Body Mass Index-dependent Pharmacokinetic Analysis of an Investigational Recombinant Factor IX Product, IB1001 (trenonacog alfa) and a Commercial Factor IX product, Nonacog Alfa (BeneFIX®) in Hemophilia B Patients

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Introduction and Objectives

IB1001 (trenonacog alfa) is an investigational recombinant factor IX (rFIX) for the treatment and prevention of bleeding in individuals with hemophilia B. It is a single chain glycoprotein derived from Chinese hamster ovary (CHO) cells and has an amino acid sequence comparable to the Thr148 (Malmo A) allelic form of plasma-derived factor IX. IB1001 is currently being evaluated in an ongoing phase 1/2/3 study (NCT00768287) to establish efficacy and safety in individuals with hemophilia B.

Pharmacokinetics (PK) of IB1001 and a commercial factor IX product, Nonacog alfa (BeneFIX®) were investigated in a randomized, double-blind, cross-over study design in previously treated adolescent and adult patients with moderately severe or severe hemophilia B (factor IX activity ≤2 IU/dL).

The objective of body mass index (BMI)-dependent analysis was to investigate the effect of BMI on IB1001 and nonacog alfa PK, as participants in the study had a broad weight-range with correspondingly wide absolute dose range for the PK infusions.

Materials and Methods

Thirty two study participants were randomized to receive either a single intravenous dose of IB1001 or nonacog alfa in a double-blind fashion.

In brief, following a washout period of a minimum of 5 days from any factor IX product, study participants were administered a single intravenous 75 ± 5 U/kg dose of rFIX (exact dose recorded).

Blood samples were collected pre-infusion and post-infusion at 30 minutes, 1, 3, 6, 9, 12, 24, 36, 48, 60 and 72 hours. After a minimum washout of 5 days and up to a maximum of 28 days after the last assessment (assuming no other treatment with factor IX), study participants were administered a single intravenous 75 ± 5 U/kg dose of the opposite rFIX product that was received in the first cross-over period (with the exact dose recorded), and an identical set of pre-infusion and post-infusion factor IX samples was performed.

The PK parameters [$AUC_{0-\infty}$, AUC_{0-t}, Cmax, alpha-phase half life, terminal half life, clearance (CL), mean residence time (MRT), incremental recovery and volume of distribution (Vss)][1] were derived using factor IX (FIX) concentration levels and actual PK sampling times and the PK parameters were computed using Demitasse 2000 Software.

A correlation analysis was performed (Spearman rank correlation coefficients for IB1001 and nonacog alfa) to assess the relationship between individual subjects' PK parameters and BMI (kg/m^2).

A descriptive summary of IB1001 and nonacog alfa PK parameters by BMI category (<25, 25-30 and >30) was generated.

Results

A correlation analysis has been performed to assess the relationship between individual subjects' pharmacokinetic parameters and BMI. Table 1 provides the Spearman rank correlation coefficients for both IB1001 and BeneFIX®, along with the p-value testing the null hypothesis that there is no correlation (ρ = 0).

Table 1: Spearman Correlation Coefficients between BMI and PK Parameters

Group	PK Parameter							
	$AUC_{0-\infty}$	AUC_{0-t}	Cmax	Alpha Half Life	Terminal Half Life	CL	MRT	Vss
IB1001	0.614**	0.683**	0.636**	0.387*	0.289	-0.614**	0.236	-0.489*
BeneFIX®	0.666**	0.575**	0.547*	0.298	0.080	-0.666**	0.036	-0.458*

* Correlation coefficient is statistically significant (p-value < 0.05)
** Correlation coefficient is statistically significant (p-value < 0.001)
CL: clearance; MRT: mean residence time; Vss: volume of distribution

A summary of the PK parameters by study group and BMI category was generated to further evaluate the impact of BMI in the patient population (see Table 2).

Table 2: Summary of PK Parameters by BMI

PK Parameter (mean ± SD)	Baseline BMI Category					
	< 25 (n=16)		25-30 (n=10)		>30 (n=6)	
	BeneFIX®	IB1001	BeneFIX®	IB1001	BeneFIX®	IB1001
Incremental Recovery (IU/dL per IU/kg)	0.83 ± 1.07	0.84 ± 1.25	1.06 ± 1.37	1.06 ± 1.33	1.20 ± 1.49	1.24 ± 1.51
Cmax (IU/dL)	62.1 ± 80.0	62.9 ± 94.0	79.7 ± 103.0	79.4 ± 100.0	89.8 ± 112.0	93.0 ± 113.0
Alpha Half Life (hours)	9.9 ± 14.7	8.7 ± 14.3	10.8 ± 13.8	10.5 ± 12.7	11.0 ± 13.6	11.0 ± 14.2
Terminal Half Life (hours)	28.0 ± 36.4	24.9 ± 44.1	43.0 ± 126.7	27.3 ± 44.4	32.0 ± 40.9	45.8 ± 118.4
$AUC_{0-\infty}$ (IU/dL/hr)	1435.9 ± 1733.6	1319.6 ± 1778.0	1939.9 ± 3170.5	1785.5 ± 2734.6	2162.8 ± 2609.4	2398.3 ± 3682.0
CL (IU/dL/hr/kg)	0.05 ± 0.07	0.06 ± 0.08	0.04 ± 0.05	0.04 ± 0.07	0.04 ± 0.04	0.03 ± 0.05
MRT (hours)	35.3 ± 45.5	31.6 ± 49.8	47.6 ± 114.9	33.3 ± 55.7	38.7 ± 50.2	51.4 ± 124.4

AUC: area under curve; SD = standard deviation; CL: clearance; MRT: mean residence time

Conclusions

- Dose dependent parameters of AUC, Cmax, CL and Vss are strongly correlated with BMI, reflecting the larger total dose for larger individuals
- The terminal half-life and MRT are not significantly correlated with BMI, reflecting the linear pharmacokinetics of factor IX
- The marginal significance of the alpha-phase half-life likely reflects the limited data points that make up the equilibrium phase, one of which is the Cmax
- IB1001 has similar pharmacokinetic activity as BeneFIX® across a broad BMI range

References

[1] Lee ML, Schroth P, Bray G, Gomperts ED. The use of robust regression techniques to obtain improved coagulation factor half-life estimates. XVIth Congress of the International Society for Thrombosis and Hemostasis, Florence, Italy, 1997.

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