CLINICAL PHARMACOLOGY BLA REVIEW
Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)
Office of Tissues & Advance Therapies (OTAT)

STN 125671

Sponsor: Novo Nordisk

Product: Antihemophilic Factor (Recombinant), GlycoPEGylated (ESPEROCT)

Indication: Adults and children with hemophilia A (on demand and routine prophylaxis)

Submission Date: February 27, 2018

Reviewer: Iftekhar Mahmood, Ph. D.

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INTRODUCTION

Recombinant human Factor VIII is produced in Chinese Hamster Ovary (CHO) cells and contains (b) (4) of the endogenous B-domain. Esperoct is a preservative-free, sterile, non-pyrogenic lyophilized powder for reconstitution for intravenous injection. Esperoct is a purified recombinant human Factor VIII product with a 40 kDa polyethylene-glycol (PEG)

conjugated to the O-linked glycan in the truncated B-domain. When Esperoct is activated by thrombin at the site of injury, the B-domain containing the PEG moiety (b) (4) cleaved off, thus generating activated Factor VIII (FVIIIa), which is similar in structure to native Factor VIIIa.

The protein part of Esperoct is a polypeptide with a molecular mass of 166 kDa and the PEG moiety. It contains a heavy chain of (b) (4) and a light chain of (b) (4) held together by non-covalent interactions. No additives of human or animal origin are used in the cell culture, purification, conjugation or formulation of Esperoct.

Recommendations

The study design, pharmacokinetic analyses, and the results of the studies are acceptable from clinical pharmacology perspective.

Study #1

Study Title: A multi-national, open-label, dose escalation trial, evaluating safety and pharmacokinetics of intravenous doses of NNC 0129-0000-1003 in patients with hemophilia A (NN7088-3776).

The objectives of the study were to evaluate the safety and pharmacokinetics (PK) of single intravenous (IV) administration of 40K pegylated recombinant FVIII (N8-GP) at three dose levels in subjects with hemophilia A (factor FVIII activity (FVIII:C) < 1%).

This was a dose escalation trial. Three cohorts of at least six subjects in each cohort were administered a single dose of 25 U/kg, 50 U/kg or 75 U/kg N8-GP. All subjects were male and the mean age was 36.8 years (ranging from 20 to 60 years). The majority of subjects were Caucasian. The median height was 1.75 m (ranging from 1.57 to 1.90 m), and the median weight was 79 kg (ranging from 58 to 103 kg). The median BMI was 24.7 kg/m^2 (ranging from 19.4 to 34.7 kg/m^2).

Blood samples for analyses of FVIII activity of N8-GP were collected at pre-dosing and at 0.5, 1, 4, 8, 12, 24, 30, 48, 72, 96, 120, 144 and 168 hours post-dosing. Pre-dose sampling was done within 1 hour prior to the dose. The pharmacokinetic parameters were based on FVIII activity based on chromogenic and clot assays (plasma calibrator). The PK parameters were estimated using non-compartmental analysis and are shown in Tables 1-2. The concentration-time profiles of N8-GP are shown in Figures 1-2.

The PK parameters of N8-GP assessed by chromogenic assay (plasma calibrator) are summarized in Table 1. The half-life and clearance of N8-GP ranged from 17 to 22 hours and 1.1 to 1.6 hours, respectively, across three doses. The values of half-life and clearance of N8-GP indicate that 50 IU/kg dose of N8-GP do not fall linearly between 25 IU/kg and 75 IU/kg.

Table 1: PK parameters for N8-GP (U/mL) using chromogenic assay (plasma calibrator)

Parameters	25 IU/kg	50 IU/kg	75 IU/kg
# Subjects	7	8	10
AUC$_{0\text{-infinity}}$ (U*h/mL)	20.4 ± 7.6	49.7 ± 14.2	58.4 ± 24.5
CL (mL/hour/kg)	1.4 ± 0.4	1.1 ± 0.3	1.6 ± 1.0
Half-life (hours)	20 ± 8	22 ± 6	17 ± 4
MRT (hours)	26 ± 8	33 ± 8	24 ± 7
V$_{ss}$ (mL/kg)	35 ± 17	34 ± 9	35 ± 14
IR (U/mL/U/kg)	0.034 ± 0.005	0.031 ± 0.007	0.031 ± 0.007
Time to 1% (days)	4.8 ±1.3	6.7 ±1.7	5.5 ±1.6

MRT = Mean residence time; V$_{ss}$ = Volume of distribution at steady state; IR = Incremental recovery.

The PK parameters of N8-GP assessed by clotting assay (N8-GP calibrator) are summarized in Table 2. The values of half-life and clearance indicate that 50 IU/kg dose of N8-GP do not fall linearly between 25 IU/kg and 75 IU/kg.

Table 2: PK parameters for N8-GP (U/mL) using clot assay
(plasma calibrator)

Parameters	25 IU/kg	50 IU/kg	75 IU/kg
# Subjects	7	8	10
$AUC_{0\text{-infinity}}$ (U*h/mL)	8.4 ± 3.9	27.2 ± 9.5	31.9 ± 13.6
CL (mL/hour/kg)	3.5 ± 1.4	2.1 ± 0.8	3.1 ± 2.2
Half-life (hours)	16 ± 5	26 ± 9	18 ± 5
MRT (hours)	23 ± 7	37 ± 12	26 ± 8
V_{ss} (mL/kg)	74 ± 17	69 ± 14	71 ± 41
IR (U/mL/U/kg)	0.013 ± 0.002	0.015 ± 0.003	0.016 ± 0.004
Time to 1% (days)	3.5 ± 1.1	6.6 ± 2.1	5.0 ± 1.6

MRT = Mean residence time; V_{ss} = Volume of distribution at steady state; IR = Incremental recovery.

Conclusions: The PK parameters of N8-GP were not comparable between chromogenic and clot assays using plasma calibrators. The clearance of N8-GP estimated by clot assay using plasma calibrator was almost 2-fold higher than the clearance of N8-GP estimated by chromogenic assay. The incremental recovery of N8-GP by the clot assay was approximately 50% lower than that by the chromogenic assay. The half-life of N8-GP was comparable by these two analytical methods.

Figure 1: Mean concentration-time profiles of N8-GP using chromogenic assay (plasma calibrator)
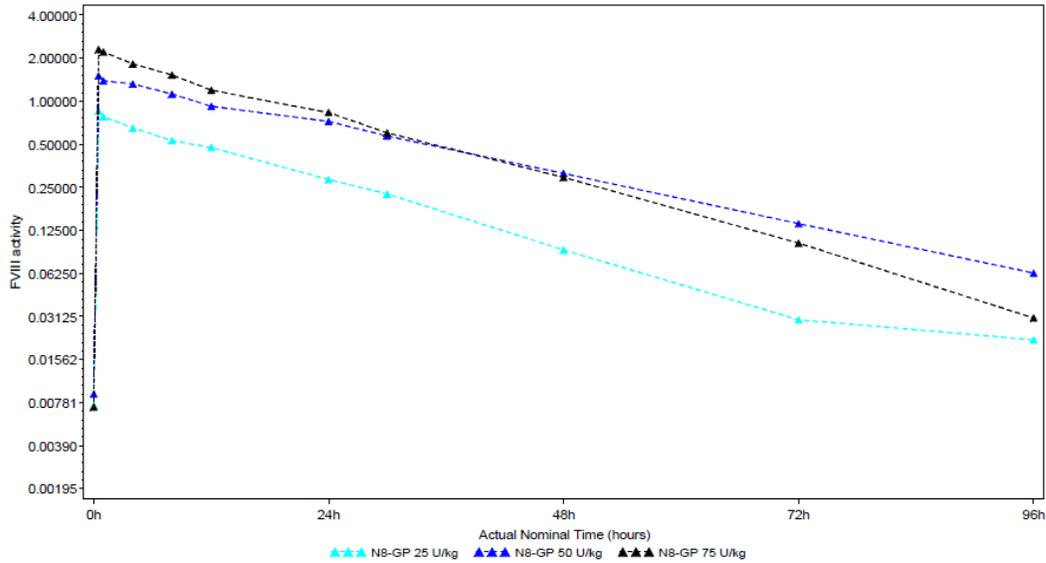
Values below LLOQ prior to last quantifiable value are set to LLOQ/2.
The first value below LLOQ after last quantifiable value is set to LLOQ/2, thereafter values are set to zero
The bars show the standard errors.

Figure 2: Mean concentration-time profile of N8-GP using clot assay (plasma calibrator)
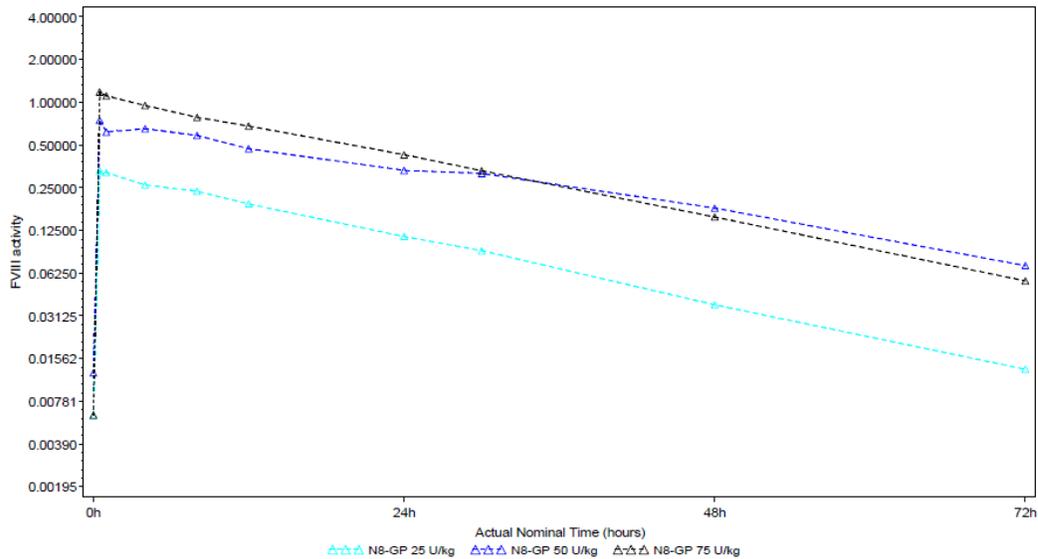
Values below LLOQ prior to last quantifiable value are set to LLOQ/2.
The first value below LLOQ after last quantifiable value is set to LLOQ/2, thereafter values are set to zero
The bars show the standard errors.

Study #2

Study Title: A multinational, open-label, non-controlled trial on safety, efficacy and pharmacokinetics of NNC 0129-0000-1003 in previously treated pediatric patients with severe hemophilia A (pathfinder™5)

This was a multi-national, open-label single-arm, and uncontrolled trial to assess safety including immunogenicity, efficacy, and pharmacokinetics (PK) of N8-GP. N8-GP was given for prophylaxis and treatment of bleeding episodes to subjects below 12 years of age with severe hemophilia A where >50 exposure days (EDs) in the 1-5-year age group and >150 EDs in the 6-11-year age group with previous FVIII products were required.

For the PK study, there were 15 male subjects with severe congenital hemophilia A (FVIII activity level below 1%) in the 1-5-year age-group and 12 subjects in the 6-11-year age-group. The mean body weights were 17.3 kg (13.5-23 kg) and 33.4 kg (17-59.8 kg) for 1-5-year and 6-11-year age-groups, respectively. Blood samples were collected at time 0, 0.5, 1, 6, 24, 30, 72, and 96 hours. FVIII plasma activity was measured by clot and chromogenic assays. The pharmacokinetic parameters of N8-GP in the two age groups are summarized in Tables 1 and 2. Concentration-time profiles of N8-GP are shown in Figures 1 and 2.

Table 1: PK parameters of N8-GP in children 1-5 years of age

	Chromogenic assay		Clot assay	
	NHP	PSS	PSS (chrom)	PSS (clot)
# of Subjects	9	9	8	8
$AUC_{0\text{-infinity}}$ (U*h/mL)	33 ± 12	26 ± 11	27 ± 8	17 ± 5
CL (mL/hour/kg)	1.9 ± 0.6	2.4 ± 0.9	2.3 ± 0.8	3.7 ± 1.3
Half-life (hours)	16 ± 3	15 ± 3	16 ± 3	16 ± 3
V_{ss} (mL/kg)	38 ± 12	45 ± 15	46 ± 11	74 ± 19

NHP: normal human plasma, PSS: product specific standard

Table 2: PK parameters of N8-GP in children 6-11 years of age

	Chromogenic assay		Clot assay	
	NHP	PSS	PSS (chrom)	PSS (clot)
# of Subjects	9	9	8	8
$AUC_{0\text{-infinity}}$ (U*h/mL)	33 ± 15	26 ± 13	22 ± 8	17 ± 12
CL (mL/hour/kg)	1.9 ± 0.6	2.5 ± 0.9	2.8 ± 1.1	4.3 ± 1.9
Half-life (hours)	15 ± 4	15 ± 4	15 ± 5	16 ± 6
V_{ss} (mL/kg)	34 ± 7	44 ± 11	51 ± 15	79 ± 26

NHP: normal human plasma, PSS: product specific standard

Although the half-life of N8-GP was similar between adults and children <12 years of age, body weight-adjusted clearance was approximately two-fold higher in children <12 years of age than adults. Therefore, dose adjustment is warranted in children <12 years of age as compared with adults.

Figure 1

PK N8-GP - mean profiles of FVIII activity (IU/mL) (log scale)
(0-5 years) - full analysis set
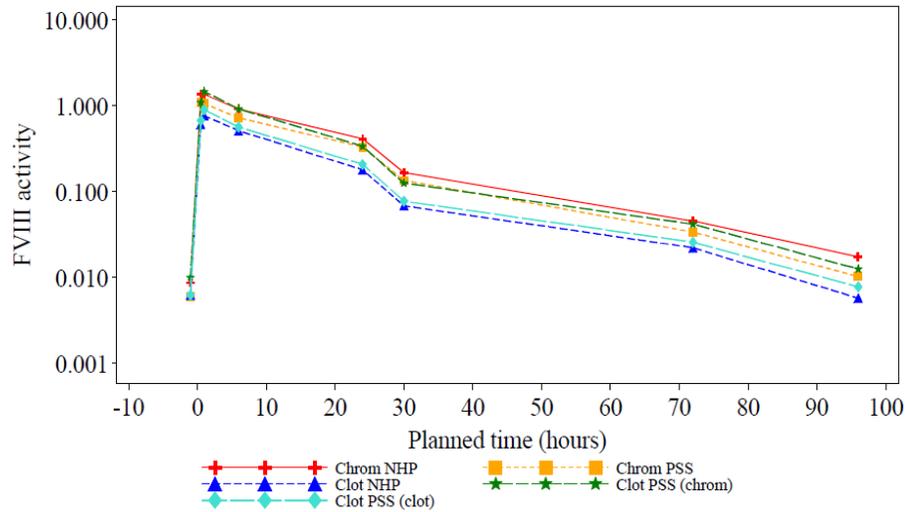
Chrom: chromogenic, NHP: normal human plasma, PSS: product specific standard
nn7088-3885/current - 19NOV2015 - f_1420_pkplot_m.sas/142019006052_PK_plots_logm_1.cgm

Figure 2

PK N8-GP - mean profiles of FVIII activity (IU/mL) (log scale)
(6-11 years) - full analysis set
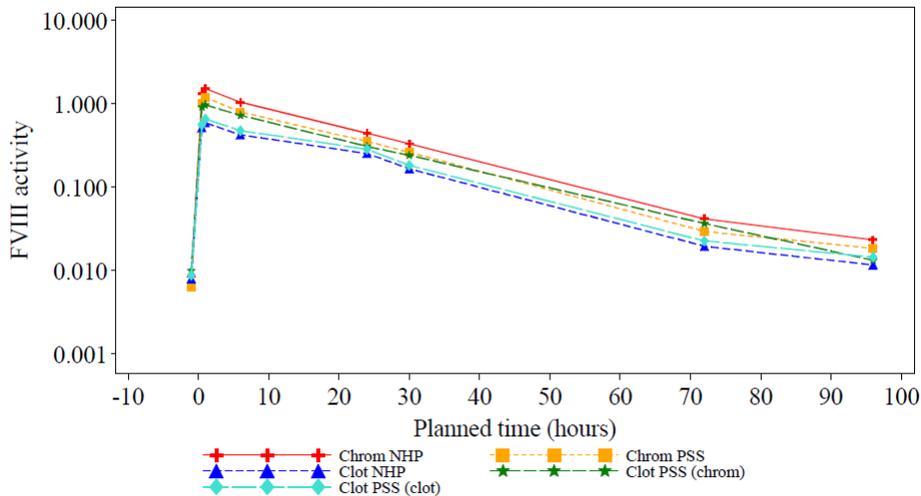
Chrom: chromogenic, NHP: normal human plasma, PSS: product specific standard
nn7088-3885/current - 19NOV2015 - f_1420_pkplot_m.sas/142019006054_PK_plots_logm_2.cgm

Study #3

Study Title: A multi-center, comparative, double blind, randomized 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 hemophilia A (NN7088-4033)

The primary objective of this study was 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 subjects with severe hemophilia A. The secondary objective was to assess the safety of N8-GP from the pivotal process and N8-GP from the commercial process after single intravenous doses of 50 U/kg in subjects with severe hemophilia A.

This was a multi-center, comparative, double-blinded, randomized cross-over trial investigating single-dose pharmacokinetics and safety of N8-GP from the pivotal process and N8-GP from the commercial process in subjects with severe hemophilia A. The subjects were all males with severe congenital hemophilia A (FVIII activity <1%) without previous or current FVIII inhibitors and were treated with >150 documented exposure days to FVIII products. Two batches of N8-GP were evaluated in the trial; one batch of N8-GP from the pivotal process (2000 IU/Vial) and one batch of N8-GP from the commercial process (2000 IU/Vial).

A total of 22 subjects were screened to receive N8-GP from the pivotal and commercial processes in a randomized cross-over design for 18 subjects to complete the study. The mean age and body weight of the subjects were 42.4 years (range: 25-71 years) and 84 kg (range: 61-125 kg), respectively.

Blood samples for pharmacokinetic (PK) study were taken at 0.5, 1, 4, 6, 8, 24, 28, 48, 72, 96 hours post dosing. FVIII plasma activity was measured using chromogenic normal human plasma (NHP), chromogenic product specific standard (PSS), clot PSS (chromogenic), and clot PSS (clot) assays. PK parameters were estimated using non-compartmental analysis.

In order to assess that the two batches of N8-GP from different processes are comparable, a 2-sided 90% confidence interval on the $AUC_{0\text{-infinity}}$ was applied and the two batches of N8-GP were declared comparable if the 90% confidence interval on natural log transferred data was between 0.8-1.25.

The results of the study are summarized in Table 1. The estimated $AUC_{0\text{-infinity}}$ was 41.0 ± 11.4 U*h/mL for the pivotal process and 40.3 ± 12.4 U*h/mL for the commercial process when using a chromogenic assay with NHP as the calibrator. The estimated ratio (commercial process/pivotal process) of 0.98 and the confidence interval ranged from 94%-102%. The remaining three analytical methods provided the similar results using the chromogenic or clot assay (Table 1). The concentration-time profiles of the two products are shown in Figure 1.

**Table 1: PK parameters and 90% confidence interval (CI) on AUC
for N8-GP from the commercial and the pivotal processes**

	Chromogenic assay		Clot assay	
	NHP	PSS	PSS (chrom)	PSS (clot)
# of Subjects	18	18	18	18
Commercial				
AUC_{0-96} (U*h/mL)	38.8 ± 10.1	40.6 ± 11.7	46.8 ± 10.9	28.3 ± 6.6
Pivotal				
AUC_{0-96} (U*h/mL)	38.8 ± 8.9	40.6 ± 9.6	46.8 ± 8.4	28.3 ± 5.1
90% confidence interval	0.95-1.03	0.91-1.03	0.94-1.02	0.94-1.02
Commercial				
$AUC_{0-infinity}$ (U*h/mL)	40.3 ± 12.4	41.4 ± 14.1	49.6 ± 14.5	29.9 ± 6.8
Pivotal				
$AUC_{0-infinity}$ (U*h/mL)	41.0 ± 11.4	43.1 ± 12.4	50.6 ± 12.1	30.5 ± 7.3
90% confidence interval	0.94-1.02	0.90-1.03	0.94-1.03	0.94-1.03
Commercial				
CL (mL/hour/kg)	1.34 ± 0.48	1.30 ± 0.58	1.09 ± 0.31	1.80 ± 0.51
Pivotal				
CL (mL/hour/kg)	1.34 ± 0.39	1.27 ± 0.33	1.09 ± 0.23	1.80 ± 0.38
Commercial				
Half-life (hours)	19 ± 7	20 ± 8	23 ± 9	23 ± 9
Pivotal				
Half-life (hours)	21 ± 7	21 ± 9	23 ± 9	23 ± 9

Conclusions: The 90% confidence interval on AUC for N8-GP from the commercial and the pivotal processes is within the acceptable range (0.8-1.25) indicating that both products are comparable.

Figure 1: Mean concentration-time profile of FVIII activity (U/mL) for N8-GP from the commercial processes
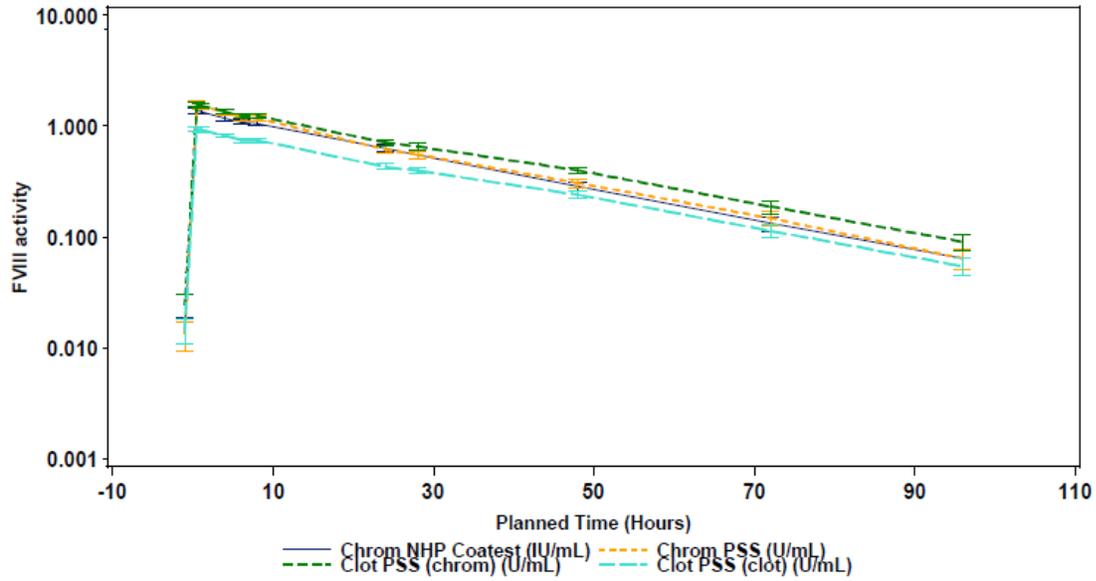
Mean +/- SEM
Chrom: chromogenic, NHP: normal human plasma, PSS: product specific standard
nn7088-4033/ctr_20170928_er - 28-SEP-2017 - f_1420_mean_plots/f_14201140_mean_com_log.cgm