BLA Clinical and Clinical Pharmacology Review Memorandum

Application Type	BLA
STN	125822/0
CBER Received Date	September 26, 2024
PDUFA Goal Date	September 25, 2025
Division / Office	DCEGM/OTP
Priority Review (Yes/No)	No
Reviewer Name(s)	Clinical: Sairah Thommi, MD, MS Clinical Pharmacology: Xiaofei Wang, PhD
Review Completion Date / Stamped Date	September 25, 2025
Associate Director of Labeling (Acting), OCE/OTP	Afsah Amin, MD, MPH
Supervisory Concurrence Team Lead/Branch Chief (Acting), GMB1 Division Director (Acting), DCEGM Office Director, OCE	 Shelby Elenburg, MD Asha Das, MD
Applicant	Kedrion SpA
Established Name	immune globulin, human- kthm 10% solution
(Proposed) Trade Name	QIVIGY
Pharmacologic Class	Biologic: Immune Globulin
Formulation(s), including Adjuvants, etc.	Immune Globulin Infusion (Human) 10% Liquid
Dosage Form(s) and Route(s) of Administration	300- 800 mg/kg (body weight) Intravenous
Dosing Regimen	Every 3-4 weeks
Indication(s) and Intended Population(s)	Treatment of adults with primary humoral immunodeficiency
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
AUC	area under the curve
AUC_{0-t}	AUC-time curve from time 0 to the time t of the last
AUC_{tau}	AUC over a dosing interval
AWC	adequate and well-controlled study
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
C_{last}	last quantifiable concentration
CLss	clearance over a dosing interval
C_{max}	maximum observed concentration
CMC	Chemistry, Manufacturing, and Controls
C_{min}	minimum observed concentration
COVID-19	Coronavirus Disease 2019
CSR	complete study report
Ctau	concentration at the end of dosing interval
CV	coefficient of variation
CVID	common variable immunodeficiency
DSMB	Data Safety Monitoring Board
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMT	geometric mean titer
ICH	International Conference for Harmonization
IG	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IGIV	immunoglobulin intravenous
IND	Investigational New Drug
iPSP	initial pediatric study plan
IR	information request
PedsQL	Pediatric Quality of Life Inventory™ Questionnaire
PD	pharmacodynamics
PI	primary humoral immunodeficiency
PID	primary immunodeficiency
PK	pharmacokinetics
PKS	pharmacokinetic evaluation set
PMR	post marketing requirement
PPS	per protocol set
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SAF	safety analysis set

SBI	serious bacterial infection
SD	standard deviation
SP	serotype-specific Pneumococcal
$t_{1/2}$	terminal elimation half life
T_{last}	time of last quantifiable concentration
T_{max}	time to maximum concentration
TEAE	treatment emergent adverse event
USPI	United States Prescribing Information
Vd	volume of distribution

1. EXECUTIVE SUMMARY

Kedrion SpA submitted Biologics License Application (BLA) 125822/0 on September 26, 2024 to license their immunoglobulin intravenous (IGIV) product QIVIGY (KIG10) for the treatment of adults with primary humoral immunodeficiency (PI).

The Applicant submitted data from one open-label, prospective, single-arm, historically controlled, multicentered study conducted from April 30, 2019 to December 21, 2020. The primary efficacy endpoint was annualized rate of acute serious bacterial infections (SBIs) defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscesses, or bacterial meningitis consistent with the 2008 FDA Guidance for Industry "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency," which will be referred to as the IGIV Guidance throughout the review memo.

During the study, 47 adult subjects received QIVIGY doses between 266 to 826 mg/kg every 3 or 4 weeks, for a treatment period of approximately 12 months. Most subjects were white (n=45; 95.7%) and female (n=30; 63.8%). The most common underlying cause of PI was common variable immunodeficiency (n=34; 72.3%). Two subjects were treated with doses outside the planned ranges. No adverse events were assessed as related to the increased doses. Doses were adjusted as necessary for changes in body weight or to maintain targeted immunoglobulin G (IgG) levels.

No acute SBIs occurred during the study, yielding an estimated incidence rate of 0 acute SBIs per person-year. The associated upper bound of the one-sided 99% confidence interval was <1, meeting the study success threshold as defined by the IGIV Guidance. Pharmacokinetic (PK) and additional infection-related outcomes were supportive of product efficacy. No deaths occurred in the study, and no serious adverse events were related to the product. The most commonly reported adverse reactions were headache, fatigue, nausea, infusion-related reactions, positive direct Coombs test, sinusitis, dizziness, and diarrhea. The overall safety profile was similar to other commercial IGIV products.

The Clinical and Clinical Pharmacology review teams have determined there is substantial evidence of effectiveness based on the acute SBI rate and supportive secondary infectious and PK outcomes in an adequate and well-controlled study, and there is a favorable benefit-risk profile to support traditional approval of QIVIGY for the treatment of adults with PI.

Considering the importance of ensuring that children have access to these therapies and our current knowledge of this disease and similar immunoglobulin products (including similarities in disease manifestations between adult and pediatric patients, expectations that efficacy in the pediatric population will be similar to that observed in the adult population, and a well-characterized safety profile among other intravenous immunoglobulin commercial products to treat both adult and pediatric populations), the FDA exerted regulatory flexibility in the requested number of pediatric patients and duration of follow-up previously agreed to for fulfillment of the Pediatric Research Equity Act (PREA) post marketing requirement (PMR). Additional extrapolation from PK data will allow product availability sooner for the pediatric population.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

A total of 47 subjects were treated. No pediatric subjects were included in the study. Table 1 shows the baseline demographics for all subjects.

Table 1: Demographic Information of the Full Analysis Set

Parameter	**21-Day Klg10 Dosing Schedule (n = 8)**	**28-Day Klg10 Dosing Schedule (n = 39)**	**Overall (n = 47)**
Age (years)	-	-	-
Mean (SD)	50.8 (15.2)	53 (12.5)	52.6 (12.9)
Median	55.5	56	56
Min, Max	22, 68	20, 70	20, 70
Age Category, n (%)	-	-	-
18-64 years	7 (87.5%)	33 (84.6%)	40 (85.1%)
65-70 years	1 (12.5%)	6 (15.4%)	7 (14.9%)
Sex, n (%)	-	-	-
Male	1 (12.5%)	16 (41%)	17 (36.2%)
Female	7 (87.5%)	23 (59%)	30 (63.8%)
Race	-	-	-
White	7 (87.5%)	18 (78.3%)	45 (95.7%)
Other	1 (12.5%)	1 (2.6%)	2 (4.3%)[1]
Ethnicity	-	-	-
Hispanic or Latino	0	2 (5.1%)	2 (4.3%)
Not Hispanic or Latino	8 (100%)	36 (92.3%)	44 (93.6%)
Unknown	0	1 (2.6%)	1 (2.1%)
Baseline Weight (kg)	-	-	-
Mean (SD)	84 (26.4)	84 (23.4)	84 (23.6)
Median	78.9	78.7	78.7
Min, max	48.8, 131.1	37.5, 158.7	37.5, 158.7

Source: Applicant Table 13, Clinical Study Report, KIG10_US3_PID01
Abbreviations: kg= kilogram; min, minimum; max, maximum; n= total number of subjects; SD= standard deviation
1-Other includes Mexican and White/African-American.

1.2 Patient Experience Data

Patient-reported outcomes included a pediatric quality of life assessment (PedsQL), which was assessed as a secondary endpoint. Clinician-reported outcomes included acute SBIs, infections other than SBIs, duration of infections, duration of antibiotic use, days hospitalized, and days hospitalized due to infection.

Data Submitted in the Application

Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
☒	Patient-reported outcome	6.1
☐	Observer-reported outcome	-
☒	Clinician-reported outcome	6.1

☐	Performance outcome	-
☐	Patient-focused drug development meeting summary	-
☐	FDA Patient Listening Session	-
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	-
☐	Observational survey studies	-
☐	Natural history studies	-
☐	Patient preference studies	-
☐	Other: (please specify)	-
☐	If no patient experience data were submitted by Applicant, indicate here.	-
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	-
☐	Patient-focused drug development meeting	-
☐	FDA Patient Listening Session	-
☐	Other stakeholder meeting summary report	-
☐	Observational survey studies	-
☐	Other: (please specify)	-

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Primary immunodeficiencies (PIDs) are a large heterogenous group of disorders resulting from inborn errors of immunity. They are characterized by absent or poor function in one or more components of the immune system. Consequently, affected subjects are unable to mount an immune response to microorganisms and may experience recurrent protozoal, bacterial, fungal, and viral infections. The estimated overall prevalence of PIDs in the United States is approximately 1 in 1,200 live births; an exception is IgA deficiency, which occurs in approximately 1 in 200 to 1 in 500 persons. PIDs are broadly classified based on the component of the immune system that is primarily disrupted. Disorders of the adaptive immune system include B-cell (humoral) immune deficiencies (also referred to as antibody deficiencies), T-cell (cellular) immune deficiencies, and combined (B-cell and T-cell) immunodeficiencies. Primary humoral immunodeficiency (PI) is a humoral form of PID that is characterized by impaired B-cell immunity, and thus, impaired ability to produce specific antibodies in response to pathogenic microorganisms. PI diseases include, but are not limited to, X-linked agammaglobulinemia, common variable immunodeficiency (CVID), Wiskott-Aldrich syndrome, severe combined immunodeficiency, and congenital agammaglobulinemia. Subjects with PI present with recurrent, often severe bacterial and viral infections affecting the respiratory tract, gastrointestinal system, skin, and other organs.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Replacement therapy, comprised of polyclonal human normal immunoglobulin (IG) infusions, is standard treatment for PI. IG is manufactured through fractionation of plasma pooled from many plasmapheresis donors and contains immune antibodies. IG restores serum Immunoglobulin G (IgG) to protective levels and provides subjects specific antibodies to prevent or minimize the frequency or severity of bacterial and viral infections. Therapy is expected to be lifelong and increase life expectancy.

Additional infection prevention includes infection avoidance measures, vaccination, and prophylactic antibiotics. Treatment of infections often requires broad antimicrobial coverage and prolonged treatment courses. Bone marrow transplantation is a treatment option for some forms of PI (such as severe combined immunodeficiency) but is limited by availability of appropriate donors and is associated with multiple risks, including graft versus host disease, rejection of the graft, complications of conditioning agents, and death.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are numerous marketed IG products, which can be administered intravenously or subcutaneously.

There are currently 15 licensed (Human) immune globulin intravenous (IGIV) products in the United States: Alyglo (GC Biopharma), Asceniv (ADMA Biologics, Inc.), Bivigam (Biotest Pharmaceuticals Corporation), Carimune (CSL Behring AG), Flebogamma DIF 5% and 10% (Instituto Grifols), Gammagard Liquid and Gammagard S/D (Baxter HealthCare Corp), Gammagard Liquid ERC (Takeda Pharmaceuticals), Gammaked (Kedrion Biopharma), Gammaplex 5% & 10% (Bio Products Laboratory), Octagam and Panzyga (Octapharma Pharmazeutika Produktionsges), Privigen (CSL Behring AG), and Yimmugo (Biotest AG). All are indicated as replacement therapy in subjects with PI.

The safety profile for IGs as a class is well-established. The incidence of adverse reactions (ARs) reported in clinical studies supporting licensure varies according to the product, route of administration, and maximum infusion rate. Severe hypersensitivity reactions may occur with IGIV products. Common ARs for IGs (including those administered subcutaneously) include local infusion site reactions, headache, fatigue, nausea, diarrhea, vomiting, and/or pyrexia. IGIV as a drug class carries an obligatory boxed warning for thrombosis, renal dysfunction, and acute renal failure. Other rare risks associated with the use of IGIV include hypersensitivity/anaphylaxis, transmission of infectious agents (e.g., viruses), hemolysis, aseptic meningitis, transfusion-associated lung injury, hyperproteinemia, and increased serum viscosity.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

QIVIGY has not been marketed in any country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 2: Submission Correspondence

Submission Type	Correspondence
Pre-IND	Written Response dated May 12, 2017
Type C	Written Response dated March 19, 2020
Pre-BLA	Meeting August 16, 2022 and meeting minutes dated September 15, 2022
iPSP	FDA agreed November 2, 2022 with the proposed iPSP plan submitted October 5, 2022
Type C	Written Response dated August 30, 2023
Type D	Written Response dated December 8, 2023
BLA	BLA was submitted September 26, 2024
iPSP update	The Applicant submitted an updated timeline, which was agreed to, based on amended expectations for fulfillment of the PREA PMR on September 19, 2025.

Source: Adapted from Table 1.6.3 in the Reviewers' Guide (BLA 125822.0)
Abbreviations: BLA= Biologics License Application; IND= Investigational New Drug; iPSP= Initial Pediatric Study Plan

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was sufficiently organized and integrated to accommodate the conduct of a complete clinical review. It was submitted electronically and formatted as an electronic Common Technical Document according to the FDA Guidance for electronic submissions. The submission contained the five modules in the common technical document structure.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The applicant reported that the study was conducted in accordance with the guidelines of the Declaration of Helsinki on biomedical research involving human subjects and in accordance with International Conference for Harmonization (ICH): Good Clinical Practice (GCP) guidelines, European Union (EU) Directives 2001/20/EC and 2005/28/EC and the US FDA Title 21 CFR, as well as the demands of national drug and data protection laws, other applicable regulatory requirements, and any new directives or regulations that became enforceable during the course of the study.

3.3 Financial Disclosures

Table 3: Financial Disclosures

Covered clinical study (**KIG10_US3_PID01**):
Was a list of clinical investigators provided? X Yes ☐ No
Total number of investigators identified: 12
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0

Number of investigators with disclosable financial interests/arrangements: 0
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 Is an attachment provided with the reason? ☐ Yes ☒ No (Request explanation from applicant)- Not required

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC review memo for details.

4.2 Assay Validation

Please refer to the CMC review memo for details.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical pharmacology/toxicology review for details. No nonclinical pharmacology/toxicology review issues were identified.

4.4 Clinical Pharmacology

Clinical pharmacology assessment of QIVIGY was included in Study IG10_US3_PID01, a Phase 3, open-label, prospective, multicenter study.

4.4.1 Mechanism of Action

QIVIGY contains a broad spectrum of immunoglobulin G (IgG) antibodies, some of which are directed toward infectious agents. QIVIGY is intended to restore serum IgG to protective levels and provide subjects with specific antibodies to prevent or minimize the occurrence or severity of infections.

4.4.2 Human Pharmacodynamics (PD)

Human normal immunoglobulin contains mainly IgG with a broad spectrum of antibodies against infectious agents. Human normal immunoglobulin contains the IgG antibodies present in the normal population. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of QIVIGY may restore abnormally low IgG levels to the normal range.

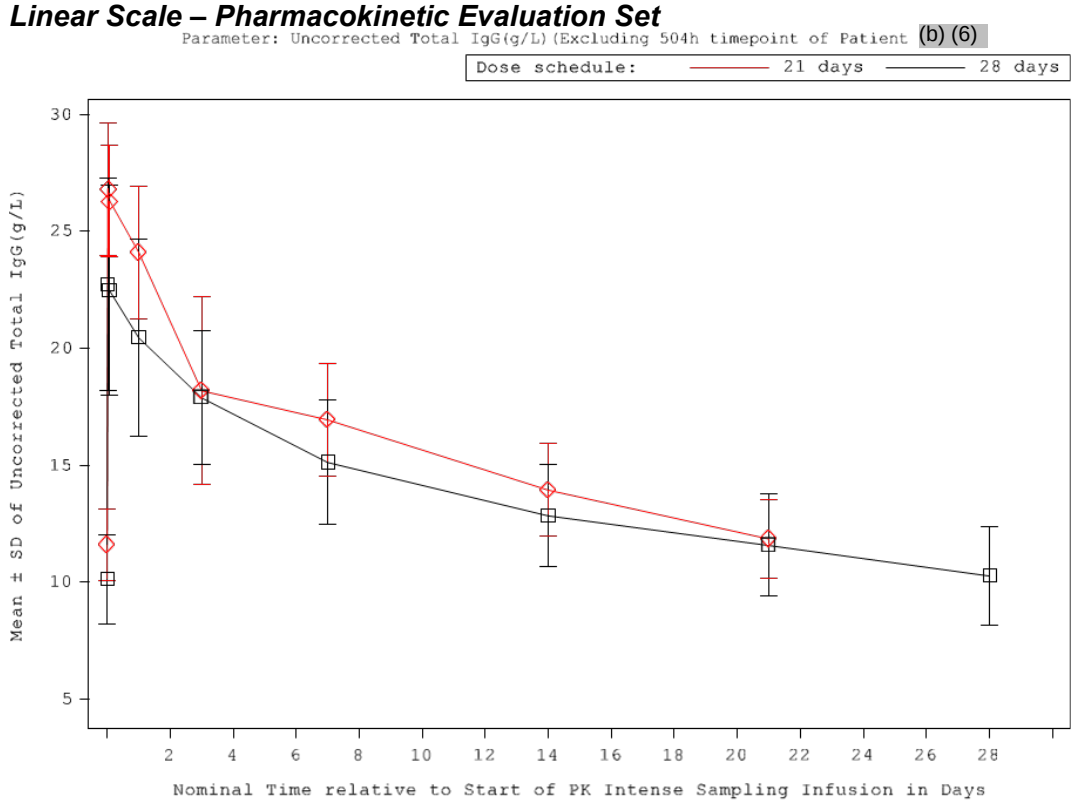
4.4.3 Human Pharmacokinetics (PK)

The pharmacokinetic (PK) analysis of QIVIGY was assessed in 23 adult subjects (5 subjects for the 3-week dosing schedule and 18 subjects for the 4-week dosing schedule) in Study KIG10_US3_PID01. Serum concentrations of total IgG were measured in 23 subjects following the 5th infusion of QIVIGY for subjects on the 4-week dosing schedule, or the 7th infusion for subjects on the 3-week dosing schedule. The dose of QIVIGY used in these subjects ranged from (b) (4) mg/kg to 826 mg/kg. After infusion, blood samples for PK analyses were collected until Day 21 or Day 28 for subjects treated according to the 3-week and 4-week schedule, respectively.

4.4.3.1 Pharmacokinetics of Total IgG

As shown in Figure 1, following the administration of QIVIGY, the uncorrected serum concentrations of total IgG increased rapidly before gradually declining and had returned to close to their baseline levels by the end of the dosing interval for both dosing regimens. The PK parameters of QIVIGY based on uncorrected serum concentration of total IgG are summarized in Table 4. The estimated mean serum half-life for uncorrected total IgG was 24.5 days (587 h) for subjects on the 21-day infusion schedule and 37.3 days (896 h) for subjects on the 28-day schedule. The mean Cmax (mean±SD) for subjects on the 21-day infusion schedule was 2680±282 mg/dL, and for subjects in the 28-day schedule it was 2300±466 mg/dL. The respective Cmin (mean±SD) were 1140±150 and 994±200 mg/dL. The median Tmax for subjects on the 21-day or 28-day infusion schedules was approximately 30 minutes from the start of infusion. The AUCtau(0-21 days) for subjects on the 21-day infusion schedule was 34,000±3630 day*mg/dL, and for subjects on the 28-day infusion schedule (0 to 28 days) it was 38,000±6500 day*mg/dL. For subjects on 21-day infusion schedules, the mean estimated Vd was 0.667 dL/kg and for subjects on the 28-day schedule was 0.697 dL/kg. The mean estimated CLss was 0.0193 and 0.0140 dL/day/kg for the 21-day and 28-day regimens, respectively.

Figure 1. Mean ± SD of Serum Uncorrected Total IgG Concentration Versus Nominal Time Relative to Start of Pharmacokinetic Intense Sampling Infusion, Linear Scale – Pharmacokinetic Evaluation Set



Source: Applicant. Study KIG10-US3-OID01 CSR, Figure 5.
IgG: immunoglobulin G; PK: pharmacokinetic; SD: standard deviation.

Table 4 4: Summary of Pharmacokinetic Parameters for Uncorrected Total IgG by Dosing Schedule – Pharmacokinetic Evaluation Set

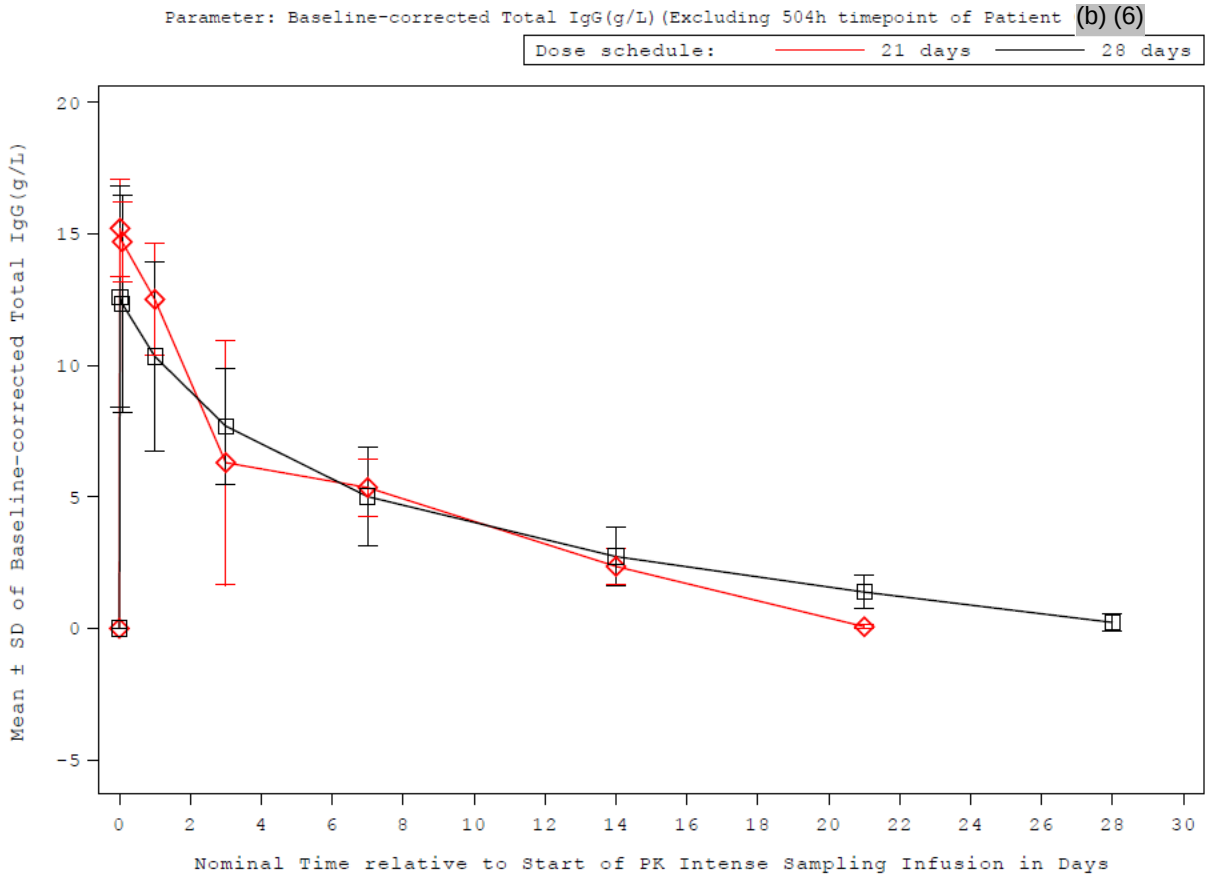
Parameter	Statistic	21-Day Regimen (7^{th} infusion)	28-Day Regimen (5^{th} infusion)
C_{max} (mg/dL)	n	5	18
-	Mean (SD)	2680 (282)	2300 (466)
-	Geometric Mean	2670	2250
-	%CV	10.5	20.3
T_{max} (h)	n	5	18
-	Median	0.530	0.515
-	Min, Max	0.500, 2.02	0.500, 23.8
C_{min} (mg/dL)	n	5	18
-	Mean (SD)	1140 (150)	994 (200)
-	Geometric Mean	1130	976
-	%CV	13.2	20.2
C_{last} (mg/dL)	n	5	18
-	Mean (SD)	1200 (148)	1020 (201)
-	Geometric Mean	1190	1000
-	%CV	12.4	19.7
T_{last} (h)	n	5	18
-	Median	502	669
-	Min, Max	334, 502	479, 718
C_{tau} (mg/dL)	n	4	18
-	Mean (SD)	1190 (169)	1010 (206)
-	Geometric Mean	1180	991
-	%CV	14.2	20.4
AUC_{0-t} (day*mg/dL)	n	5	18
-	Mean (SD)	31700 (6030)	37300 (7720)
-	Geometric Mean	31200	36400
-	%CV	19.0	20.7
AUC_{tau} (day*mg/dL)	n	4	18
-	Mean (SD)	34000 (3630)	38000 (6500)
-	Geometric Mean	33800	37500
-	%CV	10.7	17.1
C_{avg} (mg/dL)	n	4	18
-	Mean (SD)	1630 (175)	1370 (239)
-	Geometric Mean	1620	1350
-	%CV	10.8	17.5
Fluctuation (%)	n	4	18
-	Mean (SD)	95.0 (7.92)	94.3 (30.6)
-	Geometric Mean	94.7	90.3
-	%CV	8.34	32.4
CL_{ss} (dL/day/kg)	n	4	18
-	Mean (SD)	0.0193 (0.00305)	0.0140 (0.00355)
-	Geometric Mean	0.0191	0.0135
-	%CV	15.8	25.5
V_d (dL/kg)	n	4	18
-	Mean (SD)	0.667 (0.0398)	0.697 (0.118)
-	Geometric Mean	0.666	0.687
-	%CV	5.97	16.9
$t_{1/2}$ (h)	n	4	18

Parameter	Statistic	21-Day Regimen (7^{th} infusion)	28-Day Regimen (5^{th} infusion)
-	Mean (SD)	587 (58.2)	896 (269)
-	Geometric Mean	-	-
-	%CV	9.92	30.1

Source: Applicant. Study KIG10-US3-OID01 CSR, Table 30.
Abbreviations: AUC, area under the serum concentration-time curve; AUC0-t, Area under the concentration-time curve from time 0 to the time t of the last quantifiable concentration; AUCtau, AUC over a dosing interval; Cavg, average concentration over a dosing interval; Clast, last quantifiable concentration; CLss, clearance over a dosing interval; Cmax, maximum observed concentration; Cmin, minimum observed concentration; Ctau, concentration at the end of dosing interval; CV, coefficient of variation of mean; IgG, immunoglobulin G; Max, maximum; Min, minimum; n, number of observations contributing to statistic; PK, pharmacokinetic; SD, standard deviation; t½, terminal elimination half-life; Tlast, time of last quantifiable concentration; Tmax, time to Cmax; Vd, volume of distribution at steady-state.

The mean baseline-corrected total IgG concentration-time profiles for both the 21-day and 28-day dosing regimens was shown in Figure 2 . Table 5 summarizes PK parameters of QIVIGY based on baseline-corrected serum concentration of total IgG.

Figure 2. Mean ± SD of Serum Baseline-Corrected Total IgG Concentration Versus Nominal Time Relative to Start of Pharmacokinetic Intense Sampling Infusion, Linear Scale - Pharmacokinetic Evaluation Set



Source: Applicant. Study KIG10-US3-OID01 CSR, Figure 2.
IgG: immunoglobulin G; PK: pharmacokinetic; SD: standard deviation.

Table 55: Summary of Pharmacokinetic Parameters for Baseline-Corrected Total IgG by Dosing Schedule - Pharmacokinetic Evaluation Set

Parameter	Statistic	21-Day Regimen (7^{th} infusion)	28-Day Regimen (5^{th} infusion)
C_{max} (mg/dL)	n	5	18
-	Mean (SD)	1520 (185)	1280 (433)
-	Geometric Mean	1510	1210
-	%CV	12.1	33.8
T_{max} (h)	n	5	18
-	Median	0.530	0.515
-	Min, Max	0.500, 2.02	0.500, 23.8
C_{min} (mg/dL)	n	5	18
-	Mean (SD)	0 (0)	0 (0)
-	Geometric Mean	-	-
-	%CV	-	-
C_{last} (mg/dL)	n	5	18
-	Mean (SD)	131 (122)	95.8 (68.8)
-	Geometric Mean	67.1	73.7
-	%CV	92.9	71.8
T_{last} (h)	n	5	18
-	Median	337	505
-	Min, Max	334, 502	334, 672
C_{tau} (mg/dL)	n	5	18
-	Mean (SD)	22.2 (35.3)	23.2 (32.6)
-	Geometric Mean	24.6	37.7
-	%CV	159	141
AUC_{0-t} (day*mg/dL)	n	5	18
-	Mean (SD)	8380 (1670)	9520 (3310)
-	Geometric Mean	8250	8870
-	%CV	20.0	34.7
AUC_{tau} (day*mg/dL)	n	5	18
-	Mean (SD)	8860 (1630)	9840 (3330)
-	Geometric Mean	8740	9210
-	%CV	18.4	33.9
C_{avg} (mg/dL)	n	5	18
-	Mean (SD)	424 (78.6)	354 (117)
-	Geometric Mean	418	332
-	%CV	18.6	33.1
Fluctuation (%)	n	5	18
-	Mean (SD)	360 (56.3)	364 (70.7)
-	Geometric Mean	357	358
-	%CV	15.6	19.4
CL_{ss} (dL/day/kg)	n	5	18
-	Mean (SD)	0.0763 (0.00342)	0.0559 (0.0102)
-	Geometric Mean	0.0762	0.0550
-	%CV	4.48	18.3
V_d (dL/kg)	n	5	18
-	Mean (SD)	0.563 (0.161)	0.532 (0.108)
-	Geometric Mean	0.546	0.522
-	%CV	28.6	20.3
$t_{1/2}$ (h)	n	5	18
-	Mean (SD)	107 (45.4)	158 (48.4)
-	Geometric Mean	-	-

Parameter	Statistic	21-Day Regimen (7^{th} infusion)	28-Day Regimen (5^{th} infusion)
-	%CV	42.3	30.7

Source: Applicant. Study KIG10-US3-OID01 CSR, Table 29.
Abbreviations: AUC, area under the serum concentration-time curve; AUC0-t, Area under the concentration-time curve from time 0 to the time t of the last quantifiable concentration; AUCtau, AUC over a dosing interval; Cavg, average concentration over a dosing interval; Clast, last quantifiable concentration; CLss, clearance over a dosing interval; Cmax, maximum observed concentration; Cmin, minimum observed concentration; Ctau, concentration at the end of dosing interval; CV, coefficient of variation of mean; IgG, immunoglobulin G; Max, maximum; Min, minimum; n, number of observations contributing to statistic; PK, pharmacokinetic; SD, standard deviation; t½, terminal elimination half-life; Tlast, time of last quantifiable concentration; Tmax, time to Cmax; Vd, volume of distribution at steady-state.

4.4.3.2. Total IgG Trough Levels

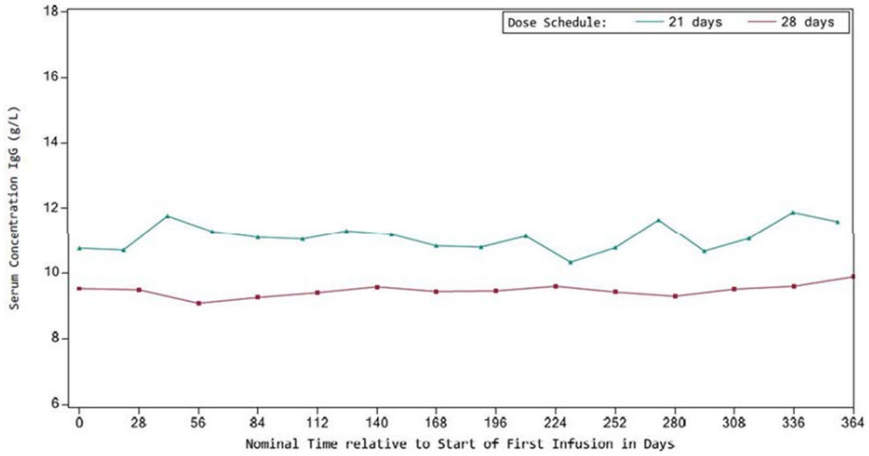
As shown in Figure 3, there was no trend observed in IGG trough levels during the study.

In the 21-day (3-week) dosing schedule (n=8):
- IgG trough levels at baseline ranged from 5.17 to 12.23 g/L, with a mean of 10.055 g/L.
- IgG trough levels at study termination visit ranged from 8.95 to 14.53 g/L, with a mean of 11.433 g/L.

In the 28-day (4-week) dosing schedule (n=39):
- IgG trough levels at baseline ranged from 6.44 to 27.39 g/L, with a mean of 10.371 g/L.
- IgG trough levels at study termination visit ranged from 7.15 to 17.04 g/L, with a mean of 10.297 g/L.

Overall (n=47):
- IgG trough levels at baseline ranged from 5.17 to 27.39 g/L, with a mean of 10.317 g/L.
- IgG trough levels at study termination visit ranged from 7.15 to 17.04 g/L, with a mean of 10.490 g/L.

Figure 3. Median of Serum Total IgG Concentration vs Nominal Time Relative to Start of First Infusion, Linear Scale - Full Analysis Set



Source: Applicant. Study KIG10-US3-OID01 CSR, Figure 1.

4.4.3.3. IgG Subclass Levels

The pattern of serum levels versus time profiles for IgG subclasses (IgG1, IgG2, IgG3, and IgG4) match with total IgG levels. The distribution of IgG subclasses overall, considering the lowest and the highest mean serum total IgG levels for each dosing schedule, varied between 53% to 59% for IgG1, 31% to 39% for IgG2, 2% to 4% for IgG3, and 2% to 3% for IgG4.

In the 21-day dosing schedule, IgG1, IgG2, and IgG4 levels increased from baseline and IgG3 levels decreased from baseline. In the 28-day dosing schedule, IgG1, IgG2, and IgG3 levels decreased from baseline at Visit 5 and Visit 9. At Visit 13, IgG1 and IgG3 continued to be at a decreased level compared to baseline but IgG2 increased slightly. IgG4 levels increased from baseline at all visits.

Overall, all the mean values of IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were maintained within the normal reference ranges. A summary of IgG subclasses is presented in Table 6 .

Table 6. Mean Trough Levels of IgG Subclasses By Visit for 21 Day and 28 Day Dosing Schedules- Full Analysis Set

Parameter	**21 Day Dosing Schedule (N=8)**	-	-	**28 Day Dosing Schedule (N=39)**	-	-
IgG Subclass (unit)	**Visit Number**	**n**	**Mean Trough**	Visit Number	**n**	**Mean Trough**
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

Source: Applicant. Study KIG10-US3-OID01 CSR, Table 20.
Abbreviations: IgG, immunoglobulin G; N, total number of subjects in each dosing schedule; n, number of subjects in each subset.
Baseline was defined as the last non-missing assessment prior to the first dose of study drug.

4.4.3.4. Specific IgG Antibody Levels

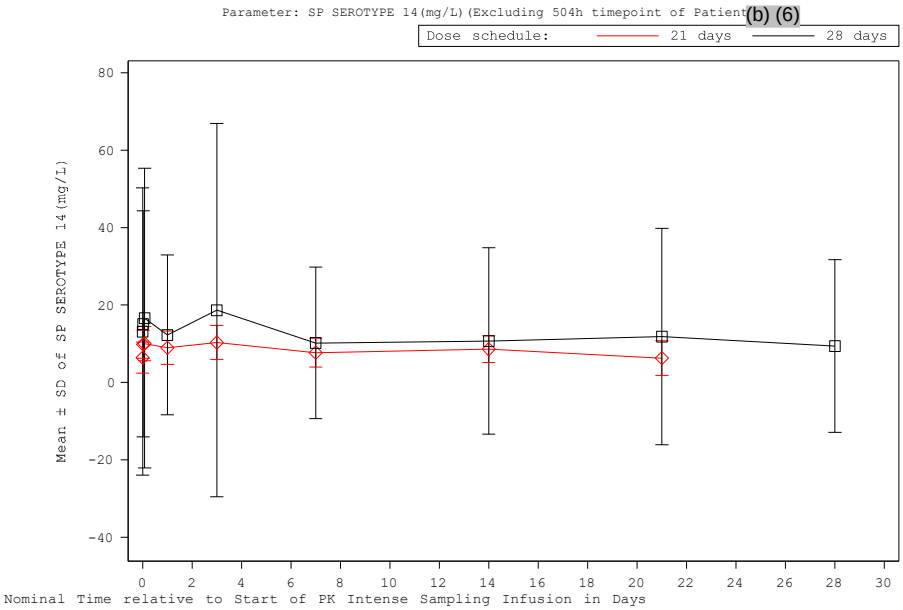
Specific IgG antibody levels were measured in Study KIG10-US3-OID01, such as anti-haemophilus influenzae type B, anti-pneumococcal capsular polysaccharide (SP serotype 14), anti-tetanus toxoid, and anti-pneumococcal capsular polysaccharide (23 serotypes other than serotype 14).

In general, the IgG-specific antibody serum levels follow an overall similar pattern as that of total IgG, i.e., sharp rise by the end of infusion and slow decline back towards baseline levels over 7 to 14 days. In the study, the overall mean levels of anti-haemophilus influenzae type B antibody, per visit, from Visit 1 were maintained above 1.00 µg/mL, which was considered protective. All mean values of anti-pneumococcal capsular polysaccharide antibodies per visit were above 0.35 mg/L which is considered a protective level. All anti-tetanus toxoid antibody levels during the study were maintained above 0.10 IU/mL which is considered protective.

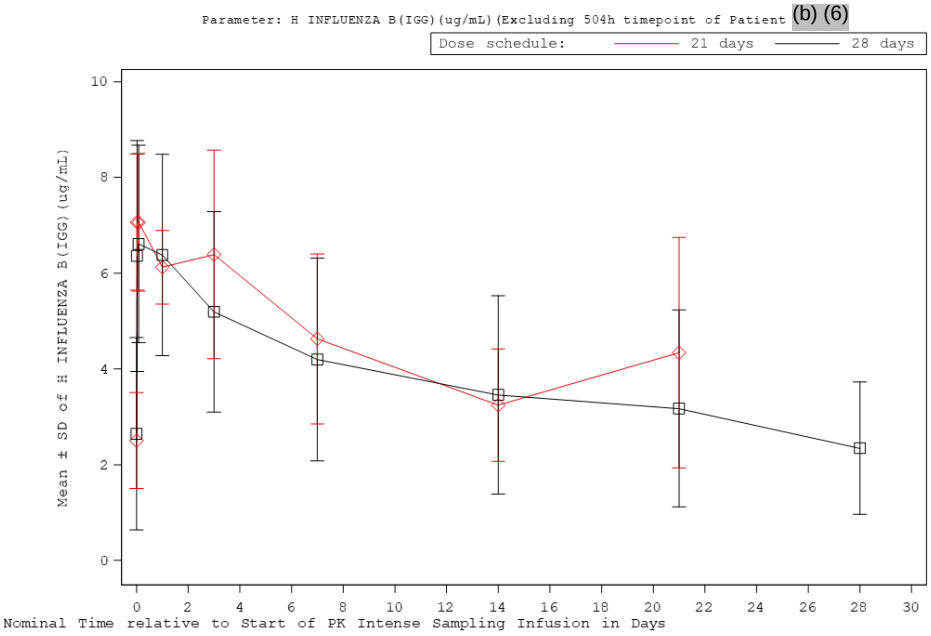
Figure 4 shows the mean concentration-time profiles of following specific IgG antibodies: anti-haemophilus influenzae type B, anti-pneumococcal capsular polysaccharide (SP serotype 14), and anti-tetanus toxoid.

Figure 4. Mean ± SD of Serum Concentration of IgG-Specific Antibodies (Anti-Pneumococcal Capsular Polysaccharide SP Serotype 14, Anti-Haemophilus Influenzae Type B, and Anti-Tetanus Toxoid) Versus Nominal Time Relative to Start of Pharmacokinetic Intense Sampling Infusion, Linear Scale – Pharmacokinetic Evaluation Set

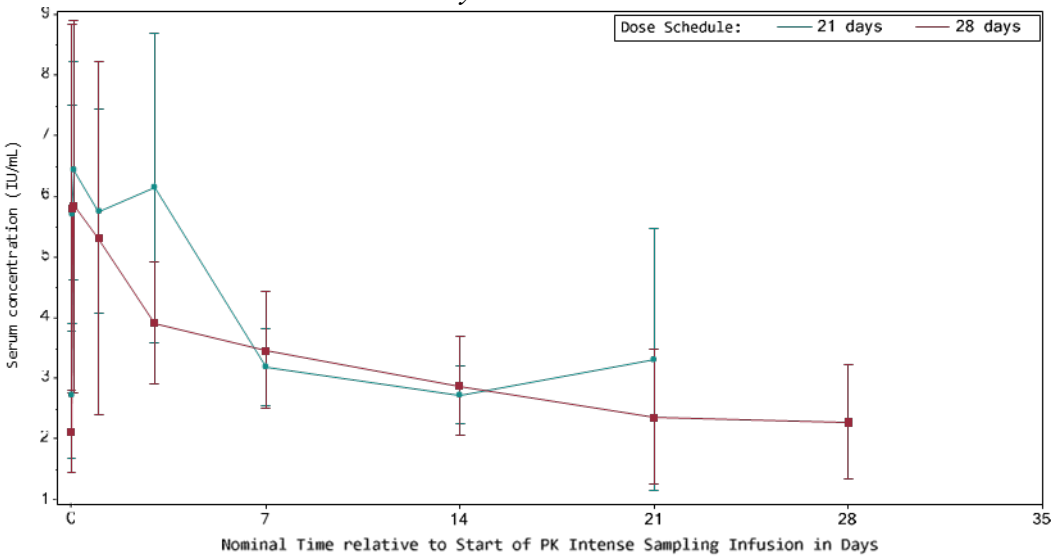
a. *Anti-Pneumococcal Capsular Polysaccharide SP Serotype 14 Antibody*



b. *Anti-Haemophilus Influenzae Type B Antibody*



c. Anti-Tetanus Toxoid Antibody



Source: Applicant. Study KIG10-US3-OID01 CSR, Figures 11 & 12.

4.5 Statistical

The statistical reviewer reviewed the submitted data used to support the primary study endpoint analyses and no statistical concerns were identified. Please refer to the memo from the statistical reviewer for additional information.

4.6 Pharmacovigilance

The Division of Pharmacovigilance recommended routine pharmacovigilance. Please refer to Division of Pharmacovigilance memo for complete details.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Data from only one clinical study was submitted in this BLA. Clinical review was completed by Dr. Sairah Thommi and clinical pharmacology review was completed by Dr. Xiaofei Wang. Dr. Thommi completed the efficacy review, and verified and updated the safety review conducted by another reviewer who left FDA prior to completion of the BLA review.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Source documents for this review include documents filed under the original application for BLA 125822, documents under IND 18648 and Applicant responses to information requests (IRs) sent during BLA review period.

5.3 Table of Studies/Clinical Trials

There is only one clinical study submitted in this BLA, KIG10_US3_PID01, discussed in Section 6.1.

5.4 Consultation

5.4.1 Advisory Committee Meeting (if applicable)

No advisory committee meeting was held.

5.4.2 External Consults/Collaborations

No external consultations were obtained.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 (of 1)

Title: A Phase III, Open-label, Prospective, Multicenter Study to Assess Efficacy, Safety and Pharmacokinetics of Kedrion Intravenous Immunoglobulin 10% in Primary Immunodeficiency Disease Patients

6.1.1 Objectives

The objective of the study was to assess the efficacy, safety, and pharmacokinetics of QIVIGY in subjects with PID.

6.1.2 Design Overview

The study was an open-label, prospective, single-arm, historically controlled, multicenter study. Subjects who were previously treated with an IGIV product were enrolled in the study and continued on their previous treatment regimen. Study visits were every 21 or 28 days (depending on the treatment regimen) and subjects were followed for 1 year. Pharmacokinetic evaluations were done at the fifth infusion for the 28-day dosing regimen or the seventh infusion for the 21-day dosing regimen.

6.1.3 Population

Subjects who had a confirmed clinical diagnosis of PID, documented agammaglobulinemia or hypogammaglobulinemia, required treatment with IGIV, and were treated with a commercially available IGIV therapy for at least 3 infusion cycles with at least 2 IgG troughs of 6 g/L or more within 12 months were enrolled. Subjects were excluded if they were naïve to IgG replacement therapy, had a history of severe or serious reactions to IGIV (including hypersensitivity reactions), previous thrombotic events, IgA deficiency, an acute infection, or were women planning a pregnancy.

> ***Clinical Reviewer Comment:*** *These eligibility criteria are consistent with other studies assessing IGIV therapy in PI. However, because subjects were excluded if they have had severe or serious reactions to IGIV or if they were IGIV-naïve, adverse reactions, including serious and severe adverse reactions, may be underestimated based on study results.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

Immune globulin intravenous (human) 10% solution.

6.1.5 Directions for Use

Not applicable.

6.1.6 Sites and Centers

Eleven study sites in the United States enrolled subjects for this study. An additional study site in Canada screened subjects but did not enroll any subjects. The lead investigator was Chaim Roifman at the Hospital for Sick Children, Toronto, Canada.

6.1.7 Surveillance/Monitoring

A Data Safety Monitoring Board (DSMB) periodically monitored this study for safety and efficacy of KIg10.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was the incidence rate of acute serious bacterial infections (SBIs) per subject-year. Acute SBIs were defined per the “FDA Guidance for Industry: Safety, Efficacy and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency” (June 2008). The 1-sided 99% upper confidence limit was required to be <1 acute SBIs per subject-year to demonstrate efficacy.

Acute SBIs included bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, and osteomyelitis/septic arthritis.

Secondary efficacy endpoints included:

- Serum IgG trough levels before each infusion
- IgG subclass (IgG1, IgG2, IgG3, IgG4) trough levels

- Frequency of subjects with total IgG below 6 g/L criteria
- Anti-tetanus toxoid antibody, anti-pneumococcal capsular polysaccharide antibody, anti-measles antibody, and anti-*Haemophilus influenza* type b antibody trough levels
- Incidence rate and duration of any infection other than acute SBIs
- Incidence rate and duration of fever episodes
- Overall hospitalization days
- Days of hospitalization due to infection
- Incidence rate and duration of antibiotics treatment for an infection
- Days of missed work, school, and other major activities due to infections
- PedsQL score at baseline, week 24, and the study termination visit

Clinical Reviewer Comment: *The primary and secondary endpoints are consistent with the IGIV Guidance and recommendations for IGIV products in PI. Of note, the rubella antibody panel was erroneously completed instead of the anti-measles antibody tests. Therefore, results for anti-measles antibody testing were not available.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please refer to the statistical review memo.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Fifty-nine subjects were enrolled in the study of which 47 were eligible and completed the study.

- The Full Analysis Set (FAS) and Safety Analysis Set (SAF) included all subjects (n=47) who received at least one dose of study medication.
- The Pharmacokinetic Evaluation Set (PKS) included all subjects who consented to pharmacokinetic (PK) analysis and had PK testing performed.
- The Per-Protocol Set (PPS) included subjects who did not have any major protocol deviations that were thought to affect efficacy.

Table 7: Analysis Sets

Analysis Set	n
FAS	47
SAF	47
PKS	23
PPS	44

Source: Reviewer table.
Abbreviations: FAS= full analysis set; n= number; PKS= pharmacokinetic evaluation set; PPS= per-protocol set; SAF= safety analysis set.

6.1.10.1.1 Demographics

Of 59 enrolled subjects, 47 were eligible and received QIVIGY. All 47 subjects completed the study. The median age was 56 years (range: 20 to 70 years). Although pediatric subjects were eligible for enrollment, enrollment numbers were achieved with adult subjects prior to enrollment of any pediatric subjects. Therefore, no children were

enrolled. Most subjects were white (n=45; 95.7%) and female (n=30; 63.8%). Full demographics are included in Table 1.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The most common underlying cause of PI was common variable immunodeficiency (n=34; 72.3%). Other diagnoses included primary immunodeficiency syndrome, congenital hypogammaglobulinemia, and hypogammaglobulinemia.

6.1.10.1.3 Subject Disposition

Of 59 enrolled subjects, 47 were eligible and received QIVIGY. All 47 subjects completed the study.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary analysis intended to demonstrate that the acute SBI rate (upper limit of the 1-sided 99% Confidence Interval [CI]) was < 1.0 per subject-year in the FAS. There were no acute SBIs during study follow-up, meeting the pre-specified endpoint for efficacy.

Because no acute SBIs were reported, subgroup analyses for age, sex, race, and sensitivity were not completed.

> ***Clinical Reviewer Comment:*** *During interactive review, the clinical team adjudicated eight adverse events (described below) that were reported in five subjects to ensure that these adverse events did not represent acute SBIs. The initial descriptions in the dataset are described initially with the bullet points corresponding to the Applicant's response to Information Requests (IR). This clinical reviewer considers there is not sufficient evidence to readjudicate any of the events and thus concurs with the Applicant's finding of no acute SBIs in the study.*

Subject (b) (6):

1. Starting on Day 2, the subject received 11 days of clarithromycin for acute bronchitis.
    - The Applicant clarified that this subject has a history of chronic bronchitis since 2003, which was ongoing at study entry.
    - Symptoms were reported over the phone between visits and antibiotics were prescribed without diagnostic testing.
    - The adverse event of mild acute bronchitis lasted the duration of the antibiotic treatment.

Subject (b) (6) (continued):

2. Starting on Day 57, the subject received 12 days of clarithromycin for acute bronchitis.
    - Symptoms were reported over the phone between visits.
    - The Applicant noted that the mild acute bronchitis lasted for 31 days, including 7 days after completion of the antibiotic course.
    - No additional diagnostic testing was reported.

    Clinical Reviewer Comment: *Testing (including a physical exam) was not completed prior to starting antibiotics to rule-out pneumonia in this subject for either event. From the description of these adverse events, it is not clear if these were pneumonia or exacerbation of the subject's chronic bronchitis. Although the treatment course may represent common clinical practice, inadequate testing was completed for an assessment of a primary outcome endpoint in a pivotal study.*

Subject (b) (6) (continued):

3. Starting on Day 106, the subject received 23 days of doxycycline for exacerbation of chronic bronchitis.
    - Exacerbation of chronic bronchitis lasted 24 days.
    - It was reported to be diagnosed during a physical examination at Visit 6.
    - No additional diagnostic tests were reported.
    - The Investigator responded that the subject did not experience any serious bacterial infection.

    Clinical Reviewer Comment: *The review team requested the case report form to assess the specific physical exam findings that led to diagnosis of chronic bronchitis exacerbation and treatment with 23 days of doxycycline. Per the case report form, there were no clinically significant findings on physical exam. No description of the exacerbation of chronic bronchitis was included. The review team noted that there was an inconsistency in the case report form and data recording.*

    The reviewed documentation does not indicate that this event was a pneumonia. However, the prolonged antibiotic course without an appropriate justification (i.e., bacterial infection) and in the context of a bronchitis exacerbation is inappropriate for a pivotal study assessing IGIV in PI.

Subject (b) (6):

1. Starting on Day 25, the subject received 18 days of amoxicillin/clavulanic acid for bronchial infection.
    - The Applicant clarified that this subject has a history of chronic bronchitis since 2014, which was ongoing at study entry.
    - The Applicant noted that the adverse event on mild bronchial infection started on the day after Visit 2 and lasted for 22 days.
    - No additional diagnostic tests were reported.

Clinical Reviewer Comment: *Testing (including a physical exam) was not completed prior to starting antibiotics to rule-out pneumonia in this subject. From the description of this adverse event, it is not clear if this was a pneumonia or exacerbation of the subject's chronic bronchitis. Although the treatment course may represent common clinical practice, inadequate testing was completed prior to starting antibiotics in a pivotal study for PI.*

Subject (b) (6) (continued):

2. Starting on Day 132, the subject received 15 days of amoxicillin/clavulanic acid for bacterial infection and on Day 148, the subject started a 21-day course of doxycycline.
    - The investigator reported "mild respiratory tract inflammation" lasting 37 days and starting on the day of amoxicillin/clavulanic acid initiation.
    - Mild acute sinusitis was also reported starting 2 days after the initiation of antibiotics (at a study visit).
    - The doxycycline was initiated upon completion of the amoxicillin/clavulanic acid course.
    - No additional diagnostic tests were reported.

Clinical Reviewer Comment: *These two antibiotic courses (starting at Day 132 and 148) treated "mild respiratory tract inflammation." A study visit was scheduled 2 days after the initiation of symptoms and antibiotics. This may have allowed a physical exam to rule out signs of a pneumonia, but findings were not specified. It is not clear what findings led the Investigator to prescribe a 36-day course of antibiotics for pulmonary symptoms that were not described as pneumonia, but additional testing/reporting of physical exam findings would have been helpful to rule in or out a pneumonia in this pivotal study for an IGIV treatment.*

Subject (b) (6):

3. Starting on Day 76, the subject received 18 days of azithromycin for bronchitis.
    - The subject had a history of chronic bronchitis, which was ongoing at study entry.
    - The medication was started and discontinued in between study visits.
    - No additional diagnostic testing was completed.

Clinical Reviewer Comment: *Additional testing would have been helpful to rule in or out a pneumonia in this pivotal study for an IGIV treatment. Although the treatment course may represent common clinical practice, inadequate testing was completed prior to starting antibiotics in a pivotal study for PI.*

Subject (b) (6):

4. Starting on Day 77, the subject received 13 days of cefdinir for acute viral bronchitis.
    - The subject reported cough, sore throat, vomiting and diarrhea. The subject was reported to have a viral gastroenteritis and viral bronchitis.
    - No additional diagnostic tests were reported.

Clinical Reviewer Comment: *The subject's viral gastroenteritis support the likelihood that the etiology of this subject's respiratory symptoms were viral.*

Subject (b) (6):

5. Starting on Day 222, the subject received 7 days of levofloxacin for "patchy airspace lower left lobe."
    - The subject had a history of recurrent bronchitis and chronic sinusitis.
    - The subject had an unscheduled visit presenting with "body aches, post nasal drip, cough, hoarse voice, and exposure to sick contact."
    - Scattered wheezing was noted on physical exam.
    - An X-ray was completed with "Linear Scar/atelectasis right lower lobe just above the hemidiaphragm, new. New patchy airspace disease left lower lobe is present and may be due to atelectasis or infiltrate."
    - The subject tested positive for influenza and Tamiflu was prescribed.
    - Per the subject's request, levofloxacin was also prescribed.

Clinical Reviewer Comment: *The clinical review team agreed that, given positive influenza testing, diffuse lung findings on exam, and systemic viral-like symptoms, the localized "new patchy airspace disease" was likely consistent with atelectasis rather than infiltrate, and thus this was unlikely to be an acute bacterial pneumonia.*

Summary of Review Team Adjudications: Although the clinical review team agreed that there was not adequate evidence for each of these adverse events to be described as an acute SBI, the team noted that for six of these adverse events, inadequate testing was done to rule out an acute SBI in the context of antibiotic administration. Of note, the study was conducted from April 30, 2019 to December 21, 2020, during the COVID-19 pandemic. In that context, it may have been appropriate to forego additional diagnostic testing in these high-risk subjects with an immunodeficiency.

Even if all six events were counted as an acute SBI, the product would have met its primary efficacy endpoint. The mean rate of acute SBIs/year would have been 0.13 acute SBIs per subject-year with an upper 99% CI of 0.31.

6.1.11.2 Analyses of Secondary Endpoints

Serum IgG trough levels before each infusion
At baseline, IgG trough levels ranged from 5.17 to 27.39 g/L. At study termination, IgG trough levels ranged from 7.15 to 17.04 g/L. No trends were identified in IgG trough level assessments.

IgG subclass (IgG1, IgG2, IgG3, IgG4) trough levels
Mean IgG subclass values were maintained within the normal ranges during study follow-up.

Frequency of subjects with total IgG below 6 g/L criteria
One subject was enrolled in the study with a baseline IgG trough below 6 g/L. During treatment with QIVIGY, one subject had an IgG trough < 6 g/L at one visit. At three visits,

one subject's IgG trough was not able to be analyzed due to either hemolysis or insufficient sample availability.

Anti-tetanus toxoid antibody, anti-pneumococcal capsular polysaccharide antibody, anti-measles antibody, and anti-*Haemophilus influenza* type b antibody trough levels
All anti-tetanus toxoid antibody levels were above the thresholds considered protective.

All anti-pneumococcal capsular polysaccharide antibody levels had *mean* levels above the thresholds considered protective. However, antibody levels for serotypes 12, 22, 23, 26, 34, and 9 (28-day dosing schedule) and 4 (both dosing schedules) had some values that were below thresholds considered protective during study follow-up.

Anti-measles antibody was not tested erroneously. Therefore, results are not available.

Anti-*Haemophilus influenzae* type b antibodies had *mean* levels above thresholds considered protective. However, four subjects who were dosed every 4 weeks had levels below protective levels at some visits during study follow-up.

Incidence rate and duration of any infection other than acute SBIs

A total of 98 infections occurred in 36 (76.6%) subjects resulting in a mean of 2.1 (SD 1.44) infections per subject-year. The median duration of infections that were not acute SBIs was 12 days (range 1-344 days). The maximum value (344) was reached by a subject who had cellulitis. Six additional subjects had infections (sinusitis, urinary tract infection, chronic bronchitis, giant papillary conjunctivitis, onychomycosis, and bronchitis) that lasted longer than 100 days.

> ***Clinical Reviewer Comment:*** *During interactive review, the Applicant updated their analyses to include four additional reports of infections that were not acute SBIs. The Applicant noted that two infections were inadvertently not coded in the correct system organ class (using infections and infestations) and two additional infections were reported as adverse events, but not included in the final database.*
>
> *The dataset did not include an end date for the patient who had cellulitis lasting 344 days. However, the study report specified that the duration of the adverse event lasted 344 days.*
>
> *Some of the infections had missing end dates and therefore durations were not calculated in the dataset. So, some AE durations may be over-estimations due to missing data.*

Incidence rate and duration of fever episodes

Seven (14.9%) of all subjects had fevers during study follow-up. All subjects who had fevers were dosed on the every 4 week schedule. This resulted in a mean rate of 0.1 fevers per subject-year with a standard deviation of 0.36. The median duration of fever episodes was 2.0 days (range 1- 7 days).

Overall hospitalization days

Four subjects were hospitalized during the study, with hospitalization durations ranging from 2 to 6 days. Reasons for hospitalization included worsening depression, hyperglycemia, hypotension, acute on chronic cholecystitis, and worsening left knee osteoarthritis.

Days of hospitalization due to infection

No subjects were hospitalized due to infection.

Incidence rate and duration of antibiotics treatment for an infection

Overall, 36 (76.6%) subjects took antibiotics for treatment of infections resulting in a mean incidence rate of 2.4 (SD 1.55) antibiotic episodes per subject-year. The median duration of antibiotic treatment was 10 days (with a range of 1 to 334 days).

Days of missed work, school, and other major activities due to infections

Nine (19.1%) subjects missed school/work due to infections for a median of 6 days (range 1- 53 days).

PedsQL score at baseline, week 24, and the study termination visit

Higher values in the PedsQL score indicate a better quality of life. PedsQL scores were stable (baseline mean 76.7 and termination 77.3) during study follow-up.

> ***Clinical Reviewer Comment:*** *No pediatric subjects were enrolled in this study. The utility of the PedsQL in this subject population is not clear.*

6.1.11.3 Subpopulation Analyses

Because no acute SBIs occurred in the study, no subpopulation analyses were completed for the primary efficacy endpoint. Subpopulation analyses for other efficacy endpoints were considered unnecessary as differences in infectious outcomes or PK assessments are not expected based on baseline demographic factors or disease characteristics in the PI population evaluated.

6.1.11.4 Dropouts and/or Discontinuations

There were no dropouts or early study discontinuations in the study.

6.1.11.5 Exploratory and Post Hoc Analyses

The Applicant performed post hoc analyses, but these analyses were not used to support the review of the BLA considering the analyses for the pre-specified endpoints constitute substantial evidence of effectiveness.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety analyses were conducted by pooling all subjects treated in the development program in the SAF (n=47) and separating by dosing schedule.

6.1.12.2 Overview of Adverse Events

A total of 46 subjects (97.9%) reported 403 treatment emergent adverse events (TEAEs), of which 75 TEAEs (occurring in 22 [46.8%] subjects) were considered by the Applicant to be related to QIVIGY.

6.1.12.3 Deaths

There were no deaths.

6.1.12.4 Nonfatal Serious Adverse Events

Four subjects experienced five serious adverse events (SAEs) all of which resulted in hospitalization or prolongation of a hospitalization. None of the SAEs were QIVIGY-related. No events were life-threatening or resulted in study withdrawal. All SAEs were reported as resolved.

Table 8: Serious Adverse Events

SAE	Severity
Depression	Severe
Hypotension	Moderate
Hyperglycemia	Moderate
Cholecystitis acute	Moderate
Osteoarthritis	Severe

Source: Adapted from Clinical Study Report KIG10_US3_PID01.

> ***Clinical Reviewer Comment:*** *Narrative reports were reviewed for each of the SAEs and adjudicated to be unrelated to QIVIGY.*

6.1.12.5 Adverse Events of Special Interest

The Applicant reported 4 adverse events of special interest (AESI) in 3 subjects.

- Three non-serious, hypersensitivity reactions were reported. One of these events was reported as related to QIVIGY, a skin reaction that occurred 1 day after QIVIGY infusion. The others were deemed not related to QIVIGY as they occurred 15 and 17 days after infusion.
- Five subjects had positive direct Coombs tests that were categorized as adverse reactions. One of these was reported as an AESI.

There were no thrombotic events, aseptic meningitis, transfusion-related acute lung injury, or acute renal failure reported during the study.

During the study, one subject tested positive for COVID-19. The infection was mild and the subject was able to continue treatment with QIVIGY according to the study protocol.

6.1.12.7 Adverse Events

The majority of adverse events (AEs) were mild or moderate in intensity. Two adverse events (depression and osteoarthritis) were severe and unrelated to QIVIGY.

Table 9: Number of Subjects with TEAEs in ≥ 5% Subjects

System Organ Class **Preferred Term**	**21-Day Dosing Schedule (N = 8)** n (%)	**28-Day Dosing Schedule (N = 39)** n (%)	**Total (N = 47)** n (%)
Subjects with any TEAE	8 (100)	38 (97.4)	46 (97.9)
Gastrointestinal disorders	-	-	-
Nausea	1 (12.5)	10 (25.6)	11 (23.4)
Diarrhea	1 (12.5)	6 (15.4)	7 (14.9)
Toothache	1 (12.5)	2 (5.1)	3 (6.4)
General disorders and administration site conditions	-	-	-
Fatigue	3 (37.5)	9 (23.1)	12 (25.5)
Pyrexia	0	6 (15.4)	6 (12.8)
Chills	0	3 (7.7)	3 (6.4)
Pain	1 (12.5)	2 (5.1)	3 (6.4)
Infections and infestations	-	-	-
Bacterial infection	6 (75)	16 (41.0)	22 (46.8)
Upper respiratory tract infection	0	8 (20.5)	8 (17)
Bronchitis	2 (25)	2 (5.1)	4 (8.5)
Influenza	1 (12.5)	2 (5.1)	3 (6.4)
Injury, poisoning and procedural complications	-	-	-
Infusion-related reaction	0	5 (12.8)	5 (10.6)
Skin laceration	2 (25)	1 (2.6)	3 (6.4)
Investigations	-	-	-
Coombs direct test positive	2 (25)	3 (7.7)	5 (10.6)
Musculoskeletal and connective tissue disorders	-	-	-
Myalgia	1 (12.5)	3 (7.7)	4 (8.5)
Arthralgia	0	3 (7.7)	3 (6.4)
Musculoskeletal pain	0	3 (7.7)	3 (6.4)
Neck pain	0	3 (7.7)	3 (6.4)
Pain in extremity	1 (12.5)	2 (5.1)	3 (6.4)
Nervous system disorders	-	-	-
Headache	1 (12.5)	18 (46.2)	19 (40.4)
Dizziness	1 (12.5)	2 (5.1)	3 (6.4)
Psychiatric disorders	-	-	-
Depression	1 (12.5)	4 (10.3)	5 (10.6)
Insomnia	2 (25)	1 (2.6)	3 (6.4)

Source: Applicant Table 5, 2.7.4 Summary of Clinical Safety

Table 10 demonstrates the number of subjects that experienced adverse reactions that occurred in 5% or more subjects. Adverse reactions were included if they were temporally (within 72 hours of an infusion) or causally related to QIVIGY.

Table 10: Adverse Reactions Occurring in ≥ 5% Subjects

System Organ Class / Preferred Term	**21-Day Dosing (N = 8)** n (%)	**28-Day Dosing (N = 39)** n (%)	**Total (N = 47)** n (%)
Gastrointestinal disorders	-	-	-
Nausea	1 (12.5)	5 (12.8)	6 (12.8)
Diarrhea	1 (12.5)	2 (5.1)	3 (6.4)
General disorders and administration site conditions	-	-	
Fatigue	2 (25)	5 (12.8)	7 (14.9)
Infections and infestations	-	-	-
Sinusitis	2 (25)	1 (2.6)	3 (6.3)
Injury, poisoning and procedural complications	-	-	
Infusion-related reaction	0	5 (12.8)	5 (10.6)
Investigations	-	-	-
Coombs direct test positive	2 (25)	3 (7.7)	5 (10.6)
Nervous system disorders	-	-	-
Headache	1 (12.5)	13 (33.3)	14 (29.8)
Dizziness	1 (12.5)	2 (5.1)	3 (6.4)

Source: Reviewer analysis of ADAE dataset

Table 11 demonstrates the total number of drug-related adverse reactions per infusion that occurred in 5% or more of subjects.

Table 11: Number of Adverse Reactions per Infusions

System Organ Class / Preferred Term	**Number of Events**	**Event per Infusions (N = 643)**
Gastrointestinal disorders	-	-
Nausea	6	<1%
Diarrhea	4	<1%
General disorders and administration site conditions	-	-
Fatigue	10	1.5%
Infections and infestations	-	-
Sinusitis	3	<1%
Injury, poisoning and procedural complications	-	-
Infusion-related reaction	7	1.1%
Investigations	-	-
Coombs direct test positive	8	1.2%
Nervous system disorders	-	-
Headache	26	4%
Dizziness	3	<1%

Source: Reviewer analysis of ADAE dataset

6.1.12.7 Clinical Test Results

As reported above, five subjects had positive direct Coombs tests that were reported as adverse reactions. No other relevant trends in laboratory testing were observed.

Clinical Reviewer Comment: *The Applicant reports that 17 (36%) of the enrolled patients had positive Coombs tests during the study, but only 5 subjects had tests that were considered by investigators to be clinically significant. Of note, a positive direct Coombs test rate of 36% is not an outlier compared to other IGIV products reported in the literature.[1] No hemolysis events were reported.*

6.1.12.8 Dropouts and/or Discontinuations

There were no dropouts or discontinuations.

6.1.13 Study Summary and Conclusions

The study met its primary endpoint assessing efficacy as no patients had acute SBIs during study follow-up. No deaths or life-threatening events occurred. The only SAEs that occurred were not related to QIVIGY-treatment. Adverse reactions reported in ≥5% of subjects treated with QIVIGY include: headache (29.8%), fatigue (14.9%), nausea (12.8%), infusion-related reactions (10.6%), direct Coombs test positive (10.6%), sinusitis (6.3%), dizziness (6.4%), and diarrhea (6.4%). The study provides substantial evidence of effectiveness and reasonable assurance of safety, and supports a favorable risk-benefit assessment for QIVIGY in adults with PI.

7. Integrated Overview of Efficacy

Since one study was submitted in this BLA, an integrated efficacy analysis was not necessary.

8. Integrated Overview of Safety

Since one study was submitted in this BLA, an integrated safety analysis was not necessary.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No new human reproduction or pregnancy data was submitted in this original BLA. The safety of immunoglobulins for use in human pregnancy has not been established in clinical studies and therefore should only be given with caution to pregnant women. Clinical experience suggests that immunoglobulin products can cross the placenta, increasingly during the third trimester. Therefore, QIVIGY should be given to pregnant women if clearly needed.

9.1.2 Use During Lactation

No new human lactation data was submitted in this original BLA. Immune globulins are excreted into the milk. There is no data to understand the safety of QIVIGY on the

[1] Schroeder Jr, H. W., and C. J. Dougherty. "Review of intravenous immunoglobulin replacement therapy trials for primary humoral immunodeficiency patients." Infection 40.6 (2012): 601-611.

breastfed newborns/infants. Therefore, QIVIGY should incorporate consideration of the benefits of breastfeeding, the potential adverse effects on the breastfed infant and the underlying maternal condition.

9.1.3 Pediatric Use and PREA Considerations

No pediatric subjects were enrolled in this study. The safety, efficacy, and PK data for children 2 to <17 years of age are being assessed in an ongoing deferred pediatric study as part of a PREA post-marketing requirement (PMR). The pediatric study requirement for age 0 to <2 years is waived as PI is rarely diagnosed in this age group, and therefore conducting studies in this age group is impossible or highly impractical.

> ***Clinical Reviewer Comment:*** *During interactive review, the Applicant requested an updated iPSP due to difficulties enrolling subjects in their ongoing pediatric study. An informal teleconference was held September 12, 2025 to discuss the Applicant's progress assessing their product in pediatric subjects. Fourteen international subjects had completed the study. In a few months, 5 subjects treated in the U.S. would have at least 6 months of data.*
>
> *Considering the importance of ensuring that children have access to these therapies and our current knowledge of this disease and product class (including similarities in disease manifestations between adults and pediatric subjects, expectations that the product meet the same efficacy requirement for the pediatric population that was met in the adult population, and a known safety profile among numerous commercially available intravenous immunoglobulin products to treat both adult and pediatric populations), the FDA agreed to exert regulatory flexibility in the requested number of subjects and duration of follow-up previously agreed to for fulfillment of the PREA PMR. Utilizing the 2024 Guidance "E11 Clinical Investigation of Medicinal Products in the Pediatric Population," the FDA requested that additional extrapolation from pharmacokinetic data be used to fill gaps particularly in 2-5 year old group where enrollment was sparse, and allow product availability sooner for the pediatric population.*

9.1.4 Immunocompromised Subjects

Not applicable as the product is indicated for subjects with immunodeficiency. All subjects have PI.

9.1.5 Geriatric Use

Seven adults ≥ 65 years of age were enrolled and treated with QIVIGY in the study. This sample size is too small to derive meaningful conclusions.

10. CONCLUSIONS

The study submitted as the basis of this BLA is an adequate and well- controlled (AWC) study. Based on the submitted data, treatment with QIVIGY appears safe and effective in adults with PI. The data supports the use of QIVIGY 300- 800 mg/kg every 3 or 4 weeks for the treatment of adults with PI.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

The risk-benefit assessment is detailed in Table 12.

Table 12: Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Primary humoral immunodeficiency (PI) is characterized by impaired B-cell immunity, and thus, impaired ability to produce specific antibodies in response to pathogenic microorganisms. • Subjects with PI are at increased risk for recurrent, severe infections.	• PI diseases are serious, chronic conditions associated with considerable morbidity and mortality. • Immunoglobulin replacement therapy (administered either intravenously or subcutaneously) has been shown to reduce the incidence of serious infections through the provision of passive immunity.
Unmet Medical Need	• There are numerous approved immunoglobulin replacement products, and therefore there is not an unmet medical need for additional products except during periods of product shortages.	• There is not currently unmet medical need due to similar products on the market, but even with available products there remain treatment burdens that impact quality of life for patients. • Given the potential of product shortages, there is a benefit to having multiple products on the market.
Clinical Benefit	• QIVIGY has demonstrated its ability to prevent acute serious bacterial infections in adults with PI. • PK assessments support the ability of QIVIGY to achieve protective IgG levels.	• Subjects with PI benefit from treatment with immunoglobulin replacement therapy.
Risk	• In general, immunoglobulin products have the following risks: thrombosis, hypersensitivity reactions, acute renal failure and renal dysfunction, aseptic meningitis, hemolysis, transfusion-related acute lung injury, transmission of infectious agents, hyperproteinemia, hyperviscosity, hyponatremia or pseudohyponatremia, and laboratory test interference. • Adverse reactions reported in ≥5% of subjects treated with QIVIGY include: headache (29.8%), fatigue (14.9%), nausea (12.8%), infusion-related reactions (10.6%), direct Coombs test positive (10.6%), sinusitis (6.3%), dizziness (6.4%), and diarrhea (6.4%).	• There were no new safety signals or new risks associated with QIVIGY compared to those observed with the use of other IGIV products.
Risk Management	• No new serious risks were identified related to QIVIGY compared to other approved IGIV products.	• The package insert and pharmacovigilance plan are adequate to manage risks. Routine post-marketing surveillance is recommended.

11.2 Risk-Benefit Summary and Assessment

Data submitted in the BLA provide substantial evidence of effectiveness and safety in adults with PI. QIVIGY is effective in reducing the number of SBIs to less than one per subject-year in adults with PI. The most commonly reported adverse reactions (including adverse events within 72 hours of an infusion and any causally related event) were headache, fatigue, nausea, infusion-related reactions, positive direct Coombs direct test, sinusitis, dizziness, and diarrhea. Adverse reactions were consistent with those anticipated for this class of medications. For immunoglobulin therapy for PI, the Agency accepts a single AWC study with confirmatory data from other AWC studies within the class for the same indication. Overall, the benefit-risk profile for adults with PI treated with QIVIGY is favorable.

11.3 Discussion of Regulatory Options

The regulatory options for this BLA efficacy supplement are approval or complete response.

When considering approval, additional options include modification of the indication or the dosing regimen (e.g., to modify the minimum dose) with considerations for post-marketing requirements.

11.4 Recommendations on Regulatory Actions

Based on a favorable risk-benefit assessment for this product, we recommend traditional approval of the original Biologics License Application (BLA) for QIVIGY for the treatment of adults with PI.

11.5 Labeling Review and Recommendations

Several revisions were made to the Applicant's proposed United States Prescribing Information. Please see Table 13 below for a summary of significant changes to the United States Prescribing Information.

Table 13: Summary of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 1: Indication and Usage	For the treatment of Primary Humoral Immunodeficiency in patients 18 years of age and older.	For the treatment of adults with Primary Humoral Immunodeficiency
Section 2: Dosage and administration	Section 2: Proposed dose (b) (4) mg/kg to 800mg/kg	Recommended dose range was revised to 300 mg/kg to 800mg/kg since the minimum dose administered in the trial was 266mg/kg and no patients received a dose (b) (4) mg/kg.

Section 5: Warnings and Precautions		The subheadings in this section were reordered based on clinical significance.
	Section 5.9 Monitoring Laboratory Tests	Section 5.9 was added to specify monitoring recommendations related to adverse events similar to other recently approved IVIG products.
Section 6: Adverse Reactions (Safety)		The information in this section was revised based on the current labeling practice for to include description of the safety database and exposure information.
	AR table included events considered to be possibly, probably, or definitely related to the product.	AR table was revised to include all adverse events occurring within 72 hours of infusion or any causally related event occurring within the study period.
	No section on post marketing experience	Section 6.2 was added to list adverse reactions reported in the postmarking setting.
Section 8: Use in Special Population	Section 8.5 Geriatric Use	Section 8.5 was revised to specify the number of geriatric patients followed by recommendations for administration of QIVIGY in this population.
Section 12: Clinical Pharmacology	Missing Section 12.2 Pharmacodynamics	Section 12.2 was added with PD information related to QIVIGY.
Section 14: Clinical Studies	-	Section 14 was revised to describe the study design, intervention, population characteristics, and results. Table 5 with efficacy results was revised to include outcomes based on review team analysis including annualized rate of acute SBI, annualized rate of other infections, patients hospitalized due to infection, number and duration of antibiotic treatment for any kind of infection, and missed work/school/other major activities due to infections

Section 15: References	Section 15 with a list of published articles.	This section was deleted as FDA could not endorse data in these publications.
Section 17: Patient Counseling Information	-	This section was revised for clarity, use of command language, and to include important risks listed in section 5 (Warning and Precautions).

Source: Created by FDA Clinical Reviewer and Associate Director of Labeling
Abbreviations: AR=adverse reaction, IVIG=intravenous immunoglobulin, SBI=serious bacterial infection

11.6 Recommendations on Post Marketing Actions

A PREA post marketing requirement (PMR) and multiple CMC post marketing commitments (PMCs) will be required as conditions of approval. Refer to Section 9.1.3 for additional details related to changes to the PREA PMR (in adjustment of dates to satisfy the PREA PMR earlier than originally planned), and refer to the CMC review memo for details of the PMCs. The following is the agreed-upon PREA PMR with updated milestone dates:

1. Deferred pediatric study under PREA for the treatment of primary immune deficiency in pediatric patients ages 2 years to less than 17 years.

   Final Protocol Submission: December 30, 2025

   Study/Trial Completion: April 30, 2026

   Final Report Submission: July 30, 2026