Pharmacokinetics of a New Intravenous Immunoglobulin 10% in Patients With Primary Immunodeficiency

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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 (PK) 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
- In this study, the PK objectives were to:
  - Assess the distribution, metabolism, and elimination of KIg10, total immunoglobulin G (IgG), IgG subclasses, and antigen-specific IgGs at steady state in 20 adult patients with PI who received the product through 2 different infusion schedules
  - Evaluate trough concentrations of total IgG and compare them to IVIg trough concentrations prior to study entry

METHODS

- PK assessments were to be performed in approximately 24 adult patients to ensure ≥20 evaluable patients before and after Infusion 5 (28-day infusion schedule) or Infusion 7 (21-day infusion schedule), when steady state was estimated to have been achieved based on the published half-life of IVIg (after 5 half-lives)
- The PK evaluation set (PKS) included all patients who consented to this part of the protocol and who had PK analysis performed as noted below
- Blood samples were obtained at 10 to 30 minutes preinfusion and at the following time points postinfusion: 30 minutes, 2 hours, 24 hours, 72 hours, 7 days, 14 days, 21 days, and 28 days (only for the 28-day infusion schedule)
- Primary PK endpoints of the study included:
  - Total IgG levels, IgG subclass levels, and selected specific antibody levels before and after Infusion 5 (28-day infusion schedule) or Infusion 7 (21-day infusion schedule)
  - PK parameters of total IgG before and after Infusion 5 (28-day infusion schedule) or Infusion 7 (21-day infusion schedule)
  - PK parameters of specific IgG antibodies before and after Infusion 5 (28-day infusion schedule) or Infusion 7 (21-day infusion schedule): anti–*Haemophilus influenzae* type b, anti–tetanus toxoid, and anti–pneumococcal capsular polysaccharide
- The PK analyses were performed for patients in the PKS; noncompartmental PK parameters were calculated using Phoenix WinNonlin (Certara USA Inc, Radnor, PA)
  - Actual sampling times were used in the determination of the individual PK parameters
  - The linear-up/log-down trapezoidal method was used for derivation of area under the curve (AUC)
- Correlation between health outcomes (number of acute bacterial infections, number of any infections other than acute serious bacterial infections [SBIs], and duration of any infections other than acute SBIs) and PK parameters (maximum serum concentration [C_{max}] and AUC over a dosing interval [AUC_{tau}]), as well as mean steady-state trough concentrations of total IgG levels, was explored graphically

References

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RESULTS

- The PK analysis was based on the PKS, which included data from 23 adult patients (5 for the 21-day infusion schedule and 18 for the 28-day infusion schedule) who completed intense PK sampling at Visit 7 for the 21-day schedule or Visit 5 for the 28-day schedule
- The estimated mean serum half-life ($t_{1/2}$) for uncorrected total IgG was 24.5 days, or 587 hours, and 37.3 days, or 896 hours, for patients on the 21- and 28-day infusion schedules, respectively (**Table 1**)

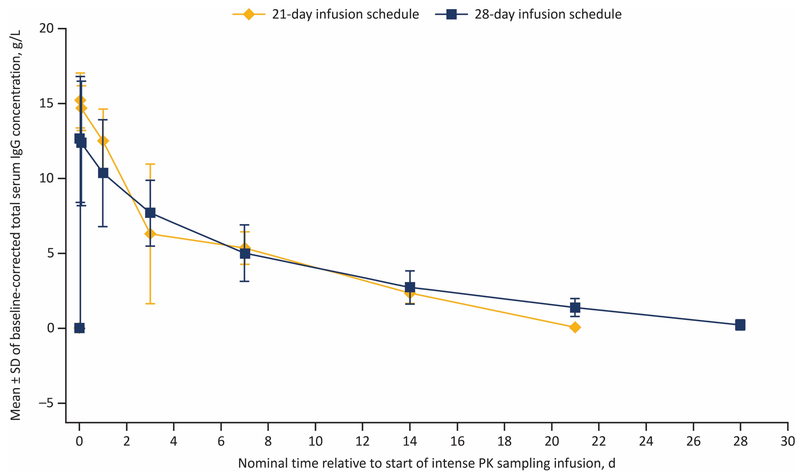
Table 1. $t_{1/2}$ for Uncorrected Total IgG

	21-day infusion schedule (n = 4[a])	28-day infusion schedule (n = 18)
$t_{1/2}$ for uncorrected total IgG (SD), h	587 (58.2)	896 (269)
$t_{1/2}$ for uncorrected total IgG, d	24.5	37.3

IgG, immunoglobulin G; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, mean serum half-life.
[a]Five patients on the 21-day infusion schedule underwent PK assessments, and 4 were taken into account in the analysis. One patient's half-life was excluded from the summary because the terminal elimination phase was not estimable.

- The total serum IgG PK profiles were comparable between the 2 infusion schedules, with a numerically higher exposure for the 21-day infusion schedule (**Figure 1**)

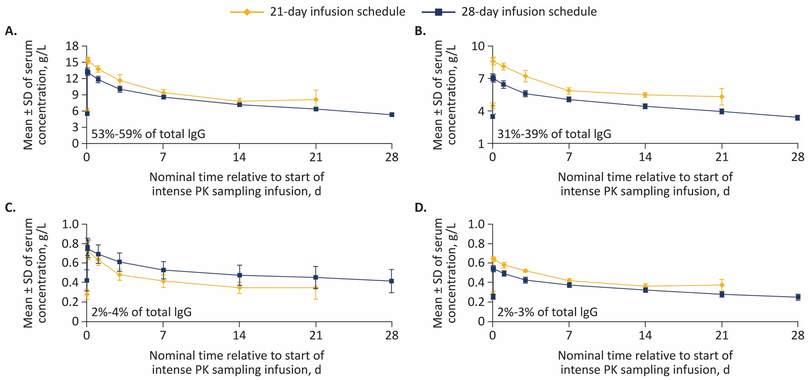
Figure 1. Baseline-Corrected Total Serum IgG Concentration



IgG, immunoglobulin G; PK, pharmacokinetic; SD, standard deviation.

- All the mean values of IgG subclasses were maintained within the reference ranges following intravenous (IV) infusion of KIg10
  - The distribution of IgG subclasses overall, considering the lowest and the highest mean total serum IgG levels for each infusion schedule, varied between 53% to 59% for IgG1, 31% to 39% for IgG2, 2% to 4% for IgG3, and 2% to 3% for IgG4 (**Figure 2**)
  - The pattern of serum levels versus time profiles of IgG subclasses matched that of total serum IgG levels
- The IgG-specific antibody (anti–*Haemophilus influenzae* type b, anti–tetanus toxoid, and anti–pneumococcal capsular polysaccharide) serum levels followed an overall similar pattern as that of total serum IgG
- The estimated $t_{1/2}$ for baseline-corrected total serum IgG was 4.46 days, or 107 hours, for patients on the 21-day infusion schedule and 6.58 days, or 158 hours, for those on the 28-day infusion schedule (**Table 2**)
- The mean C_{max} (standard deviation [SD]) for patients on the 21-day infusion schedule was 1520 (185) mg/dL; for those on the 28-day infusion schedule, it was 1280 (433) mg/dL (**Table 2**)
- The mean area under the curve from time 0 to time t of the last quantifiable concentration ($AUC_{0\text{-}t}$ [SD]) for patients on the 21-day infusion schedule was 8380 (1670) day·mg/dL; for patients on the 28-day infusion schedule, it was 9520 (3310) day·mg/dL (**Table 2**)

Figure 2. Serum IgG Concentration Versus Time for (A) IgG1, (B) IgG2, (C) IgG3, and (D) IgG4 Subclasses



IgG, immunoglobulin G; PK, pharmacokinetic.

Table 2. PK Parameters for Baseline-Corrected Total Serum IgG by Infusion Schedule in the PKS (N = 23)

PK parameter, mean (SD)	KIg10 infusion schedule	
	21-day infusion schedule (n = 5)	28-day infusion schedule (n = 18)
C_{max}, mg/dL	1520 (185)	1280 (433)
$t_{1/2}$, h	107 (45.4)	158 (48.4)
$AUC_{0\text{-}t}$, day·mg/dL	8380 (1670)	9520 (3310)
AUC_{tau}, day·mg/dL	8860 (1630)	9840 (3330)

$AUC_{0\text{-}t}$, area under the curve from time 0 to time t of the last quantifiable concentration; AUC_{tau}, area under the curve over a dosing interval; C_{max}, maximum serum concentration; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; PK, pharmacokinetic; PKS, pharmacokinetic evaluation set; $t_{1/2}$, mean serum half-life.

CONCLUSIONS

- PK parameters estimated based on total serum IgG in the present study are typical of the values obtained for other US-licensed IVIg products[11-16]
- The estimated mean elimination half-life was 4 to 7 days for baseline-corrected total serum IgG and 25 to 37 days for uncorrected total serum IgG; patients on the 28-day infusion schedule reported longer half-lives
- The total serum IgG PK profiles between both infusion schedules are comparable, with a slightly higher exposure for the 21-day infusion schedule reflecting the more frequent infusions
- The distribution of IgG subclasses observed following IV infusion of KIg10 is similar to the reported normal serum IgG subclass values in the literature[17]; the pattern of serum levels versus time profiles of IgG subclasses matched that of total serum IgG levels

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

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