Pharmacokinetics of a novel extended half-life glycoPEGylated factor IX, nonacog beta pegol (N9-GP) in previously treated adult, adolescent, and pediatric patients with hemophilia B – results from two phase 3 trials

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Objective

- Evaluate the pharmacokinetics (PK) of nonacog beta pegol (N9-GP) in adult/adolescent and pediatric patients with hemophilia B in two phase 3 trials (paradigm™2 and paradigm™5).

Conclusions

- Due to the long half-life of N9-GP, the mean trough value for most patients (≥17%) was in the range of mild hemophilia (factor IX [FIX] activity 5–40%)[1] after once-weekly dosing at 40 IU/kg.
- As expected, children exhibited lower plasma FIX activity levels and incremental recoveries versus adults/adolescents. All these values were higher than data from standard FIX products.
- The mono-exponential decay of FIX plasma activity profile (which differs from other long-acting products)[2] favorably supports once weekly N9-GP prophylactic dosing in patients with hemophilia B.

Introduction

- Nonacog beta pegol (N9-GP), a glycoPEGylated recombinant factor IX (FIX) product with an extended half-life, was developed for the prevention and treatment of bleeds with less frequent dosing in patients with hemophilia B.[3,4]
- In two phase 3 trials, N9-GP was well tolerated and provided effective once-weekly prophylaxis and bleed control in adult/adolescent (paradigm™2)[4] and pediatric (paradigm™5)[5] patients with hemophilia B.
- Here, we evaluate the pharmacokinetic (PK) characteristics of N9-GP across all age groups.

Methods

- N9-GP PK parameters were assessed in adults/adolescents (paradigm™2) and children (paradigm™5).
- Previously treated patients with hemophilia B (FIX activity ≤2%), no history of FIX inhibitors, and ≥50 or ≥150 exposure days to any FIX product (children aged 0–12 yrs and adults/adolescents aged ≥13 yrs, respectively) were included.
- PK data are presented for N9-GP 40 IU/kg across all age groups.
- Predose FIX activity levels were measured in all patients to assess steady-state trough levels.
- Single-dose PK were assessed across all ages, while steady-state PK were assessed in adults/adolescents.
- Blood samples for PK assessment were collected up to 168 h (1 week) after N9-GP administration.
- Standard PK parameters were estimated based on plasma FIX activities assessed with the 1-stage clotting assay and N9-GP as the reference standard.
- PK parameters were also assessed according to race and body mass index (BMI) for adults/adolescents.

Results

- Thirty-four patients with full PK profiles (9 adults/adolescents and 25 children) on 40 IU/kg were included in the analysis.
- Fifty-four patients (29 adults/adolescents and 25 children) with predose FIX measurements at steady state were included in the analysis of trough levels at steady state.
- PK parameters for all patients dosed with N9-GP at 40 IU/kg are shown in Table 1.

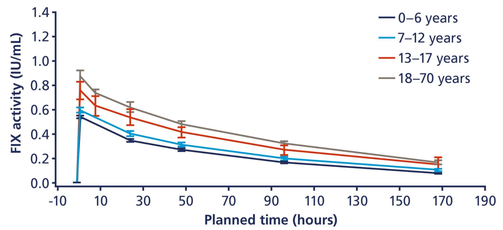
Table 1 PK parameters for N9-GP 40 IU/kg (geometric means).

Geometric mean (CV%)	Children (single-dose PK only) 0–6 yrs[a] (n=12)	Children (single-dose PK only) 7–12 yrs[a] (n=13)	Adults/adolescents[a] Single dose (n=9)	Adults/adolescents[a] Steady state (n=9)
IR, IU/mL / IU/kg	0.015 (7.3)[b]	0.016 (16.18)	0.022 (14.5)	0.019 (21.06)
Clearance, mL/h/kg	0.8 (13.0)	0.6 (21.9)	0.4 (20.4)	0.4 (12.3)
Half-life, h	69.6 (15.8)	76.3 (25.5)	85.1 (21.8)	110.8 (11.8)
FIX activity 168 h postdose[c], IU/mL	0.084 (16.28)	0.109 (18.89)	0.16 (34.4)	0.31[d] (17.3)
$AUC_{(0–inf)}$, IU×h/mL	46.2 (14.1)	56.2 (19.1)	86.9 (22.3)	141.3 (17.4)

$AUC_{(0–inf)}$, area under the curve–from time zero to infinity; CV, confidence interval; FIX, factor IX; IR, incremental recovery at t=30 min; n, number of patients for each PK parameter; PK, pharmacokinetic. [a]Samples were not available for all patients for some PK parameters. [b]n=11. [c]FIX activity 168 h postdose; values based on n=11, 12, 8, and 8, respectively. [d]Steady-state value corresponding to predosing for next dose, i.e., trough level.

- After single-dose administration, half-life was 85.1 h in adults/adolescents versus 69.6 and 76.3 h in children aged 0–6 and 7–12 yrs, respectively (Table 1).
- Single-dose PK profiles were as expected for the different age groups (Figure 1).
- There were no apparent differences in single-dose PK parameters:
  - Across race groups for all ages (White, n=21; Black, n=1; Asian, n=9; and Others, n=3).
  - Between normal-weight (BMI 18.5–24.9 kg/m²; n=5) and overweight (BMI ≥25 kg/m²; n=4) individual adult/adolescent patients.

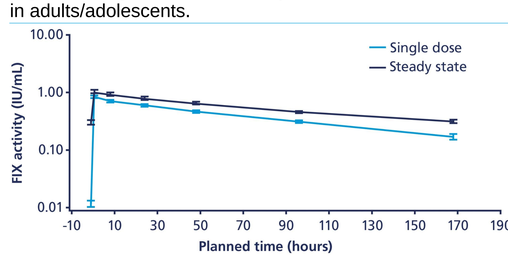
Figure 1 Single-dose PK of N9-GP 40 IU/kg in all age groups.



Data show mean ± standard error. FIX, factor IX; N9-GP, nonacog beta pegol; PK, pharmacokinetic.

- Overall, plasma FIX activity levels were lower in children of all ages than in adults/adolescents.
  - Incremental recovery for single-dose PK was lower for children of all ages versus adults/adolescents, whereas clearance per kg of body weight was higher (Table 1).
- At steady state, N9-GP half-life was 110.8 h and mean trough FIX level was 0.31 IU/mL at 168 h postdose in adults/adolescents (Table 1).
  - Estimated FIX trough at steady state based on predose measurements were 0.17 and 0.27 IU/mL for ≤12 and ≥13 yrs, respectively.

Figure 2 Single-dose and steady-state PK of N9-GP 40 IU/kg in adults/adolescents.



Data show mean ± standard error. FIX, factor IX; N9-GP, nonacog beta pegol; PK, pharmacokinetic.

- In adults/adolescents, plasma FIX activity profiles followed a mono-exponential decay after both single-dose administration and at steady state (Figure 2).
  - At all time points, FIX activity was proportionally higher at steady state than after single-dose administration.

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Conflict of interest disclosure

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