



Clinical trial results:

An Open-label, Multi-centre, Un-controlled Trial to Assess Efficacy and Safety of NNC-0156-0000-0009 during Surgical Procedures in Patients with Haemophilia B.

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2010-023070-40 |
| Trial protocol | FR GB NL DE IT ES GR AT |
| Global end of trial date | 02 December 2013 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 15 March 2016 |
| First version publication date | 28 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | NN7999-3773 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01386528 |
| WHO universal trial number (UTN) | U1111-1121-4554 |

Notes:

Sponsors

| | |
|------------------------------|---------------------------------------------------------------------------------------|
| Sponsor organisation name | Novo Nordisk A/S |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2860 |
| Public contact | Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |
| Scientific contact | Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |

Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000731-PIP01-09 |
| 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 | 27 May 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 02 December 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 December 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the haemostatic effect of nonacog beta pegol (N9-GP) during surgical procedures in patients with haemophilia B.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Seoul, October 2008), the ICH Good Clinical Practice (Geneva, May 1996) and FDA 21 CFR 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

| | |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment | 08 June 2012 |
| 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 | United Kingdom: 2 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | Romania: 1 |
| Country: Number of subjects enrolled | Malaysia: 2 |
| Country: Number of subjects enrolled | South Africa: 2 |
| Country: Number of subjects enrolled | Taiwan: 1 |
| Country: Number of subjects enrolled | Turkey: 1 |
| Country: Number of subjects enrolled | United States: 3 |
| Worldwide total number of subjects | 13 |
| EEA total number of subjects | 4 |

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) | 1 |
| Adults (18-64 years) | 12 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The 10 sites in 8 countries enrolled patients: Italy (1 site), Malaysia (1 site), Romania (1 site), South Africa (1 site), Taiwan (1 site), Turkey (1 site), UK (2 sites), US (2 sites).

Pre-assignment

Screening details:

Patients enrolled in the present trial could be recruited from the pivotal trial (NN7999-3747) or the extension trial (NN7999-3775). In addition, new patients could also be recruited into the present trial.

Period 1

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

Blinding implementation details:

Not applicable.

Arms

| | |
|-----------|--------------------|
| Arm title | nonacog beta pegol |
|-----------|--------------------|

Arm description:

New patients as well as transferred patients from the pivotal trial (NN7999-3747) or the extension trial (NN7999-3775) received nonacog beta pegol at screening and followed a preventive treatment regimen with nonacog beta pegol until one week before the day of surgery. No more than 4 hours prior to the planned surgical procedure, all patients received a single bolus injection of 80 U/kg of nonacog beta pegol. Postoperatively, the patients received fixed doses of 40 U/kg repeated at the investigator's discretion aiming for no less than the FIX levels recommended by the World Federation of Hemophilia. Nonacog beta pegol was administered intravenously (into the vein).

| | |
|----------------------------------------|----------------------------------------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | nonacog beta pegol (N9-GP) |
| Investigational medicinal product code | NNC 0156-0000-009 |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection, Solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The new patients were dosed once with 40 U/kg nonacog beta pegol at screening. The FIX (coagulation factor 9) activity after 30 minutes at this visit, was used to determine if dose adjustments were necessary during the peri-operative period. For patients who had been on prophylaxis with 40 U/kg in the preceding trial, the most recent FIX activity level 30 minutes post-dose was used instead. All patients received a pre-operative dose of nonacog beta pegol 15 minutes to 4 hours prior to the surgery and before any procedures were undertaken including anaesthesia. The pre-operative dose was a single bolus injection of 80 U/kg. It was recommended to give a dose of 40 U/kg 24-48 hours after the pre-operative dose depending on the desired FIX activity level. From the day after surgery (Day 1) and through Day 6, nonacog beta pegol dosing was adjusted to aim for a FIX activity level of approximately 0.50 U/mL.

| Number of subjects in period 1 | nonacog beta pegol |
|---------------------------------------|--------------------|
| Started | 13 |
| Completed | 13 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description:

The demographics and baseline characteristics are presented for the full analysis set (FAS) which included all patients exposed to nonacog beta pegol.

| Reporting group values | Overall Study | Total | |
|------------------------------------------------------------------|----------------|-------|--|
| Number of subjects | 13 | 13 | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years median full range (min-max) | 39 15 to 56 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 13 | 13 | |

End points

End points reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | nonacog beta pegol |
|-----------------------|--------------------|

Reporting group description:

New patients as well as transferred patients from the pivotal trial (NN7999-3747) or the extension trial (NN7999-3775) received nonacog beta pegol at screening and followed a preventive treatment regimen with nonacog beta pegol until one week before the day of surgery. No more than 4 hours prior to the planned surgical procedure, all patients received a single bolus injection of 80 U/kg of nonacog beta pegol. Postoperatively, the patients received fixed doses of 40 U/kg repeated at the investigator's discretion aiming for no less than the FIX levels recommended by the World Federation of Hemophilia. Nonacog beta pegol was administered intravenously (into the vein).

Primary: Haemostatic effect during surgery evaluated by the four-point response scale, assessed by the investigator/surgeon at the day of surgery – Four-point response scale: Excellent, good, moderate, poor.

| | |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Haemostatic effect during surgery evaluated by the four-point response scale, assessed by the investigator/surgeon at the day of surgery – Four-point response scale: Excellent, good, moderate, poor. ^[1] |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Haemostatic effect during surgery was evaluated immediately after surgery (last stitch) using a four-point response scale:

– Four-point response scale: Excellent, good, moderate, poor.

The evaluation was done by the surgeon, anaesthesiologist and/or investigator based on experience as follows:

1. Excellent: Better than expected/predicted in this type of procedure.
2. Good: As expected in this type of procedure.
3. Moderate: Less than optimal for the type of procedure but haemostatic response maintained without change of treatment regimen.
4. Poor: Bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required.

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

End point timeframe:

During surgery (assessed immediately after surgery (last stitch)).

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: Endpoint is summarised as well as listed. No statistical analyses were planned for this endpoint.

| End point values | nonacog beta pegol | | | |
|-----------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: Frequency | | | | |
| number (not applicable) | | | | |
| Excellent | 10 | | | |
| Good | 3 | | | |
| Moderate | 0 | | | |
| Poor | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of N9-GP (U/kg BW) during surgery and post-operative period

| | |
|-----------------|-------------------------------------------------------------------------|
| End point title | Consumption of N9-GP (U/kg BW) during surgery and post-operative period |
|-----------------|-------------------------------------------------------------------------|

End point description:

Mean consumption of nonacog beta pegol (U/kg) used for treatment per patient before surgery, during surgery (the time from knife to skin until last stitch) and post-operative period.

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

End point timeframe:

Before surgery is defined as the time from the patient entered the trial until the surgery. During surgery is defined as the time from knife to skin until last stitch. The post-operative period is defined as the time from Day 1 to Day 13

| | | | | |
|--------------------------------------------|--------------------|--|--|--|
| End point values | nonacog beta pegol | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: U/Kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Consumption used for treatment per patient | 328.2 (± 113.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Transfusion requirements (fulfilling transfusion criteria) during surgery and the post-operative

| | |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | Transfusion requirements (fulfilling transfusion criteria) during surgery and the post-operative |
|-----------------|--------------------------------------------------------------------------------------------------|

End point description:

Mean quantity of transfusion during surgery (the time from knife to skin until last stitch) and the post-operative period (Day 1-13).

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

End point timeframe:

During surgery is defined as the time from knife to skin until last stitch. The post-operative period is defined as the time from Day 1 to Day 13.

| End point values | nonacog beta pegol | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 ^[2] | | | |
| Units: mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| During surgery | 275 (± 35.4) | | | |
| Post operative period (Days 1-6) | 266.7 (± 28.9) | | | |

Notes:

[2] - Only 2 patients received transfusions.

Statistical analyses

No statistical analyses for this end point

Secondary: Haemoglobin pre and post surgery start (0, 1h, 24 h)

| | |
|------------------------|----------------------------------------------------------|
| End point title | Haemoglobin pre and post surgery start (0, 1h, 24 h) |
| End point description: | The mean pre-surgery and post surgery haemoglobin level. |
| End point type | Secondary |
| End point timeframe: | Prior to surgery and post surgery start (0, 1h, 24 h) |

| End point values | nonacog beta pegol | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 ^[3] | | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Prior to surgery | 8.98 (± 0.67) | | | |
| 1 hour post-surgery | 8.37 (± 0.78) | | | |
| 24 hours post-surgery | 7.99 (± 1.13) | | | |

Notes:

[3] - 10 and 12 subjects contributed to the analysis during 1 hour and 24 hour post-surgery respectively.

Statistical analyses

No statistical analyses for this end point

Secondary: Haemoglobin post surgery start - every 24 hours in the post-operative period.

| | |
|------------------------|-------------------------------------------------------------------------------|
| End point title | Haemoglobin post surgery start - every 24 hours in the post-operative period. |
| End point description: | Mean haemoglobin level, every 24 hours in the post-operative period. |

| | |
|----------------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Every 24 hours in the post-operative period. | |

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | nonacog beta pegol | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[4] | | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | () | | | |

Notes:

[4] - Patients could be discharged on Day 3 and so Hb could not be measured every 24 hrs post surgery.

Statistical analyses

No statistical analyses for this end point

Secondary: AE and SAEs reported during the trial period until the last visit.

| | |
|-----------------|--------------------------------------------------------------------|
| End point title | AE and SAEs reported during the trial period until the last visit. |
|-----------------|--------------------------------------------------------------------|

End point description:

The number of adverse events and serious adverse events per patient years of exposure, reported during the trial period.

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

End point timeframe:

Adverse events from the first trial related activity after the patient had signed the informed consent and until post treatment follow-up period.

| | | | | |
|--------------------------------------------|--------------------|--|--|--|
| End point values | nonacog beta pegol | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: Events per patient year of exposure | | | | |
| number (not applicable) | | | | |
| Adverse events | 12.12 | | | |
| Serious adverse events | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of inhibitors against FIX (≥0.6 BU) until the last visit

| | |
|-----------------|--------------------------------------------------------------------|
| End point title | Incidence of inhibitors against FIX (≥0.6 BU) until the last visit |
|-----------------|--------------------------------------------------------------------|

End point description:

Number of patients with inhibitory antibodies.

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

End point timeframe:

During the trial from screening until last visit. The last visit is defined as the end of trial visit if the patient continues in the extension trial and as the follow-up visit if the patient does not continue in the extension trial.

| | | | | |
|-----------------------------|-----------------------|--|--|--|
| End point values | nonacog beta pegol | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: Number of patients | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs from screening visit (day 0) and until post treatment follow-up period. Patients not continuing in the extension trial attended a follow-up visit 4 weeks \pm 2 weeks after the last dose of nonacog beta pegol.

Adverse event reporting additional description:

The safety analysis set consists of all patients exposed to nonacog beta pegol.

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

Dictionary used

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

| | |
|--------------------|---------|
| Dictionary version | unknown |
|--------------------|---------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Nonacog beta pegol |
|-----------------------|--------------------|

Reporting group description:

New patients as well as transferred patients from Paradigm™ 2 (NN7999-3747) or Paradigm™ 4 (NN7999-3775) trials received nonacog beta pegol at screening, just prior to and during surgical intervention, administered intravenously (into the vein).

| Serious adverse events | Nonacog beta pegol | | |
|---------------------------------------------------|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | Nonacog beta pegol | | |
|-------------------------------------------------------|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 13 (69.23%) | | |
| Investigations | | | |
| Serum ferritin increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Excoriation | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | | |
| occurrences (all) | 1 | | |
| Fall | | | |

| | | | |
|----------------------------------------------------------------------------------------------------------------------------|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Vascular disorders Haemorrhage subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Hypertension subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| General disorders and administration site conditions Face oedema subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Gastrointestinal disorders Epigastric discomfort subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Oral mucosal erythema subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Vomiting | | | |

| | | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | | |
| Musculoskeletal and connective tissue disorders Musculoskeletal discomfort subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10 January 2012 | Linguistic revision to one of the stopping rules. In addition, the protocol was amended on some operational issues and inconsistencies. |
| 11 May 2012 | Changes in the visual appearance of the trial product. Information on stop time of bleeding episode. Information on number of months on on-demand treatment. Information on screening of antibodies. |
| 02 January 2013 | The following countries were added to the list of participating countries: Austria, Greece, Latvia, Lithuania and Romania. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported