



## Clinical trial results:

### Evaluation of safety following Immune Tolerance Induction treatment with turoctocog alfa in patients with haemophilia A following inhibitor development in NN7170-4213 trial

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-003821-40 |
| Trial protocol           | GB AT BG DE    |
| Global end of trial date | 19 June 2019   |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 27 December 2019 |
| First version publication date | 27 December 2019 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | NN7170-4345 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT03588741     |
| WHO universal trial number (UTN)   | U1111-1187-7323 |

Notes:

#### Sponsors

|                              |                                                                                                                   |
|------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Novo Nordisk A/S                                                                                                  |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880                                                                               |
| Public contact               | Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 866 8677178, clinicaltrials@novonordisk.com |
| Scientific contact           | Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 866 8677178, clinicaltrials@novonordisk.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 31 October 2019 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 19 June 2019    |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 19 June 2019    |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate safety of immune tolerance induction treatment with turoctocog alfa in patients who have developed neutralising antibodies against coagulation factor VIII (FVIII) after exposure to subcutaneous turoctocog alfa pegol during participation in NN7170-4213.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (October 2013), ICH Good Clinical Practice, including archiving of essential documents (June 1996), and 21 CFR 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 12 June 2018 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Germany: 1 |
| Worldwide total number of subjects   | 1          |
| EEA total number of subjects         | 1          |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |
| Adolescents (12-17 years)                 | 0 |
| Adults (18-64 years)                      | 1 |
| From 65 to 84 years                       | 0 |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at 1 trial site in Germany.

### Pre-assignment

Screening details:

Previously treated subjects with severe haemophilia A (FVIII activity <1% according to medical records) who had developed clinically relevant FVIII inhibitors in trial NN7170-4213 were offered immune tolerance induction (ITI) treatment with turoctocog alfa.

### Period 1

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

### Arms

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Turoctocog alfa |
|------------------|-----------------|

Arm description:

The subject received intravenous (i.v.) injection of 65 international units per kilogram (IU/kg) turoctocog alfa 3 times per week.

|                                        |                                               |
|----------------------------------------|-----------------------------------------------|
| Arm type                               | Experimental                                  |
| Investigational medicinal product name | Turoctocog alfa                               |
| Investigational medicinal product code |                                               |
| Other name                             | NovoEight                                     |
| Pharmaceutical forms                   | Powder and solvent for solution for injection |
| Routes of administration               | Intravenous use                               |

Dosage and administration details:

The subject received i.v. injection of 65 IU/kg turoctocog alfa 3 times per week. The total consumption of turoctocog alfa comprised of a total of 8 administrations of between 63 and 65 IU/kg each.

| Number of subjects in period 1 | Turoctocog alfa |
|--------------------------------|-----------------|
| Started                        | 1               |
| Completed                      | 0               |
| Not completed                  | 1               |
| Withdrawal by subject          | 1               |

## Baseline characteristics

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Turoctocog alfa |
|-----------------------|-----------------|

Reporting group description:

The subject received intravenous (i.v.) injection of 65 international units per kilogram (IU/kg) turoctocog alfa 3 times per week.

| Reporting group values                                                                                                                                               | Turoctocog alfa | Total |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-------|--|
| Number of subjects                                                                                                                                                   | 1               | 1     |  |
| Age Categorical                                                                                                                                                      |                 |       |  |
| Units: Subjects                                                                                                                                                      |                 |       |  |
| Adults (18-64 years)                                                                                                                                                 | 1               | 1     |  |
| Age Continuous                                                                                                                                                       |                 |       |  |
| Since the study enrolled a single subject, the age continuous data is not provided as this could be against General Data Protection Regulation (EU) 2016/679 (GDPR). |                 |       |  |
| Units: years                                                                                                                                                         |                 |       |  |
| arithmetic mean                                                                                                                                                      | 0               |       |  |
| standard deviation                                                                                                                                                   | ± 0             | -     |  |
| Gender Categorical                                                                                                                                                   |                 |       |  |
| Units: Subjects                                                                                                                                                      |                 |       |  |
| Male                                                                                                                                                                 | 1               | 1     |  |

## End points

### End points reporting groups

|                                                                                                                                                                    |                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Reporting group title                                                                                                                                              | Turoctocog alfa     |
| Reporting group description:<br>The subject received intravenous (i.v.) injection of 65 international units per kilogram (IU/kg) turoctocog alfa 3 times per week. |                     |
| Subject analysis set title                                                                                                                                         | Full analysis set   |
| Subject analysis set type                                                                                                                                          | Full analysis       |
| Subject analysis set description:<br>Full analysis set (FAS) comprised of all subjects who initiated ITI treatment with turoctocog alfa.                           |                     |
| Subject analysis set title                                                                                                                                         | Safety analysis set |
| Subject analysis set type                                                                                                                                          | Safety analysis     |
| Subject analysis set description:<br>Safety analysis set (SAS) comprised of all subjects who initiated ITI treatment with turoctocog alfa.                         |                     |

### Primary: Number of adverse events

|                                                                                                                                                                                                                                                                                                   |                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| End point title                                                                                                                                                                                                                                                                                   | Number of adverse events <sup>[1]</sup> |
| End point description:<br>An adverse event (AE) was any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. SAS comprised of all subjects who initiated ITI treatment with turoctocog alfa. |                                         |
| End point type                                                                                                                                                                                                                                                                                    | Primary                                 |
| End point timeframe:<br>During immune tolerance induction treatment with turoctocog alfa.                                                                                                                                                                                                         |                                         |

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: The primary endpoint investigated safety and was analysed using descriptive statistics, and thus no statistical analysis was performed.

|                             |                  |  |  |  |
|-----------------------------|------------------|--|--|--|
| <b>End point values</b>     | Turoctocog alfa  |  |  |  |
| Subject group type          | Reporting group  |  |  |  |
| Number of subjects analysed | 1 <sup>[2]</sup> |  |  |  |
| Units: Events               | 6                |  |  |  |

Notes:

[2] - SAS.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Response to immune tolerance induction treatment (success, partial success, failure, other)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Response to immune tolerance induction treatment (success, partial success, failure, other) |
| End point description:<br>ITI treatment response was categorized as: 1. Success: Undetectable inhibitor titre <0.6 bethesda units (BU) (or lower limit of quantification [LLOQ] if above 0.6 BU); Normalised FVIII in vivo recovery, defined as $\geq 0.013$ international units (IU) per milliliter per IU per kilogram ((IU/ml)/(IU/kg)) (66% of expected incremental recovery); turoctocog alfa half-life $\geq 7$ hours (based on FVIII activity) after 72 hours treatment-free washout period. 2. Partial success: Inhibitor titre $\leq 5$ BU; Clinical effect of turoctocog alfa therapy as judged by the investigator. 3. Failure (one criterion had to be fulfilled): Failure to attain |                                                                                             |

defined success or partial success after 24 months of ITI treatment with turoctocog alfa; Decrease in inhibitor titre after 12 months of ITI treatment <20% compared to peak titre. 4. Other: Subjects not fulfilling the above criteria e.g. early withdrawal from ITI treatment, lack of adherence to recommended ITI protocol etc. FAS.

|                                                                              |           |
|------------------------------------------------------------------------------|-----------|
| End point type                                                               | Secondary |
| End point timeframe:                                                         |           |
| Within a maximum immune tolerance induction treatment duration of 24 months. |           |

| End point values            | Turoctocog alfa  |  |  |  |
|-----------------------------|------------------|--|--|--|
| Subject group type          | Reporting group  |  |  |  |
| Number of subjects analysed | 1 <sup>[3]</sup> |  |  |  |
| Units: Subjects             |                  |  |  |  |
| Success                     | 0                |  |  |  |
| Partial success             | 0                |  |  |  |
| Failure                     | 0                |  |  |  |
| Other                       | 1                |  |  |  |

Notes:

[3] - FAS.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

up to 31 months

Adverse event reporting additional description:

Evaluation of safety was based on SAS which comprised of all subjects who initiated ITI treatment with turoctocog alfa.

'Number of deaths causally related to treatment' is the data considered to present under 'total number of deaths resulting from adverse events'.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Turoctocog alfa |
|-----------------------|-----------------|

Reporting group description:

Subjects received intravenous (i.v.) injection of 65 international units per kilogram (IU/kg) turoctocog alfa 3 times per week. The total consumption of turoctocog alfa comprised of a total of 8 administrations of between 63 and 65 IU/kg each.

| Serious adverse events                            | Turoctocog alfa |  |  |
|---------------------------------------------------|-----------------|--|--|
| Total subjects affected by serious adverse events |                 |  |  |
| subjects affected / exposed                       | 0 / 1 (0.00%)   |  |  |
| number of deaths (all causes)                     | 0               |  |  |
| number of deaths resulting from adverse events    | 0               |  |  |

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

| Non-serious adverse events                            | Turoctocog alfa |  |  |
|-------------------------------------------------------|-----------------|--|--|
| Total subjects affected by non-serious adverse events |                 |  |  |
| subjects affected / exposed                           | 1 / 1 (100.00%) |  |  |
| Nervous system disorders                              |                 |  |  |
| Headache                                              |                 |  |  |
| subjects affected / exposed                           | 1 / 1 (100.00%) |  |  |
| occurrences (all)                                     | 1               |  |  |
| Musculoskeletal and connective tissue disorders       |                 |  |  |
| Muscle disorder                                       |                 |  |  |

|                                                                                                    |                      |  |  |
|----------------------------------------------------------------------------------------------------|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                   | 1 / 1 (100.00%)<br>2 |  |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 1 (100.00%)<br>3 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 28 January 2019 | 1) To align with new internal procedures in Novo Nordisk. Summary of Product Characteristics will no longer be the source of the Reference Safety Information (RSI) for assessment of AE expectedness. 2) Change in treatment of patient section, in order to allow investigators to treat the patients as deemed relevant and according to local guidelines. 3) Testing for non-neutralising antibodies will only be performed if deemed relevant or for safety reasons, e.g. in case of adverse events suspected of being related to antibodies. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported