Immune Globulin Intravenous (Human) 10% Liquid is Safe and Efficacious in Pediatric Patients with Primary Immune Deficiency Disorders

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IgNS 2023
Poster #110

INTRODUCTION

Immune globulin intravenous (human) 10% liquid (IGIV 10%) is FDA-approved for the treatment of primary humoral immunodeficiency (PI).[1] In its pivotal trial, pediatric subjects with PI were limited to 9 subjects aged 6 to 16 years old.[1] To further characterize the safety in children and adolescents (>2 to 16 years of age), Study 994 was conducted as part of a post-marketing requirement.[2]

OBJECTIVE

The primary objective was to evaluate the safety of IGIV 10%, including the incidence and profile of adverse events (AEs), treatment emergent adverse events (TEAEs), serious adverse events (SAEs), temporally associated adverse events (TAAEs), and infusion associated adverse events. Additional secondary outcomes included efficacy based on the rate of serious bacterial infections (SBIs), number of days missed from school/work, and number of hospitalizations.

METHODS

This Phase IV prospective, open-label, single-arm, multi-center clinical trial evaluated the safety and efficacy of IGIV 10% (BIVIGAM® 10%) in pediatric subjects with confirmed and documented clinical diagnosis of PI. This study took place at 6 US sites from December 2016 to June 2021.

Subjects 2 to 16 years old were eligible if they had a documented diagnosis of PI and were receiving immune globulin replacement therapy (IgRT) at a steady dose (±25% of the mean dose) for at least 3 months prior to study entry with an immune globulin G (IgG) trough level of at least 500 mg/dL. Subjects received IGIV 10% at a dose of 300 to 800 mg/kg every 3 or 4 weeks for 5 months of study infusions. Dose adjustments were permitted during the study to maintain trough total IgG concentrations at > 500 mg/dL. Study product was infused at a starting rate of 0.5 mg/kg/min and increased by 0.8 mg/kg/min every 20 minutes and could be increased to a maximum of 6 mg/kg/min if tolerated at intermediate rates in previous infusions.

Safety data are summarized utilizing descriptive statistics in the modified intent to treat (mITT) population. The primary efficacy outcome was analyzed using Poisson model in the mITT population; secondary efficacy outcomes are summarized with descriptive statistics.

This study was sponsored by ADMA Biologics, Inc. Ramsey, NJ

RESULTS

PATIENTS

Sixteen patients across 6 US sites received a median dose of 484 mg/kg (range 312 mg/kg to 1077 mg/kg). The most common PI diagnosis was hypogammaglobulinemia (*Figure* 1). Additional patient baseline characteristics are summarized in *Table 1*.

Figure 1. PI diagnosis indicating IgRT (N=16)

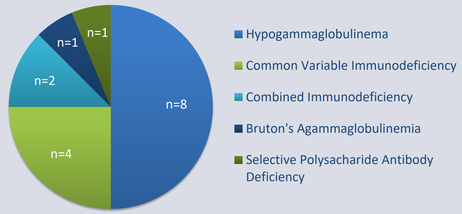


Table 1. Summary of baseline characteristics and demographic data for the mITT patient population

Demographics	3-week regimen (N=8)	4-week regimen (N=8)	Total (N=16)
Age, mean (SD) years	11 (5.2)	9.5 (3.1)	10.3 (4.2)
2-5 years old, n (%)	2 (25)	1 (12.5)	3 (18.8)
6-11 years old, n (%)	1 (12.5)	4 (50)	5 (31.3)
12-16 years old, n (%)	5 (62.5)	3 (37.5)	8 (50)
Male, n (%)	8 (100)	8 (100)	16 (100)
Weight, mean (SD) kg	50.1 (32.7)	37.4 (17.2)	43.7 (26.1)
Median (min,max)	45.9 (16.3,119)	31.7 (18.6,67.1)	39.5 (16.3,119)
Years since PI diagnosis, mean (SD)*	3.9 (2.2)	4.7 (4.2)	4.3 (3.3)
Median (min,max)	3.3 (1.6, 7.1)	3.2 (0.9,10.8)	3.3 (0.9,10.8)
IgG trough levels pre-infusion 1, mean (SD) mg/dL	964 (128)	760 (183)	862 (185)
Median (min,max)	1014 (761,1112)	810 (459,1022)	874 (459,1112)

*Data available for 14 subjects; max=maximum; min=minimum; SD=standard deviation

SAFETY

In the total safety set (N=16), 7 of the 96 (7.3%) IGIV 10% infusions administered had TAAEs with the mean proportion of infusions with TAAEs per subject being 8.75 (95% Confidence Limit [CL], -0.2 to 17.7). The one-sided 95% upper CL (17.7%) in the overall population was well below the established IGIV product safety threshold of 40%.

TEAEs occurring in ≥10% of subjects in the total population included: headache (31.3%), upper respiratory infection (18.8%), bronchitis, cough, fatigue, influenza, nasal congestion, oropharyngeal pain, pyrexia, and sinus congestion (12.5% each). A single SAE occurred in the study (hemiparesis) and was deemed unrelated to the study product. Three subjects experienced a total of 7 TEAEs related to the study product (procedural headache, fatigue, and headache) all determined to be mild or moderate. No patients reported significant, life-threatening TEAEs, and no AEs led to study discontinuation.

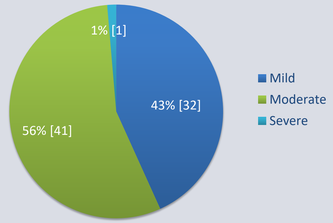
Seven adverse infusion reactions were reported in 3 subjects. No infusion site reactions were reported.

Table 2. Safety data for the mITT population

Category	3-week regimen (N=8)		4-week regimen (N=8)		Total (N=16)	
	Total Events	Subjects n (%)	Total Events	Subjects n (%)	Total Events	Subjects n (%)
Any adverse event	69	8 (100)	17	5 (62.5)	86	13 (81.3)
Any TEAE	62	8 (100)	12	5 (62.5)	74	13 (81.3)
Serious	1	1 (12.5)	0	0	1	1 (6.3)
Product-related	5	2 (25)	2	1 (12.5)	7	3 (18.8)
TAAE within 72 hours of infusion	7*	3 (37.5)	2	1 (12.5)	9**	4 (25)
Adverse events of special interest†	0	0	0	0	0	0
Adverse infusion reactions	5	2 (25)	2	1 (12.5)	7	3 (18.8)
Infusion site reactions	0	0	0	0	0	0

*Occurred within 1 hour of infusion; **TAAEs reported (9 total) include procedural headache (3), fatigue (2), nausea (1), rash (1), headache (2);
† Defined as hemolysis or thrombosis

Figure 2. TEAEs by severity (74 total TEAEs, % [total])



RESULTS, Cont.

EFFICACY

No acute SBIs occurred during the observation period (mean 152 days) in either the 3- or 4-week regimen groups. This resulted in a mean number of acute SBI episodes per person-year of 0.0 that is below the 1.0 threshold set by the FDA. No serious infections or hospitalizations due to infection were reported. One subject in the 3-week infusion regimen group missed a total of 9 days from school due to infection; there were no days missed from school in the 4-week group. Trough IgG levels were maintained over 500 mg/dL in all subjects throughout the study.

DISCUSSION/CONCLUSIONS

Study 994 met its primary objective by demonstrating the safety of IGIV 10% in pediatric subjects aged 2 to 16 years. Six months of treatment with IGIV 10% was well tolerated, with no deaths, no SAEs attributed to the study product, and no AEs necessitating a change in study product dose or regimen, discontinuation of an infusion, or withdrawal from the study. There were no findings indicative of intravascular hemolysis, thrombosis, or viral transfer. The type and frequency of AEs were consistent with the known safety profile of IGIV 10%, and IGIV treatment in general.

The study also demonstrated efficacy in preventing the occurrence of acute SBIs in the study population. No acute SBIs occurred during the 6-month observation period, yielding a mean number of acute SBI episodes per person-year of 0.0. Furthermore, no other serious infections or hospitalizations due to infections occurred.

REFERENCES

1. ADMA Biologics, Inc. Ramsey, NJ. BIVIGAM® (immune globulin intravenous (human) 10% liquid) [prescribing information]. Accessed September 2023.
2. S.830 - 105th Congress (1997-1998): Food and Drug Administration Modernization Act of 1997. (1997, November 21). https://www.congress.gov/bill/105th-congress/senate-bill/830