Statistical Analysis Plan

Sponsor Name: Kedrion S.p.A.

Protocol Number: KIG10_US3_PID01
Protocol Title: A Phase III, Open-label, Prospective, Multicenter Study to Assess Efficacy, Safety and Pharmacokinetics of Kedrion Intravenous Immunoglobulin (IVIg) 10% in Primary Immunodeficiency Disease (PID) Patients

Protocol Version and Date: Version 1, 19-Sep-2018
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Authors: PPD

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	19-Oct-2018	PPD	Initial Release Version
2.0	24-Jan-2019	PPD	In section 4.2, the criteria in third secondary efficacy endpoint "Frequency of patients with total IgG below 5 g/L criteria", changed from 5 g/L to 6 g/L. The change is also made in the corresponding endpoint analysis section 8.2.1 Hematology, chemistry and urinalysis will be performed at the central lab and clarified such in section 10.4 The day of study termination is renamed as duration of study in section 6.2.7. Added clarification for the subgroup analyses for the primary and secondary efficacy endpoints.
3.0	27-May-2019	PPD	Definition of fever as body temperature >38°C (>100.4°F) given in section 6.2.15 is changed to body temperature ≥38°C (≥100.4°F). Urobilinogen testing will not performed, as a result this test is removed from the urinalysis given in section 10.4. Removed the lists of tables, listings and figures given in sections 14, 15 and 16, and the readers are requested to refer to the table, listing and figure shells instead.

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
4.0	15-Sep-2020	PPD	In Section 5.6, clarifications on major protocol deviations are added. Changes based on Protocol amendment from Version 2 to Version 3 are made in Section 3.4, 3.5.1, 3.5.2, and Table 1.1 and Table 1.2. PK paramenter Vd is added in Section 9.2.3. Handling of below limit of quantification (BLQ) or above upper limit of quantification (ULOQ) are modified in Sections 9.4.1 and 9.4.2. Study Day Definition is updated in Section 6.2.19. Following changes are made to address FDA comments: • Subgroup analysis by sex, race for primary efficacy endpoint are added in Section 6.6. • Relative change from Baseline is added in Sections 8.2.1 - 8.2.6, and 10.4-10.6. • The estimate and 1-sided 99% upper confidence limit using Poisson model are added for the secondary endpoints in Section 8.2.7, 8.2.8 and 8.2.10. • Process for programming the primary efficacy endpoint dataset based on adverse event data is added in Section 8.1.2. • Multiple imputation method to impute the missing data on the primary efficacy endpoint due to the subjects who discontinued from study, and sensitivity analyses of primary efficacy endpoint with imputed data are added in Section 8.1.4.5.

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

PPD Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
PPD Pharmacokineticist	Signature	Date (DD-Mmm-YYYY)
PPD Senior Reviewing Biostatistician	Signature	Date (DD-Mmm-YYYY)

Kedrion S.p.A. Approval

PPD , PPD Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

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1. Glossary of Abbreviations

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
AIC	Akaike's information criterion
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
$AUC_{(0\text{-}inf)}$	Area under the concentration-time curve from time zero extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the plasma concentration vs. time curve from time 0 to the time t of the last quantifiable concentration
AUC_{tau}	Area under the concentration-time curve calculated from start to end of the dosing interval
BLQ	Below Limit of Quantification
BMI	Body Mass index
C_{avg}	Average concentration
CI	Confidence Interval
CL_{ss}	Steady-state clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
Ig(s)	Immunoglobulin(s)
IVIg	Intravenous Immunoglobulin

Abbreviation	Description
K_{el}	Elimination constant
KIg10	Kedrion intravenous immunoglobulin 10%
Λz (lambda z)	Terminal elimination rate constant
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MSB	Between-groups mean squares
MSW	Within-groups mean squares
MI	Multiple Imputation
MAR	Missing at Random
MNAR	Missing Not at Random
N/A	Not Applicable
NA	Not Applicable
CCI	
PedsQL™	Pediatric Quality of Life Inventory™
PID(s)	Primary immunodeficiency disease(s)
PK	Pharmacokinetic(s)
PPS	Per-Protocol Set
PT	Preferred Term
QC	Quality Control
QoL	Quality of Life
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event

Abbreviation	Description
TLF	Table, Listing and Figure
$t_{1/2}$	Terminal elimination half-life
t_{max}	Time to reach maximum concentration
ULOQ	Upper Limit of Quantification
V_d	Volume of Distribution (compartmental)
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

An interim pharmacokinetic (PK) analysis is planned after at least CCI patients with complete intense PK sampling before and after infusion 5 for 28 days schedule or infusion 7 for 21 days schedule. An interim PK report will be produced by the study PK scientist.

The primary analysis of safety and efficacy and pharmacokinetics is planned after all patients complete the final study visit or terminate early from the study.

An independent Data and Safety Monitoring Board (DSMB) will review the full documentation for specific AEs and determine whether they meet the criteria for acute serious bacterial infections (as described in protocol Section 8.1.1, Serious Bacterial Infections), defining the study's primary endpoint. Furthermore, DSMB will be asked to review safety and efficacy data (in terms of IgG trough levels) on at least CCI adolescent or adult patients with CCI infusions (i.e. CCI months of exposure). After a positive evaluation, Kedrion intends to continue studying the efficacy and safety of KIg10 in the young age group of PID patients (children < CCI years of age). DSMB will also review data that are indicative of intravascular hemolysis.

The timing and content of the DSMB reviews will be described in the DSMB charter.

3. Study Objectives

3.1. Primary Objective

3.1.1. Primary Efficacy Objective

To assess the efficacy of KIg10 administered to patients with PID to demonstrate that the rate of acute serious bacterial infections (i.e., the mean number of acute serious bacterial infections per patient-year) is less than 1.0 to provide substantial evidence of efficacy from day 1 to week 51/52.

3.1.2. Safety Objective

To assess the safety of KIg10 in the overall study population from day 1 to week 51/52.

3.1.3. Pharmacokinetic Objectives

To assess the distribution, metabolism, and elimination of KIg10, total IgG, IgG subclasses, and antigen-specific IgGs at steady state in 20 adult PID patients with different dosing schedules.

To evaluate trough concentrations of total IgG and compare to IVIg trough concentrations prior to the study entry.

3.2. Secondary Objective(s)

To assess the efficacy of KIg10 administered to patients with PID as measured by:

1. IgG trough levels before each infusion and at the study termination visit (week 51/52).
2. IgG subclasses levels (IgG1, IgG2, IgG3, IgG4) before infusions 1, 5, 9, and 13 for the 28-day infusion schedule and at infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
3. Anti-tetanus toxoid, anti-pneumococcal capsular polysaccharide, anti-Haemophilus influenza, and anti-measles antibodies levels before infusions 1, 5, 9, and 13 for the 28-day infusion schedule and before infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
4. Occurrence and duration of any infection other than acute serious bacterial infections, from day 1 to week 51/52.
5. Occurrence and length of fever episodes, from day 1 to week 51/52.
6. Occurrence and duration of overall hospitalization, from day 1 to week 51/52
7. Occurrence and duration of hospitalization due to infection, from day 1 to week 51/52.
8. Occurrence and duration of patients on antibiotics for the treatment of any kind of infections, from day 1 to week 51/52.
9. The missed days of work/school/other major activities due to infections, from day 1 to week 51/52.
10. Quality of life using the PedsQL™ questionnaires collected at baseline, at 24 weeks (infusion 7 for the 28-day schedule and infusion 9 for the 21-day schedule), and at the study termination visit.

CCI [redacted]

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3.4. Brief Description

This is a phase III, open-label, prospective, single arm, historically controlled, multicenter study to evaluate efficacy, safety, and PK of KIg10 in patients, aged 2 to 70 years at the time of screening, and affected by PID.

Enrollment of the 2 to 11 year old pediatric patients will be delayed until acceptable safety and efficacy of KIg10 for the PID treatment of adolescents (12 to 17 years) or adults are demonstrated.

All patients will receive an intravenous infusion of KIg10 every 21 days 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 KIg10 will mark the beginning of the investigation period and enrollment.

Visits will be performed every 21 (±3) days or 28 (±4) days after each infusion until week 51, or 52 (i.e., study termination visit), depending on the patient's treatment schedule (please refer to the table below).

Procedure **28-day regimen** **(21-day regimen in parentheses)**	**Timing**	**Comments**
Screening	Day -28 to day 0 (Day -21 to day 0)	up to 3/4 weeks prior to the first infusion
Infusion 1	Week 1, Day 1 Baseline	Enrollment
Infusion 2-4 (Infusion 2-4)	Week 4 to 12 (Week 3 to 9)	
PK Assessment	Infusion 5, Week 16 (Infusion 7, Week 18)	For PK Evaluation Set only
Infusion 6 to 13 (Infusion 6 to 17)	Week 20 to 48 (Week 15 to 48)	
Study termination visit: 28 days after last infusion (21 days after last infusion)	Week 52 (Week 51)	Up to 4 weeks after the last study infusion

3.5. Patient Selection

3.5.1. Inclusion Criteria

1. Written informed consent/assent obtained from patients/patients' parent(s) or legally acceptable representative indicating that they understand the purpose of and procedures required for the study and are willing to participate in it.
2. Confirmed clinical diagnosis of a PID as defined by 2017 International Union of Immunological Societies (IUIS) Phenotypic Classification for Primary Immunodeficiencies (Bousfiha A, 2018) and requiring treatment with IVIg. 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 [ie, at least 2 standard deviations under the mean level per age]).
3. Male or female, ages 2 to 70 years at screening.
4. Received 200 to 800 mg/kg of a commercially available IVIg therapy

   in the range of 21- or 28-day intervals (±3 days or ±4 days, respectively) for at least 3 infusion cycles prior to screening.

   (NOTE: Other IVIgs will be prohibited after ICF signature and until study end, week 51/52).
5. At least 2 documented IgG trough levels while receiving an IVIg, of ≥ 6 g/L obtained at 2 infusion cycles within 12 months (1 must be within 6 months) prior to ICF signature.
6. Patient (and parent/guardian where applicable) is willing to comply with all requirements of the protocol.
7. Females of child-bearing potential with a negative urine pregnancy test and who agree to employ adequate birth control measures during the study.
8. Authorization to access personal health information.
9. Patients previously participating in a clinical trial with another experimental IVIg may be enrolled if they have received stable commercially available IVIg therapy for at least 3 infusion cycles (21 or 28 days) prior to screening.
10. Patients currently on treatment with any subcutaneous immunoglobulin (SCIG) can be enrolled if they are switched to stable commercially available IVIg therapy at least 3 infusion cycles (21 or 28 days) prior to screening.

3.5.2. Exclusion Criteria

1. Newly diagnosed PID and naïve to IgG replacement therapy.
2. Dysgammaglobulinemia (defined as a deficiency in one or more classes of antibodies, but not severe enough to require substitutive therapy) or isolated IgG subclass deficiency, or profound primary T-cell deficiency (defined as the absence or severe reduction of T lymphocytes [CD3+ <300 cell/mm^3] and an absent or particularly low proliferative response [10% of the lower normal range] to phytohaemagglutinin P [PHA]).
3. History of severe or serious reactions or hypersensitivity to IVIg or other injectable forms of IgG.
4. History of thrombotic events including deep vein thrombosis, cerebrovascular accident, pulmonary embolism, transient ischemic attacks, or myocardial infarction, as defined by at least 1 event in patient's lifetime.
5. IgA deficiency with documented antibodies to IgA.
6. Received blood products that have not undergone viral inactivation measures within 12 months prior to ICF signature..
7. Significant protein losing enteropathy, nephrotic syndrome, or lymphangiectasia.
8. An acute infection as documented by culture or diagnostic imaging and/or a body temperature ≥ 38°C (≥ 100.4°F) within 7 days prior to screening.

9. Acquired immunodeficiency syndrome (AIDS) and/or hepatitis B/C active disease at at ICF signature .
10. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times of the upper limit of normal for the laboratory designated for the study.
11. Using an implanted venous access device.
12. Profound anemia (hemoglobin < 10 g/dL) or persistent severe neutropenia (≤ 1000 neutrophils per mm^3) or lymphopenia of less than 500 cells per microliter.
13. A severe chronic condition such as renal failure (creatinine concentration > 2.0 times the upper limit of normal) with proteinuria, congestive heart failure (New York Heart Association III/IV), cardiomyopathy, cardiac arrhythmia associated with thromboembolic events (e.g., atrial fibrillation), unstable or advanced ischemic heart disease, hyperviscosity, or any other condition that the Investigator believes is likely to interfere with evaluation of the study drug or with satisfactory conduct of the trial. * normal values for serum creatinine are the following: a) Female (18+ years): 45 - 84 µmol/L or 0.51 - 0.95 mg/dl; b) Male (18+ years): 59 - 103 µmol/L or 0.67 - 1.17 mg/dl
14. History of a malignant disease other than properly treated carcinoma in situ of the cervix or basal cell or squamous cell carcinoma of the skin within 24 months ICF signature .
15. History of pharmacoresistant epilepsy or multiple episodes of migraine (defined as at least 1 episode within 6 months of ICF signature) not completely controlled by medication.
16. Patient must not be receiving the following medication:

    a) Steroids, oral or parenteral, at a daily dose of ≥ 0.15 mg/kg/day of prednisone or equivalent).

    b) Other immunosuppressive drugs (including monoclonal antibodies) or chemotherapy.
17. Females who are pregnant, breast feeding or planning a pregnancy during the course of the study. Women who become pregnant during the study will be withdrawn from the study.
18. Participated in another clinical study within 3 weeks prior to study ICF signature.
19. Active drug or alcohol abuse or history of drug or alcohol abuse within the 6 months before screening.
20. Employed or a direct relative of an employee of the CRO, the study site, or the Sponsor.
21. Previously treated under this protocol.
22. Unable to provide informed consent or provide informed consent by a legally authorized representative.

3.6. Determination of Sample Size

A sample size of at least 40 evaluable patients is considered a sufficient number to evaluate the primary study endpoint according to the relevant FDA (1) and EMA (2) guidelines. A sample size of 40 achieves 90% power to reject the null hypothesis of an acute serious bacterial infection incidence rate greater or equal to 1.0 by means of a 1-sided test and a Type 1 error of 0.01 assuming a true underlying rate of acute serious bacterial infections of 0.49 per year (assuming a Poisson process). CCI [redacted] Thus, about 50 patients are planned to be screened to account for drop outs (10%) and screening failures (10%).

Within the planned CCI patients, up to CCI pediatric patients will be enrolled in order to collect preliminary evidence in this population.

The enrollment of 2 to 11 year old patients will be delayed until the efficacy (in terms of IgG trough levels) and the safety of the product have been demonstrated in at least 10 adolescent (≥ 12 years) or adult patients with at least 3 infusions (i.e., 3 months of exposure).

Approximately CCI adults of the CCI patients will have a PK profile analyzed before and after the 5th study infusion (28-day infusion schedule) or 7th infusion (21-day infusion schedule) to ensure data collection from at least 20 evaluable adult patients.

3.7. Treatment Assignment & Blinding

All patients will receive an intravenous infusion of KIg10 at the same dose and interval as used for their previous IVIg maintenance therapy. KIg10 will be administered every 21 or 28 days for a period of 48 weeks (depending on the treatment regimen determined by their attending physician).

The study is open label. No blinding and randomization procedures will be applied.

3.8. Administration of Study Medication

Before administration, the solution must be allowed to reach room temperature. The average time to reach room temperature after storage at CCI °C is approximately CCI hours. Once a vial has been opened under aseptic conditions the product must be used within the same day.

The study drug will be administered intravenously. Prior to infusion of KIg10, the Investigator or his/her delegate must ensure that the patient is adequately hydrated.

The bottle should not be shaken because excessive shaking will cause foaming (existing foam does not prevent use as foam will stay in the bottle). The product should be visually inspected for particulate matter, turbidity and discoloration, prior to administration. Products which are not clear or have sediment must not be used. A slight yellow discoloration is not of concern.

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Infusion rate

- First infusion: infusion will proceed at an initial rate of 1 mg/kg/minute (0.01 mL/kg/min) for 30 minutes. If well tolerated, the rate of administration may be increased to a maximum of 8 mg/kg/minute (2mg/kg/min - 0.02mL/kg/min; 4mg/kg/min – 0.04mL/kg/min; 6mg/kg/min - 0.06 mL/kg/min; 8mg/kg/min – 0.08 mL/kg/min) at 30 minute intervals.
- Subsequent infusions: infusions will proceed at an initial rate of 2 mg/kg/minute (0.02 mL/kg/min) for 15 minutes. If well tolerated, the rate of administration may be increased to a maximum of 8 mg/kg/minute (4mg/kg/min – 0.04mL/kg/min; 6mg/kg/min - 0.06 mL/kg/min; 8mg/kg/min 0.08 mL/kg/min) at 15 minute intervals.

If an AE occurs, either the rate of administration must be reduced to the previous step or the infusion stopped. The treatment required depends on the nature and severity of the AE.

Patients should be monitored for pulmonary adverse reactions during the infusion since there have been reports of thrombotic events and non-cardiogenic pulmonary edema (Transfusion-Related Acute Lung

Injury [TRALI]) in patients administered IVIg products. If TRALI is suspected, appropriate tests will be performed for the presence of anti-neutrophil antibodies in both the product and the patient serum.

Patients may be treated with different lots of KIg10 over the course of the 48 week treatment period. Different lots may not be mixed for a single infusion.

3.9. Study Procedures and Flowchart

Table 1.1: Time and Events Table for 28-day Infusion Schedule

Study Week		1 (Day 1)	4	8	12	16	20	24	28	32	36	40	44	48	52
Visit Number	Screening	Baseline Visit 1	Treatment Visits												Study Termination Visit
			2	3	4	5	6	7	8	9	10	11	12	13	
Visit Window (Days)	-28 to 0	n/a	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	± 4	±4	±4
Infusion Number		1	2	3	4	5	6	7	8	9	10	11	12	13	
STUDY EVENT															
Study Treatment															
IVIg infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	
Screening and safety															
Informed Consent[1]	X														
Medical History	X														
Demography	X														
Physical examination[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intravascular hemolysis testing[4]	X	X				X									X
Chest X-ray[5]	X														
Urinalysis[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X														

Study Week		1 (Day 1)	4	8	12	16	20	24	28	32	36	40	44	48	52
Visit Number	Screening	Baseline Visit 1	Treatment Visits												Study Termination Visit
			2	3	4	5	6	7	8	9	10	11	12	13	
Visit Window (Days)	-28 to 0	n/a	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	± 4	±4	±4
Infusion Number		1	2	3	4	5	6	7	8	9	10	11	12	13	
STUDY EVENT															
Exclusion/Inclusion Criteria	X														
Retention sample blood drawn[6]	X														X
Patient Diary reviewed and data collected[7]			X	X	X	X	X	X	X	X	X	X	X	X	X
Assess any AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy															
Assess serious bacterial infections		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fever episodes[8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations		X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgG levels[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgG subclasses levels (Pre-infusion)		X				X				X				X	
Ab anti-measles and specific antibodies[9] levels (Pre-infusion)		X				X				X				X	

Study Week		1 (Day 1)	4	8	12	16	20	24	28	32	36	40	44	48	52
Visit Number	Screening	Baseline Visit 1	Treatment Visits												Study Termination Visit
			2	3	4	5	6	7	8	9	10	11	12	13	
Visit Window (Days)	-28 to 0	n/a	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	± 4	±4	±4
Infusion Number		1	2	3	4	5	6	7	8	9	10	11	12	13	
STUDY EVENT															
PK parameters of total IgG and specific antibodies[9] (Pre and post infusion)						X									
Quality of life questionnaires[10]		X						X							X
Health care utilization		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient satisfaction questionnaire[11]								X							
Study completion procedures															
Study termination[12]															X

Abbreviations: Ab=antibody; AE=adverse events; IgG=immunoglobulin G; n/a = not applicable; CCI [redacted]; PedsQL™ = Pediatric Quality of Life Inventory; PK=pharmacokinetic(s).

1. Confirm consent and assent is obtained and the form(s) signed prior to any procedures.
2. Measure body weight at every visit for patients < 18 years of age. For adults (≥ 18 years of age), measure body weight every at screening, baseline and weeks 12, 24, 36, and 48.
3. To be collected pre-infusion at all infusion visits.
4. Perform direct Coombs and tests for intravascular hemolysis (serum haptoglobin, plasma free hemoglobin, urine hemosiderin) post-infusion at all infusion visits.
5. If baseline X-ray within last 6 months is not available.
6. Two mL serum (approximately 4 mL of blood).
7. Reminder phone calls will be performed on day 2 or 3 after each scheduled in fusion to remind the patient/parent(s)/legal guardian(s) about completion of the Patient Diary. The call follows the reminder telephone script provided to the site, and is not intended to be an interview for collection of safety data.
8. Fever will be defined as any temperature ≥ 38°C (≥ 100.4°F).
9. Specific antibodies refer to anti-tetanus toxoid, anti-pneumococcal polysaccharide and anti-haemophilus influenza.
10. Quality of life questionnaires will include PedsQL™, and CCI [redacted].
11. The patient satisfaction questionnaire is provided in Appendix A to the protocol.

12. When a patient is withdrawn from treatment or withdraws from the study early, the Investigator will notify the Sponsor and, when possible, will perform the procedures as specified for the study termination visit.

Table 1.2: Time and Events Table for 21-day Infusion Schedule

Study Week		**1 (Day 1)**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**51**
			Treatment Visits																
Visit Number	**Screening**	**Baseline Visit 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Study Termination Visit**
Visit Window (Days)	**-21 to 0**	**n/a**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Infusion Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
STUDY EVENT																			
Study Treatment																			
IVIg infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Screening and safety																			
Informed Consent [1]	X																		
Medical History	X																		
Demography	X																		
Physical Examination[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intravascular hemolysis testing[4]	X	X						X											X
Chest X-ray[5]	X																		
Urinalysis[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Week		**1 (Day 1)**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**51**
			Treatment Visits																
Visit Number	**Screening**	**Baseline Visit 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Study Termination Visit**
Visit Window (Days)	**-21 to 0**	**n/a**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Infusion Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
STUDY EVENT																			
Pregnancy Test	X																		
Exclusion/Inclusion Criteria	X																		
Retention sample blood drawn[6]	X																		X
Patient Diary reviewed and data collected[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess any AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy																			
Assess serious bacterial infections		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fever episodes[8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgG levels[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Week		**1 (Day 1)**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**51**
			Treatment Visits																
Visit Number	**Screening**	**Baseline Visit 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Study Termination Visit**
Visit Window (Days)	**-21 to 0**	**n/a**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Infusion Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
STUDY EVENT																			
IgG subclasses (Pre-infusion)		X						X				X						X	
Ab anti-measles and specific antibodies (Pre-infusion)[9]		X						X				X						X	
PK parameters of total IgG and specific antibodies (Pre and post-infusion)[9]								X											
Quality of life questionnaires[10]		X								X									X
Healthcare utilization		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient satisfaction questionnaire[11]										X									
Study completion procedures																			
Study termination[12]																			X

Abbreviations: Ab=antibody; AE=adverse events; IgG=immunoglobulin G; n/a = not applicable; CCI ; PedsQL™ = Pediatric Quality of Life Inventory; PK=pharmacokinetic(s).

1. Confirm consent and assent is obtained and the form(s) signed prior to any procedures.
2. Measure body weight at every visit for patients < 18 years of age. For adults (≥ 18 years of age), measure body weight at screening, baseline and weeks 12, 24, 36, and 48.
3. To be collected pre-infusion at all infusion visits.
4. Perform direct Coombs and tests for intravascular hemolysis (serum haptoglobin, plasma free hemoglobin, urine hemosiderin) post-infusion at all infusion visits.
5. If baseline X-ray within last 6 months is not available.
6. Two mL serum (approximately 4 mL of blood).
7. Reminder phone calls will be performed on day 2 or 3 after each scheduled in fusion to remind the patient/parent(s)/legal guardian(s) about completion of the Patient Diary. The call follows the reminder telephone script provided to the site, and is not intended to be an interview for collection of safety data.
8. Fever will be defined as any temperature ≥ 38°C (≥ 100.4°F).
9. Specific antibodies refer to anti-tetanus toxoid, anti-pneumococcal polysaccharide and anti-haemophilus influenza.
10. Quality of life questionnaires will include PedsQL™, and CCI .
11. The patient satisfaction questionnaire is provided in Appendix A to the protocol.
12. When a patient is withdrawn from treatment or withdraws from the study early, the Investigator will notify the Sponsor and, when possible, will perform the procedures as specified for the study termination visit.

4. Endpoints

4.1. Primary Efficacy Endpoint

Incidence rate (i.e., the mean number of acute serious bacterial infections per patient-year) of acute serious bacterial infections (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) according to FDA (1) and EMA (2) guidelines and the criteria described in the relevant FDA (1) guidance.

4.2. Secondary Efficacy Endpoints

1. Serum IgG trough levels before each infusion of KIg10 and at the study termination visit (week 51/52).

2. IgG subclasses levels (IgG1, IgG2, IgG3, IgG4) before infusions 1, 5, 9 and 13 for the 28-day infusion schedule, and before infusions 1, 7, 11 and 17 for the 21-day infusion schedule.

3. Frequency of patients with total IgG below 6 g/L criteria.

4. Anti-tetanus toxoid antibody level (quantitative assay) before infusions 1, 5, 9 and 13 for the 28-day infusion schedule and before infusions 1, 7, 11 and 17 for the 21-day infusion schedule.

5. Anti-pneumococcal capsular polysaccharide antibody level (quantitative assay) before infusions 1, 5, 9 and 13 for the 28-day infusion schedule and before infusions 1, 7, 11 and 17 for the 21-day infusion schedule.

6. Anti-measles antibody level (quantitative assay) before infusions 1, 5, 9 and 13 for the 28-day infusion schedule and before infusions 1, 7, 11 and 17 for the 21-day infusion schedule.

7. Anti-Hemophilus influenza type b antibody level (quantitative assay) before infusions 1, 5, 9 and 13 for the 28-day infusion schedule and before infusions 1, 7, 11 and 17 for the 21-day infusion schedule.

8. Incidence rate (i.e., the mean number per patient-year) of any infection other than acute serious bacterial infections from day 1 to week 51/52.

9. Duration of any infection other than acute serious bacterial infections from day 1 to week 51/52.

10. Incidence rate (i.e. the mean number per patient-year) of fever episodes, from day 1 to week 51/52.

11. Duration of fever episodes, from day 1 to week 51/52.

12. Overall hospitalization days from day 1 to week 51/52.

13. Days of hospitalizations due to infection from day 1 to week 51/52.

14. Incidence rate (i.e. the mean number per patient-year) of patients on antibiotics for the treatment of any kind of infection from day 1 to week 51/52.

15. Duration of patients on antibiotics for the treatment of any kind of infection from day 1 to week 51/52.

16. Days of missed work/school/other major activities due to infections from day 1 to week 51/52.

17. 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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4.4. Pharmacokinetic Endpoints

The following PK endpoints will be derived for the PK Evaluation Set only.

1. Serum total IgG levels, IgG subclasses levels and selected specific antibody levels before and after the 5th infusion (28-day infusion schedule) or 7th infusion (21-day infusion schedule).

2. PK parameters of total IgG before and after the 5th infusion (28-day infusion schedule) or 7th infusion (21-day infusion schedule).

3. PK parameters of specific IgG antibodies before and after the 5th infusion (28-day infusion schedule) or 7th infusion (21-day infusion schedule).

   a. Anti-haemophilus influenza type b

   b. Anti-tetanus toxoid

   c. Anti-pneumococcal capsular polysaccharide

4. Plasma concentration-time curve, C_{max}, T_{max}, AUC_{0-t}, other parameters such as steady state parameters AUC_{tau}, average concentration of drug over the dosing interval (C_{ave}), and steady state clearance (CL_{ss}) may also be derived. Elimination parameters such as elimination rate constant, elimination half-life. AUC_{0-inf}, volume of distribution will be derived if data allow based on PK acceptance criteria.

5. Exploratory correlation analysis between health outcomes and PK parameters or trough concentrations may be included in the analysis.

4.5. Safety Endpoints

1. Number of AEs (%) and proportion of patients experiencing at least 1 AE.

2. Number of SAEs (%) and proportion of patients experiencing at least 1 SAE.

3. Number of related infusion AEs (%) occurring during infusion or within 1, 24, and 72 hours after the end of infusion and proportion of patients experiencing at least 1 of such related infusion AE.

4. The proportion and number of KIg10 infusions for which the infusion rate is decreased due to AEs.

5. Number and proportion of infusions with 1 or more infusion (temporally-associated) AE.

6. Changes in vital signs, physical examinations, and safety laboratory tests (hematology, serum chemistry and urinalysis).

7. The proportion and number of patients with a positive Coomb's test following the 5th infusion for the 28-day infusion schedule and the 7th infusion for the 21-day infusion schedule.

8. The proportion and number of patients with a positive urine hemosiderin test following the 5th infusion for the 28-day infusion schedule and the 7th infusion for the 21-day infusion schedule.

9. Plasma-free hemoglobin level following the 5th infusion for the 28-day infusion schedule and the 7th infusion for the 21-day infusion schedule.

10. Serum haptoglobin level following the 5th infusion for the 28-day infusion schedule and the 7th infusion for the 21-day infusion schedule.

5. Analysis Sets

5.1. All Patients Enrolled Set

The All Patients Enrolled Set will include all patients who have given informed consent/assent to this study. Unless specified otherwise, this set will be used for patient listings and for summaries of patient disposition.

5.2. Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who have received at least 1 dose of study medication.

5.3. Safety Set

The Safety Set (SAF) comprises all patients who have received at least 1 dose of study medication. In this study, the SAF and FAS are coincident as no randomization occurred.

5.4. Pharmacokinetic (PK) Evaluation Set

The PK Evaluation Set includes all adult patients that consent to this part of the protocol and who have PK analysis performed at the 5th infusion (28-day infusion schedule) or the 7th infusion (21-day infusion schedule). The population includes all patients following the principles of the SAF for whom at least 1 concentration of total IgGs, IgG subclasses 1-4, or IgG specific antibody levels (anti-haemophilus influenza type b, anti-tetanus toxoid, anti-pneumococcal capsular polysaccharide), measured in the dense sampling period (i.e., before and after the 5th infusion of the 28-day infusion schedule and before and after the 7th infusion for the 21-day infusion schedule).

PK concentrations are listed for all patients in the PK Evaluation Set.

5.5. Per-protocol Set

The Per-protocol Set (PPS) includes all patients who are compliant with the study protocol without any major protocol deviations that could affect efficacy. An analysis based on the PPS will be performed for the primary efficacy endpoint as an additional supportive analysis.

5.6. Protocol Deviations

Deviations from the protocol will be defined in advance and documented on an ongoing basis during conduct of the clinical study based on monitoring reports (e.g., failure of eligibility criteria), data management checks, medical review and statistical programming (e.g., prohibited medications based on drug codes) and stored in the clinical study database.

Patients with major protocol deviations that affect efficacy will be excluded from the PPS based on deviations assessement in case they may have an impact on the efficacy analysis.

Major protocol deviations may include the following categories:

- Deviation from Inclusion/Exclusion criteria
- Deviations in study medication administration (infusion not administered, infusion administered late, infusion dose is <200 mg/kg or >800 mg/kg)
- Missed sampling required for dose adjustment
- Use of prohibited concomitant medications (use of other IVIG or SCIg while on trial, use of high dose oral/parenteral steroids or other immunosuppressive drugs while on trial)

- No diary data collected
- Lab results not reviewed at Screening
- Lab results related to SBI definition not completed (See Sec 8.1.1 in study protocol)
- Study visit missed

Further major protocol deviations will be defined during the Data Review Meeting (DRM) prior to database lock. Full list of major protocol deviations will be documented on the Protocol Deviation and Noncompliance Workbook.

The investigator should not implement any deviation from, or changes to the protocol, without agreement from the sponsor and prior review and documented approval/favorable opinion of an amendment from the IRB/IEC, except where necessary to eliminate an immediate hazard(s) to study patients. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

6. General Aspects for Statistical Analysis

6.1. General Methods

- Unless otherwise specified, summaries will be presented for each treatment schedule (21-day and 28-day infusion schedule) and overall.
- Unless otherwise specified, continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of patients.
- All relevant patient data will be included in listings. All patients entered into the database will be included in patient data listings.
- Unscheduled assessments will not be included in summary tables unless specified otherwise, but will be included in the patient listings.

6.2. Key Definitions

6.2.1. Age

Age (years) = floor((date of informed consent – date of birth)/365.25)

6.2.2. Baseline

For purpose of the analysis, the baseline value is defined as the last nonmissing valid observation before the first infusion. In most cases this will be the Day 1 pre-dose value. However, if the Day 1 pre-dose value is missing or was obtained after the first infusion of study drug is administered, then the most recent value obtained prior to the initiation of study drug will serve as the baseline measurement and may be measured at an unscheduled visit.

6.2.3. Absolute Change from Baseline

Absolute change from baseline:
Absolute change = Post-baseline value – Value at baseline

6.2.4. Relative change from baseline

Relative change = [(Post-baseline value – Value at baseline)/ Value at baseline] x100

6.2.5. Completion

A patient will be defined as “completed” if s/he has received all intended doses of KIg10 and has completed the 3 or 4 weeks (according to the treatment regimen) safety study termination visit after the last dose of KIg10.

6.2.6. Date of first infusion (Day 1)

Date of first infusion is the earliest day/time that infused KIg10 is first initiated. Day 1 is associated to this date.

6.2.7. Duration of Study

Duration of study = Date of termination – Date of first infusion + 1

6.2.8. Duration of infection

Duration of infection [days] = Date of stop of infection – Date of start of infection + 1

6.2.9. Duration of antibiotics for the treatment of any kind of infection

Duration of antibiotic treatment [days] = Date of stop of antibiotic treatment – Date of start of antibiotic treatment + 1

6.2.10. Duration of fever

Duration of fever [days] = (Date of stop of fever – Date of start of fever +1)

6.2.11. Duration of KIg10 exposure

Duration of KIg10 exposure is defined as the number of weeks from Day 1 to the date of Last Dose of KIg10

6.2.12. Duration of KIg10 infusion

Duration of KIg10 infusion is defined, for each infusion, as
Duration of KIg10 infusion [minutes] = Date/time of stop of KIg10 infusion – Date/time of start of KIg10 infusion

6.2.13. Duration of infusional AE

Infusional AEs are AEs that begin during or within 72 hours after an infusion.
Duration of AE [hours] = Date/time of stop of AE – Date/time of start of AE

6.2.14. Duration of noninfusional AE

Duration of AE [days] = Date of stop of AE – Date of start of AE + 1

6.2.15. Fever

Fever is defined as a body temperature ≥38°C (≥100.4°F).

6.2.16. Pediatric

A patient will be considered as a pediatric, if he/she is between ≥ 2 to ≤17 years old at the time of the screening. Here, age is defined as calendar year age (e.g., 11.99 years = 11 years old).

6.2.17. Prior/Concomitant medication

A medication is regarded as "prior" if the stop date of the event is prior to the date of first infusion, irrespective of the start date.
The medication is regarded as "concomitant" if the start date or stop date is between the date of first infusion (included) and the day of study termination (included).
The medication is regarded as "concomitant" if ticked as ongoing on the CRF.

6.2.18. Start Day of previous/concomitant medication

If medication starts before date of first infusion:
Start Day of Medication = Date of start of medication – Date of first infusion
If medication starts at/after date of first infusion:
Start Day of Medication = Date of start of medication – Date of first infusion + 1
Incomplete start dates of medication will not be imputed. Start day of medication will be missing.

6.2.19. Study Day

Study Day is defined relative to Day 1. Thus, the study day of an event is calculated as:
Study Day = Event date – Date of Day 1 + 1.

6.2.20. Study Duration/Length

Study Duration (in days) is computed as (Date of termination – Date of first infusion + 1)
This is equivalent to the definition of Day of Study Termination.

6.2.21. Study Visit

Study Visit is the nominal visit as recorded on the CRF.

6.2.22. Time since PID Diagnosis

Time since diagnosis [months] = ((Date of Screening – Date of diagnosis)+1)/30

6.2.23. Time to Onset of infusional AE

Time to Onset of AE [hours] = Date/time of start of AE – Date/time of start of infusion at respective infusion (1st infusion, 2 infusion, etc.)

6.2.24. Time to Onset of noninfusional AE

Time to onset of AE [days] = Date of start of AE – Date of first infusion

6.3. Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all patients. All available data will be included in the analyses and will be summarized as far as possible. Unless otherwise specified, there will be no substitution of missing data, i.e., missing data will not be replaced; missing data will be

handled as 'missing' in the statistical evaluation. Imputation methods used to analyze the primary efficacy endpoint and other efficacy endpoints will be detailed in the relevant sections where it applies.

6.3.1. Efficacy endpoints

Patients who discontinued before completing the study will lead to missing data on the primary efficacy endpoint. Multiple Imputation (MI) will be used to imputate the missing data in primary efficacy endpoint. The details of the imputation process and sensitivity analyses to assess the robustness the primary efficacy results are described in Section 8.1.4.5. Methods for dealing with missing or incomplete data where any imputation of the data is planned for other efficacy endpoints are covered in the relevant sections.

6.3.2. Safety endpoints

Partial or missing dates of safety data will be imputed according to the most conservative approach.

6.3.2.1. *AEs*

For missing or incomplete start dates, if the month/year is the same as the Day 1 month/year then the date will be set to the date of Day 1. In other cases, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1.
Incomplete end dates are assumed to have ended on the study completion date.
Actual values will be presented in data listings.

6.3.2.2. *Concomitant medications:*

No data will be imputed.

6.3.2.3. *Other safety end points*

No data will be imputed.

6.4. Visit Windows

Visits will be performed every 21 (± 3) days or 28 (± 4) days after each infusion until week 51, or 52 (i.e., study termination visit), depending on the patient's treatment schedule. All visits will be summarized according to the nominal visit.
For PK data analysis see Section 9.1.

6.5. Pooling of Centers

Data from all centers will be pooled together.

6.6. Subgroups

Subgroup analyses by age and treatment schedule are planned to be performed for the primary and secondary efficacy endpoints and for safety endpoints, including AEs (infusional AEs and treatment-emergent AEs). Additional subgroup analyses by sex, race are planned to be performed for the primary efficacy endpoint. Subgroup analysis by region will not be performed because only sites of USA enrolled subjects.

6.6.1. Age

The age categories for the subgroup analysis are
- children (2 to 11 years, inclusive)
- adolescents (12 to 17 years, inclusive)
- adults (18 to 70 years, inclusive).

The age categories will be consistent for all subgroup analyses with the exception of PK, where blood samples will only be taken from adults.

Age will be the age recorded at screening (initial visit). The same age will be used per patient during the entire study (i.e., if a patient's age changes from 17 to 18 years during the study, the patient will remain in the age category of 12 through 17 years during the entire study).

6.6.2. Treatment Schedule

The treatment categories for the subgroup analyses will be 21 days and 28 days.

6.6.3. Race

The race categories for the subgroup analyses will be White and polled group of all other races.

7. Demographic, Other Baseline Characteristics and Medication

7.1. Patient Disposition and Withdrawals

Patient disposition will be summarized by presenting the number and percentage of patients eligible for the study, treated with study medication and completed or discontinued from the study together with the primary reason for premature termination. The number of patients enrolled at each site will be presented. The summaries will be done by dosage interval (21- or 28-day) and overall for the 'All patients enrolled set'.

Major protocol deviations will be summarized for patients in FAS by dosage interval (21- or 28-day) and overall.

A further summary table will be presented detailing the number of patients in each analysis set. Furthermore, the number of patients excluded from each analysis set will be summarized by reason for exclusion. These summaries will be presented by dosage interval (21- or 28-day) and overall. All data will be summarized and listed.

7.2. Demographic and Other Baseline Characteristics

Demographic (age, gender, weight at baseline, race and ethnicity) and baseline characteristics (child-bearing potential status, tolerance of previous IgG treatment and antibody response to pneumococcal vaccination (if available)) will be presented in a summary table and a listing. The summary table will be based on the FAS, PPS and PK Evaluation set and will be done by dosage interval (21- or 28-day) and overall.

Age will be summarized as both a continuous variable and using the subgroup categories defined in Section 6.6.1.

Separate summaries will also be presented by age category for FAS.

All data will be listed.

7.3. Medical History and Concomitant Diseases

Medical history terms (including infection history) will be coded using MedDRA to give a preferred term (PT) and a system organ class (SOC) term for each medical history term. At the end of the study, medical history will be recoded applying the latest available MedDRA version available at this time point.

7.3.1. PID history

PID history will be summarized by the number and percentage of patients within each SOC and PT. Time since disease diagnosis will be presented by means of descriptive statistics.

The summary table will be based on the FAS and will be done by dosage interval (21- or 28-day) and overall. All data will be listed.

7.3.2. Non PID Medical History

Medical history (previous and concomitant diseases) will be summarized by the number and percentage of patients within each SOC and preferred term. This summary will be done overall based on the FAS.

Medical history terms with ongoing ticked 'No' will be considered as previous diseases, with ongoing ticked 'Yes' as concomitant diseases.

Summaries will be based on the FAS. All data will be listed.

7.4. Other Baseline Characteristics

Prior IVIG therapy for treatment of PID (taken in the last 3 months prior to start of this study) will be coded using WHO-DD using Anatomical Therapeutic Chemical (ATC) Classification Level 2 and 3 plus any applicable sorting (e.g. type of therapy and/or setting). The latest available version of WHO-DD available at the end of study will be used.

The number and percentage of patients with prior PID therapies will be presented by ATC Levels 2 and 3, and the preferred term.

In addition, patients currently receiving IVIG infusions/other medications yes/no, number of IgG trough levels of ≥ 6 g/L within 12 months prior to enrolment and patient's baseline IgG levels will be summarized,

The summary tables will be based on the FAS and will be done by dosage interval (21- or 28-day) and overall. All data will be listed.

7.5. Medication

Rules for discriminating prior/concomitant medications are defined within Section 6.2.17.
Medication will be coded using WHO-DD using Anatomical Therapeutic Chemical (ATC) Classification Level 2 and 3 plus any applicable sorting (e.g. type of therapy and/or setting). The latest available version of WHO-DD available at the end of study will be used.

The number and percentage of patients taking previous and concomitant other medications (excluding immunoglobulins) will be summarized overall by ATC Levels 2 and 3.

The number and percentage of patients taking premedications, to avoid AEs occurring in conjunction with the infusion of IVIg products during the study will also be summarized overall by ATC Levels 2 and 3. These will be identified by a review of the coded medications and include antihistamines, antipyretics, and/or steroids with indication - prophylaxis.

The number and percentage of patients taking previous antibiotic medications will be summarized overall by ATC Levels 2 and 3. Concomitant antibiotic medication is one of the secondary efficacy endpoints and is described in the Section 8.2.10.

The number and percentage of patients taking prohibited medication or treatment during the study will be summarized overall by ATC Levels 2 and 3. Prohibited medication or treatment includes the use of other polyclonal IgG (SCIG or IVIg) between the first infusion of KIg10 and the study termination visit. High dose steroids (oral and parenteral, daily ≥ 0.15 mg of prednisone equivalent/kg/day), and other immunosuppressive (including monoclonal antibodies)/cytotoxic drugs are prohibited during the study period except when required for emergency use, and their use must be recorded. These will be identified by a review of the coded medications.

All presentations will be done based on the FAS.

All available information will be listed.

8. Efficacy

Efficacy endpoints are based on data from different sources: eCRF, patient diary and questionnaires.
The summaries will be based on the FAS.
All data will be listed.

8.1. Primary Efficacy Endpoint and Analysis

8.1.1. Definition

Incidence rate (i.e., the mean number of acute serious bacterial infections per patient-year) of acute serious bacterial infections (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) according to FDA (1) and EMA (2) guidelines and the criteria described in the relevant FDA (1) guidelines.

8.1.2. Main Analysis

Primary analysis of the primary endpoint will be performed on the FAS. Primary efficacy will be analyzed using a Poisson model using as offset the length of the observation period after the start of treatment per patient. The unit of measurements of time is years. The estimate and 1-sided 99% upper confidence limit will be reported. Efficacy will be claimed if this limit is less than 1.0.
Any intra-patients correlations of acute serious bacterial infections are not considered to follow a conservative approach for the infection rates.

SAS code:

```
proc genmod;
     model [Number of Infections] =  / dist=poisson link=log
     offset=log(observation period after the start of treatment per patient
     in years) alpha=0.02 ;
run;
```

The primary efficacy analysis will be tested overall, e.g., without separation by dosing interval.

A per-subject primary endpoint analysis dataset will be derived from AE data. The following terms will be searched in AE prefered term to determine if an acute serious bacterial infection occurred: bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis. For each subject, the number of acute serious bacterial infections will be derived.

8.1.3. Main Analysis – Output

The following information will be summarized:

- Number and percentage of patients with 0 / 1 / 2 / 3 or more events

- Estimate of mean and SD of the incidence rate by the simple estimator.

The following steps will be applied for the simple estimator:
1. For each patient calculate the observation period (see Section 6.2.20)
2. The number of patient years will be calculated by summing the total patient days and dividing by 365.

3. An estimate of the mean (simple estimator) of acute serious bacterial infection rate for KIG10 will be obtained by dividing the total number of acute serious bacterial infections by the total number of patient years.
4. An estimate of the SD will be produced

- Estimate and 1-sided 99% upper confidence limit of the incidence rate from the Poisson model.

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8.2. Secondary Efficacy Endpoint(s) and Analyses

Secondary efficacy endpoints will be summarized using descriptive statistics by age categories, treatment schedule and overall, unless otherwise specified.

8.2.1. Serum IgG Trough Levels (Total IgG)

Serum IgG Trough Levels are collected before each infusion and at the study termination visit (week 51/52) and are analyzed at a central laboratory. The following information will be summarized for each visit:

- Actual value, change from baseline and relative change from baseline
- Number and percentage of patients with target level of ≥ 6 g/L (8) for actual value reached/not reached

Definition of baseline is given in Section 6.2.2.

8.2.2. IgG subclasses levels (IgG1, IgG2, IgG3, IgG4)

IgG subclasses levels are collected before infusions 1, 5, 9 and 13 for the 28-day infusion schedule, and before infusions 1, 7, 11 and 17 for the 21-day infusion schedule and are analyzed at a central laboratory. The following information will be summarized for each visit:

- Actual value, change from baseline and relative change from baseline

Definition of baseline is given in Section 6.2.2.

8.2.3. Anti-tetanus toxoid antibody level (quantitative assay)

Anti-tetanus toxoid antibody levels are collected before infusions 1, 5, 9 and 13 for the 28-day infusion schedule, and before infusions 1, 7, 11 and 17 for the 21-day infusion schedule and are analyzed at a central laboratory. The following information will be summarized for each visit:

- Actual value,change from baseline and relative change from baseline

Definition of baseline is given in Section 6.2.2.

8.2.4. Anti-pneumococcal capsular polysaccharide antibody level (quantitative assay)

Anti-pneumococcal capsular polysaccharide antibody levels are collected before infusions 1, 5, 9 and 13 for the 28-day infusion schedule, and before infusions 1, 7, 11 and 17 for the 21-day infusion schedule and are analyzed at a central laboratory. The following information will be summarized for each visit:

- Actual value, change from baseline and relative change from baseline

Definition of baseline is given in Section 6.2.2.

8.2.5. Anti-measles antibody level (quantitative assay)

Anti-measles antibody levels are collected before infusions 1, 5, 9 and 13 for the 28-day infusion schedule, and before infusions 1, 7, 11 and 17 for the 21-day infusion schedule and are analyzed at a central laboratory. The following information will be summarized for each visit:

- Actual value, change from baseline and relative change from baseline

Definition of baseline is given in Section 6.2.2.

8.2.6. Anti-Hemophilus influenza type b antibody level (quantitative assay)

Anti-hemophilus influenza type b antibody levels are collected before infusions 1, 5, 9 and 13 for the 28-day infusion schedule, and before infusions 1, 7, 11 and 17 for the 21-day infusion schedule and are analyzed at a central laboratory. The following information will be summarized for each visit:

- Actual value, change from baseline and relative change from baseline

Definition of baseline is given in Section 6.2.2.

8.2.7. Any infection other than acute serious bacterial infections

The following information will be summarized for infections between day 1 and week 51/52:

- Estimate of mean and SD of the incidence rate by the simple estimator.
- Duration of the considered infection(s)
- The estimate and 1-sided 99% upper confidence limit using Poisson model.

The length of the observation period after the start of treatment per patient will be used as offset in the Poisson model. The unit of measurements of time is years.

Definition of incidence rate is given in Section 8.1.1.
Computation of the estimate and 1-sided 99% upper confidence limit using Poisson model is given in Section 8.1.2.
Computation of the simple estimator is given in Section 8.1.3.
Definition of duration of infection is given in Section 6.2.8.

8.2.8. Fever episodes

The following information will be summarized for fever episodes between day 1 and week 51/52:

- Estimate of mean and SD of the incidence rate by the simple estimator.
- Duration of fever
- The estimate and 1-sided 99% upper confidence limit using Poisson model.

The length of the observation period after the start of treatment per patient will be used as offset in the Poisson model. The unit of measurements of time is years.

Definition of incidence rate is given in Section 8.1.1.
Computation of the estimate and 1-sided 99% upper confidence limit using Poisson model is given in Section 8.1.2.
Computation of the simple estimator is given in Section 8.1.3.
Definition of duration of fever is given in Section 6.2.10.

8.2.9. Hospitalization/ Hospitalization due to Infection

The following information will be summarized for hospitalizations between day 1 and week 51/52:

- Total days of hospitalization (any cause)

- Total days of hospitalization (any infection)

8.2.10. Antibiotics for the treatment of any kind of infection

The following information will be summarized for antibiotic treatment of any kind of infection between day 1 and week 51/52:

- Percentage of patients taking at least an antibiotics for treatment of infections
- Estimate of mean and SD of the incidence rate by the simple estimator
- Duration on antibiotics for the treatment of any kind of infection
- The estimate and 1-sided 99% upper confidence limit using Poisson model.

The length of the observation period after the start of treatment per patient will be used as offset in the Poisson model. The unit of measurements of time is years.

Definition of incidence rate is given in Section 8.1.1.
Computation of the estimate and 1-sided 99% upper confidence limit using Poisson model is given in Section 8.1.2.
Computation of the simple estimator is given in Section 8.1.3.
Definition of duration of antibiotics for the treatment of any kind of infectionis given in Section 6.2.9.

In addition, the number and percentage of patients taking concomitant antibiotic medications will be summarized by ATC Levels 2, 3 and 4.

8.2.11. Days of missed work/school/other major activities due to infections

The following information will be summarized for missed work/school/other major activities due to infections between day 1 and week 51/52:

- Total days of missed work/school/other major activities due to infections

8.2.12. Pediatric Quality of Life Inventory (PedsQL™) (Generic Core Scales)

For the analysis of PedsQL™ (4) three scores will be calculated:

- Total Scale Score (all 23 items)
- Physical Health Summary (8 items)
- Psychosocial Health Summary (15 items)

The parent proxy-report for children aged 2-4 years consists of 21 items.

The following information will be summarized at baseline, week 24 and at the study termination visit (week 51/52) for the summary scores and the single dimension scores (physical functioning, emotional functioning, social functioning, school functioning) by age group (2-4 years, 5-7 years, 8-12 years, 13-18 years, 18-25 years, >25 years):

- Actual value,change from baseline and relative change from baseline

Both child self-reports and parent proxy-reports will be presented, if applicable.
Scoring and handling of missing values will be done as recommended in the user manual.

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[redacted]

9. Pharmacokinetic Evaluation

The PK analyses will be performed using PK evaluation set.

9.1. PK sampling Schedule

Pharmacokinetic assessments will be performed in approximately [redacted] adult patients in order to have 20 evaluable patients before and after the 5th study infusion (28-day infusion schedule) or the 7th study infusion (21-day treatment schedule), when steady state is expected to be achieved (after 5 half-lives of regular infusion of the IMP). Interim PK analysis will be performed when approximately [redacted] adult patients (20 evaluable patients) complete intense PK sampling before and after infusion 5 for the 28-day schedule or infusion 7 for 21-day schedule.

Blood samples (approximately 20 mL) will be obtained at the following time-points at 5th (28-day schedule) or 7th (21-day schedule) study infusion:

- 30 minutes to 10 minutes pre-infusion
- 30 minutes (± 5 minutes) post-infusion
- 2 hours (± 15 minutes) post-infusion
- 24 hours (± 2 hours) post-infusion
- 72 hours (± 2 hours) post-infusion
- 7 days (± 1 day) post-infusion
- 14 days (± 1 day) post-infusion
- 21 days (± 1 day) post-infusion
- 28 days (± 2 days) post-infusion (only for 28 days treatment schedule)

9.2. PK Parameters

Non-compartmental PK parameters will be calculated using Phoenix WinNonlin 8.0 or higher version. Actual sampling times will be used in the determination of the individual PK parameters. Linear up log down method will be used for derivation of AUC.

9.2.1. Total IgG PK

Total IgG levels will be listed individually by time point, and serum concentration-time curve (individually and mean±SD) will be plotted. The serum levels will be presented in g/L units.

Following PK parameters will be evaluated:

- $T_{1/2}$, AUC_{0-t}, AUC_{0-inf}, AUC_{tau}, Vd, CL_{ss}, C_{max}, C_{min}, T_{max}, and K_{el}, C_{avg} and % Fluctuation

AUC_{0-inf} will be evaluated if data meet PK acceptance criteria to elimination parameters; AUC over dosing interval (21-day or 28-day) (AUC_{tau}) and other parameters may be derived.

9.2.2. IgG subclass levels

Blood samples for the analysis of IgG subclasses levels (IgG1, IgG2, IgG3, IgG4) will be taken before (as for all patients) and after the infusion 5 (28-day infusion schedule) or infusion 7 (21-day infusion schedule) at the time points indicated above in Section 9.1.

The IgG subclass levels will be listed individually by time point, and serum concentration-time curve (individually and mean±SD) will be plotted. The serum levels will be presented in g/L units.

9.2.3. PK parameters of specific IgG antibodies

Blood samples for the analysis of PK parameters for specific IgG antibodies (anti-Haemophilus influenza type b, anti-pneumococcal capsular polysaccharide, and anti-Tetanus toxoid) will be taken before and after the infusion 5 (28-day infusion schedule or infusion 7 (21-day infusion schedule) at the time-points indicated in Section 9.1.

The specific antibodies levels will be listed individually by time point, and serum concentration-time curve (individually and mean±SD) will be plotted. The serum levels will be presented in µg or IU/mL units.

Following PK parameters will be evaluated:

- $T_{1/2}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, AUC_{tau}, Vd, CL_{ss}, C_{max}, C_{min}, T_{max}, and K_{el}, C_{avg} and % Fluctuation.

$AUC_{0\text{-}inf}$ will be evaluated if data meet PK acceptance criteria to elimination parameters; AUC over dosing interval (21-day or 28-day) (AUC_{tau}) and other parameters may be derived.

9.3. Reliability of PK parameters

The following PK acceptance criteria will be applied to assess the reliability of the elimination parameters:

- 1. R2adj for the goodness of fit of the regression line through the data points must be ≥0.80;
- 2. The AUC extrapolation to infinity must be ≤20%.

For patients with unreliable K_{el} (criteria 1-2 are not met), K_{el}, $T_{1/2}$, $AUC_{0\text{-}inf}$, CL_{ss} and Vd will be flagged in the individual data.

For patients with unreliable $AUC_{0\text{-}inf}$ (only criterion 3 is not met), $AUC_{0\text{-}inf}$, CL_{ss} and Vd will be listed and flagged in the individual data.

Flagged PK parameters will be excluded from summaries and statistical analyses.

9.4. Presentation of PK data

9.4.1. Handling of Dropouts, Missing Data

Missing concentration data for all patients who are administered study drug will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

The sampling time of predose samples relative to dosing will also be treated as zero; if the actual time of sampling is missing, the planned time can be used.

9.4.2. Handling of BLQ and ULOQ

For calculation of PK parameters, summary statistics and individual serum concentration vs time curves of total IgG, IgG subclasses (sp serotypes) and specific antibodies (anti-Haemophilus influenza type b, anti-pneumococcal capsular polysaccharide, and anti-Tetanus toxoid) following rules will be applied if values are below lower limit of quantification (BLQ) or above upper limit of quantification (ULOQ):

1. All the ULOQ values will be imputed to the highest limit of quantification
2. During the full PK profile curves (visit 5 and 7), If there are more than 4 ULOQ value in the curve, values will be imputed as above, but no PK parameters will be calculated for that visit.
3. All the BLQ values will be imputed to BLQ/2.
4. During the full PK profile curves (visit 5 and 7), If there are more than 4 BLQ value in the curve, values will be imputed as above, but no PK parameters will be calculated for that visit.

9.4.3. Listing and Presentation of Individual PK Data

Following presentations of individual PK concentrations will be produced:

- Listing of PK sampling times including nominal and actual time elapsed from dose with the deviation from the nominal time and measured concentrations of the drug. The PK samples taken outside the scheduled window will be flagged in listing and can be excluded from summary statistics if the deviation will be deemed to affect the summary result.
- Individual PK profiles in linear scale for all patients within the same dosing schedule combined on one graph and plotted vs. actual time of the samples elapsed from the start of infusion.
- Individual trough concentrations vs. time elapsed from the start of 1st infusion or infusion number.

9.4.4. PK data summarization

- The mean/median value at a time point where 1 or more samples have BLQ values will be reported (in tabular or graphical fashion) even if the mean/median value is BLQ.
- Zero mean or median values will be included in summary tables.
- SD will not be displayed if more than 30% of values are missing or BLQ.

Tables of summary statistics for concentration-time data will report N (number of patients in the analysis population), n (number of actual observations) and the percentage of BLQ values relative to the total number of observations.

Following presentations of mean PK concentrations will be produced:

- Table of PK concentrations summarized by nominal time for each dosing schedule.
- Mean PK profiles in linear and log-linear scale by dosing schedule and plotted vs. nominal time relative to the start of intense sampling infusion
- Median trough concentrations vs. nominal time elapsed from the start of 1st infusion or infusion number by dosing schedule

Pharmacokinetic parameters and serum concentration data will be summarized by each dosing schedule using the following descriptive statistics:

Table 1: Concentration Summary Statistics

Variable	**Summarized with:**
Serum concentration at each time point	n, number and % BLQ, arithmetic mean, SD, coefficient of variance (CV) %, minimum, median and maximum
Continuous PK parameters (C_{max}, AUCs, …)	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
Categorical PK parameters (T_{max})	n, minimum, Q1, median, Q3 and maximum
Semi-continuous PK parameters ($T_{1/2}$, K_{el})	n, arithmetic mean, SD, CV%, minimum, median, maximum

CV% = SD/mean in %.
%BLQ = 100 * (total number of patients who have BLQ values/total number of patients within each dose level at each time point)

Table 2: Precision of PK Data Reporting

Statistics	**Degree of Precision**
Minimum, Maximum	3 significant digits or as needed based on actual measured values (for example PK concentrations)
Mean (arithmetic and geometric), Median, Q1, Q3	4 significant digits or as needed based on actual measured values (for example PK concentrations)
SD	5 significant digits or as needed based on actual measured values (for example PK concentrations)
CV% and Geometric CV%	1 decimal place or as needed based on actual measured values (for example PK concentrations)
AUCs, C_{max}, C_{min}, CL_{ss}, Vd, (same for ss parameters) Kel, C_{avg},% fluctuation	4 significant digits
T_{max}, R2adj	2 decimal places
$T_{1/2}$	1 decimal place

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9.6. Comparison of Total IgG trough concentrations

The evaluation of trough concentrations of Total IgG during the study compared to IVIg trough concentrations prior to the study entry will be carried out descriptively, separately for each dosing schedule.

The Total IgG trough concentrations prior to study entry will be compared to the mean of steady state trough concentrations as defined in previous section.

The comparison will be explored graphically using box plots for both dosing schedules separately.

10. Safety

All analyses described in this section will be performed using the SAF. The results will be descriptive in nature. All data will be summarized and listed.

Safety will be assessed on the basis of AEs, laboratory parameters (routine safety and intravascular hemolysis), vital signs, and physical examination.

10.1. Extent of Exposure

10.1.1. Overall

The duration of exposure will be expressed as the time in weeks from the first infusion of KIg10 through to the last visit (inclusive), with treatment administration and will be summarized.

The total number of administered infusions will be summarized for continuous variable and by categorizing the data according to the following categories:

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The actual calculated dose in mg/kg, based on the total dose administered and body weight at a given visit, will also be calculated at each infusion. The actual dose in mg/kg, the actual dose in mg and ml, number of patients with dose modification or dose interruption will be summarized for each infusion together with the reason for changes in the dose. Changes of planned infusion rate [ml/kg/min] during any infusion and the reason for change will be summarized. In addition, the total dose administered in mg and ml across all infusions will be summarized.

Duration of infusion in min will also be summarized for each infusion.

All data will be presented overall and by infusion schedule.

Additionally, extent of exposure will be presented for age categories defined in the Section 6.6.1.

All available information will be listed.

10.1.2. AE related

The following information will be summarized overall and by infusion schedule:

- Number and proportion of KIg10 infusions for which the infusion rate is decreased due to AEs (from infusion 1 to infusion 17)
- Number and proportion of KIg10 infusions with 1 or more infusional (temporally-associated) AE (from infusion 1 to infusion 17).
- A 1-sided 95% confidence interval (CI) will be produced for the proportion of infusions with 1 or more temporally-associated AEs (including AEs determined not to be product-related) using an exact binomial method. Due to the clustered nature of the data, a Design Effect will be applied to the confidence interval. An analysis of variance method will be used to calculate the Intra Cluster Correlation Coefficient (5).

For this analysis, safety will be declared if the upper 1-sided 95% confidence is less than 0.4 (counting overall infusions).

For producing such CI the following steps will be performed:

1 Calculate the raw 1-sided 95% CI: This will be done using an exact binomial method (e.g. Clopper Pearson)

2 Calculate the intracluster correlation coefficient: The point estimate via ANOVA method is given by Wu (5) as:

$$\widehat{\rho_A} = \frac{MSB - MSW}{MSB + (n_A - 1) * MSW}$$

where

$$n_A = \frac{1}{(k-1)}(N - \frac{\sum n_i^2}{N})$$

$$MSB = \frac{1}{(k-1)}(\sum \frac{Z_i^2}{n_i} - \frac{(\sum Z_i)^2}{N})$$

$$MSW = \frac{1}{(N-k)}(\sum Z_i - \sum \frac{Z_i^2}{n_i})$$

and
MSB and MSW: between-group and within-group mean squares from a one-way analysis of variance of the binary data
k: number of clusters (patients)
n_i : number of observations (infusions) on the i^{th} cluster (patient)
Y_{ij}: the response of patient j in cluster i (with Y_{ij}: 0 meaning negative to the event of interest and Y_{ij}: *1* meaning positive to the event of interest where the event of interest having at least one associated infusional Adverse Event*)*. The sum Y_{ij} is equal to the number of successes on the i^{th} cluster and it is labelled as Z_i i.e.

$$Z_i = \sum_j Y_{ij}$$

N is the number of total observations (infusions) in the considered analysis i.e.

$$N = \sum n_i$$

3 Calculate the Design Effect: A conservative approach is given by Eldridge (6). The Design effect can be written as:

$$DE = 1 + (\left[\left\{cv^2 \frac{(k-1)}{k} + 1\right\} * \overline{m}\right] - 1) * \widehat{\rho_A}$$

Where:

cv: ratio of the standard deviation of cluster sizes s_m to the mean cluster size, $\overline{m}$

$$S_m^2 = \frac{\sum(m_i - \overline{m})^2}{(k-1)}$$

m_i: size of the cluster i
k: number of clusters
$\widehat{\rho_A}$: calculated in step 2

4 Apply the Design Effect to the CI: Upper Confidence Limit to be reported = Design effect * Upper Confidence Limit (from exact binomial)

At the DRM prior to database lock it will be evaluated if other methods that take in account the clustered nature of the data should be performed (e.g., Generalized Estimating Equation).

The raw CI and the results of the supportive analyses that take the clustering into account will be reported.

All available information will be listed.

10.2. Treatment Compliance

Not applicable.

10.3. Adverse Events / Adverse Drug Reactions

Adverse events (AEs) will be coded using MedDRA to give a PT and a SOC term for each event. At the end of the study, AEs will be recoded applying the latest available MedDRA version available at this time point.

Adverse events temporally associated with the infusion are AEs occurring during infusion or within 72 hours after the end of infusion and are defined as infusional AEs.

Summary tables will be based on treatment-emergent adverse events (TEAEs), defined as those events with onset date/time at or after the first KIg10 infusion until the patient's last study visit.

10.3.1. Overall

An overall summary of AEs will show the number and percentage of patients (and the corresponding number of AEs) for infusional and noninfusional AEs and overall:

- any AEs
- any TEAEs
- any TEAEs by intensity
  any drug related TEAEs
- any serious TEAE
- any serious drug related TEAE
- any TEAEs leading to study drug infusion interruption / dose missed

- any TEAEs leading to study discontinuation / withdrawal
- any TEAEs leading to death

This table will be repeated by dosage interval (21- or 28-day) and by age category.

Infusional AEs:
Separate overall summaries of the infusional AEs will show the number and percentage of patients (and the corresponding number of AEs) who report during infusion or within 1, 24 or 72 hours after the end of infusion

- any infusional AEs,
- any nonserious infusional AEs,
- any related infusional AEs,
- any serious infusional AEs,
- any infusional AEs by intensity

The information will be presented overall and for each infusion.

This table will be repeated by dosage interval (21- or 28-day) and by age category.

Listings will be generated on the SAF for

- any AEs
- any drug related AEs
- any AEs leading to study discontinuation
- any serious AEs
- any fatal AEs
- any infusional AEs

10.3.2. By SOC/PT

An AE summary displaying SOC and PT will be presented for infusional and noninfusional AEs and overall:

- any TEAEs
- any severe TEAEs
- any drug related TEAEs
- any TEAEs leading to study discontinuation
- any serious TEAEs
- any serious drug related TEAEs
- any serious TEAEs leading to study discontinuation
- any fatal TEAEs

In addition, infusional AEs will be summarized by SOC and PT stratified by within 1, 24 or 72 hours after the end of infusion.

10.3.3. Relationship between infusional related AEs and speed of infusion

A 2-way table will summarize the frequency and proportion of infusion related AE by speed of infusion which will be grouped into different cohorts. This table will be produced overall and by the number of infusional related AE experienced per patient (e.g., 1 event experienced, 2 events experienced, 3+ events experienced).

10.4. Laboratory Evaluations

Blood chemistry, hematology, urinalysis, IgG levels, IgG subclasses and specific antibodies samples, intravascular hemolysis testing and PK blood sampling will be analyzed at a central laboratory. Direct Coombs and urine hemosiderin can be tested either centrally or at site level.The pregnancy test on urine will be performed locally at each site. This section describes the statistical analyses for blood chemistry, hematology and urinalysis. The statistical analyses for the rest of the laboratory evaluations are described in relevant Sections 8.2.1 – 8.2.6, 9.2 and 10.7. Please refer also to Table 1.1 and Table 1.2 for the timepoints for the collection of the specimen for the laboratory tests.

The tests listed below will be performed at screening visit, at each visit before the infusion, and at the study termination visit (week 51/52):

- Blood profile:
  hemoglobin, hematocrit, RBC count, WBC count with formula, number of platelets;
- Blood chemistry profile:
  total bilirubin, creatinine, blood urea nitrogen, ALT, AST, alkaline phosphatase, lactate dehydrogenase, glucose, sodium, potassium, chloride, and calcium;
- Urinalysis (qualitative and quantitative/semi-quantitative):
  bilirubin, pH, protein, blood, nitrite, specific gravity, leukocyte esterase, RBCs, WBCs.

These safety laboratory assessments will be categorized with respect to the central laboratory reference ranges as normal/abnormal. Abnormal values will be further classified with respect to clinical relevance: not clinically significant (NCS) or clinically significant (CS). Changes over time will be described by means of “shift-tables”, comparing the post-baseline values versus baseline value. Definition of baseline is given within Section 6.2.2. Absolute change and relative change from baseline are defined in 6.2.3 and 6.2.4, respectively.

The raw data will be listed. Values below or above the reference values in the data listings will be flagged. All laboratory values will be converted into standard units for presentation reasons.

The pregnancy test on urine (for patients of childbearing age) will be also performed at the screening visit. All data will be listed.

10.5. Vital Signs

The vital signs, including blood pressure, heart rate and temperature will be collected at each visit (including screening and study termination visit) and recorded in the eCRF.

Temperature method should be consistent throughout the study for any given patient.

All post-screening vital sign measurements will have an allowable window of ±5 minutes. For each infusion, vital signs will be measured at rest at the following time points:

- 10 to 15 min pre-infusion
- After start of infusion: 5 minutes before each increase of the infusion rate
- 30 minutes after reaching the maximum infusion rate; every 60 minutes thereafter
- Immediately after completion of the infusion

The following information will be summarized for each scheduled visit:
- Actual value of the parameter

- Change from baseline of the parameter
- Relative change from baseline for parameter

Definition of baseline is given within Section 6.2.2.

All available information will be listed.

10.6. Physical Examination

A physical examination will be performed at screening, at each visit before the infusion, and at the study termination visit. The general physical examination will include an evaluation of all body systems, as per normal standard of care at each site. Body weight measurement will be collected at each visit for pediatric patients and every 12 weeks (weeks 12, 24, 36, and 48) for adults.

For physical examination at screening, the number and percentage of patients with assessments of normal, abnormal or Not Done will be displayed in a summary table for each body system.

At the post-screening visits any abnormal, clinically significant findings are recorded as AEs. Therefore, abnormal findings of physical examination at these visits will be analyzed through the AE analysis.

For body weight, absolute values, changes from baseline and relative change from baseline will be presented for each scheduled study visit.

Definition of baseline is given within Section 6.2.2.Absolute change and relative change from baseline are defined in 6.2.3 and 6.2.4, respectively.

All available information will be listed.

10.7. Intravascular hemolysis

Intravascular hemolysis testing will be performed at the screening visit, after the first study infusion, after the 5th infusion for the 28-day infusion schedule or the 7th infusion for the 21-day infusion schedule, and at the study termination visit (week 51/52). Direct Coombs, serum haptoglobin, plasma-free hemoglobin, and urine hemosiderin tests will be performed. All blood samples related to intravascular hemolysis testing and Direct Coombs assessment will be analyzed at a central laboratory.

If a Direct Coombs test is positive, the test and serum haptoglobin, plasma-free hemoglobin, and urine hemosiderin tests must be repeated immediately after the initial positive results.

Intravascular hemolysis laboratory assessments (Coombs' test, serum haptoglobin, plasma-free hemoglobin, and urine hemosiderin) will be summarized by the number and percentage of patients with the given results at each scheduled visit. In case of positive Coombs' test results, further evaluations and/or time points will be included in the summaries. In case of intravascular hemolysis (drop in hemoglobin level by ≥2.0 g/dL and drop in serum haptoglobin to below the lower limit of normal and a rise in serum lactate dehydrogenase compared to the screening level), summaries will be presented for those patients meeting the conditions.

All information will be listed.

11. Interim Analyses

An interim PK analysis is planned after at least 20 patients will complete intense PK sampling before and after infusion 5 for 28 days schedule or infusion 7 for 21 days schedule. An interim PK report will be produced by the study PK scientist.

12. Changes from Analysis Planned in Protocol

Not applicable

13. Reference List

1. FDA/CBER. Guidance for industry: safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency, 2008.

2. European Medicines Agency (EMA) - Committee for Medicinal Products for Human Use (CHMP): Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). EMA/CHMP/BPWP/94033/2007 rev. 3; 28 June 2018.

3. Analysis of Count Data Using the SAS® System. Alex Pedan, Vasca Inc., Tewksbury, MA. SUGI 26; Paper 247-26, 2001. Available from: http://www2.sas.com/proceedings/sugi26/p247-26.pdf

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5. Wu S, Crespi CM, Wong WK. Comparison of methods for estimating the intraclass correlation coefficient for binary responses in cancer prevention cluster randomized trials. Contemp Clin Trials. 2012. 33(5):869-80.

6. Sandra M Eldridge Deborah Ashby Sally Kerry. International Journal of Epidemiology, Volume 35, Issue 5, 1 October 2006, Pages 1292–1300, https://doi.org/10.1093/ije/dyl129

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8. European Medicines Agency (EMA) - Committee for Medicinal Products for Human Use (CHMP): Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg). EMA/CHMP/BPWP/94038/2007 Rev. 5; 28 June 2018.

14. Index of Tables

Please refer to the table shells.

15. Index of Figures

Please refer to the figure shells.

16. Index of Listings

Please refer to the listing shells.

17. Appendices

Appendix 1: Study-specific Patient Satisfaction Questionnaire

STUDY-SPECIFIC QUESTIONNAIRE

Additional questions for PID patients

in the context of the Kedrion IVIG clinical study

1.	How satisfied you were with your *previous* IVIG treatment **before** entering in this clinical study? ☐ unsatisfied ☐ rather unsatisfied ☐ neither unsatisfied nor satisfied ☐ rather satisfied ☐ satisfied
2.	How satisfied you are with your *current* IVIG treatment **during** this clinical study? ☐ unsatisfied ☐ rather unsatisfied ☐ neither unsatisfied nor satisfied ☐ rather satisfied ☐ satisfied
3.	Is there something that disturbs or bothers you with your *current* IVIG treatment **during** this clinical study? _____ _____ _____ _____
4.	What was your motivation to participate in this clinical study? _____ _____ _____ _____
5.	Based on your experience during this clinical study with KEDRION IVIG, would you recommend a friend with primary immunodeficiency (PID) to use this IVIG treatment? 0 ——— 100 not at all ——— completely

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

PPD	PPD	PPD	
PPD		Signature	Date (DD-Mmm-YYYY)
Lead Biostatistician			
	PPD	PPD	
PPD		Signature	Date (DD-Mmm-YYYY)
Pharmacokineticist			
	PPD	PPD	
PPD		Signature	Date (DD-Mmm-YYYY)
Senior Reviewing Biostatistician			

Kedrion S.p.A. Approval

	PPD		PPD
PPD	PPD	Signature	Date (DD-Mmm-YYYY)
Sponsor Contact			