subjects affected / exposed      | 6 / 14 (42.86%) |  |  |
| occurrences (all)                | 18              |  |  |
| Atonic seizures                  |                 |  |  |
| subjects affected / exposed      | 3 / 14 (21.43%) |  |  |
| occurrences (all)                | 4               |  |  |
| Dystonia                         |                 |  |  |
| subjects affected / exposed      | 3 / 14 (21.43%) |  |  |
| occurrences (all)                | 3               |  |  |
| Partial seizures                 |                 |  |  |
| subjects affected / exposed      | 3 / 14 (21.43%) |  |  |
| occurrences (all)                | 28              |  |  |
| Seizure                          |                 |  |  |
| subjects affected / exposed      | 3 / 14 (21.43%) |  |  |
| occurrences (all)                | 8               |  |  |
| Speech disorder developmental    |                 |  |  |
| subjects affected / exposed      | 3 / 14 (21.43%) |  |  |
| occurrences (all)                | 3               |  |  |
| Dyskinesia                       |                 |  |  |
| subjects affected / exposed      | 2 / 14 (14.29%) |  |  |
| occurrences (all)                | 34              |  |  |
| Epilepsy                         |                 |  |  |
| subjects affected / exposed      | 2 / 14 (14.29%) |  |  |
| occurrences (all)                | 3               |  |  |
| Tremor                           |                 |  |  |
| subjects affected / exposed      | 2 / 14 (14.29%) |  |  |
| occurrences (all)                | 2               |  |  |
| Athetosis                        |                 |  |  |
| subjects affected / exposed      | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                | 1               |  |  |
| Febrile convulsion               |                 |  |  |
| subjects affected / exposed      | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                | 2               |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| Headache                                       |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 2               |  |  |
| Language disorder                              |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 2               |  |  |
| Myoclonic epilepsy                             |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 4               |  |  |
| Partial seizures with secondary generalisation |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 2               |  |  |
| Petit mal epilepsy                             |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 3               |  |  |
| Pleocytosis                                    |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Seizure cluster                                |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Status epilepticus                             |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Ear and labyrinth disorders                    |                 |  |  |
| Deafness unilateral                            |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Ear haemorrhage                                |                 |  |  |
| subjects affected / exposed                    | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Eye disorders                                  |                 |  |  |
| Visual impairment                              |                 |  |  |
| subjects affected / exposed                    | 2 / 14 (14.29%) |  |  |
| occurrences (all)                              | 2               |  |  |
| Dry eye  |                 |  |  |

|                                  |                 |  |  |
|----------------------------------|-----------------|--|--|
| subjects affected / exposed      | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                | 1               |  |  |
| Eye movement disorder            |                 |  |  |
| subjects affected / exposed      | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                | 11              |  |  |
| Gastrointestinal disorders       |                 |  |  |
| Vomiting                         |                 |  |  |
| subjects affected / exposed      | 5 / 14 (35.71%) |  |  |
| occurrences (all)                | 7               |  |  |
| Dysphagia                        |                 |  |  |
| subjects affected / exposed      | 4 / 14 (28.57%) |  |  |
| occurrences (all)                | 5               |  |  |
| Constipation                     |                 |  |  |
| subjects affected / exposed      | 3 / 14 (21.43%) |  |  |
| occurrences (all)                | 3               |  |  |
| Abdominal pain                   |                 |  |  |
| subjects affected / exposed      | 2 / 14 (14.29%) |  |  |
| occurrences (all)                | 2               |  |  |
| Dental caries                    |                 |  |  |
| subjects affected / exposed      | 2 / 14 (14.29%) |  |  |
| occurrences (all)                | 3               |  |  |
| Diarrhoea                        |                 |  |  |
| subjects affected / exposed      | 2 / 14 (14.29%) |  |  |
| occurrences (all)                | 5               |  |  |
| Stomatitis                       |                 |  |  |
| subjects affected / exposed      | 2 / 14 (14.29%) |  |  |
| occurrences (all)                | 2               |  |  |
| Aphthous ulcer                   |                 |  |  |
| subjects affected / exposed      | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                | 1               |  |  |
| Gastrointestinal fistula         |                 |  |  |
| subjects affected / exposed      | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                | 1               |  |  |
| Gastrooesophageal reflux disease |                 |  |  |
| subjects affected / exposed      | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                | 1               |  |  |



|   |                      |  |  |
|---|----------------------|--|--|
| Toothache<br>subjects affected / exposed<br>occurrences (all)         | 1 / 14 (7.14%)<br>1  |  |  |
| Skin and subcutaneous tissue disorders                                |                      |  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)              | 3 / 14 (21.43%)<br>4 |  |  |
| Dermatitis atopic<br>subjects affected / exposed<br>occurrences (all) | 1 / 14 (7.14%)<br>1  |  |  |
| Eczema<br>subjects affected / exposed<br>occurrences (all)            | 1 / 14 (7.14%)<br>1  |  |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)          | 1 / 14 (7.14%)<br>1  |  |  |
| Rash generalised<br>subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1  |  |  |
| Rash macular<br>subjects affected / exposed<br>occurrences (all)      | 1 / 14 (7.14%)<br>1  |  |  |
| Renal and urinary disorders   |                      |  |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)        | 1 / 14 (7.14%)<br>1  |  |  |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all) | 1 / 14 (7.14%)<br>1  |  |  |
| Musculoskeletal and connective tissue disorders                       |                      |  |  |
| Pain in jaw<br>subjects affected / exposed<br>occurrences (all)       | 1 / 14 (7.14%)<br>1  |  |  |
| Infections and infestations   |                      |  |  |
| Upper respiratory tract infection                                     |                      |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed             | 12 / 14 (85.71%) |  |  |
| occurrences (all)                       | 26               |  |  |
| Gastroenteritis                         |                  |  |  |
| subjects affected / exposed             | 7 / 14 (50.00%)  |  |  |
| occurrences (all)                       | 10               |  |  |
| Influenza                               |                  |  |  |
| subjects affected / exposed             | 4 / 14 (28.57%)  |  |  |
| occurrences (all)                       | 6                |  |  |
| Corona virus infection                  |                  |  |  |
| subjects affected / exposed             | 3 / 14 (21.43%)  |  |  |
| occurrences (all)                       | 4                |  |  |
| Rhinitis                                |                  |  |  |
| subjects affected / exposed             | 3 / 14 (21.43%)  |  |  |
| occurrences (all)                       | 5                |  |  |
| Viral upper respiratory tract infection |                  |  |  |
| subjects affected / exposed             | 3 / 14 (21.43%)  |  |  |
| occurrences (all)                       | 4                |  |  |
| Bronchitis                              |                  |  |  |
| subjects affected / exposed             | 2 / 14 (14.29%)  |  |  |
| occurrences (all)                       | 3                |  |  |
| Otitis media                            |                  |  |  |
| subjects affected / exposed             | 2 / 14 (14.29%)  |  |  |
| occurrences (all)                       | 2                |  |  |
| Parainfluenzae virus infection          |                  |  |  |
| subjects affected / exposed             | 2 / 14 (14.29%)  |  |  |
| occurrences (all)                       | 2                |  |  |
| Tonsillitis                             |                  |  |  |
| subjects affected / exposed             | 2 / 14 (14.29%)  |  |  |
| occurrences (all)                       | 2                |  |  |
| Ear infection                           |                  |  |  |
| subjects affected / exposed             | 1 / 14 (7.14%)   |  |  |
| occurrences (all)                       | 1                |  |  |
| Escherichia urinary tract infection     |                  |  |  |
| subjects affected / exposed             | 1 / 14 (7.14%)   |  |  |
| occurrences (all)                       | 2                |  |  |
| Exanthema subitum                       |                  |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 1              |  |  |
| Fungal skin infection       |                |  |  |
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 1              |  |  |
| Hordeolum                   |                |  |  |
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 3              |  |  |
| Infection                   |                |  |  |
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 1              |  |  |
| Laryngitis                  |                |  |  |
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 1              |  |  |
| Mycoplasma infection        |                |  |  |
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 1              |  |  |
| Otitis externa              |                |  |  |
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 1              |  |  |
| Paronychia                  |                |  |  |
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 1              |  |  |
| Pharyngitis                 |                |  |  |
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 1              |  |  |
| Pharyngotonsillitis         |                |  |  |
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 1              |  |  |
| Pneumonia                   |                |  |  |
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 3              |  |  |
| Pneumonia chlamydial        |                |  |  |
| subjects affected / exposed | 1 / 14 (7.14%) |  |  |
| occurrences (all)           | 1              |  |  |
| Pyelonephritis              |                |  |  |

|                                       |                |  |  |
|---------------------------------------|----------------|--|--|
| subjects affected / exposed           | 1 / 14 (7.14%) |  |  |
| occurrences (all)                     | 1              |  |  |
| Pyuria                                |                |  |  |
| subjects affected / exposed           | 1 / 14 (7.14%) |  |  |
| occurrences (all)                     | 1              |  |  |
| Respiratory syncytial virus infection |                |  |  |
| subjects affected / exposed           | 1 / 14 (7.14%) |  |  |
| occurrences (all)                     | 1              |  |  |
| Respiratory tract infection viral     |                |  |  |
| subjects affected / exposed           | 1 / 14 (7.14%) |  |  |
| occurrences (all)                     | 2              |  |  |
| Rhinovirus infection                  |                |  |  |
| subjects affected / exposed           | 1 / 14 (7.14%) |  |  |
| occurrences (all)                     | 1              |  |  |
| Rotavirus infection                   |                |  |  |
| subjects affected / exposed           | 1 / 14 (7.14%) |  |  |
| occurrences (all)                     | 1              |  |  |
| Urinary tract infection bacterial     |                |  |  |
| subjects affected / exposed           | 1 / 14 (7.14%) |  |  |
| occurrences (all)                     | 1              |  |  |
| Viral infection                       |                |  |  |
| subjects affected / exposed           | 1 / 14 (7.14%) |  |  |
| occurrences (all)                     | 1              |  |  |
| Metabolism and nutrition disorders    |                |  |  |
| Hypernatraemia                        |                |  |  |
| subjects affected / exposed           | 1 / 14 (7.14%) |  |  |
| occurrences (all)                     | 1              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 31 January 2017 | <p>Implemented following agreed measures from modified BMN 190 paediatric investigation plan as set out in European Medicines Agency decision(P/0248/2016)dated 05 September 2016. This global protocol amendment superseded the previously implemented original &amp; US-specific versions of protocol:</p> <ul style="list-style-type: none"><li>o Added secondary study objective to assess serial CSF &amp; plasma PK on Day 1,&amp; Weeks 25, 49, &amp; 97 to characterize the PK profile at the recommended doses</li><li>o Added secondary study objective to assess time to disease manifestation for asymptomatic participants to better characterize the development of symptoms not captured by change in the CLN2 ML scale</li><li>o Per Agency request, removed inclusion criterion requiring the participant to have at least 1 sibling with confirmed CLN2 disease who was enrolled in Study 190-201</li><li>o Added inclusion criterion requiring abstinence or a highly effective method of contraception while participating in the study &amp; until 6 months after the study has been completed(or withdrawal from the study)</li><li>o Modified BMN 190 dosing plan from 300mg administered every 14 days(+/-3 days)to dosing every 14 days (+/-3 days) according to the participant's age:<ul style="list-style-type: none"><li>▪ birth to &lt;6 months:100mg</li><li>▪ 6 months to &lt;1 year:150mg</li><li>▪ 1 year to &lt;2 years:200mg(first 4 doses),300 mg(subsequent doses)</li><li>▪ &gt;=2 years:300mg</li></ul></li></ul> <p>This change was implemented in order to describe dosing for participants who may be enrolled &amp; are younger than 2 years of age</p> <ul style="list-style-type: none"><li>o Changed timing of Hamburg CLN2 disease rating scale administration from once every 12 weeks to once every 4 weeks in order to have more frequent assessments of clinical function; the complete Hamburg CLN2 scale(motor, language, vision, &amp; seizure subscales)will be administered for each assessment. Rating scale assessments will be videotaped every 12 weeks</li><li>o Added follow-up plan that all participants will be offered participation in a follow-up registry that will assess long-term safety &amp; efficacy of BMN 190 for patients</li></ul> |
| 17 March 2017   | <ul style="list-style-type: none"><li>o Clarified that vital signs (SBP, DBP, heart rate, respiration rate, and temperature) will be measured within 30 (±5) minutes before infusion start (or restart), every 30 (±5 minutes) during infusion, 0.5 hours (±5 minutes), 1 hour (±5 minutes), and 4 hours (±15 minutes) after infusion end, and then every 4 hours (±15 minutes) for the next 16 hours.</li><li>o In order to collect more accurate blood pressure measurements, added that blood pressure will be measured in the upper arm using an appropriately sized blood pressure cuff. If the participant's blood pressure is abnormal (as compared to site-specific reference ranges), a manual blood pressure will be obtained by a trained healthcare professional.</li><li>o Added that in participants with present or past bradycardia, conduction disorders, or with structural heart disease, an ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities) will be performed within 30 minutes before the start of infusion (±5 minutes), at 2 hours (±15 minutes) during infusion, within 15 (±5) minutes after infusion end, and 12 hours (±3 hours) after infusion end for each study drug administration.</li><li>o Clarified that a standard ECG (12-lead) will be performed at the first infusion and every 24 weeks thereafter within 15 (±5) minutes after infusion end.</li><li>o Added cardiovascular and ECG adverse events as AESI that require reporting to BioMarin Pharmacovigilance (BPV), irrespective of severity, seriousness, or causality within 24 hours of a study site awareness.</li><li>o Clarified that in the event that the ICV device is replaced, the next infusion will occur at least 14 days and no more than 28 days after surgery.</li><li>o Added dose selection rationale supporting the uniform infusion rate of 2.5 mL/hour for all participants, thus requiring shorter total infusion times for participants administered doses lower than 300 mg.</li></ul>  |

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|------------------|---|
| 05 May 2017      | <p>Implemented Regulatory Agency recommendation to increase ECG monitoring to further characterize possible acute cardiac effects of BMN 190; and to enroll at least 5 participants &lt; 2 years of age. Significant changes were as follows:</p> <ul style="list-style-type: none"> <li>o For the first infusion of BMN 190, continuous ECG monitoring (3- or 5-lead) will be performed for all participants. The ECG should begin 15 (<math>\pm</math> 5) minutes prior to infusion start, continue through infusion of BMN 190, and end after infusion of flushing solution. In the event that the participant has already received the first infusion of BMN 190, the next infusion will be monitored as above. If a 12-lead ECG is required during this time, continuous monitoring should be interrupted in order to obtain the 12-lead ECG.</li> <li>o Revised 12-lead ECG assessment to occur 30 (<math>\pm</math> 5) minutes after infusion end for all participants to provide adequate time for the infusion of flushing solution and completion of telemetry prior to the 12-lead ECG assessment.</li> <li>o Added requirement that at least 5 participants &lt; 2 years of age are enrolled.</li> <li>o Added requirement that all removed or replaced implantable ICV devices must be returned to BioMarin in order to evaluate the material integrity of the reservoir, and any other devices (as defined in the protocol) should also be returned.</li> </ul>   |
| 20 October 2017  | <p>Extended the study duration from 96 to 144 weeks and clarified study procedures during the extended study duration. Significant changes were as follows:</p> <ul style="list-style-type: none"> <li>o Modified the study duration to 144 weeks globally. The 48-week increase in treatment was implemented to increase the power of the study to show a treatment benefit for the study drug and to obtain additional safety data.</li> <li>o Revised Schedule of Events to indicate study procedures that will be performed from Week 96 to 144.</li> <li>o Frequency of complete physical examination changed from every 24 weeks to every 48 weeks to decrease burden to the participants. The frequency of the brief physical exam remains unchanged (every 2 weeks).</li> <li>o Updates were made to the immunogenicity assessment section to include serum neutralizing antibodies (Nab) sample collection. This change was made in response to Regulatory Agency request to evaluate the presence of neutralizing antibodies to BMN 190 in serum. No changes are being made to the frequency or schedule of assessments.</li> </ul>   |
| 17 December 2018 | <ul style="list-style-type: none"> <li>o Added clarification that for participants who do not participate in an extension study or registry after last dose of study drug, 4-week device safety follow-up visit &amp; 6-month safety follow-up visit will capture information regarding ongoing events at the time of last dose or new events related to study drug</li> <li>o Added that central laboratories(or a central reviewer)will be used to evaluate EEG scans in order to standardize review &amp; data presentation, &amp; limit siteassociated variability</li> <li>o Added CLN2 disease rating scale assessment to 4-week device safety follow-up visit &amp; 6-month safety follow-up visit in order to ascertain whether there were any functional changes associated with any reported adverse events</li> <li>o Removed Infant-Toddler Quality of Life Questionnaire in order to decrease study burden &amp; in acknowledgement that other Quality of Life questionnaires administered may be more relevant to this patient population</li> <li>o Removed EQ-5D-5L Questionnaire in order to decrease study burden &amp; in acknowledgement that other Quality of Life questionnaires administered may be more relevant to this patient population</li> <li>o Clarified that EEGs should be performed every 24 weeks, including end of treatment visit</li> <li>o Added updated information that material degradation of ICV device reservoir has occurred after approximately 105 perforations of ICV device in benchtop testing, &amp; has been observed in clinical trials with approximately 4 years of BMN 190 administration. Access device replacement should be considered prior to 4 years of regular administration of BMN 190; with decision made on an individual participant level based on medical judgment of investigator</li> <li>o Assessment of height &amp; body weight has been changed from every 48 weeks to every 24 weeks to permit additional monitoring of growth milestones</li> <li>o Clarified that, in event of a device-related AE where device &amp; its components should be returned to BioMarin for further testing, infusion pump does not need to be returned</li> </ul> |

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| 05 February 2019 | Corrected an error in Protocol 190-203 Amendment 5 in which "Ophthalmology Assessments" (Baseline/First Infusion, Q48W, Study Completion/Early Termination) was inadvertently removed from the Schedule of Events (Table 9.1.1) and Study Procedures (Section 12). Ophthalmologic assessments for the 190-203 protocol should continue to be performed before the first infusion and every 48 weeks for the duration of the study. |
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported