Safety and Tolerability of a New Intravenous Immunoglobulin 10% in Patients With Primary Immunodeficiency

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KEDRION BIOPHARMA

INTRODUCTION

- Primary immunodeficiency (PI) disorders, or inborn errors of immunity, are a heterogeneous group of disorders with a congenital basis that result in the deficiency of different components of the adaptive and innate immune system
  - These disorders result in inadequate antibody production and may increase patients' susceptibility to recurrent infections, autoimmunity, and malignancy[1-4]
- Lifelong treatment with intravenous immunoglobulin (IVIg) replacement therapy is foundational to the standard of care for many patients with PI
  - However, uncertainties regarding the degree of improvement in patients' quality of life and variability in tolerability profiles with various agents, in addition to overall limitations in IVIg supply, create unmet needs for new treatment options for patients and clinicians[5-10]
- KIg10 is a new ready-to-use liquid, normal IVIg product (100 mg/mL) developed from source plasma collected in the United States
- The manufacturing process features Cohn-Oncley fractionation, caprylate precipitation treatments, and anion-exchange chromatography to produce an IVIg with low levels of procoagulant activity and impurities in the final product
- Three manufacturing steps have been validated for pathogen (virus and prion agents) clearance: caprylate precipitation and inactivation treatment, nanofiltration (20 nm), and low-pH treatment for viral removal/inactivation

OBJECTIVES

- An open-label, prospective, single-arm, multicenter, phase 3 study (KIg10_US3_PID01; ClinicalTrials.gov Identifier: NCT01581593) was conducted to evaluate the efficacy, safety, and pharmacokinetics of this new IVIg 10% product (KIg10) administered at doses of 200 to 800 mg/kg every 21 or 28 days for 48 weeks in adult patients with PI who were previously treated with other IVIg products
- Safety and tolerability data from this study are reported here and include treatment-emergent adverse events (TEAEs) from Day 1 to Week 51/52

METHODS

- This open-label, prospective, single-arm, historically controlled, multicenter, phase 3 study was conducted in patients with PI treated with KIg10 at doses of 200 to 800 mg/kg every 21 or 28 days for 48 weeks
- Patients eligible for enrollment were aged 2 to 70 years with a confirmed clinical diagnosis of PI and documented agammaglobulinemia or hypogammaglobulinemia, but, ultimately, only adult patients were enrolled and evaluated in this study
- Prior to screening, enrolled patients had received commercially available IVIg products at doses of 200 to 800 mg/kg for ≥3 infusion cycles (21 or 28 days) and had ≥2 documented immunoglobulin G trough levels of ≥6 g/L while receiving IVIg treatment during 2 infusion cycles within 12 months of providing informed consent
- The first infusion was administered at an initial rate of 1 mg/kg/min for 30 minutes
  - If well tolerated, the rate was progressively increased to a maximum of 8 mg/kg/min at 30-minute intervals
- Subsequent infusions were administered at an initial rate of 2 mg/kg/min for 15 minutes
  - If well tolerated, the rate was progressively increased to a maximum of 8 mg/kg/min (4, 6, and 8 mg/kg/min) at 15-minute intervals
- If an adverse event (AE) occurred, either the rate of administration was reduced to the previous step or the infusion was stopped; the treatment required depended on the nature and severity of the AE
- Evaluations were performed after each infusion until Week 51 or Week 52, depending on the infusion schedule
- The primary safety objective was to assess the safety profile of KIg10 in the overall study population from Day 1 to Week 51/52, including the incidence of overall and infusional AEs, defined as those that began during or within 72 hours after an infusion

References

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RESULTS

- Forty-seven patients were enrolled and received study treatment; enrolled patients completed all study requirements and were analyzed for safety and efficacy
- Four (8.5%) patients, all on the 28-day infusion schedule, received premedication, and most of them (3 [6.4%] patients) took analgesics (**Table 1**)
  - Premedication was defined as any medication taken to avoid AEs occurring in conjunction with the infusion of IVIg products during the study and may have included antihistamines, antipyretics, and/or steroids with an indication of prophylaxis

Table 1. Number of Patients Who Received Premedications by Infusion Schedule

Patients who received premedication, n (%)	KIg10 infusion schedule		Overall (N = 47)
	21-day infusion schedule (n = 8)	28-day infusion schedule (n = 39)	
Any premedication	0	4 (10.3)	4 (8.5)
Analgesics and antipyretics	0	3 (7.7)	3 (6.4)
Antimigraine preparations	0	1 (2.6)	1 (2.1)
Anti-inflammatory and antirheumatics	0	1 (2.6)	1 (2.1)
Antiemetics and antinauseants	0	1 (2.6)	1 (2.1)
Antihistamines for systemic use	0	1 (2.6)	1 (2.1)
Corticosteroids for systemic use	0	1 (2.6)	1 (2.1)

ATC, Anatomical Therapeutic Chemical.
Classification according to ATC levels 2 and 3.

- All patients overall received all infusions on both the 21-day (17 infusions) and 28-day (13 infusions) infusion schedules, for a total of 643 infusions administered
  - The majority (96.9%) of infusions were completed without infusion rate reduction, interruption, or discontinuation
- All patients were treated with a dose within the allowed range of 200 to 800 mg/kg, except for 2 patients
  - One patient was treated with a dose of 826 mg/kg for the entire study duration
  - One patient was treated with a dose of 802 mg/kg for Infusions 9 to 12 and a dose of 958 mg/kg for the last infusion (Infusion 13)
- Forty-four of 47 (93.6%) patients reached the maximum infusion rate of 8 mg/kg/min
- Forty-six (97.9%) patients reported ≥1 TEAE; drug-related TEAEs were reported by 22 (46.8%) patients (**Table 2**)

Table 2. TEAEs

Patients, n (%)	KIg10 infusion schedule		Overall (N = 47)
	21-day infusion schedule (n = 8)	28-day infusion schedule (n = 39)	
Any TEAE	8 (100)	38 (97.4)	46 (97.9)
Mild	5 (62.5)	34 (87.2)	39 (83.0)
Moderate	8 (100)	27 (69.2)	35 (74.5)
Severe	1 (12.5)	1 (2.6)	2 (4.3)
Drug-related TEAE	3 (37.5)	19 (48.7)	22 (46.8)
Serious drug-related TEAE	0	0	0

AE, adverse event; TEAE, treatment-emergent adverse event.
For the summary of TEAEs by intensity, a patient was counted more than once if the patient had >1 TEAE of different intensities. For example, if a patient had an AE of mild intensity and an AE of moderate intensity, the patient was counted in both categories.

- Four (8.5%) patients reported 5 serious TEAEs that required hospitalization or prolonged hospitalization; all were assessed as not related to the study drug (**Table 3**)
- Overall, 22 (46.8%) patients reported drug-related TEAEs; the most frequently reported (≥5%) drug-related TEAEs were headache in 12 (25.5%) patients; infusion-related reaction in 5 (10.6%) patients; and nausea, fatigue, and Coombs direct test positive in 4 (8.5%) patients each (**Table 3**)
- Two severe TEAEs were reported in the study; both were deemed not related to the study treatment by the investigators

Table 3. Drug-Related TEAEs Occurring in ≥5% of Patients

	Patients, n (%)			Events, n	Infusions, n (%) (N = 643)
	KIg10 infusion schedule				
	21-day infusion schedule (n = 8)	28-day infusion schedule (n = 39)	Overall (N = 47)		
Any drug-related TEAE	3 (37.5)	19 (48.7)	22 (46.8)	75	45 (7.0)
Headache	1 (12.5)	11 (28.2)	12 (25.5)	27	23 (3.6)
Infusion-related reaction	0	5 (12.8)	5 (10.6)	9	7 (1.1)
Nausea	0	4 (10.3)	4 (8.5)	4	3 (0.5)
Fatigue	0	4 (10.3)	4 (8.5)	7	3 (0.5)
Coombs direct test positive	1 (12.5)	3 (7.7)	4 (8.5)	7	7 (1.1)
Serious drug-related TEAE	0	0	0	0	0

TEAE, treatment-emergent adverse event.

- No hemolysis events were reported, and no laboratory findings were suggestive of hemolysis associated with positive Coombs direct tests, such as decreased hemoglobin levels
- Thirty (63.8%) patients reported ≥1 infusional AE; drug-related infusional AEs were reported by 19 (40.4%) patients (**Table 4**)
  - The most frequently reported (≥5%) infusional AEs were headache (25.5%); fatigue (14.9%); infusion-related reaction, nausea, and Coombs direct test positive (10.6% each); and diarrhea, dizziness, and sinusitis (6.4% each)
- Notably, no patient had infusional AEs during Infusions 14, 15, 16, and 17 (the last infusions of the 28-day infusion schedule)

Table 4. Infusional AEs

Patients, n (%)	KIg10 infusion schedule		Overall (N = 47)
	21-day infusion schedule (n = 8)	28-day infusion schedule (n = 39)	
Any infusional AE	5 (62.5)	25 (64.1)	30 (63.8)
Drug related	2 (25.0)	17 (43.6)	19 (40.4)
During infusion	0	7 (17.9)	7 (14.9)
Within 1 h after end of infusion	3 (37.5)	7 (17.9)	10 (21.3)
Within 24 h after end of infusion	1 (12.5)	10 (25.6)	11 (23.4)
Within 72 h after end of infusion	4 (50.0)	11 (28.2)	15 (31.9)

AE, adverse event.

CONCLUSIONS

- No safety concerns were observed during the study period, and none of the reported AEs were life-threatening or led to treatment discontinuation
- No hemolysis events were reported, and no laboratory findings were suggestive of hemolysis associated with positive Coombs direct tests, such as decreased hemoglobin levels
- The most frequently reported (≥5%) drug-related TEAEs were headache in 12 (25.5%) patients; infusion-related reaction in 5 (10.6%) patients; and nausea, fatigue, and Coombs direct test positive in 4 (8.5%) patients each
- No serious TEAE was considered related to the study drug
- The most frequently reported (≥5%) infusional AEs were headache (25.5%); fatigue (14.9%); infusion-related reaction, nausea, and Coombs direct test positive (10.6% each); and diarrhea, dizziness, and sinusitis (6.4% each)
- The maximum infusion rate was reached in 44/47 (93.6%) patients and in 599/643 (93.2%) total infusions administered
- No cases of thrombotic events, aseptic meningitis, transfusion-related acute lung injury (TRALI), acute renal failure, or neutropenia were reported during the study
- No safety signals were evident from the review of physical examination, vital signs, and laboratory data
- At the infusion schedules and rates used in this phase 3 study, treatment with KIg10 was effective and well tolerated in patients with PI

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Scan the QR code to view a plain language summary of the data presented in this poster.

Acknowledgments and Disclosures

This study was funded by Kedrion Biopharma Inc. Medical writing support was provided by Chan Yoon, PharmD, of Lumanity Scientific Inc., and was funded by Kedrion Biopharma Inc.

MN, **EG**, and **RC** are employees of Kedrion Biopharma Inc. or its subsidiaries. **EP** received research funding from Kedrion Biopharma Inc. for the study presented; received consultant/speaker fees from AbbVie, ADMA Biologics, Blueprint Medicine, CSL Behring, and Grifols; and is a member of the FDA Blood Product Advisory Committee. **CMR** served as the chair of the data and safety monitoring board for the study presented; received grants from AstraZeneca, Grifols, and Takeda; is a member of advisory committees for the Canadian Blood Services and Blood Products Ontario; and is the chairman of Immunodeficiency Canada.

Presented at the Clinical Immunology Society (CIS) Annual Meeting; May 1-4, 2025; Philadelphia, PA, USA