



Clinical trial results:

A multi-centre, comparative, double blind, randomised cross-over trial investigating single dose pharmacokinetics and safety of turoctocog alfa pegol from the pivotal process and turoctocog alfa pegol from the commercial process in patients with severe haemophilia A

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-005327-63 |
| Trial protocol | NL DK DE ES FR |
| Global end of trial date | 07 April 2017 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 12 April 2018 |
| First version publication date | 12 April 2018 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | NN7088-4033 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02920398 |
| WHO universal trial number (UTN) | U1111-1176-9253 |

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, clinicaltrials@novonordisk.com |
| Scientific contact | Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, 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 | 28 November 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 April 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 April 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate and compare the single-dose pharmacokinetic of N8-GP (turoctocog alfa pegol) from the pivotal process with N8-GP from the commercial process, each given as intravenous administrations of 50 U/kg to patients with severe haemophilia A.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008), International Conference on Harmonisation (ICH) Good Clinical Practice (1996) and United States Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

| | |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment | 04 October 2016 |
| 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 | Denmark: 3 |
| Country: Number of subjects enrolled | France: 1 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Spain: 2 |
| Country: Number of subjects enrolled | United States: 11 |
| Worldwide total number of subjects | 21 |
| EEA total number of subjects | 10 |

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 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 19 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 11 sites in 6 countries, as follows: Denmark: 1 site; France: 1 site; Germany: 1 site; Netherlands: 1 site; Spain: 2 sites; United States: 5 sites.

Pre-assignment

Screening details:

Study Design: Subjects were recruited from trial NN7088-3859 (EudraCT number: 2011-001142-15) and returned to trial NN7088-3859 upon completion of this trial. This cross over trial included two identical pharmacokinetic (PK) visits (each consisting of 5 days) with a wash-out period of at least 7 days prior to each PK visit.

Period 1

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

Blinding implementation details:

N8-GP was packed blinded and allocated via the interactive web response system (IWRS) to ensure the blinding of the trial product. The N8-GP from the pivotal manufacturing process and N8-GP from the commercial manufacturing process were visually identical.

Arms

| | |
|-----------|--------------------|
| Arm title | Overall population |
|-----------|--------------------|

Arm description:

This was a two period cross-over study. All subjects were randomised in a 1:1 manner to receive one of the two possible treatment sequences of trial products, turoctocog alfa pegol (N8-GP) from the commercial process and N8-GP from the pivotal process. Subjects, who received N8-GP from the commercial process in treatment period 1, received N8-GP from the pivotal process in treatment period 2. And subjects, who received N8-GP from the pivotal process in treatment period 1, received N8-GP from the commercial process in treatment period 2. There was a wash-out period of at least 7 days prior to dosing in both the periods.

| | |
|----------------------------------------|-----------------------------------------------|
| Arm type | Cross-over |
| Investigational medicinal product name | Turoctocog alfa pegol |
| Investigational medicinal product code | |
| Other name | N8-GP |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects were administered with a single-dose of N8-GP 50±5 IU/kg from the commercial process on day 1 of both the treatment periods. N8-GP was supplied as a sterile, freeze-dried powder in a 2–8°C (36–46°F) stable formulation single use vial with a nominal content of 2000 IU/vial was reconstituted with 4.3 mL 0.9% isotonic sodium chloride solution for intravenous (i.v.) injection. After reconstitution each vial contained 500 IU/mL N8-GP.

| | |
|----------------------------------------|-----------------------------------------------|
| Investigational medicinal product name | Turoctocog alfa pegol |
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Dosage and administration details:

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| Number of subjects in period 1 | Overall population |
|---------------------------------------|--------------------|
| Started | 21 |
| Completed | 21 |

Baseline characteristics

Reporting groups

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title | Overall population |
| Reporting group description: | |
| This was a two period cross-over study. All subjects were randomised in a 1:1 manner to receive one of the two possible treatment sequences of trial products, turoctocog alfa pegol (N8-GP) from the commercial process and N8-GP from the pivotal process. Subjects, who received N8-GP from the commercial process in treatment period 1, received N8-GP from the pivotal process in treatment period 2. And subjects, who received N8-GP from the pivotal process in treatment period 1, received N8-GP from the commercial process in treatment period 2. There was a wash-out period of at least 7 days prior to dosing in both the periods. | |

| Reporting group values | Overall population | Total | |
|------------------------|--------------------|-------|--|
| Number of subjects | 21 | 21 | |
| Age Categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 19 | 19 | |
| From 65-84 years | 2 | 2 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 42.4 | | |
| standard deviation | ± 14.2 | - | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Male | 21 | 21 | |

Subject analysis sets

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Subject analysis set title | Turoctocog alfa pegol commercial process |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Subjects received N8-GP from the commercial process in treatment period 1 (from treatment sequence, N8-GP commercial process/N8-GP pivotal process) and in treatment period 2 (from treatment sequence, N8-GP pivotal process/N8-GP commercial process). | |
| Subject analysis set title | Turoctocog alfa pegol pivotal process |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Subjects received N8-GP from the pivotal process in treatment period 1 (from treatment sequence, N8-GP pivotal process/N8-GP commercial process) and in treatment period 2 (from treatment sequence, N8-GP commercial process/N8-GP pivotal process). | |

| Reporting group values | Turoctocog alfa pegol commercial process | Turoctocog alfa pegol pivotal process | |
|------------------------|------------------------------------------|---------------------------------------|--|
| Number of subjects | 21 | 21 | |
| Age Categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 19 | 19 | |
| From 65-84 years | 2 | 2 | |

| | | | |
|--------------------|--------|--------|--|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 42.4 | 42.4 | |
| standard deviation | ± 14.2 | ± 14.2 | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Male | 21 | 21 | |

End points

End points reporting groups

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Reporting group title | Overall population |
| Reporting group description: This was a two period cross-over study. All subjects were randomised in a 1:1 manner to receive one of the two possible treatment sequences of trial products, turoctocog alfa pegol (N8-GP) from the commercial process and N8-GP from the pivotal process. Subjects, who received N8-GP from the commercial process in treatment period 1, received N8-GP from the pivotal process in treatment period 2. And subjects, who received N8-GP from the pivotal process in treatment period 1, received N8-GP from the commercial process in treatment period 2. There was a wash-out period of at least 7 days prior to dosing in both the periods. | |
| Subject analysis set title | Turoctocog alfa pegol commercial process |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects received N8-GP from the commercial process in treatment period 1 (from treatment sequence, N8-GP commercial process/N8-GP pivotal process) and in treatment period 2 (from treatment sequence, N8-GP pivotal process/N8-GP commercial process). | |
| Subject analysis set title | Turoctocog alfa pegol pivotal process |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects received N8-GP from the pivotal process in treatment period 1 (from treatment sequence, N8-GP pivotal process/N8-GP commercial process) and in treatment period 2 (from treatment sequence, N8-GP commercial process/N8-GP pivotal process). | |

Primary: Area under the FVIII activity-time curve - dose normalised to 50 U/kg (AUC0-96h, norm)

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| End point title | Area under the FVIII activity-time curve - dose normalised to 50 U/kg (AUC0-96h, norm) |
| End point description: Area under the FVIII plasma activity versus time profile from time zero to 96h normalised to 50 U/kg (AUC0-96h, norm). i.e., Measure of FVIII plasma exposure in the time interval 0 to 96h. Blood samples were analysed using both chromogenic and one-stage clotting assays. The results are based on the full analysis set (FAS), which included all subjects with at least one evaluable PK profile. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned 'Measure Type' should be read as 'Geometric Mean (Coefficient of Variation in Percentage)'. | |
| End point type | Primary |
| End point timeframe: From 0 to 96 h post injection | |

| End point values | Turoctocog alfa pegol commercial process | Turoctocog alfa pegol pivotal process | | |
|-----------------------------------------------------|------------------------------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: IU*h/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Chromogenic assay | 34.250 (± 32.091) | 34.064 (± 28.715) | | |
| One-stage clotting assay | 40.965 (± 29.241) | 41.731 (± 19.964) | | |

Statistical analyses

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Statistical analysis title | N8-GP commercial process vs N8-GP pivotal process |
| Statistical analysis description: | |
| The primary endpoint was log-transformed and analysed using an analysis of variance (ANOVA) model with product, period, sequence and patient within sequence as factors. The following 'comparison groups' should be read as 'N8-GP commercial process versus (vs) N8-GP pivotal process'. Due to cross-over design of the trial, the following 'number of subjects included in analysis' is being erroneously displayed as 40. Actual 'number of subjects included in analysis' is 20. | |
| Comparison groups | Turoctocog alfa pegol commercial process v Turoctocog alfa pegol pivotal process |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Treatment ratio |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.97 |
| upper limit | 1.04 |

Secondary: FVIII activity 30 min post administration - dose normalised to 50 U/kg

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| End point title | FVIII activity 30 min post administration - dose normalised to 50 U/kg |
| End point description: | |
| The FVIII activity recorded 30 minutes after end of injection normalised to 50 U/kg. Blood samples were analysed using both chromogenic and one-stage clotting assays. The following timeframe should be read as 'from time of trial product administration to 30 minutes post-dose'. The results are based on the FAS. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned 'Measure Type' should be read as 'Geometric Mean (Coefficient of Variation in Percentage)'. | |
| End point type | Secondary |
| End point timeframe: | |
| From time of trial product administration to 96 hours post-dose | |

| End point values | Turoctocog alfa pegol commercial process | Turoctocog alfa pegol pivotal process | | |
|-----------------------------------------------------|------------------------------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: IU/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |

| | | | | |
|--------------------------|-----------------------|-----------------------|--|--|
| Chromogenic assay | 1.183 (\pm 16.568) | 1.157 (\pm 18.982) | | |
| One-stage clotting assay | 1.420 (\pm 22.105) | 1.320 (\pm 19.032) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the FVIII activity-time curve from 0 to infinity

| | |
|-----------------|-------------------------------------------------------------|
| End point title | Area under the FVIII activity-time curve from 0 to infinity |
|-----------------|-------------------------------------------------------------|

End point description:

Area under the FVIII activity versus time profile from time zero to infinity (AUC0-inf). i.e., Measure of total FVIII plasma exposure. Blood samples were analysed using both chromogenic and one-stage clotting assays. The following timeframe should be read as 'from time of trial product administration to infinity'. The results are based on the FAS. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned 'Measure Type' should be read as 'Geometric Mean (Coefficient of Variation in Percentage)'.

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

End point timeframe:

From time of trial product administration to 96 hours post-dose

| End point values | Turoctocog alfa pegol commercial process | Turoctocog alfa pegol pivotal process | | |
|-----------------------------------------------------|------------------------------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: IU*h/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Chromogenic assay | 40.305 (\pm 32.112) | 40.987 (\pm 27.532) | | |
| One-stage clotting assay | 49.598 (\pm 28.704) | 50.594 (\pm 22.384) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance

| | |
|-----------------|-----------|
| End point title | Clearance |
|-----------------|-----------|

End point description:

Total plasma clearance (CL) of drug after intravenous administration. Blood samples were analysed using both chromogenic and one-stage clotting assays. The following timeframe should be read as 'from time of trial product administration to infinity'. The results are based on the FAS. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned 'Measure Type' should be read as 'Geometric Mean (Coefficient of Variation in Percentage)'.

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

End point timeframe:

From time of trial product administration to 96 hours post-dose

| End point values | Turoctocog alfa pegol commercial process | Turoctocog alfa pegol pivotal process | | |
|--------------------------------------------------------|---------------------------------------------------|---------------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: mL/h/kg | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Chromogenic assay | 1.340 (\pm 31.753) | 1.340 (\pm 27.141) | | |
| One-stage clotting assay | 1.089 (\pm 28.218) | 1.085 (\pm 22.120) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental recovery

| | |
|-----------------|----------------------|
| End point title | Incremental recovery |
|-----------------|----------------------|

End point description:

Dose-normalised FVIII activity recorded 30 min after end of injection and reported as [U/mL]/[U/kg]. Expected to be the highest dose-normalised activity observed. Blood samples were analysed using both chromogenic and one-stage clotting assays. The following timeframe should be read as 'from time of trial product administration to 30 min post-dose'. The results are based on the FAS. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned 'Measure Type' should be read as 'Geometric Mean (Coefficient of Variation in Percentage)'.

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

End point timeframe:

From time of trial product administration to 96 hours post-dose

| End point values | Turoctocog alfa pegol commercial process | Turoctocog alfa pegol pivotal process | | |
|--------------------------------------------------------|---------------------------------------------------|---------------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: (IU/mL) / (U/kg) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Chromogenic assay | 0.023 (\pm 17.284) | 0.023 (\pm 19.909) | | |
| One-stage clotting assay | 0.028 (\pm 24.325) | 0.026 (\pm 20.728) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal half-life

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|-----------------|--------------------|
| End point title | Terminal half-life |
|-----------------|--------------------|

End point description:

Terminal half-life ($t_{1/2}$) = $\ln(2) / \lambda_z$, where λ_z was the terminal elimination rate estimated using linear regression on the terminal part of the log(activity) versus time profile. Blood samples were analysed using both chromogenic and one-stage clotting assays. The following timeframe should be read as 'from 24 hours post-dose to 96 hours post-dose'. The results are based on the FAS. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned 'Measure Type' should be read as 'Geometric Mean (Coefficient of Variation in Percentage)'.

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

End point timeframe:

From time of trial product administration to 96 hours post-dose

| End point values | Turoctocog alfa pegol commercial process | Turoctocog alfa pegol pivotal process | | |
|--------------------------------------------------------|---------------------------------------------------|---------------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: hour (h) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Chromogenic assay | 19.469 (\pm 37.648) | 20.648 (\pm 30.984) | | |
| One-stage clotting assay | 22.908 (\pm 37.168) | 23.405 (\pm 35.313) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

All AEs reported after exposed to N8-GP were defined as TEAEs. Since all patients were transferred from trial NN7088-3859, all AEs reported in this trial were considered as treatment emergent even if the AE occurred prior to the first dosing in this trial

Adverse event reporting additional description:

Analysis population: Safety analysis set, which included all subjects transferring from trial NN7088-3859 into this trial. All reported adverse events in this trial were treatment emergent adverse events (TEAEs).

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

Dictionary used

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

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

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious adverse events with a prevalence of 5% are available for this trial. In total, 2 subjects in the turoctocog alfa pegol pivotal process arm had non-serious adverse events and no subject in the turoctocog alfa pegol commercial process arm had non-serious adverse events.

Additionally 3 AEs were reported outside the PK visits

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 04 November 2016 | Changes were done in exclusion criteria. A criterion on hypersensitivity was added. The wording of the criterion is identical to the exclusion criterion in trial NN7088-3859's protocol from where all patients were recruited. |
| 23 March 2017 | This protocol amendment was prepared to clarify the assays used for assessment of coagulation factor VIII (FVIII) activity in trial NN7088-4033 in order to align with updates in the assay strategy for all pathfinder™ trials. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported