Supplemental Material

Clinical evaluation of pharmacokinetics, efficacy, and safety of a 10% immunoglobulin in primary immunodeficiency disease (CARES10 study)

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Investigator Working Group Statement

This study was conducted by the CARES10 investigator study group. The full list of investigators who contributed to this work is provided in the supplemental material in alphabetical order. All group members named as authors met the authorship criteria established by *Advances in Therapy* and approved the final manuscript.

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1. List of Investigators

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2. Table S1. Diagnosis and Main Criteria for Inclusion/Exclusion

Main Inclusion Criteria

- Male or female
- 2 to 70 years old at screening
- Provided written informed consent/assent (ICF)
- Confirmed clinical diagnosis of PI
- Documented agammaglobulinemia or hypogammaglobulinemia
- Received 200 to 800 mg/kg of a commercially available IVIg therapy for at least 3 infusion cycles (21 or 28 days) prior to screening
- Had at least 2 documented IgG trough levels while receiving an IVIg of ≥6 g/L obtained at 2 infusion cycles within 12 months prior to providing informed consent.
- Willing to comply with all requirements of the protocol
- Gave authorization to collect personal data information.
- Female patients of childbearing potential with a negative urine pregnancy test and who agreed to employ adequate birth control measures during the study were allowed to participate.
- Patients who previously participated in a clinical trial with another experimental IVIg could be enrolled if they had received stable commercially available IVIg therapy for at least 3 infusion cycles (21 or 28 days) prior to screening.
- Patients who were on treatment with any subcutaneous immunoglobulin (SCIG) could be enrolled if they were switched to stable commercially available IVIg therapy for at least 3 infusion cycles (21 or 28 days) prior to screening.

Main Exclusion Criteria

- Newly diagnosed PI and naïve to IgG replacement therapy
- Dysgammaglobulinemia (defined as a deficiency in one or more classes of antibodies, but not severe enough to require substitutive therapy)
- Isolated IgG subclass deficiency
- Profound primary T-cell deficiency (defined as the absence or severe reduction of T lymphocytes [CD3+ <300 cell/mm] [3] and an absent or particularly low proliferative response [10% of the lower normal range] to phytohemagglutinin P [PHA]).
- Immunoglobulin A (IgA) deficiency with documented antibodies to IgA
- Received blood products that had not undergone viral inactivation measures within 12 months prior to ICF signature.
- Significant protein losing enteropathy, nephrotic syndrome, or lymphangiectasia.
- An acute infection as documented by culture or diagnostic imaging and/or a body temperature ≥38°C (≥100.4°F) within 7 days prior to screening.
- Acquired immunodeficiency syndrome (AIDS) and/or hepatitis B/C active disease at ICF signature
- Alanine aminotransferase or aspartate aminotransferase >2.5 times the upper limit of normal
- Was using an implanted venous access device
- Profound anemia (hemoglobin <10 g/dL) or persistent severe neutropenia (≤1000 neutrophils per mm^3) or lymphopenia of less than 500 cells per microliter
- A severe chronic condition such as:
    - renal failure (creatinine concentration >2.0 times the upper limit of normal*) with proteinuria
        - * Normal values for serum creatinine were the following:
            Female (≥18years): 45 – 84 µmol/L or 0.51 – 0.95 mg/dL
            Male (≥18 years): 59 – 103 µmol/L or 0.67 – 1.17 mg/dL
    - congestive heart failure (New York Heart Association III/IV),

    - cardiomyopathy,
    - cardiac arrhythmia associated with thromboembolic events (e.g., atrial fibrillation),
    - unstable or advanced ischemic heart disease,
    - hyperviscosity,
    - or any other condition that the Investigator believed was likely to interfere with evaluation of the study drug or with satisfactory conduct of the trial.
- History of:
    - severe or serious reactions or hypersensitivity to IVIg or other injectable forms of Ig.
    - thrombotic events including deep vein thrombosis, cerebrovascular accident, pulmonary embolism, transient ischemic attacks, or myocardial infarction, as defined by at least 1 event in patient's lifetime.
    - malignant disease other than properly treated carcinoma in situ of the cervix or basal cell or squamous cell carcinoma of the skin within 24 months prior to ICF signature.
    - pharmacoresistant epilepsy or multiple episodes of migraine (defined as at least 1 episode within 6 months of ICF signature) not completely controlled by medication.
- Patients were not to be receiving the following medication:
    - Steroids, oral or parenteral, at a daily dose of ≥0.15 mg/kg/day of prednisone or equivalent).
    - Other immunosuppressive drugs (including monoclonal antibodies) or chemotherapy.
- Female patients who were pregnant, breast feeding, or planning a pregnancy during the study.
    - Women who became pregnant during the study were to be withdrawn from the study
- Participated in another clinical study within 3 weeks prior to the study ICF signature
- Active drug or alcohol abuse or history of drug or alcohol abuse within the 6 months before screening
- Employed or a direct relative of an employee of the Contract Research Organization (CRO), the study site, or the Sponsor.
- Previously treated under this protocol.
- Unable to provide informed consent or provide informed consent by a legally authorized representative.

AIDS, acquired immunodeficiency syndrome; CD, cluster of differentiation; CRO, contract research organization; ICF, informed consent form; Ig, immunoglobulin; IgA, immunoglobulin A; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; PHA, phytohemagglutinin P; PI, principal investigator; SCIG, subcutaneous immunoglobulin.

3. Table S2. Study Endpoints

Primary Endpoint

Incidence rate (i.e., the mean number of acute SBIs per patient-year) of acute SBIs (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, and osteomyelitis/septic arthritis).

Secondary Endpoints

- IgG trough levels before each infusion of KIg10 and at the study termination visit (Week 51/52).
- IgG subclasses levels (IgG1, IgG2, IgG3, and IgG4) before Infusions 1, 5, 9, and 13 for the 28-day infusion schedule and before Infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
- Frequency of patients with total IgG below 6 g/L criteria.
- Anti-tetanus toxoid antibody level (quantitative assay) before Infusions 1, 5, 9, and 13 for the 28-day infusion schedule and before Infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
- Anti-pneumococcal capsular polysaccharide antibody level (quantitative assay) before Infusions 1, 5, 9, and 13 for the 28-day infusion schedule and before Infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
- Anti-measles* antibody level (quantitative assay) before Infusions 1, 5, 9, and 13 for the 28-day infusion schedule and before Infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
    - *Note: Rubella antibody panel (IgG and IgM) test was erroneously performed for the study instead of anti-measles antibody test; therefore, results are not available (see Section 9.8.2 for details).
- Anti-Haemophilus influenzae type b antibody level (quantitative assay) before Infusions 1, 5, 9, and 13 for the 28-day infusion schedule and before Infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
- Incidence rate (i.e., the mean number per patient-year) of any infection other than acute SBIs from Day 1 to Week 51/52.
- Duration of any infection other than acute SBIs, from Day 1 to Week 51/52.
- Incidence rate (i.e., the mean number per patient-year) of fever episodes, from Day 1 to Week 51/52.
- Duration of fever episodes, from Day 1 to Week 51/52.
- Overall hospitalization days, from Day 1 to Week 51/52.
- Days of hospitalizations due to infection from Day 1 to Week 51/52.
- Incidence rate (i.e., the mean number per patient-year) of patients on antibiotics for the treatment of any kind of infection, from Day 1 to Week 51/52.
- Duration of patients on antibiotics for the treatment of any kind of infection, from Day 1 to Week 51/52.
- Days of missed work/school/other major activities due to infections, from Day 1 to Week 51/52.
- PedsQL™ score at baseline, Week 24 (Infusion 7 for the 28-day schedule and Infusion 9 for the 21-day schedule), and at the study termination visit.

Exploratory Endpoints

- Total score of PADQOL-16 at baseline, Week 24 (Infusion 7 for the 28-day schedule and Infusion 9 for the 21-day schedule), and study termination visit.
- HCU data as measured by the need for any care in addition to the protocol-defined standard of care visits and items listed in the Schedule of Events; (e.g., additional visits to health clinic, doctor office, urgent care center, hospital; additional prescription medications; additional therapies; etc.).
- Patient satisfaction with participation and treatment during the study, based on a separate study-specific questionnaire.

Safety Endpoints

- Number of AEs (%) and proportion of patients who experienced at least 1 AE.
- Number of SAEs (%) and proportion of patients who experienced at least 1 SAE.
- Number of related infusion AEs (%) that occurred during infusion or within 1, 24, and 72 hours after the end of infusion and proportion of patients who experienced at least 1 related infusion AE.
- The proportion and number of KIg10 infusions for which the infusion rate was decreased due to AEs.

- Number and proportion of infusions with 1 or more infusion (temporally) associated AE.
- Changes in vital signs, physical examinations, and safety laboratory tests (hematology, chemistry, and urinalysis).
- The proportion and number of patients with a positive Coombs test following Infusion 5 for the 28-day infusion schedule and Infusion 7 for the 21-day infusion schedule.
- The proportion and number of patients with a positive urine hemosiderin test following Infusion 5 for the 28-day infusion schedule and Infusion 7 for the 21-day infusion schedule.
- Plasma-free hemoglobin level following infusion 5 for the 28-day infusion schedule and Infusion 7 for the 21-day Infusion schedule.
- Serum haptoglobin level following Infusion 5 for the 28-day infusion schedule and Infusion 7 for the 21-day infusion schedule.

Pharmacokinetic Endpoints

- Total IgG levels, IgG subclasses 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 the Infusion 7 (21-day infusion schedule).
- Serum concentration-time curve,
    - maximum concentration (Cmax),
    - time to reach Cmax (Tmax),
    - area under the concentration-time curve (AUC) from time 0 to time of last quantifiable concentration (AUC0-t),
    - other parameters such as steady-state parameters AUC calculated from start to end of the dosing interval (AUCtau),
    - average concentration of drug over the dosing interval (Cavg),
    - and steady-state clearance (CLss) were derived.
- Elimination parameters such as
    - elimination rate constant,
    - elimination half-life,
    - AUC from time 0 extrapolated to infinity (AUC0 inf), and
    - volume of distribution were derived if data allowed based on PK acceptance criteria.
- 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
    - Anti-pneumococcal capsular polysaccharide
- Exploratory correlation analysis between health outcomes and PK parameters or trough concentrations was included in the analysis.

AEs, adverse events; AUC, area under the concentration-time curve; AUC0 inf. AUC from time 0 extrapolated to infinity; AUC0-t, AUC from time 0 to time of last quantifiable concentration; AUCtau, AUC calculated from start to end of the dosing interval; Cavg, average concentration of drug over the dosing; CLss, steady-state clearance; Cmax, maximum concentration; IgG, immunoglobulin G; IgM, immunoglobulin M; HCU, healthcare utilization; PADQOL-16, Primary Antibody Disease Quality of Life -16; PedsQL™, Pediatric Quality of Life Inventory™; PK, pharmacokinetics; SAEs, serious adverse events; SBIs, serious bacterial infections; Tmax, time to reach Cmax .

4. Table S3. Mean Trough Levels of IgG Subclasses - Full Analysis Set

	21-Day (N = 8)			28-Day (N = 39)		
Subclass (unit)	Visit	**n**	**Mean**	Visit	**n**	**Mean**
IgG1 (g/L)						
	Baseline	8	5.623	Baseline	39	5.834
	Visit 7	8	5.968	Visit 5	39	5.605
	Visit 11	8	5.979	Visit 9	39	5.679
	Visit 17	8	6.210	Visit 13	37	5.634
IgG2 (g/L)						
	Baseline	8	3.840	Baseline	39	3.463
	Visit 7	8	4.113	Visit 5	39	3.419
	Visit 11	8	4.079	Visit 9	39	3.458
	Visit 17	8	4.234	Visit 13	37	3.475
IgG3 (g/L)						
	Baseline	8	0.346	Baseline	39	0.417
	Visit 7	8	0.271	Visit 5	39	0.351
	Visit 11	8	0.249	Visit 9	39	0.352
	Visit 17	8	0.253	Visit 13	37	0.329
IgG4 (g/L)						
	Baseline	8	0.2363	Baseline	39	0.2182
	Visit 7	8	0.2744	Visit 5	39	0.2388
	Visit 11	8	0.2838	Visit 9	39	0.2425
	Visit 17	8	0.2950	Visit 13	37	0.2396

IgG, immunoglobulin G; N, total number of patients in each dosing schedule; n, number of patients in each subset. Baseline was defined as the last non-missing assessment prior to the first dose of study drug.