Immune Globulin Intravenous, human – slra 10% is Safe and Efficacious in Pediatric Patients with Primary Immune Deficiency Disorders

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INTRODUCTION

Immune globulin intravenous, human – slra 10% (IGIV-slra 10%) was approved in 2019 for the treatment of primary humoral immunodeficiency (PI) in adults and adolescents 12 years of age and older.[1] This Phase IV open-label, single-arm, multi-center clinical trial study was conducted to further characterize efficacy, safety, and pharmacokinetics in the pediatric population (≥2 to 11 years) as part of a post-marketing requirement.[2]

OBJECTIVE

Primary Objective:
Evaluate the pharmacokinetic (PK) profile of IGIV-slra 10% in pediatric subjects with primary immunodeficiency diseases (PI)

Secondary Objectives:

- Efficacy and safety of dosing with IGIV-slra 10%, including:
  - Adverse events (AEs)
  - Serious adverse events (SAEs)
  - Infusion associated adverse events (IAAEs).
- Additional secondary outcomes included trough total IgG levels at regular intervals and levels of specific antibodies

METHODS

This Phase IV open-label, single-arm, multi-center clinical trial evaluated the safety and efficacy of IGIV-slra 10% (ASCENIV™) in pediatric subjects with confirmed and documented clinical diagnosis of PI. This study took place at 5 US sites from March 2023 to October 2024.

Subjects 2 to 11 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 IgG trough level of at least 500 mg/dL.

Subjects received IGIV-slra 10% at a dose of 300 to 800 mg/kg every 3 or 4 weeks for a total of 7 or 6 doses, respectively. 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 in 15-minute intervals to 1 mg/kg/min at 15 minutes, 2 mg/kg/min at 30 minutes, 4 mg/kg/min at 45 minutes, 6 mg/kg/min at 60 minutes, to a final maximum rate of 8 mg/kg/min at 75 minutes after the start of infusion if tolerated.

Safety data are summarized utilizing descriptive statistics in the modified intent to treat (mITT) population. The primary efficacy outcome is analyzed as the annualized rate of acute SBIs per patient; secondary efficacy outcomes are summarized with descriptive statistics. Pharmacokinetic parameters are calculated using non-compartmental analysis of serum concentration data.

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

RESULTS

SUBJECTS

Sixteen subjects across 5 US sites received a median dose of 547 mg/kg (range 316 mg/kg to 960 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)

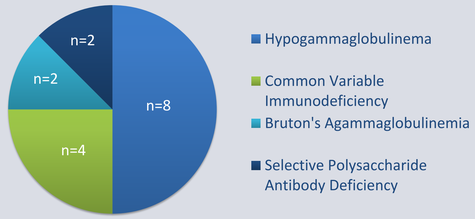


Table 1. Summary of baseline characteristics and demographic data for the mITT patient population

Demographics	3-week regimen (N=3)	4-week regimen (N=13)	Total (N=16)
Age, mean (SD) years	10.3 (1.15)	6.4 (3.23)	7.1 (3.32)
2-6 years old, n (%)	—	7 (53.8)	7 (43.8)
7-11 years old, n (%)	3 (100)	6 (46.2)	9 (56.3)
Male, n (%)	1 (33.3)	10 (76.9)	11 (68.8)
Weight, mean (SD) kg	41 (8.9)	25.4 (9.9)	28.3 (11.3)
Median (min, max)	37.4 (34.5, 51.2)	25.8 (11.4, 37.5)	30.25 (11.4, 51.2)
Years since PI diagnosis, mean (SD)*	4.13 (4.1)	2.31 (1.9)	2.65 (2.4)
Median (min, max)	3.76 (0.2, 8.4)	1.70 (0.4, 5.5)	1.96 (0.2, 8.4)
IgG trough levels pre-infusion 1, mean (SD) mg/dL	981 (758, 1255)	887 (650, 1271)	909 (650, 1271)
Median (min, max)	931	887	909

*Data available for 16 subjects; max=maximum; min=minimum; SD=standard deviation

SAFETY

In the total safety set (N=16), 11 of the 91 (12.1%) infusions administered were temporally associated with an AE. The mean proportion of infusions with ≥1 TAAE (defined as AEs occurring during or within 72 hours after a study drug infusion) was 15.63%, and the upper limit of the 95% one-sided confidence interval for the mean was 27.5%. Therefore, the study met its primary safety endpoint by demonstrating that the one-sided 95% upper confidence limit (CL) of the probability that an infusion was associated with an AE was below 40%.

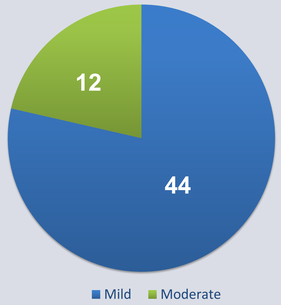
Treatment-Emergent Adverse Events (TEAEs) occurring in ≥10% of subjects in the total population included: headache (31.3%), nausea, pyrexia (18.8% each), cough, COVID-19, epistaxis, nasal congestion, nasopharyngitis, otitis media, procedural headache, sinusitis, skin abrasion, and vomiting (12.5% each). No deaths occurred during the study. A single treatment-emergent SAE occurred (hypersensitivity, reported as acute allergic reaction) and resolved within the same day. The subject was discontinued from the study as a result, and the event was assessed as moderate in severity and probably related to the study treatment. Nine adverse infusion reactions were reported in 6 subjects. No infusion site reactions were reported.

Table 2. Summary of Adverse Events, Safety Population

Category	3-week regimen (N=3)		4-week regimen (N=13)		Total (N=16)	
	Total Events	Subjects n (%)	Total Events	Subjects n (%)	Total Events	Subjects n (%)
Any adverse event	8	3 (100)	54	11 (84.6)	62	14 (87.5)
Any TEAE	7	3 (100)	49	11 (84.6)	56	14 (87.5)
Serious	0	0	2	2 (15.4)	2	2 (12.5)
Product-related	5	1 (33.3)	8	5 (38.5)	13	6 (37.5)
TAAE within 72 hours of infusion	5	1 (33.3)	14	6 (46.2)	19	7 (43.8)
Adverse events of special interest[†]	0	0	0	0	0	0
Adverse infusion reactions	2	1 (33.3)	7	5 (38.5)	9	6 (37.5)
Infusion site reactions	0	0	0	0	0	0

TEAE: defined as an AE that started on or after the first IMP infusion
TAAE: defined as an AE with onset within 72 hours after the end of the infusion.
[†] Defined as hemolysis or thrombosis

Figure 2. TEAEs by severity (56 total TEAEs)



RESULTS, Cont.

EFFICACY

No acute serious bacterial infections (SBIs) occurred during the observation period (mean 158 days). This resulted in a mean number of acute SBI episodes per person-year of 0.0, meeting the threshold set by the FDA of below 1.0.

A total of 17 infections (bacterial and viral combined, all non-serious) occurred in 10 subjects (62.5%) in the mITT population. No serious infections or hospitalizations due to infection were reported. Apart from a single IV dose of ceftriaxone sodium administered for the treatment of otitis media, antibiotic treatment for infections was taken orally.

PHARMACOKINETICS

None of the 14 subjects with Total IgG data available prior to their last infusion (2 subjects in the 3-week infusion regimen and 12 subjects in the 4-week infusion regimen cohort) had trough Total IgG levels below 500 mg/dL. Within each subject, trough IgG concentrations were reasonably constant across all visits regardless of age and frequency of dosing, suggesting that an apparent steady-state was maintained.

CONCLUSIONS

The study met its primary objective by demonstrating the safety of IGIV-slra 10% in pediatric subjects aged 2 to 11 years.

- **No acute SBIs observed during the 6-month observation period**
- **No other serious infections or hospitalizations due to infections occurred**

Six months of treatment with IGIV-slra 10% was well tolerated, with no deaths, no findings indicative of intravascular hemolysis, thrombosis, or viral transfer. One treatment-emergent SAE (hypersensitivity, occurring during an IMP infusion) was attributed to the study treatment, and resulted in discontinuation from the study. The type and frequency of AEs was consistent with the known safety profile of IGIV-slra 10%, and IGIV treatment in general.

Immune globulin intravenous, human – slra 10% was safe, effective, and well tolerated in patients 2 to 11 years old with PI, supporting an expanded age indication that includes younger pediatric patients.

REFERENCES

1. ADMA Biologics, Inc. Ramsey, NJ. ASCENIV® (immune globulin intravenous (human-slra) 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