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Division / Office	DCEGM/OCE/OTP
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Priority Review	No
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Applicant	Kedrion SpA
Established Name	Immune Globulin Intravenous (Human) 10%
(Proposed) Trade Name	QIVIGY
Dosage Form(s) and Route(s) of Administration	Solution for intravenous infusion
Dosing Regimen	(b) (4) to 800 mg/kg of body weight every 3 to 4 weeks, adjusted over time to achieve adequate trough levels and clinical responses
Indication(s) and Intended Population(s)	Treatment of adults with primary humoral immunodeficiency

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## GLOSSARY

Abbreviation	Definition
AE	Adverse Event
BLA	Biologics License Application
CI	Confidence Interval
CVID	Common variable immunodeficiency
FAS	Full Analysis Set
ICF	Informed consent form
IgG	Immunoglobulin Gamma
IGIV	Immune globulin Intravenous
IND	Investigational new drug
KIg10	Kedrion 10% Immune Globulin Intravenous
PADQOL	Primary Antibody Deficiency Quality of Life
PedsQL	Pediatric Quality of Life Inventory
PI	primary humoral immunodeficiency
PID	Primary Immunodeficiency Disease
PK	Pharmacokinetic(s)
PKS	PK Evaluation Set
PPS	Per-Protocol Set
QoL	Quality of Life
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBI	Serious bacterial infection
TEAE	Treatment-emergent adverse event
USA	United States of America

### 1. Executive Summary

This original Biologics License Application (BLA STN 125822/0) was submitted for QIVIGY, an immune globulin intravenous (Human) 10% solution, for the proposed indication of treatment of adults with primary humoral immunodeficiency (PI). The efficacy and safety databases consist of data on 47 patients treated in Study KIG10\_US3\_PID01, a phase 3, open-label, prospective, multicenter study to assess efficacy, safety, and pharmacokinetics of QIVIGY in PI patients.

The primary efficacy endpoint of Study KIG10\_US3\_PID01 was the occurrence of acute serious bacterial infections (SBIs). No acute SBIs occurred during the study, yielding an estimate of the incidence rate of at 0 acute SBIs per person-year. The associated upper bound of the one-sided 99% confidence interval was  $<1$ , meeting the study success criterion. Study results on secondary efficacy endpoints, including incidence of infections, days missed from work/school, and hospitalizations, further supported efficacy of QIVIGY.

No deaths occurred during the study.

In conclusion, the efficacy results support the proposed indication. I therefore recommend approval of this BLA.

## 2. Clinical and Regulatory Background

QIVIGY was referred to as KIG10 during clinical development. Kedrion 10% Immune Globulin Intravenous (IGIV) or KIG10, a plasma-derived, ready-to-use liquid normal Ig (100 mg/mL) with a formulation that is appropriate for an IGIV product, and its main component is  $\geq 96\%$  Immunoglobulin Gamma (IgG).

### 2.1 Disease or Health-Related Condition(s) Studied

The proposed indication is treatment of adults with primary humoral immunodeficiency (PI).

Primary Immunodeficiency Disease (PID) occurs in individuals with a genetic defect in the immune system. These patients are affected by recurrent protozoal, bacterial, fungal, and viral infections. Antibody deficiencies, also referred to as B-cell or humoral immunodeficiencies, comprise the largest group of PIDs and are characterized by an impaired ability to produce specific antibodies in response to antigens. Many of these disorders are caused by mutations in the Ig genes or in genes involved in the regulation of B-cell growth and differentiation.

The largest group of patients with antibody deficiency are classified as common variable immunodeficiency (CVID) with an estimated prevalence of 1 in 50,000. It is defined principally as low IgG together with a significant impairment of specific antibody production in response to bacterial vaccine or natural infectious challenge. Males and females are equally affected, and diagnosis is most common between the ages of 20 to 40 years with only about 20% of patients diagnosed in childhood.

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

Replacement Ig therapy is the standard practice for patients with PID to prevent infections and control the frequency and severity of infections in affected individuals. Most patients receive IGIV infusions at intervals of 3 or 4 weeks. Reductions in hospitalization and infection rates are well documented in patients who receive high dose ( $>400$  mg/kg every 3 weeks) of IGIV. IGIV dosage is individualized based upon the patient's clinical response.

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

QIVIGY has not been approved in any country.

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

Table 1 lists the regulatory meetings between the applicant and the Agency.

**Table 1: Meetings between the applicant and the Agency**

Meeting Number	Meeting Date	Meeting Type
CRMTS 10677	5/12/2017	Pre IND written response meeting
CRMTS 12315	3/19/2020	Written response Type C meeting
CRMTS 14174	9/15/2022	Pre-BLA Type B meeting
CRMTS 15083	8/30/2023	Written response Type C meeting
CRMTS 15388	12/8/2023	Written response Type D meeting

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

### 3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to the clinical and bioresearch and monitoring (BIMO) reviews.

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

### 5.1 Review Strategy

This review memo is based on the efficacy and safety analyses of the study KIG10\_US3\_PID01, conducted under IND 18648.

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

For the statistical review of the BLA submission the following documents/modules have been referred to:

- Module 1.6 Meetings for IND 18648
- Module 1.14 Labelling
- Module 2.5 Clinical overview
- Module 2.7.3 Summary of Clinical efficacy
- Module 5.2 Tabular Listing of all Clinical Studies

- Module 5.3 Clinical study reports including protocol amendments and Statistical Analysis Plan (SAP) for IND 18648 and related datasets

### 5.3 Table of Studies/Clinical Trials

Type of Study	Study ID	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis of Patients	Treatment Duration	Study Status; Type of Report
Efficacy, Safety and Pharmacokinetics	KIG10_US3_PID01	Module 5.3.5.1	<p><b>Primary objective:</b> to assess the efficacy of Kedrion 10% IGIV in patients with PID by demonstrating the rate of acute serious bacterial infections.</p> <p><b>Safety objective:</b> to assess the safety of Kedrion 10% IGIV in the overall study population from Day 1 to Week 51/52.</p> <p><b>PK objectives:</b></p> <ul style="list-style-type: none"> <li>Assess the distribution, metabolism, and elimination of Kedrion 10% IGIV, total IgG, IgG subclasses, and antigen-specific IgGs at steady state in 20 adult PID patients with different dosing schedules.</li> <li>Evaluate trough concentrations of total IgG and compare to IVIg trough concentrations prior to the study entry.</li> </ul> <p><b>Secondary objectives:</b> to assess the efficacy of Kedrion 10% IGIV in patients with PID in various other efficacy measures.</p>	<p>Phase III, open-label, prospective, single-arm, historically controlled, multicenter study to evaluate the efficacy, safety, and PK of Kedrion 10% IGIV in non-naïve adult patients affected by PID.</p> <p><i>Although not designed to claim efficacy and safety in pediatric patients, children and adolescents were planned to be enrolled to collect preliminary data in this population. However, a sufficient number of evaluable adult patients was reached before any pediatric patients were screened therefore no children and adolescents were enrolled.</i></p>	<p><b>Test Product:</b> Kedrion 10% IGIV intravenous immune globulin</p> <p><b>Dosage Regimen:</b> Patients received an IV infusion of Kedrion 10% IGIV at the same dose and interval as used for their previous IGIV maintenance therapy. Kedrion 10% IGIV was administered every 21 or 28 days, depending on the treatment regimen.</p> <p><b>Rate of First Infusion:</b> Initial rate of 1 mg/kg/minute (0.01 mL/kg/min) for 30 minutes. If well tolerated, the rate of administration was to be increased to a maximum of 8 mg/kg/minute (2 mg/kg/min [0.02 mL/kg/min]; 4 mg/kg/min [0.04 mL/kg/min]; 6 mg/kg/min [0.06 mL/kg/min]; 8 mg/kg/min [0.08 mL/kg/min]) at 30-minute intervals.</p> <p><b>Rate of Subsequent Infusions:</b> Initial rate of 2 mg/kg/minute (0.02 mL/kg/min) for 15 minutes. If well tolerated, the rate of administration was to be increased to a maximum of 8 mg/kg/minute (4 mg/kg/min [0.04 mL/kg/min]; 6 mg/kg/min [0.06 mL/kg/min]; 8 mg/kg/min [0.08 mL/kg/min]) at 15-minute intervals.</p> <p><b>Route of Administration:</b> Intravenous infusion (not mixed with other medications or fluids).</p>	47	Confirmed diagnosis of primary immunodeficiency disease.	The treatment period was 48 weeks.	<p>Study Status: Completed</p> <p>Type of report: CSR Full; Final Analysis.</p>

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Study KIG10\_US3\_PID01

Study Title: A Phase III, Open-label, Prospective, Multicenter Study to Assess Efficacy, Safety and Pharmacokinetics of Kedrion Intravenous Immunoglobulin (IVIg) 10% in PID Patients.

#### 6.1.1 Objectives

The **primary efficacy objective** was to assess the efficacy of QIVIGY in patients with PID by demonstrating the rate of acute serious bacterial infections (SBIs) was less than 1 per person-year from Day 1 to Week 51/52.

The **secondary objectives** were to assess the efficacy of QIVIGY in patients measuring trough total IgG and specific antibody levels, all infections of any kind/seriousness, non-serious infections, time to resolution of infections, antibiotic treatment, hospitalizations due to infection, episodes of fever, days lost from school and/or work due to infections and their treatment, and additional Quality of Life (QoL) measures.

The **safety objective** of the study was to assess the safety of QIVIGY in the overall study population from Day 1 to Week 51/52.

### 6.1.2 Design Overview

This was a phase III, open-label, prospective, single-arm, historically controlled, multicenter study to evaluate the efficacy, safety, and PK of QIVIGY in adult patients with PID.

Enrollment of 2- to 11-year-old pediatric patients was to be delayed until acceptable safety and efficacy of QIVIGY for the PID treatment of adolescents (12 to 17 years) or adults are demonstrated. However, a sufficient number of evaluable adult patients were reached before any pediatric patients were screened, therefore no children and adolescents were enrolled.

The study planned to evaluate at least 40 patients with a confirmed diagnosis of PID. Patients received an IV infusion of QIVIGY (200 to 800 mg/kg) every 21 or 28 days (depending on the treatment regimen determined by their attending physician) for a period of 48 weeks at the study site. The first infusion of QIVIGY marked the beginning of the investigation period and enrollment. Visits were performed every 21 ( $\pm 3$ ) days or 28 ( $\pm 4$ ) days after each infusion until Week 51, or Week 52 (i.e., study termination visit), depending on the patient's treatment schedule.

### 6.1.3 Population

Key inclusion criteria:

- Confirmed clinical diagnosis of a PID which required treatment with IGIV. Documented agammaglobulinemia (defined as the total absence of one or more classes of antibodies) or hypogammaglobulinemia (defined as low levels of one or more classes [i.e., at least 2 standard deviations under the mean level per age]).
- Male or female, aged 2 to 70 years at screening.
- Had received 200 to 800 mg/kg of a commercially available IGIV therapy in a range of 21- or 28-day intervals ( $\pm 3$  days or  $\pm 4$  days, respectively) for at least 3 infusion cycles prior to screening.
- Had at least 2 documented IgG trough levels while receiving an IGIV, of  $\geq 6$  g/L obtained at 2 infusion cycles within 12 months (1 must be within 6 months) prior to Informed consent form (ICF) signature.

Patients with newly diagnosed PID and naïve to IgG replacement therapy were excluded.

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

All eligible patients received an IV infusion of QIVIGY (200 to 800 mg/kg) at the same dose and interval as used for their previous IGIV maintenance therapy. QIVIGY was administered every 21 or 28 days for a period of 48 weeks (depending on the treatment regimen). The first infusion of QIVIGY was based on the patient's baseline weight.

### 6.1.6 Sites and Centers

Eleven sites in the United States (US) each enrolled at least 1 patient.



#### 6.1.7 Surveillance/Monitoring

Patients received infusions for 48 weeks, for a total of 17 or 13 infusions at a frequency of every 21 ( $\pm 3$ ) or 28 ( $\pm 4$ ) days, respectively. The study termination visit occurred at Week 51 or Week 52, respectively. A Patient Diary was given to patients at each infusion visit to record AEs, any medication taken including antibiotic treatment, infections of any type, fever episodes, days of hospitalizations, and days missed from major activities due to infections.

#### 6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was the occurrence of acute SBIs. SBI included bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, and osteomyelitis/septic arthritis.

The study would be considered a success if the upper limit of the 99% one-sided confidence interval (CI) on the mean incidence rate of acute SBI is less than 1.0 episode per person-year. This is consistent with recommendations in FDA's *Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*<sup>1</sup>.

Selected secondary efficacy endpoints were as follows:

1. Incidence rate (i.e., the mean number per person-year) of any infection other than acute serious bacterial infections from day 1 to week 51/52.
2. Duration of any infection other than acute serious bacterial infections from day 1 to week 51/52.
3. Incidence rate (i.e. the mean number per person-year) of fever episodes, from day 1 to week 51/52.
4. Duration of fever episodes, from day 1 to week 51/52.
5. Overall hospitalization days from day 1 to week 51/52.
6. Days of hospitalizations due to infection from day 1 to week 51/52.
7. Incidence rate (i.e. the mean number per person-year) of patients on antibiotics for the treatment of any kind of infection from day 1 to week 51/52.
8. Duration of patients on antibiotics for the treatment of any kind of infection from day 1 to week 51/52.
9. Days of missed work/school/other major activities due to infections from day 1 to week 51/52.
10. 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.

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<sup>1</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-efficacy-and-pharmacokinetic-studies-support-marketing-immune-globulin-intravenous-human>

#### 6.1.9 Statistical Considerations & Statistical Analysis Plan

##### Sample Size determination:

A sample size of at least 40 would achieve a 90% power to reject the null hypothesis of an acute SBI incidence rate of greater than or equal to 1.0 episodes/patient-year by a one-sided test with a Type 1 error rate of 0.01, assuming a true acute SBI rate of 0.49 episodes/person-year. This estimation assumed a Poisson process distribution. The applicant planned to screen about 50 patients to account for dropouts (10%) and screening failures (10%). The applicant also planned to enroll up to 12 pediatric patients out of these 50 patients.

##### Analysis population:

The All Patients Enrolled Set included all patients who have given informed consent/assent to participate in the study.

Both the Full Analysis Set (FAS) and the Safety set (SAF) comprised all patients who have received at least 1 dose of study medication. Primary analysis of the primary endpoint was performed on the FAS.

##### Efficacy analysis:

Primary efficacy was analyzed with a Poisson model using as offset the length of the observation period after the start of treatment per patient (in years). The estimate and one-sided 99% upper confidence limit were reported. Efficacy would be claimed if this limit is less than 1.0 episodes/person-year.

Secondary efficacy endpoints were summarized using descriptive statistics by treatment schedule and overall, unless otherwise specified.

##### Missing data handling:

To handle missing data on the primary efficacy endpoint due to the patient's discontinuation before completing the study, sensitivity analyses of acute SBI will be done by imputing missing data using MI (multiple imputation) under the missing at random (MAR) assumption as well as based on a pattern-mixture model under the missing not at random (MNAR) assumption.

*Reviewer's comment: I will not describe the sensitivity analysis further, as there was no missing data on the primary efficacy endpoint and no imputation was needed.*

#### 6.1.10 Study Population and Disposition

#### 6.1.10.1 Populations Enrolled/Analyzed

Out of 59 screened patients, 47 were eligible and received treatment. These 47 patients were included in the FAS and SAF. A subset of 44 patients were included in the PPS.

*Reviewer's comment: I will report all the results below using FAS, unless otherwise specified.*

##### 6.1.10.1.1 Demographics

Table 2 summarizes the demographics and baseline characteristics for the FAS (N=47): 40 (85.1%) patients were between 18 and 64 years of age and 7 (14.9%) were between 65 and 70 years of age; 30 (63.8%) patients were female, and 17 (36.2%) were male; 45 (95.7%) patients were White, and 44 (93.6%) were not Hispanic or Latino. The median baseline weight for all the patients was 78.7 kg ranging from 37.5 kg to 158.7 kg.

**Table 2: Demographics and Baseline Characteristics (FAS):**

Dosing Interval	21-Day (N=8)	28-Day (N=39)	Overall (N = 47)
<b>Age (years)</b>			
Mean (SD)	50.8 (15.2)	53.0 (12.5)	52.6(12.9)
Median	55.5	56.0	56.0
Min, Max	22, 68	20, 70	20, 70
<b>Age Category, n (%)</b>			
18 to 64 years	7 (87.5)	33 (84.6)	40 (85.1)
65 to 70 years	1 (12.5)	6 (5.4)	7 (14.9)
<b>Sex, n (%)</b>			
Male	1 (12.5)	16 (41.0)	17 (36.2)
Female	7 (87.5)	23 (59.0)	30 (63.8)
<b>Race, n (%)</b>			
White	7 (87.5)	38 (97.4)	45 (95.7)
Other	1 (12.5)	1 (2.6)	2 (4.3)
<b>Ethnicity, n (%)</b>			
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)
<b>Baseline Weight (kg)</b>			
Mean (SD)	84.0 (26.4)	84.0 (23.4)	84.0 (23.6)
Median	78.9	78.7	78.7
Min, Max	48.8, 131.1	37.5, 158.7	37.5, 158.7

<sup>1</sup> Percentages were based on the number of females within each regimen or overall.

Source: Adapted from Original BLA 125822/0; CSR – Table 13 (Section 10.4.1)

#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 3 and Table 4 summarize the baseline disease characteristics and the history of PID, respectively.

**Table 3: Baseline Disease Characteristics**

Dosing Interval	21-Day (N = 8)	28-Day (N = 39)	Overall (N = 47)
Time at 1 <sup>st</sup> infusion from Disease Diagnosis (Months)			
Mean (SD)	126.7 (84.7)	155.1 (127.5)	150.25 (121.0)
Median	114.5	113.1	113.1
Min, Max	30.1, 245.4	2.9, 445.1	2.9, 445.1
Patients Currently Receiving Other Medications for PID, n (%)			
Yes	3 (37.5)	19 (48.7)	22 (46.8)
No	5 (62.5)	20 (51.3)	25 (53.2)
Number of IgG Trough Levels $\geq$ 6 g/L within 12 Months Prior to Enrollment, n (%)			
2	8 (100)	37 (94.9)	45 (95.7)
3	0	2 (5.1)	2 (4.3)
Baseline IgG Levels (g/L)			
Mean (SD)	10.1 (2.3)	10.4 (3.3)	10.3 (3.1)
Median	10.8	9.5	9.9
Min, Max	5.2, 12.2	6.4, 27.4	5.2, 27.4

Source: Adapted from Original BLA 125822/0; CSR – Table 14 (Section 10.4.2)

*Reviewer's Note: The sponsor defined time to diagnosis in the CSR/SAP as ((Date of Screening – Date of diagnosis) +1)/30, but as per define.xml, they calculated it as (1<sup>st</sup> infusion date-diagnosis date)/30.4. Here, I have reported the results based on the definition provided in the define.xml file. The median (min, max) time between screening date and infusion date for all the patients is 0.73 (0.33, 1.2) months.*

**Table 4: Primary Immunodeficiency History (FAS)**

Dosing Interval	21-Day (N = 8) n (%)	28-Day (N = 39) n (%)	Overall (N = 47) n (%)
<b>Patients with Any PID History</b>	<b>8 (100)</b>	<b>39 (100)</b>	<b>47 (100)</b>
<b>Congenital, familial and genetic disorders</b>	4 (50.0)	10 (25.6)	14 (29.8)
Primary immunodeficiency syndrome	4 (50.0)	7 (17.9)	11 (23.4)
Congenital hypogammaglobulinaemia	0	3 (7.7)	3 (6.4)
<b>Immune system disorders</b>	4 (50.0)	30 (76.9)	34 (72.3)
Immunodeficiency common variable	4 (50.0)	30 (76.9)	34 (72.3)
Hypogammaglobulinaemia	0	1 (2.6)	1 (2.1)

Source: Original BLA 125822/0; CSR – Table 15 (Section 10.4.2)

### 6.1.10.1.3 Subject Disposition

Table 5 summarizes patient disposition. Of the 59 patients who signed the ICF, 47 patients (79.7%) were eligible and treated in the study, while the remaining 12 patients (20.3%) were screen failures. No discontinuation occurred during the study, and all 47 enrolled patients completed the study.

**Table 5: Patient Disposition**

Dosing Interval	21-Day n (%)	28-Day n (%)	Overall n (%)
Patients who signed the informed consent.			59
Screen Failures			12 (20.3)
Eligible for the Study			47 (79.7)
Full Analysis Set (FAS)	8	39	47
Safety Set (SAF) <sup>1</sup>	8 (100)	39 (100)	47 (100)
Pharmacokinetic (PK) Evaluation Set <sup>1</sup>	5 (62.5)	18 (46.2)	23 (48.9)
Per-Protocol Set (PPS) <sup>3</sup>	7 (87.5)	37 (94.9)	44 (93.6)
Patients Completed All Study Visits <sup>1</sup>	8 (100)	39 (100)	47 (100)
Patients who Discontinued the Study <sup>1</sup>	0	0	0

<sup>1</sup> Percentages were based on the number of FAS patients within each regimen.

Reviewer's Note: As informed by the BIMO reviewer, two subjects from site no. 12, (b) (6) had incorrect infusion intervals recorded. However, they are included in the FAS and have been used in the efficacy analysis, but these intervals don't affect the results.

Source: adapted from original BLA 125822/0; CSR – Table 10

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint was occurrence of acute SBIs. The primary efficacy analysis for the primary endpoint was conducted separately for the two dosing schedules: 21-day and 28-day dose intervals.

No acute SBIs occurred during the study, yielding an estimate of the incidence rate of 0 SBIs per person-year. The total observation period was 47.0 person-years for the FAS. Table 6 summarizes the observation period and the one-sided 99% upper confidence limits (CL) for the FAS analysis set and the two subgroups by dosing interval. All the CLs are less than 1 SBI/person-year, meeting the study success criterion.

**Table 6: Efficacy results on incidence rate of acute SBI**

Dosing Interval	21-Day N=8	28-Day N=39	Overall N=47
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Total Observation Period (person-years)	7.9	39.1	47.0
One-sided 99% Upper Confidence Limit	0.6	0.2	0.098

Source: Calculated by the reviewer

*Reviewer's comment:* The applicant stated that they used an approximated formula to calculate the upper limit for the overall cohort and the individual cohorts: Upper limit =  $-\ln(\alpha)/N$  ( $N$  = number of patients in FAS) and the result was 0.10. The results for the individual dosing schedule group (21-day and 28-day) appears to be erroneous as  $N$  varies for each dosing schedule cohort. I have presented the corrected values in Table 6.

#### 6.1.11.2 Analyses of Secondary Endpoints

This section covers only efficacy endpoints that have been proposed by the applicant to include in the labeling. Please refer to review of other secondary endpoints by other review discipline, e.g., clinical pharmacology.

Table 7 summarizes the results of the selected secondary efficacy endpoints, related to clinical endpoints, for the two dosing interval cohorts and overall in the FAS dataset.

**Table 7: Results on selected secondary efficacy endpoints**

Dosing Interval	21-Day N=8	28-Day N=39	Overall N=47
<b>Patients with any infections other than acute SBI, n (%)</b>	7 (87.5)	29 (74.4)	36 (76.6)
Total no. of infections other than SBI <sup>1</sup>	35	63	98
Incidence rate of infections per person-year	4.4	1.6	2.1
Duration of infections (days) <sup>3</sup>			
Median	18.0	11.0	12
Min, Max	4, 295	1, 344	1, 344
<b>Patients with any fever episodes, n (%)</b>	0	7 (17.9)	7 (14.9)
Total no. of fever episodes	0	7	7
Incidence rate of fevers per person-year	-	0.2	0.1
Duration of fever (Days)			
Median		2.0	2.0
Min, Max		1, 7	1, 7
<b>Patients hospitalized due to infection</b>	0	0	0

<b>Patients taking any antibiotics to treat infections, n (%)</b>	8 (100.0)	28 (71.8)	36 (76.6)
Total no. of antibiotics episodes <sup>2</sup>	30	83	113
Total duration on antibiotics (Days) <sup>3</sup>			
Median	11.5	10.0	10.0
Min, Max	2, 28	1, 334	1, 334
<b>Patients who lost time to School/Work due to Infections and their Treatment</b>	3	6	9
Total Days of Missed School/Work due to Infections and their Treatment			
Median	19.0	4.5	6.0
Min, Max	4, 53	1, 8	1, 53

Source: Adapted from Original BLA 125822/0; CSR – Table 22-28 (Section 11.1.3)

Reviewer's note:

1. The total number of infections, incidence rate and its duration differ from the results reported in the CSR as the applicant a revised table including 4 new infection records in an amendment IR dated 08/04/2025.
2. Every instance of an antibiotic episode for each patient have been counted separately.
3. Overall, 8 patients had infections other than SBI for which the infection resolution date was not documented and 6 patients had records of taking antibiotic with without a recorded treatment completion date.

### 6.1.11.3 Subpopulation Analyses

The results for the primary efficacy subgrouped by age, sex and race are provided in Table 8.

**Table 8: Incidence rate of acute SBI by subgroups**

	<b>21-Day N=8</b>	<b>21-Day N=8</b>	<b>28-Day N=39</b>	<b>28-Day N=39</b>	<b>Overall N=47</b>	<b>Overall N=47</b>
<b>Age Category (years)</b>	<b>18-64</b>	<b>65-70</b>	<b>18-64</b>	<b>65-70</b>	<b>18-64</b>	<b>65-70</b>
n	7	1	33	6	40	7
Total Observation Period (years)	6.9	0.98	33.1	6.01	40	6.99
1-sided 99% Upper Confidence Limit	0.667	4.7	0.139	0.766	0.115	0.659
<b>Sex</b>	<b>Female</b>	<b>Male</b>	<b>Female</b>	<b>Male</b>	<b>Female</b>	<b>Male</b>
n	7	1	23	16	30	17
Total Observation Period (years)	6.9	0.98	23.1	16	30	16.9
1-sided 99% Upper Confidence Limit	0.667	4.7	0.199	0.289	0.153	0.272
<b>Race</b>	<b>White</b>	<b>Other</b>	<b>White</b>	<b>Other</b>	<b>White</b>	<b>Other</b>
n	7	1	38	1	45	2
Total Observation Period (years)	6.9	0.98	38.1	0.99	45	1.97

1-sided 99% Upper Confidence Limit	0.667	4.7	0.121	4.65	0.102	2.34
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Source: Calculated by the reviewer

*Reviewer's comment: As no acute SBIs occurred, subgroup analyses by age, sex, and race which were to be performed according to the SAP, were not carried out by the applicant.*

#### 6.1.11.4 Dropouts and/or Discontinuations

There was no dropout/discontinuation in the study. Because all patients completed the study, sensitivity analyses using multiple imputation methods were not performed.

#### 6.1.11.5 Exploratory and Post Hoc Analyses

Primary Antibody Deficiency Quality of Life (PADQOL)-16 questionnaire is a disease-specific Health-Related Quality of Life (HR-QoL) instrument for adult patients with PID which measures the patient's self-perceived symptoms of immunodeficiency and well-being that are caused by, or related to, their treatment modalities. Lower values of score indicated an improvement in QoL, considering a total score range from 0 to 32. With 46 patients completing the questionnaire, for the overall study population quality of life was improved during the study, with a decrease in the mean total score from baseline to study termination visit, from 7.4 to 6.9.

*Reviewer's comment: Performing a paired comparison between the PADQOL scores between baseline visit and Study termination visit, the 95% CI is [-1.6, 2.7]. The QoL parameter in a single arm study limits the ability to draw clinically meaningful conclusions. Therefore, I recommended removing the results for the QoL from the labeling.*

#### 6.1.12 Safety Analyses

##### 6.1.12.3 Deaths

No deaths occurred during the study.

##### 6.1.12.4 Nonfatal Serious Adverse Events

Four patients reported five serious Treatment-emergent adverse events (TEAE) that required or prolonged hospitalization. One patient on the 21-day dosing schedule had severe depression. The other three patients on the 28-day dosing schedule experienced the following events: one patient had both moderate hypotension and hyperglycemia, while the other two patients each experienced moderate acute cholecystitis and severe osteoarthritis, respectively. The applicant stated that "All were assessed as not related to the study drug."

##### 6.1.12.7 Dropouts and/or Discontinuations

No dropouts or early study discontinuations occurred in the study.



## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

This original Biologics License Application (BLA STN 125822/0) was submitted for QIVIGY, an immune globulin intravenous (Human) 10% solution, for the proposed indication of treatment of adults with primary humoral immunodeficiency (PI). The efficacy and safety databases consist of data on 47 patients treated in Study KIG10\_US3\_PID01, a phase 3, open-label, prospective, multicenter study to assess efficacy, safety, and pharmacokinetics of QIVIGY in PI patients.

The primary efficacy endpoint was the occurrence of acute SBIs. The primary efficacy analysis for the primary endpoint was conducted separately for the two dosing schedules. No acute SBIs occurred during the study, yielding an estimate of the incidence rate of at 0 SBIs per person-year. The associated upper bound of the one-sided 99% confidence interval was  $<1$ , meeting the study success criterion. Study results on secondary efficacy endpoints further supported efficacy of QIVIGY, reflected in incidence of infections, days missed from work/school, and hospitalizations.

No deaths occurred during the study.

### 10.2 Conclusions and Recommendations

There were no major statistical issues related to this submission. I have verified all the primary results and reported them in my review. The efficacy results of the study KIG10\_US3\_PID01 supports approval of the product QIVIGY to be used in patients with PID. I therefore recommend approval of this BLA.