Safety Profile of IB1001, Recombinant Factor IX (trenonacog alfa) in the Treatment of Hemophilia B

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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.

Methods

The safety information for IB1001 is derived from a single Phase I/II/III clinical trial designed as a prospective, multicenter study to evaluate the pharmacokinetic (PK) parameters, safety, immunogenicity and efficacy of IB1001 in previously treated patients (PTPs) with severe hemophilia B (Treatment Phase and Surgery). The analysis included data from prophylaxis, on-demand and preventive (surgical) therapies. IB1001 doses were determined by Investigators except for the randomized, cross-over PK study where patients received a single 75 IU/Kg dose. The treatment doses were initially selected based upon the PK profile of IB1001 and the subject's bleeding phenotype. Doses could be adjusted at the Investigator's discretion. Patient demographics and clinical characteristics, IB1001 consumption, and safety data, including adverse events (AEs) and immunogenicity assessments, were collected and analysed.

Results

In total, 77 patients received at least one dose of IB1001 (safety population). Median age was 26 years (range 7 to 64 years). The subjects were grouped in age < 12 yrs, age12 to 18 yrs and age >18 yrs; all were male with the exception of a single carrier symptomatic female enrolled in the surgical sub-study only. Most of the subjects participating in the study were Caucasian (n=62; 79%), Black (n=3; 4%), Asian (n=8; 10%), Native Hawaiian or other Pacific Islander (n=2; 3%) or unknown (n=3; 4%) (Table 1).

Table 1: Study IB1001-01 Details

Age (years)	N (%): 77 subjects Median age: 26 yrs (range 7-64 years)
<12	3 (4)
12-18	9 (12)
>18	65 (84)
Study*	*Subjects could have participated in more than one study phase.
Randomized PK	32
Repeat PK	14
Initial Recovery	41
Surgery	17
Treatment	68
Ethnicity	
Caucasian	61 (79)
Asian	8 (10)
Black	3 (4)
Native Hawaiian/ Pacific Island	2 (3)
Unknown	3 (4)
Dose	Median 258,424 IU/yr (range 2250-961,333 IU/yr)
Infusions	116 (range 1-441)
Exposure Days	112/subject

Thirty-two subjects participated in the randomized cross-over PK study, 41 subjects in the initial recovery PK sub-study (14 subjects participated in the repeat PK sub-study), 68 subjects in the treatment phase, and 17 subjects participated in the surgery sub-study. Subjects received a mean dose per infusion of 56 IU/kg, with a median of 116 infusions (range 1 – 441) for a median of 112 exposure days (EDs)/subject. Overall, a total of 9641 infusions were administered to subjects participating in IB1001-01.

Of the 449 AEs reported by 58/77 subjects (75%), 14 AEs in 10/77 subjects (13%) were considered serious (SAEs), including 2 events of diverticulitis, and one event of each of the following: skin laceration, periprosthetic fracture, joint injury, limb injury, abdominal pain, mental status change, lumbar vertebral fracture, wound infection, femur fracture and postoperative wound infection. All SAEs were assessed as unrelated to IB1001 by the investigator (Figure 1).

There were no reports of deaths, suspected unexpected serious adverse reactions (SUSARs), hypersensitivity reactions, thromboembolism, nephrotic syndrome or development of inhibitory FIX antibodies. Most AEs were considered mild or moderate (Figure 2).

References

[1] Ingerslev J, Christiansen K, Ravn HB et al. Antibodies to heterologous proteins in hemophilia A patients receiving recombinant factor VIII (Recombinate™). Thromb Haemost 2002;87:626–34.

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[3] D Toth, E Van der Hart, S Buhay, H Price, R Jenny, J Kosman, C Weber, A Walker, L Saward. Manufacture of recombinant factor IX IB1001 with low host cell proteins through process improvements. EAHAD Abstract Feb 2014

Results, continued

There were 15 ADRs (i.e., related AEs) reported in 7 out of 77 subjects (9%); all ADRs were mild or moderate in intensity. The most common ADR was headache (5 events in 2 subjects; 3%). In addition to 5 ADRs of headache in 2 subjects, the other 10 ADRs were reported once each: asthenia, lethargy, rash, apathy, dysgeusia, injection site discomfort, influenza, depression, hemophilia and positive for non-inhibitory FIX antibodies.

Figure 1 Number of AEs, ADRs, SAEs and SUSARs

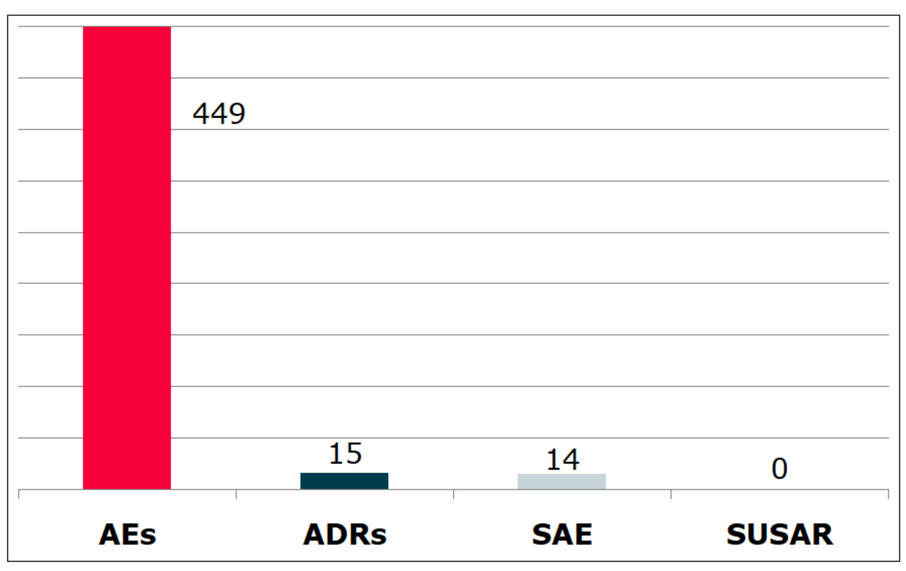
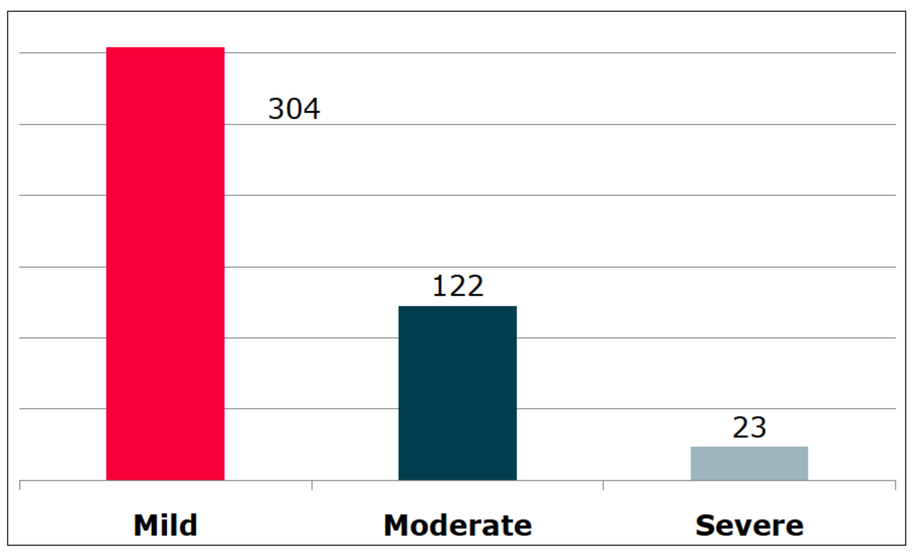


Figure 2 Number of AEs by Intensity



Immunogenicity

Studies of marketed recombinant factor products produced in CHO cells suggest that antibodies against CHO cell proteins (CHOP) can sporadically be detected in patients as well as in non-hemophilic subjects[1]. During the course of IB1001-01 clinical trial, 68 subjects were tested for anti-CHOP; 20 out of 68 subjects (29%) developed anti-CHOP reactivity, 37 subjects (54%) remained negative, while 11 subjects were indeterminate. No AEs were temporally associated with anti-CHOP reactivity and there have been no clinical characteristics that appear to be correlated with anti-CHOP seroconversion.

To address the issue of CHOP in IB1001, the manufacturing process has been minimally modified to include a hydrophobic interaction chromatography (HIC) column to increase clearance of CHOP[2,3].

Occasional and transient non-inhibitory FIX binding antibodies have also been observed in clinical trials. Of the 77 enrolled subjects, 56 subjects (73%) were negative,16 subjects (21%) showed the presence of non-inhibitory FIX antibodies at one or more time points after IB1001 infusion, while 5 subjects (6%) reported non-inhibitory FIX antibodies at baseline. These antibodies were not associated with any changes in dose and their clinical significance has not been established.

Conclusions

- The results from IB1001-01 suggest that IB1001 is generally well tolerated in a broad patient population and in a variety of treatment settings (i.e., across age groups, ethnicity and phase of study).
- The most common ADR was headache (5 events in 2 subjects; 3%).
- No reports of inhibitor development, anaphylaxis, thrombogenicity or nephritic syndrome.
- The IB1001 safety profile is comparable to other marketed recombinant FIX products; however, further evaluation is warranted

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