N9-GP (nonacog beta pegol)

Blood Products Advisory Committee
April 4, 2017
Novo Nordisk
N9-GP Introduction

Shawn Hoskin
Sr. Director, Regulatory Affairs
Novo Nordisk
Hemophilia B: Bleeding Disorder Caused by Deficiency of Protein Clotting Factor IX

- X-linked recessive congenital disorder
- ~1000 patients diagnosed with severe Hemophilia B in US
- Tendency of bleeding is inversely related to the FIX level
- Treatment focused on replacing FIX
  - Historically above 1% FIX activity level

Once-Weekly N9-GP 40 IU/kg Sustains High FIX Levels in Adolescents & Adults

![Graph showing FIX activity over time with non-hemophilia range (>40%) shaded area]

1. WFH guidelines
Once-Weekly N9-GP 40 IU/kg Achieves Higher FIX Levels in Children

Non-hemophilia range (>40%)\(^1\)

1. WFH guidelines
N9-GP Proposed Indication

Use in adults and children with hemophilia B for control and prevention of bleeding episodes, perioperative management, and routine prophylaxis
N9-GP Uses PEGylation to Extend Half-Life of Recombinant FIX

Ostergaard et al., 2011.
Nonclinical Studies Support N9-GP Safety

- No adverse nonclinical findings observed at doses >40x clinical dose
  - No adverse findings related to PEG
- Novo Nordisk will continue to monitor long-term safety
# Clinical Development Overview

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Patients</th>
<th>Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>3639</td>
<td>PK</td>
<td>&gt;12 years</td>
<td>16</td>
</tr>
<tr>
<td>3747</td>
<td>Prophylaxis, On-demand</td>
<td>&gt;12 years</td>
<td>74</td>
</tr>
<tr>
<td>3775</td>
<td>Safety Extension</td>
<td>&gt;12 years</td>
<td>71</td>
</tr>
<tr>
<td>3774</td>
<td>Prophylaxis*</td>
<td>0-12 years</td>
<td>25</td>
</tr>
<tr>
<td>3773</td>
<td>Surgery</td>
<td>&gt;12 years</td>
<td>13</td>
</tr>
</tbody>
</table>

*Extension ongoing
Benefits of Once-Weekly N9-GP 40 IU/kg

- Higher FIX levels than current FIX products
- Reduces annualized bleeding rate (ABR) and spontaneous bleeds
- Resolves target joints caused by repeated bleeding
- Safety consistent with current FIX treatments
- Fewer injections/year, reduced administration burden
# Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmet Need</td>
<td><strong>Guy Young, M.D.</strong>&lt;br&gt;Director of the Hemostasis and Thrombosis Program and Attending Physician Children’s Hospital of Los Angeles</td>
</tr>
<tr>
<td>N9-GP Clinical Efficacy</td>
<td><strong>Stephanie Seremetis, M.D.</strong>&lt;br&gt;Chief Medical Officer Novo Nordisk</td>
</tr>
<tr>
<td>Long-term PEG Safety</td>
<td><strong>Lars Wichmann Madsen, DVM, Ph.D.</strong>&lt;br&gt;Corporate Vice President Novo Nordisk</td>
</tr>
<tr>
<td>N9-GP Clinical Safety</td>
<td><strong>Stephanie Seremetis, M.D.</strong></td>
</tr>
<tr>
<td>N9-GP Benefit Risk</td>
<td><strong>Guy Young, M.D.</strong></td>
</tr>
</tbody>
</table>
Additional Experts

**Manuel Carcao, M.D.**  
Co-Director, Hemophilia Clinic  
Hospital for Sick Children  
Toronto, Canada

**Jennifer Sims, Ph.D.**  
Independent Toxicologist  
Integrated Biologix GHMH  
Basel, Switzerland

**Henry Wall, DVM, Ph.D.**  
Independent Pathologist  
Wall Pathology LLC  
Wake Forest, NC, USA
Unmet Medical Need in Hemophilia B Patients

Guy Young, M.D.
Director of the Hemostasis and Thrombosis Center, Children's Hospital Los Angeles
Professor of Pediatrics
University of Southern California Keck School of Medicine
Clinical Manifestations of Hemophilia B

- Serious, potentially life-threatening bleeding disorder
- Most common manifestation is joint bleeding
- Recurrent joint bleeding results in permanent joint damage
  - Most signs and symptoms emerge in adolescents and adults
- Results in diminished QoL

Srivastava et al., 2013; WFH guidelines.
Severity of Bleeding Correlated to FIX Activity

- **Severe <1%**
  - Frequent spontaneous bleeds
  - Untreated, develop permanent joint damage

- **Moderate (1-5%) and Mild (5-40%)**
  - Can experience spontaneous bleeds
  - Bleed with minimal trauma
  - May develop permanent joint damage

Srivastava et al., 2013; WFH guidelines; Soucie et al., 2015; Kulkarni, 2015.
Recurrent Bleeding into Joints Leads to Arthropathy

- Single bleed causes inflammation
- Recurrent bleeding results in target joints

Lafebe et al., 2008; Luck et al., 2004.
Current Prophylaxis to >1% Does Not Stop Progressive Joint Damage

- Treating to >1% factor activity does not prevent spontaneous or traumatic bleeding\(^1,2\)
- MRI joint changes occur with >1% targeted prophylaxis in absence of joint bleeds\(^3,4\)
  - Seen in ankles/knees/elbows by age 6

Epidemiology Suggests Higher Factor Activity Reduces Risk of Bleeding

Adapted from Soucie et al., 2015.
Frequent Intravenous Infusions are Treatment Burden in Hemophilia

- IV injections needed to provide replacement therapy (2-3/week with standard FIX)
- Venous access difficult for some patients (children, adults with scarred veins)
- Needle sticks can cause pain and anxiety
Unmet Need: Sustain Higher FIX Levels with Fewer Doses

- Higher FIX levels could reduce or prevent
  - Risk for bleeding
  - Development of target joints
  - Progression of joint disease
What Higher FIX Levels Could Mean to Patients

- Life free from fear of bleeding
- Ability to participate in normal activities e.g., jobs, sports, play
Hemophilia B Unmet Need Conclusion

- Need safe, efficacious products that reduce burden of treatment and disease
- Approach: Maintain higher FIX levels while reducing number of injections
N9-GP Clinical Efficacy

Stephanie Seremetis, M.D.
Chief Medical Officer
Novo Nordisk
N9-GP Development Program Hypothesis

- Maintaining higher FIX levels may help reduce bleeding and resolve target joints
- Once-weekly 40 IU/kg selected to achieve higher levels than current products for all ages
- For adults/adolescents
  - 40 IU/kg should achieve FIX >40% for most of week
  - 10 IU/kg should provide FIX levels closer to current FIX products
## 5 Clinical Trials in Patients with Hemophilia B

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</table>

*Extension ongoing
## Results Allowed Completion of Planned Hierarchical Testing

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Description/Criteria</th>
<th>Result (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>At most 1 patient incidence of inhibitory antibodies</td>
<td>0 inhibitors</td>
</tr>
<tr>
<td></td>
<td>against FIX</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary confirmatory efficacy endpoints</strong></td>
<td>Hemostatic responses for bleeding with lower limit of CI &gt;65%</td>
<td>92.2% (86.9; 95.4)</td>
</tr>
<tr>
<td></td>
<td>Number of bleeding episodes with prophylaxis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Upper level of CI &lt;4.8/yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 IU/kg dose, then 10 IU/kg dose</td>
<td>2.51 bleeds/year (1.42; 4.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.56 bleeds/year (3.01; 6.90)</td>
</tr>
</tbody>
</table>
Trial 3747 (Patients >12 Years)

Prophylaxis and On-demand
Trial 3747: Patients Blinded and Randomized to Assess Higher FIX Levels

Hypothesis

# of days in normal, non-hemophilia range (FIX >40%) is beneficial

52 weeks

Prophylaxis 40 IU/kg once-weekly (n=29)

Prophylaxis 10 IU/kg once-weekly (n=30)

FIX in “normal” non-hemophilia range* (>40%)¹

FIX comparable to currently available therapies

1. WFH guidelines
Once-Weekly 40 IU/kg Maintains Higher FIX Levels

Trial 3747: Patients randomized to either once-weekly 10 IU/kg or once-weekly 40 IU/kg
Trial 3747: 40 IU/kg Sustains Non-Hemophilia FIX Levels >5 Days/Week

<table>
<thead>
<tr>
<th>Once-weekly N9-GP FIX activity levels at steady-state</th>
<th>40 IU/kg</th>
<th>10 IU/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted days in non-hemophilia range &gt;40%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>5.4</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>1</sup> WFH guidelines
Trial 3747: 40 IU/kg Superior to 10 IU/kg in ABR (p=0.03)

<table>
<thead>
<tr>
<th>Once-weekly N9-GP Annualized Bleeding Rate</th>
<th>40 IU/kg (N=29)</th>
<th>10 IU/kg (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated ABR (95% CI)</td>
<td>2.51 (1.42; 4.43)</td>
<td>4.56 (3.01; 6.90)</td>
</tr>
<tr>
<td>Inter-arm comparison</td>
<td>p=0.03</td>
<td></td>
</tr>
<tr>
<td>Median ABR Interquartile range</td>
<td>1.04 (0.00; 4.00)</td>
<td>2.93 (0.99; 6.02)</td>
</tr>
</tbody>
</table>

ABR: annualized bleeding rate
Trial 3747: 40 IU/kg Prophylaxis Shown to Improve Target Joints

% Patients with No Bleeding Episodes at Target Joint During Trial

% of Baseline Target Joints No Longer Defined as “Target Joint” at EOT*

<table>
<thead>
<tr>
<th>Dosing Level</th>
<th>No Bleeding at Target Joint</th>
<th>No Longer Defined as Target Joint</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 IU/kg</td>
<td>67%</td>
<td>90%</td>
</tr>
<tr>
<td>10 IU/kg</td>
<td>8%</td>
<td>58%</td>
</tr>
</tbody>
</table>

EOT: end of trial

*ISTH-SSC: a target joint with ≤ 2 bleeds is no longer a target joint at 12 months; Blanchette, 2014
Trial 3747: Improvement in Quality of Life with 40 IU/kg Based on EQ-5D

Only data from patients completing both visits included.

EQ-5D VAS: Euro Quality of Life-5D Visual Analogue Scale; EOT: end of trial.
Trial 3774 (Patients 0-12 Years)

Prophylaxis
Trial 3774: Open-Labeled, Non-Controlled Study in Children

Screening
- Male
- 0–12 yrs
- FIX activity ≤2%
- Previously treated
- No inhibitor history

52 weeks

Prophylaxis
40 IU/kg once-weekly
(n=25)

Extension
Option to enroll in extension
(n=22)

Carcao et al., 2016.
Trial 3774: High FIX Trough Levels in Children

Steady-state Pre-dose FIX Activity Levels

% FIX Activity

7–12 years (n=13)
0–6 years (n=12)

Time (weeks)

FIX activity: Mean +/- SEM
Figure is adapted from Carcao et al., 2016.
## Trial 3774: Low ABR in Children

<table>
<thead>
<tr>
<th>Once-weekly N9-GP 40 IU/kg</th>
<th>0-6 Years (n=12)</th>
<th>7-12 Years (n=13)</th>
<th>Pediatric Total (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized Bleed Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated ABR* (95% CI)</td>
<td>0.87 (0.38; 2.01)</td>
<td>1.88 (1.14; 3.09)</td>
<td>1.44 (0.92; 2.26)</td>
</tr>
<tr>
<td>Median ABR Interquartile range</td>
<td>0.0 (0.00; 1.78)</td>
<td>2.0 (0.68; 2.89)</td>
<td>1.0 (0.00; 2.06)</td>
</tr>
</tbody>
</table>

*Poisson regression model

ABR: annualized bleed rate
Trial 3773 (Surgery)

Safety & Efficacy in Patients >12 Years
Trial 3773: Open-Label, Non-Controlled Study in 13 Patients >12 Years

Day 0
80 IU/kg prior to surgery

Day 1-6*
Option for two 40 IU/kg doses

Day 7-14
Additional doses at investigator discretion

*Second dose recommended in protocol
Escobar et al., 2017.
## Trial 3773: All Surgeries Elective, Non-Emergency

<table>
<thead>
<tr>
<th>Type of Surgical Procedure</th>
<th>Patients (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orthopedic Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Knee replacement</td>
<td>5</td>
</tr>
<tr>
<td>Hip replacement / fixation</td>
<td>2</td>
</tr>
<tr>
<td>Ankle fusion</td>
<td>1</td>
</tr>
<tr>
<td>Achilles tendon repair</td>
<td>1</td>
</tr>
<tr>
<td><strong>Other Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Molar extractions</td>
<td>3</td>
</tr>
<tr>
<td>Rectal surgery</td>
<td>1</td>
</tr>
</tbody>
</table>
Trial 3773: 100% Hemostatic Response Success During Surgery

- All 13 patients reported as “excellent” or “good”

<table>
<thead>
<tr>
<th>Number of N9-GP injections</th>
<th>Post-surgery through day 6</th>
<th>Post-surgery days 7–13</th>
<th>Total post-surgery until EOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>2.0 (1.2)</td>
<td>1.5 (0.8)</td>
<td>3.8 (2.3)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.0 (0-4)</td>
<td>1.5 (0-3)</td>
<td>4.0 (0-9)</td>
</tr>
</tbody>
</table>

EOT: end of trial
N9-GP Efficacy Conclusions
Efficacy Results Show Value of Higher FIX Levels and Treating to Normal Range

- 40 IU/kg statistically and clinically superior to 10 IU/kg across all endpoints
  - 10 IU/kg represents FIX levels and efficacy of standard and extended half-life products
- Higher FIX levels with 40 IU/kg N9-GP
  - Effect bleed prevention (low ABR)
  - Reduced target joint bleeding
  - Only long-acting product to achieve normal range FIX levels with once-weekly dosing

ABR: annualized bleed rate
Long-Term PEG Safety

Lars Wichmann Madsen, DVM, Ph.D.
Corporate Vice President
Novo Nordisk
Key Questions Regarding Long-Term Exposure to PEG

- PEG accumulation in tissues including the choroid plexus
  - How is PEG cleared?
  - Significance of PEG presence?
- Vacuoles observed in animals dosed with N9-GP and vehicle controls
  - Does PEG contribute to vacuole formation?
- Clinical significance of the non-clinical data?
PEG is a Well-Established Protraction Principle Used in Many Drugs

- PEG is an inert technology used widely
- No changes of toxicological relevance$^1-^3$
  - Cellular vacuolation is an adaptive response seen at high doses in some animal studies
  - Vacuoles in macrophages and choroid plexus seen with high doses of PEG 40 kDa
  - Vacuolation not associated with cellular damage

Cellular Processes Involved in Uptake and Processing of PEGylated Proteins

1. Internalization/pinocytosis
2. Transport to endo-/lysosomes
3. Metabolism
4. Excretion

Adapted from Baumann A, et al. 2014.
Vacuoles are Normal Cellular Structures

- Vacuoles: Involved in endocytosis and exocytosis

- Vacuolation: An increase in number or size
  - Not adverse in itself

Choroid Plexus is a Highly Vascularized Filtration Tissue

- Located in ventricles of brain
- Formed prior to birth
- Produces CSF (cerebrospinal fluid)
- Constitutes the blood-CSF barrier

Overview: Findings from N9-GP Non-Clinical Studies

- No PEG-related histopathological changes in any tissue
  - No vacuolation related to N9-GP treatment
- PEG detected in all vascularized tissues including choroid plexus
  - Does not cross blood-brain barrier
- PEG eliminated from plasma and tissues
  - Indicates steady-state was reached
  - No further accumulation
## No PEG-Related Toxicological Changes Seen with N9-GP in Any Tissue

<table>
<thead>
<tr>
<th>N9-GP repeat dose toxicology (duration; dose)</th>
<th>Noteworthy clinical findings</th>
<th>Toxicological assessments including histopathology (45 tissues)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowett nude rat (up to 26 weeks; up to 1200 IU/kg/5d*)</td>
<td>Normal</td>
<td>Normal, No adverse findings</td>
</tr>
<tr>
<td>Cynomolgus monkey (up to 13 weeks; up to 3750 IU/kg/wk**)</td>
<td>Normal, except tremors at 3750 IU/kg/wk</td>
<td>Normal transient No adverse findings except acquired hemophilia (cross-reacting antibodies)</td>
</tr>
</tbody>
</table>

*42-fold the weekly clinical dose of N9-GP
**94-fold the weekly clinical dose of N9-GP
Rats: Observed Vacuoles are Background Finding Not Related to N9-GP

Vacuoles observed in 68 out of >3200 tissue slides

Vehicle Control (N=32)
N9-GP 1200 IU/kg/5d (N=36)

Rat, 26-week toxicity study
Monkeys: Observed Vacuoles are Background Finding Not Related to N9-GP

<table>
<thead>
<tr>
<th>Dose (kg/week)</th>
<th>% Incidence of minimal / slight vacuoles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle 4 weeks 0 IU (N=5)</td>
</tr>
<tr>
<td>Liver</td>
<td>20%</td>
</tr>
</tbody>
</table>

Vacuoles observed in 2 out of >1800 tissue slides
# Choroid Plexus Not Affected by PEG

<table>
<thead>
<tr>
<th>N9-GP repeat dose Toxicology</th>
<th>Histopathology</th>
<th>Choroid Plexus / Brain Tissue</th>
<th>Electron Microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowett nude rat (up to 26 weeks)</td>
<td>Normal, no PEG-related vacuolation</td>
<td>PEG detected in choroid plexus connective tissue and epithelial cells, not in brain tissue</td>
<td>Lysosomes visible in epithelial cells No ultra-structural changes</td>
</tr>
<tr>
<td>Cynomolgus monkey (up to 13 weeks)</td>
<td>Normal, no PEG-related vacuolation</td>
<td>PEG detected in choroid plexus connective tissue and epithelial cells, not in brain tissue</td>
<td>Not Assessed</td>
</tr>
</tbody>
</table>
N9-GP Non-Clinical Data Show PEG is Eliminated from Plasma and Tissues

PEG Concentration (pmol/g)

Plasma

Kidney

Liver

Choroid Plexus

Days

Days

Rat, Single dose tissue distribution study, N9-GP
# Terminal Half-Life and Time to PEG Steady-State in Rats and Humans

<table>
<thead>
<tr>
<th>PEG Terminal t½ (days)</th>
<th>Species</th>
<th>Plasma</th>
<th>Kidney</th>
<th>Liver</th>
<th>Choroid Plexus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>15</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>49</td>
</tr>
<tr>
<td>Human*</td>
<td>59</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>192</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Time to steady-state**</th>
<th>Species</th>
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<th>Liver</th>
<th>Choroid Plexus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Human</td>
<td>~½ year</td>
<td>~1 year</td>
<td>~1 year</td>
<td>~1 year</td>
<td>~2 years</td>
</tr>
</tbody>
</table>

*Human t½ = rat t½ x (BW human/BW rat)^0.25

**3.3 x half-lives used for time to steady-state

1. Rowland and Tozer, 1995
PEG Plasma-Tissue Model

Kidney → Plasma → Liver → Tissue (e.g. choroid plexus) → Feces

Kidney → Plasma → Liver → Tissue (e.g. choroid plexus) → Urine
Predicted Human PEG Plasma Concentration

Children and Adolescents 0–16 years old

Total PEG Concentration (ug/mL)

Years of Treatment

Predicted Steady-State Range
Actual Plasma PEG Concentration Steady-State Was Achieved

Children and Adolescents 0–16 years old

Total PEG Concentration (ug/mL)

Years of Treatment

Predicted Steady-State Range
Steady-State Represents Equilibrium Between Rate of Input and Output
PEG Steady-State Levels Lower in Humans vs. Rats

![Graph showing PEG levels in plasma and choroid plasma over time](image)

- **Plasma**: Predicted Rat (26 weeks) vs. Measured human
- **Choroid Plasma**: Predicted Rat (26 weeks) vs. Predicted human

Time (years) vs. Total PEG concentration (μg/mL) and (μg/g)
Data Support Long-Term PEG Safety with N9-GP Treatment

- Non-clinical
  - No adverse PEG-related findings with N9-GP
  - No PEG-related vacuolation observed in any tissue including choroid plexus
  - Published data from PEGylated products does not indicate any tissue damage

- Clinical
  - Steady-state PEG levels reached for N9-GP
  - Plans to continue PEG safety surveillance
N9-GP Safety

Stephanie Seremetis, M.D.
Chief Medical Officer
Novo Nordisk
115 Patients Treated with N9-GP Totaling 226 Patient Years

<table>
<thead>
<tr>
<th>Safety analysis set*</th>
<th>0-6 years (N=12)</th>
<th>7-12 years (N=13)</th>
<th>13-17 years (N=18)</th>
<th>18-59 years (N=70)</th>
<th>≥ 60 years (N=2)</th>
<th>Total (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 months</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>15</td>
<td>–</td>
<td>16</td>
</tr>
<tr>
<td>6 to &lt;12 months</td>
<td>–</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>12 to &lt;24 months</td>
<td>–</td>
<td>–</td>
<td>4</td>
<td>23</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>24 to &lt;36 months</td>
<td>1</td>
<td>1</td>
<td>13</td>
<td>27</td>
<td>–</td>
<td>42</td>
</tr>
<tr>
<td>36 to &lt;48 months</td>
<td>8</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>12</td>
</tr>
<tr>
<td>≥ 48 months</td>
<td>2</td>
<td>6</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>8</td>
</tr>
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*Once-weekly N9-GP 40 IU/kg (Trials 3649, 3747, 3773, 3774, 3775) through cut-off date of 01-Nov-2016
# N9-GP Safety Overview

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<thead>
<tr>
<th>Safety analysis set (Trials 3639, 3747, 3773, 3774, 3775)</th>
<th>Pooled Total (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>85%</td>
</tr>
<tr>
<td>“Probably” or “Possibly” related AEs</td>
<td>20%</td>
</tr>
<tr>
<td>AEs by severity</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>81%</td>
</tr>
<tr>
<td>Moderate</td>
<td>37%</td>
</tr>
<tr>
<td>Severe</td>
<td>9%</td>
</tr>
<tr>
<td>SAEs</td>
<td>10%</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>2%</td>
</tr>
</tbody>
</table>
## Pooled Safety: AEs > 5%

<table>
<thead>
<tr>
<th>Patients reporting preferred term in safety analysis set (Trials 3639, 3747, 3773, 3774, 3775)</th>
<th>Pooled Total (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>17%</td>
</tr>
<tr>
<td>Contusion</td>
<td>13%</td>
</tr>
<tr>
<td>Cough</td>
<td>13%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11%</td>
</tr>
<tr>
<td>Headache</td>
<td>10%</td>
</tr>
<tr>
<td>Influenza</td>
<td>10%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>10%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9%</td>
</tr>
<tr>
<td>Fall</td>
<td>8%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>5%</td>
</tr>
<tr>
<td>Head injury</td>
<td>5%</td>
</tr>
<tr>
<td>Skin abrasion</td>
<td>5%</td>
</tr>
<tr>
<td>Laceration</td>
<td>5%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>5%</td>
</tr>
</tbody>
</table>
**Pooled Safety: 12 Reported SAEs**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age (yrs)</th>
<th>Preferred term</th>
<th>Day</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>3639</td>
<td>25</td>
<td>Hypersensitivity</td>
<td>1</td>
<td>Probable</td>
</tr>
<tr>
<td>3747</td>
<td>14</td>
<td>Abdominal pain</td>
<td>4</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Retroperitoneal hematoma</td>
<td>7</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>Skin ulcer</td>
<td>17</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>Hip fracture</td>
<td>19</td>
<td>Unlikely</td>
</tr>
<tr>
<td>3775*</td>
<td>42</td>
<td>Road traffic accident</td>
<td>20</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Femur fracture</td>
<td>68</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>Hepatocellular carcinoma</td>
<td>72</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>Post procedural infection, local swelling</td>
<td>75</td>
<td>Unlikely</td>
</tr>
<tr>
<td>3774</td>
<td>24</td>
<td>Fecaloma</td>
<td>78</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>Gastroenteritis</td>
<td>83</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Food poisoning</td>
<td>17</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

*Patients in extension trial received previous N9-GP treatment

Pooled Safety analysis set includes Trials 3639, 3747, 3773, 3774, 3775
N9-GP Safety Profile Similar to Other FIX Products

- Thromboembolic events
  - No AEs suggestive of TE
- Hypersensitivity
  - Risk similar to other FIX products
  - 1 reaction in 8,801 injections in previously treated patients
- Immunogenicity
  - No previously treated patients developed inhibitors

Based on safety analysis set (Trials 3639, 3747, 3773, 3774, 3775)
Neurologic Assessments Did Not Identify Safety Concerns

- Neurological assessment performed as part of physical exams in all subjects in all trials
  - Performed according to local procedures
  - General evaluation of CNS and PNS
  - Functional assessment of musculoskeletal system
  - General appearance of patient

- Retrospective analysis of neurological, psychosocial and developmental AEs
Post-Approval Monitoring Plan

1. Ongoing pediatric clinical trials
2. Post-Approval Safety Study (PASS) including monitoring of renal, hepatic and neurologic function
3. Existing registries (international/national)
4. Follow up on AEs related to renal, hepatic and neurologic systems
1. Ongoing Pediatric Clinical Trials

- Continued collection of safety data in ongoing phase 3 clinical trials with pediatric patients
  - 19 previously treated patients
  - 17 previously untreated patients (goal 40 PUPs)
- Periodic clinical evaluations include neurological assessments
- Collection of renal/hepatic biomarkers
- Collection of plasma PEG levels
2. Post-Approval Safety Study

- Planned monitoring
  - AEs
  - Physical and neurological exams
  - Renal and hepatic function
  - Development in children
  - PEG-plasma levels
- ≥ 50 previously treated patients
- Study duration ≥ 5 years
3. International and National Registries

- PedNet Registry (EU, Canada, Israel)
  - >1500 patients born after 2000
- E JHASS (EU)
  - Independent safety surveillance for inherited bleeding disorders
- ATHN (US)
  - ~1000 severe Hemophilia B patients
4. Specific Follow-up of Reported Events

- Renal function
- Hepatic function
- Neurologic function or symptoms
  - Seizures
  - Severe non-resolving or repetitive headaches
  - Developmental delays
  - Neurological exam findings
Benefit-Risk

Guy Young, M.D.
Director of the Hemostasis and Thrombosis Program and Attending Physician
Children’s Hospital of Los Angeles
Benefits of Once-Weekly N9-GP 40 IU/kg Across All Age Groups

- Maintains higher FIX levels than current products with a once-weekly dose
- Significant and clinically meaningful outcomes
  - Low AsBR and ABR
  - Target joint resolution
  - Improved quality of life

ABR: annualized bleeding rate; AsBR, annualized spontaneous bleeding rate
Current Hemophilia B Therapies Do Not Sustain FIX Levels >40%

![Graph showing FIX Activity over time for different therapies.](image)

- **Non-hemophilia range (>40%)**: The graph shows the expected FIX activity levels for non-hemophilia patients.

- **Time (days)**: The x-axis represents the time in days, ranging from 0 to 28.

- **FIX Activity**: The y-axis represents the FIX activity percentage, ranging from 0% to 120%.

- **Idelvion 40 IU/kg once-weekly**: The orange line indicates the FIX activity levels for patients receiving Idelvion at a dosage of 40 IU/kg once weekly.

- **Alprolix 50 IU/kg once-weekly**: The purple line shows the FIX activity levels for patients receiving Alprolix at a dosage of 50 IU/kg once weekly.

Only N9-GP Sustains High FIX Levels in Adolescents and Adults

Non-hemophilia range (>40%)¹

Time (days)

FIX Activity

0% 20% 40% 60% 80% 100% 120%

N9-GP 40 IU/kg once-weekly
Idelvion 40 IU/kg once-weekly²
Alprolix 50 IU/kg once-weekly³

## Low ABR Across Age Groups with 40 IU/kg Once-Weekly N9-GP

<table>
<thead>
<tr>
<th></th>
<th>40 IU/kg Prophylaxis</th>
<th>10 IU/kg Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-6 years (n=12)</td>
<td>7-12 years (n=13)</td>
</tr>
<tr>
<td><strong>Median ABR</strong></td>
<td>0.0</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Median AsBR</strong></td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Trials 3747 and 3774

ABR: annualized bleeding rate; AsBR: annualized spontaneous bleeding rate
Impact of Treatment with N9-GP

- Spontaneous bleeds
- Target joints
- Mobility
Most Patients Did Not Have Spontaneous Bleeds on Once-Weekly 40 IU/kg

Trials 3747 and 3774
Most Patients had No Bleeding in Targets Joints with 40 IU/kg N9-GP

% patients with no bleeding episodes at target joint during trial

ISTH-SSC: a target joint with ≤ 2 bleeds is no longer a target joint at 12 months; Blanchette, 2014.
Improved Mobility with 40 IU/kg in Adults and Adolescents

EQ-5D-3L Mobility

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Some problems</td>
<td>52%</td>
<td>24%</td>
</tr>
<tr>
<td>in walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No problems</td>
<td>48%</td>
<td>76%</td>
</tr>
<tr>
<td>in walking</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=25

Trial 3747: Only data from patients completing both visits are included.
EQ-5D-3L: Euro Quality of Life-5D-3L
Safety of Once-Weekly N9-GP 40 IU/kg Similar to Other FIX Therapies

- Clinical data support long-term safety of N9-GP in all age groups
  - No unexpected safety risks identified
- Over 4 years of safety data from active treatment in children (aged 0-12 years)
- Clinical and non-clinical support PEG safety
Favorable Benefit-Risk Assessment

- N9-GP sustains higher FIX levels than current products with once-weekly dosing
- High FIX levels drive
  - Low ABR
  - Resolution of target joints
  - Improved quality of life
- Effective for treatment of bleeds and during surgery
- Long-term safety of N9-GP demonstrated, with >4 years of exposure in children
N9-GP (nonacog beta pegol)

Blood Products Advisory Committee
April 4, 2017
Novo Nordisk
Hemophilia B is an Orphan Population in the US with few Older/Severe Patients

CDC HTC Population Profile
Unique patients seen between 1/1/2012-12/31/2016

<table>
<thead>
<tr>
<th>CDC</th>
<th>Total</th>
<th>&lt;2</th>
<th>2-10</th>
<th>11-19</th>
<th>20-44</th>
<th>45-64</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>4929</td>
<td>163</td>
<td>973</td>
<td>1131</td>
<td>1709</td>
<td>793</td>
<td>330</td>
</tr>
<tr>
<td>Severe</td>
<td>1385</td>
<td>55</td>
<td>266</td>
<td>267</td>
<td>553</td>
<td>191</td>
<td>53</td>
</tr>
</tbody>
</table>

www.cdc.gov accessed 4/3/2017, 1/1/2012-12/31/2016 unique patients
**Fold From Nonclinical Doses Compared to Clinical Dose - PEG alone**

(Sponsors Briefing Book, Appendix 1, Table 1)

<table>
<thead>
<tr>
<th>Discipline</th>
<th>NOAEL</th>
<th>Dose Level</th>
<th>PEG Dose</th>
<th>Fold to clinical PEG dose by Body surface area HED</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxico/ogy (40 kDa PEG alone)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks, PEG alone</td>
<td>NA</td>
<td>45,000</td>
<td>196</td>
<td>31</td>
<td>Rat</td>
</tr>
<tr>
<td>6 weeks, PEG alone</td>
<td>NA</td>
<td>117,000</td>
<td>509</td>
<td>81</td>
<td>Rat</td>
</tr>
<tr>
<td>6 weeks, PEG alone</td>
<td>NA</td>
<td>45,000</td>
<td>196</td>
<td>63</td>
<td>Cynomolgus monkey</td>
</tr>
<tr>
<td>13 weeks, PEG alone</td>
<td>NA</td>
<td>7,000</td>
<td>30</td>
<td>10</td>
<td>Cynomolgus monkey</td>
</tr>
</tbody>
</table>

- **For human equivalent dose (HED), multiply dose with 0.32 (monkey) and 0.16 (rat)**
- Once weekly clinical dose of 40 IU/kg N9-GP corresponds to 230 IU/kg/week
# Fold From Nonclinical PEG Doses N9-GP or PEG alone Compared to Clinical Dose

<table>
<thead>
<tr>
<th>Discipline</th>
<th>NOAEL Dose Level N9-GP (IU/kg)</th>
<th>PEG Dose (µg/kg/week)</th>
<th>Fold to clinical PEG dose of 230 µg/kg</th>
<th>Fold to clinical PEG dose by Body surface area (HED)</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxicology (Refixia)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks, N9-GP dosed twice weekly</td>
<td>1200$^8$</td>
<td>13800</td>
<td>60</td>
<td>10</td>
<td>Rowett nude rat</td>
</tr>
<tr>
<td>26 weeks, N9-GP dosed every 5th day</td>
<td>1200$^\bullet$</td>
<td>9660</td>
<td>42</td>
<td>7</td>
<td>Rowett nude rat</td>
</tr>
<tr>
<td>4 weeks, N9-GP weekly doses</td>
<td>1300</td>
<td>7475</td>
<td>32</td>
<td>10</td>
<td>Cynomolgus monkey</td>
</tr>
<tr>
<td>13 weeks, N9-GP weekly doses</td>
<td>200$^8$</td>
<td>1150</td>
<td>5</td>
<td>2</td>
<td>Cynomolgus monkey</td>
</tr>
<tr>
<td><strong>Toxicology (40 kDa PEG alone)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks, PEG alone</td>
<td>NA</td>
<td>45,000</td>
<td>196</td>
<td>31</td>
<td>Rat</td>
</tr>
<tr>
<td>6 weeks, PEG alone</td>
<td>NA</td>
<td>45,000$^8$</td>
<td>196</td>
<td>63</td>
<td>Cynomolgus monkey</td>
</tr>
<tr>
<td>13 weeks, PEG alone</td>
<td>NA</td>
<td>7,000</td>
<td>30</td>
<td>10</td>
<td>Cynomolgus monkey</td>
</tr>
</tbody>
</table>

$^8$Highest dose tested

$^\bullet$For human equivalent dose (HED), multiply dose with 0.32 (monkey) and 0.16 (rat), Once weekly clinical dose of 40 IU/kg N9-GP corresponds to 230 g/kg/week
Trial 3774: FIX Levels in Children on N9-GP are Predicted to be >40% 2.3 Days (33% of the Week)
# Brain Sections Examined

<table>
<thead>
<tr>
<th></th>
<th>H&amp;E</th>
<th>IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 week monkey</td>
<td>2 Sections</td>
<td>1 Sections incl. CP</td>
</tr>
<tr>
<td>13 week monkey</td>
<td>2 Sections</td>
<td>1 Sections incl. CP</td>
</tr>
<tr>
<td>6- and 26 week rat</td>
<td>4 Section</td>
<td>3 Sections</td>
</tr>
<tr>
<td>PEG alone Rat</td>
<td>4 Section</td>
<td>3 Sections</td>
</tr>
<tr>
<td>PEG alone Monkey</td>
<td>2 Sections</td>
<td>1 Sections incl. CP</td>
</tr>
</tbody>
</table>
How Cerebrum, Cerebellum and Spinal Cord Sections are Cut for Histology

1. Cerebrum at the optic chiasm
2. Cerebrum at the base of the posterior hypothalmus
3. Midcerebellum and medulla oblongata
4. Pons and middle of its protrusion
5. Cranial cervial cord

Christine Ruehi-Fehlert et al., Exp Toxic Pathol 2003; 55: 91-106
Histology of Choroid Plexus Normal, 26 Week Rat Study 1200 IU/kg/Sd N9-GP

Rat, Control (x 20)  
Rat, 1200 IU/kg/Sd N9-GP (highest dose tested), after 26 weeks exposure (x 20)

N9·GP, 26 weeks repeat-dose toxicity study in rat, study 212513
No Pathological Effects - Electron Microscopy of Choroid Plexus, 26 Week Rat Study

• Ultra-structure appeared normal
• Lysosomes with PEG micro-vesicles

US Treatment Centers

- Children's Hospital of New Orleans
- Children's Hospital of Los Angeles
- Children's Hospital Of Philadelphia
- Children's Hospitals And Clinics Of Minnesota
- Children's Medical Center (Texas)
- Georgia Regents University
- Johns Hopkins University
- Maimonides Medical Center
- Mount Sinai Medical Center
- Nemours Children's Clinic (Florida)
- Oregon Health & Science University
- St. Luke's Mountain States Tumor Institute
- St. Michael's Medical Center
- SUNY Upstate Medical University
- Texas Children's Hospital
- The Gulf States Hemophilia & Thrombophilia Center
- Univ. of CA San Fran
- University of Iowa
- University Of Nebraska Medical Center
- University of Utah Primary Children's Medical Center
- Vanderbilt Hemostasis Thrombosis Clinic
## Patients 0-6 Years of Age

<table>
<thead>
<tr>
<th>Patient</th>
<th>Country</th>
<th>Age (Years)</th>
<th>Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>United States of America</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>2</td>
<td>United Kingdom</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>3</td>
<td>Taiwan</td>
<td>1</td>
<td>0–2</td>
</tr>
<tr>
<td>4</td>
<td>Canada</td>
<td>2</td>
<td>0–2</td>
</tr>
<tr>
<td>5</td>
<td>United States of America</td>
<td>3</td>
<td>3–6</td>
</tr>
<tr>
<td>6</td>
<td>Italy</td>
<td>3</td>
<td>3–6</td>
</tr>
<tr>
<td>7</td>
<td>Germany</td>
<td>3</td>
<td>3–6</td>
</tr>
<tr>
<td>8</td>
<td>United Kingdom</td>
<td>3</td>
<td>3–6</td>
</tr>
<tr>
<td>9</td>
<td>United States of America</td>
<td>4</td>
<td>3–6</td>
</tr>
<tr>
<td>10</td>
<td>United Kingdom</td>
<td>5</td>
<td>3–6</td>
</tr>
<tr>
<td>11</td>
<td>Japan</td>
<td>5</td>
<td>3–6</td>
</tr>
<tr>
<td>12</td>
<td>Taiwan</td>
<td>6</td>
<td>3–6</td>
</tr>
</tbody>
</table>
Number of sections Monkey Brain

- 5 sections
- Includes the following regions:
  - Cerebellum (2) through hypothalamic region
  - Midbrain
  - Cerebellum
  - Medulla oblongata
Most of the Adverse Events in Children were Mild and Unlikely Related to N9-GP

<table>
<thead>
<tr>
<th></th>
<th>0-2 years # Patients (Events)</th>
<th>3-6 years # Patients (Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># of Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All AEs</td>
<td>4 (61)</td>
<td>8 (70)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs by severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>4 (57)</td>
<td>8 (66)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (4)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs by relationship(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probably or possibly</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td>4 (59)</td>
<td>8 (70)</td>
</tr>
</tbody>
</table>

Nervous System Disorders

Psychiatric Disorders

Data from Trials 3639, 3747, 3773, 3775 and 3774; AE, adverse event; PPX, prophylaxis.

\(^1\)As judged by the investigator.
Plasma PEG Concentrations in Humans and Animals at Exposures Not Associated with Vacuolation
Vacuolation Only Observed Above a Threshold of ~100 ug/mL Plasma PEG Concentration

Predicted RAT N9-GP (1200 IU/kg/5d; 26 weeks)

Measured HUMAN N9-GP (symbols)

LLOQ: 0.75 µg/ml