The safety and efficacy of IB1001 (trenonacog alfa) in children with hemophilia B: a pooled analysis

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Introduction

- Hemophilia B, an X-linked congenital bleeding disorder that results from a deficiency of factor IX, frequently presents in childhood as easy bruising, spontaneous bleeding, or excessive bleeding following trauma or surgery.
- The primary aim of care is to prevent and treat bleeding with factor IX replacement (Srivastava A, et al. Haemophilia 2013).
- IB1001 is a third generation recombinant factor IX approved for the control and prevention of bleeding episodes and for perioperative management patients ≥ 12 years of age with hemophilia B (IXINITY package insert).
- In the pivotal clinical trial, patients using a prophylactic regimen of IB1001 had a median annualized bleeding rate (ABR) of 1.52. Bleeding episodes were controlled with one infusion of IB1001 in 71% of cases, and with 2 infusions in 84% of cases (Drobic B, et al. NHF 2015).
- Data on the use of IB1001 in patients < 12 years old could help inform clinical decision-making.

Objectives

- To evaluate the safety and efficacy of IB1001 in previously treated children ≤ 12 years of age with hemophilia B.

Study Design

- Pooled analysis of 2 prospective, multi-center, non-randomized, open-label studies in previously treated patients with hemophilia B.
  - Study 1 (NCT01271868): Patients ≤ 12 years of age (n=9)
  - Study 2 (NCT00768287): Patients ≥ 12 years of age: younger patients included on an exception basis (n=3)
- Patients were treated with either a prophylactic or on demand regimen based on investigator discretion.
  - All patients were assigned a prophylactic regimen.
  - One patient erroneously received on demand treatment during the study.
- Bleed control efficacy was evaluated using:
  - Annualized bleeding rate
  - Subject's rating of efficacy for the degree of bleed control
  - Number of infusions required to treat a bleed.
- Subjects were monitored for adverse events and regularly assessed for the development of inhibitors.

Entry Criteria

Key Inclusion Criteria

- Documented severe or moderately severe hemophilia B diagnosis (factor IX activity ≤2 IU/dL); in addition, severity may be indicated by the occurrence of one or more joint bleeding episode(s) at any point in the child's medical history requiring infusion(s) to replace factor IX
- Previously treated patients with a minimum of 50 exposure days (as documented/determined by the investigator) to a preparation/blood components containing factor IX
- Immunocompetent (CD4 count >400/mm^3) and not receiving immune modulating or chemotherapeutic agents
- Platelet count at least 150,000/mm^3
- Liver function: alanine transaminase (ALT) and aspartate transaminase (AST) ≤2 times the upper limit of normal
- Total bilirubin ≤1.5 times the upper limit of the normal range
- Renal function: serum creatinine ≤1.25 times the upper limit of the normal range
- Hemoglobin ≥7 g/dL

Key Exclusion Criteria

- History of factor IX inhibitor ≥0.6 Bethesda Units (BU)
- Existence of another coagulation disorder
- Evidence of thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC)
- Use of an investigational drug within 30 days prior to study entry

Patient Characteristics

Characteristic	Number
Number of patients	12
Age; median (range)	9.5 (2-11)
Gender	
Male	12
Female	0
Race	
Asian	6
White	3
Pacific Islander	2
Other	1

Results

Efficacy (Prophylaxis Group)

	Age	Race	Exposure Days	Treatment Duration (months)	# of Bleeds	Annualized Bleed rate
Study 1	2	White	111	13	0	0.0
	4	Asian	189	46	1	0.3
	4	Asian	404	46	1	0.3
	7	White	395	48	1	0.3
	9	Asian	238	47	0	0.0
	10	White	347	46	6	1.6
	10	Asian	193	43	1	0.3
	11	Asian	203	44	2	0.5
Study 2	7	Pacific Islander	262	51	11	2.6
	10	Pacific Islander	254	51	5	1.2
	10	Other	267	30	10	4.0

Summary Results (n=11)	
Exposure days; median (range)	254 (111-404)
Dose per infusion (IU/kg); median (range)	75.3 (25.3-111.0)
Number of bleeding episodes; median (range)	1.0 (0-11)
Annualized bleed rate (ABR); median (range)	0.3 (0-4.0)
# of patients with no bleeds, N (%)	2 (18)

Efficacy (On Demand Patient)

- The one patient who received IB1001 on demand was Asian, 11 years old, had 23 bleeding episodes and had an ABR of 11.1.

Efficacy (Combined Group)

- Of the total 61 bleeding episodes in this study, 6 (10%) resolved with no infusions, 44 (72%) resolved after one infusion, 5 (8%) required two infusions, and 6 (10%) required 3, 4, or 5 infusions.
- Of the 34 bleeding episodes rated, subjects rated bleed control as "excellent" for 22 (65%) of the bleeding episodes, "good" for 11 (32%) of the bleeding episodes, "fair" for 1 (3%) of the bleeding episodes, and "poor" for no episodes.

Safety

- The adverse events considered related to IB1001 were hyperhidrosis and fever in one patient and hyperhidrosis in another.
- None of the patients developed factor IX inhibitors during the study.

Conclusions

- In this pooled analysis, IB1001 was well-tolerated and appeared effective in preventing and controlling bleeding episodes in previously treated children ≤ 12 years of age with hemophilia B.
- These results are comparable to the results of the overall population studied in the pivotal clinical trial (Study 1, age range 7 to 64).
- Patients respond to different factor IX options differently, so it is helpful to have a variety of options available.

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