

# CLINICAL STUDY PROTOCOL KIG10\_US3\_PID01

Version 4, 30-November-2020

Amendment 2 to Version 2, 17-January-2019

## 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

*Short Title: Clinical Assessment of phaRmacokinetics, Efficacy, and Safety of 10% IVIg in PID Patients (CARES10)*

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***Confidentiality Statement***

The information contained in this protocol is provided to you in confidence, for review by you, your staff and any applicable regulatory authority or Institutional Review Board/Independent Ethics Committee/Research Ethics Board. It is understood that this information may not be disclosed to any other party, in any form, without prior authorization from the Sponsor, except to the extent necessary to obtain informed consent from the persons to whom the drug may be administered.

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## PROTOCOL SIGNATURE PAGE

Protocol Number: KIG10\_US3\_PID01  
VERSION 4, 30-November-2020  
Amendment 2 to Version 2, 17-January-2019

### INVESTIGATOR STATEMENT

By signing this statement, the Investigator declares receipt of a copy of protocol number KIG10\_US3\_PID01, entitled "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" version 4 and dated 30-November-2020.

The Investigator declares that the clinical study will be carried out in compliance with the provisions of the protocol, with the Declaration of Helsinki, with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines and all applicable regulations and laws.

The Investigator also declares the following:

- To have the scientific qualifications and experience required to conduct clinical trials in the scientific area specified in the protocol;
- To have received all information needed to assess possible risks and adverse events (AEs) associated with the medical products to be used in the study, as described in the Investigator's Brochure (IB), and that staff members will be properly informed;
- No changes shall be made to the protocol unless formally agreed upon with the Sponsor, except for emergency conditions that require the protection of safety, rights and welfare of the patients;
- All patients/parents/legal representatives will receive the Informed Consent/Assent/Authorization to access personal health information form(s); the Investigator will collect patient's/parent(s)/legal representative's signature on consent forms approved by the Sponsor and by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) before patients will enter in the study;
- Any clinical materials shall be used only in accordance with the protocol. The Investigator shall be responsible for the safety and documentation regarding the use of the trial drug supplies, devices supplies and any equipment provided on loan for use;
- The electronic Case Report Forms (eCRF) shall be completed in a timely accurate manner. The "source documents" and the documents required for the study shall be archived as set forth by all applicable regulation;
- Monitoring visits will be permitted at a predetermined frequency or as needed;
- Inspections of the facilities and documents carried out by Competent Authorities (CAs) and representatives authorized by the Sponsor will be permitted, upon guarantee of confidential data protection;
- The Investigator is committed to send out all relative communications regarding the safety following the procedure described in the appropriate paragraph of the protocol;
- Any information obtained during the clinical trial must not be presented at scientific conferences or sent to scientific publications without prior authorization by the Sponsor.



**Kedrion S.p.A.** Protocol Code **KIG10\_US3\_PID01**  
**Version 4, 30-November-2020 Amendment 2 to Version 2, 17-January-2019**  
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- Each manuscript or abstract shall be sent for review to the Sponsor at least 60 days before being sent out for any purpose.

\_\_\_\_\_  
Investigator's Name (in block capitals) and signature

\_\_\_\_\_  
Date

Following signature Kedrion S.p.A./Syneos Health will certify that the present document has been compiled and that the clinical study KIG10\_US3\_PID01 will be managed in conformity to the Helsinki declaration, the GCP and all the applicable regulatory requirements.

PPD \_\_\_\_\_

Sponsor's Medical Responsible's Name (in block capitals) and signature

PPD \_\_\_\_\_

Date

PPD \_\_\_\_\_

Contract Research Organization's Representative (in block capitals) and signature

PPD \_\_\_\_\_

Date

## PROTOCOL SYNOPSIS

<b>Sponsor Name:</b> Kedrion S.p.A. - Loc. Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) Italy	
<b>Product Name:</b> NA	<b>Investigational Product:</b> Kedrion intravenous immunoglobulin (IVIg) 10%
<b>Title of Study:</b> 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.	
<b>Study Period:</b> Approximately 13 months, including a 21 or 28 days screening period, a 48 weeks treatment period, and 3 or 4 weeks follow-up (depending on treatment regimen)	<b>Clinical Phase:</b> Phase III
<b>Study Centers:</b> This study will be conducted at approximately 15 study centers in 2 countries, Canada and the United States.	
<b>Background and Rationale:</b> <p>Primary immunodeficiency diseases (PIDs) occur in individuals with a genetic defect in the immune system. As a consequence, patients are affected by recurrent protozoal, bacterial, fungal, and viral infections (Picard C, 2015). Antibody deficiencies, also referred to as B-cell or humoral immunodeficiencies, comprise the largest group of PIDs. This is a group of disorders characterized by an impaired ability to produce specific antibodies in response to antigen. Many of these disorders are caused by mutations in the immunoglobulin (Ig) genes or in genes involved in the regulation of B-cell growth and differentiation. Still, the molecular basis of most cases remains unknown.</p> <p>The first antibody deficiency and best studied is X-linked agammaglobulinemia, which is caused by mutations in the Bruton tyrosine kinase (Bruton OC 1952; Bonilla FA, 2003). Loss-of-function mutations in this gene lead to a block in B-cell maturation, a near-total absence of B-cells in the periphery, and panagammaglobulinemia. Other autosomal recessive gene defects may lead to similar phenotype. Patients with agammaglobulinemia typically present with symptoms in early childhood but are usually well for the first 9 to 12 months of life because they are passively protected by transplacentally acquired IgG from their mothers. When symptoms present, they commonly appear as recurrent pyogenic infections such as otitis media, sinusitis, meningitis, conjunctivitis, pneumonia, and pyoderma mainly due to <i>Haemophilus influenzae</i> and <i>Streptococcus pneumoniae</i> (Rosen FS, 1995). Infrequently enteroviral infections with a chronic meningoencephalitis and a syndrome resembling dermatomyositis are present. Patients are also prone to <i>mycoplasma pneumoniae</i> infections.</p>	

**Sponsor Name:**

Kedrion S.p.A. - Loc. Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) Italy

**Product Name:**

NA

**Investigational Product:**

Kedrion intravenous immunoglobulin (IVIg) 10%

The largest group of patients with antibody deficiency is classified as common variable immunodeficiency (CVID), with an estimated prevalence of 1 in 50,000. Diagnosis of CVID is based on the exclusion of other known causes of humoral immune defects (Resnick ES, 2012). It is defined principally as low IgG (often with low IgA) together with a significant impairment of specific antibody production in response to bacterial vaccine or natural infectious challenge (Conley ME, 1999; Cunningham-Rundles C, 1999). Males and females are equally affected and presentation is most common at the ages of 20 to 40 with only about 20% of patients diagnosed in childhood. While some genetic defects have been shown to cause CVID, in most patients the molecular defect remains unknown. Signs and symptoms of CVID are generally that of recurrent pyogenic sino-pulmonary infections. The patients are also prone to infection with enteric pathogens, such as *Giardia lamblia* infection, and a variety of autoimmune disorders (Resnick ES, 2012).

Polyclonal Ig preparations of human origin, including intravenous immunoglobulin (IVIg) products, have historically been used as replacement therapy to reduce the frequency of serious bacterial infections in patients with PID. Prior to the introduction of IVIg therapy, patients suffering from hypogammaglobulinemia and agammaglobulinemia due to PID experienced approximately 4 or more serious acute bacterial infections each year. However, maintenance of a trough serum level of  $\geq 5$ g IgG/L controls most recurrent infections and their chronic complications, improving the patients' quality of life (Roifman CM, 2008).

The study is being conducted to evaluate the efficacy, safety, and pharmacokinetics (PK) of Kedrion IVIg 10% (KIG10) in patients with PID, in accordance with the Food and Drug Administration (FDA) "Guidance for Industry: Safety, Efficacy and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency; June 2008" and European Medicines Agency (EMA) "Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg); EMA/CHMP/BPWP/94033/2007 rev. 3" and "Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg); EMA/CHMP/BPWP/94038/2007 Rev. 5."

<b>Sponsor Name:</b> Kedrion S.p.A. - Loc. Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) Italy	
<b>Product Name:</b> NA	<b>Investigational Product:</b> Kedrion intravenous immunoglobulin (IVIg) 10%
<b>Study Objectives:</b>	
<u>Primary Efficacy Objective</u> To assess the efficacy of Klg10 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.	
<u>Primary Safety Objective</u> To assess the safety of Klg10 in the overall study population from day 1 to week 51/52.	
<u>Pharmacokinetic Objectives</u> To assess distribution, metabolism, and elimination of Klg10 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.	
<b>Study Design:</b> This is a phase III, open-label, prospective, single arm, historically controlled, multicenter study to evaluate efficacy, safety, and PK of Klg10 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 Klg10 for the PID treatment of adolescents (12 to 17 years) or adults are demonstrated. All patients will receive an intravenous infusion of Klg10 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 Klg10 will mark the beginning of the investigation period and enrollment. Visits will be performed every 21 ( $\pm 3$ ) days or 28 ( $\pm 4$ ) 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).	

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**Investigational Product:**

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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

After obtaining a signed informed consent form (ICF), assent form (as applicable), and authorization to access personal health information, the screening procedures will be performed. Screening will include documentation of diagnosis by the site Investigator.

A Patient Diary will be given to patients at each infusion visit to record adverse events (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.

General (Pediatric Quality of Life Inventory [PedsQL™ Generic Core Scales]) and specific disease state CCI questionnaires will be administered to patients to evaluate the QoL. The PedsQL™ is a self-rated and proxy-rated questionnaire, and both versions include 23 items.

Based upon available data, health care utilization will be assessed also.

Patient satisfaction with participation and treatment during the study will be assessed.

**Number of Patients Planned:**

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 and EMA guidelines. CCI

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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

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

**Study Population and Patient Characteristics:**

Patients who have an acute infection at the time of screening (exclusion criterion #8) may be rescreened at the investigator's discretion as long as the infection is not serious and is resolved by the time of rescreening.

Inclusion Criteria

Patients must meet the following inclusion criteria to be enrolled into the study.

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 the time of screening.
4. Received 200 to 800 mg/kg of a commercially available IVIg therapy in the range of 21- or 28-day intervals ( $\pm 3$  days or  $\pm 4$  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 a IVIg, of  $\geq 6$  g/L obtained at 2 infusion cycles within 12 months (1 must be within 6 months) prior to ICF signature.

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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 for at least 3 infusion cycles (21 or 28 days) prior to screening.

Exclusion Criteria

Patient must not meet any of the exclusion criteria to be enrolled into the study.

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<sup>3</sup>] 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  $\geq 38^{\circ}\text{C}$  ( $\geq 100.4^{\circ}\text{F}$ ) within 7 days prior to screening.
9. Acquired immunodeficiency syndrome (AIDS) and/or Hepatitis B/C active disease 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.



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<b>Product Name:</b> NA	<b>Investigational Product:</b> Kedrion intravenous immunoglobulin (IVIg) 10%
<p>11. Using an implanted venous access device.</p> <p>12. Profound anemia (hemoglobin &lt; 10 g/dL) or persistent severe neutropenia (<math>\leq 1000</math> neutrophils per <math>\text{mm}^3</math>) or lymphopenia of less than 500 cells per microliter.</p> <p>13. A severe chronic condition such as renal failure (creatinine concentration &gt; 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.</p> <p>* normal values for serum creatinine are the following: a) Female (18+ years): 45 - 84 <math>\mu\text{mol/L}</math> or 0.51 - 0.95 mg/dl; b) Male (18+ years): 59 - 103 <math>\mu\text{mol/L}</math> or 0.67 - 1.17 mg/dl</p> <p>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 prior to ICF signature.</p> <p>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.</p> <p>16. Patient must not be receiving the following medication:</p> <p>a) Steroids, oral or parenteral, at a daily dose of <math>\geq 0.15</math> mg/kg/day of prednisone or equivalent.</p> <p>b) Other immunosuppressive drugs (including monoclonal antibodies) or chemotherapy.</p> <p>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.</p> <p>18. Participated in another clinical study within 3 weeks prior to study ICF signature.</p> <p>19. Active drug or alcohol abuse or history of drug or alcohol abuse within the 6 months before screening.</p> <p>20. Employed or a direct relative of an employee of the Contract Research Organization, the study site, or the Sponsor.</p> <p>21. Previously treated under this protocol.</p> <p>22. Unable to provide informed consent or provide informed consent by a legally authorized representative.</p>	

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<b>Product Name:</b> NA	<b>Investigational Product:</b> Kedrion intravenous immunoglobulin (IVIg) 10%
<b>Study Procedures:</b> <p>At the screening visit, the signed ICF and authorization to access personal health information will be obtained from the patient or the patient's parent(s)/legal guardian(s). The assent form will be also collected for children, as applicable according to local regulation.</p> <p>Screening procedures will be performed up to 21 or 28 days (depending on the treatment regimen) prior to the first Klg10 infusion. During the screening, the diagnosis of PID will be confirmed by the site Investigator.</p> <p>Each patient will be treated with the investigational product at a dose of 200 to 800 mg/kg body weight every 21 or 28 days for a period of 48 weeks (see protocol Time and Events table).</p> <p>A blood sample will be obtained from all patients for evaluation IgG trough levels at screening, before each infusion, every 21 or 28 days during all study periods, and at the study termination visit.</p> <p>Blood samples required for PK analysis will be taken before and after the 5<sup>th</sup> study infusion (for 28-day infusion schedule) and the 7<sup>th</sup> study infusion (for 21-day infusion schedule) for those patients that consent to the PK portion of the study.</p> <p>A pretreatment serum sample at the screening visit and a serum sample at the study termination visit will be collected and stored at <math>\leq -70^{\circ}\text{C}</math> for viral safety and possible future testing.</p> <p>A Patient Diary will be given to the patient at each infusion visit. The patient and/or patient's parent(s)/guardian(s) will be trained by the Investigator on how to complete the Patient Diary, starting after the first infusion. The Patient Diary will be collected at the following visit, data will be reviewed by the Investigator, and a new Patient Diary will be provided to the patient.</p> <p>The patient will be asked to complete QoL questionnaires (general and specific) at 3 visits as follows: at baseline (prior to first infusion of Klg10), at week 24 of treatment (infusion 7 for the 28-day schedule or infusion 9 for the 21-day schedule), and at the study termination visit. Patients who are unable to independently complete the questionnaires may enlist the assistance of a parent or caregiver.</p> <p>During the study [at week 24 (infusion 7 for the 28-day schedule or infusion 9 for the 21-day schedule)] the patient will be asked to complete short assessment questionnaire (Appendix A to the protocol) about personal satisfaction with participation and treatment during the study.</p>	
<b>Investigational Medicinal Product, Dosage Regimen and Route of Administration:</b> <p>Immune Globulin Intravenous (Human) 10% solution.</p> <p>The product contains 100 mg human plasma protein per 1 mL solution, of which IgG represents at least 96%.</p> <p>Dosage should be calculated so that the amount administered should match the patient's previously individualized dosing regimen.</p>	

**Sponsor Name:**

Kedrion S.p.A. - Loc. Ai Conti 55051 Castelvecchio Pascoli, Barga (Lucca) Italy

**Product Name:**

NA

**Investigational Product:**

Kedrion intravenous immunoglobulin (IVIg) 10%

**Modalities of Treatment Administration:**

- 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 (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.
- 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 (4 mg/kg/min – 0.04mL/kg/min; 6 mg/kg/min – 0.06 mL/kg/min; 8 mg/kg/min – 0.08 mL/kg/min) at 15 minute intervals.

**Efficacy Endpoints:**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 pre-specified criteria).

Secondary Efficacy Endpoints

- Serum IgG trough levels before each infusion of Klg10 and at the study termination visit (week 51/52).
- 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.
- Frequency of patients with total IgG below 6 g/L criteria.
- Anti-tetanus toxoid antibody level (quantitative assay) before infusions 1, 5, 9, and 13 for the 28-day infusion schedule and before infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
- Anti-pneumococcal capsular polysaccharide antibody level (quantitative assay) before infusions 1, 5, 9, and 13 for the 28-day infusion schedule and before infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
- Anti-measles antibody level (quantitative assay) before infusions 1, 5, 9, and 13 for the 28-day infusion schedule and before infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
- Anti-Haemophilus influenza type b antibody level (quantitative assays), before infusions 1, 5, 9, and 13 for the 28-day infusion schedule and before infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
- Incidence rate (i.e., the mean number per patient-year) of any infection other than acute

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serious bacterial infections from day 1 to week 51/52.

- Duration of any infection other than acute serious bacterial infections day 1 to week 51/52.
- Incidence rate (i.e., the mean number per patient-year) of fever episodes from day 1 to week 51/52.
- Duration of fever episodes from day 1 to week 51/52.
- Overall hospitalization days from day 1 to week 51/52.
- Days of hospitalization due to infection from day 1 to week 51/52.
- Incidence rate (i.e. the mean number per patient year) of patient on antibiotics for the treatment of any kind of infections from day 1 to week 51/52.
- Duration of patient on antibiotics for the treatment of any kind of infections from day 1 to week 51/52.
- Days of missed work/school/other major activities due to infections.
- PedsQL™ score at baseline, week 24, study termination visit.

CCI

**Safety Endpoints:**

- Number of AEs (%) and proportion of patients experiencing at least 1 AE.
- Number of serious AEs (SAEs) (%) and proportion of patients experiencing at least 1 SAE.
- 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 related infusion AE.
- The proportion and number of Klg10 infusions for which the infusion rate is decreased due to AEs.
- Number and proportion of infusions with 1 or more infusion (temporally) associated AE.
- Changes in vital signs, physical examinations, and safety laboratory tests (hematology,

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serum chemistry, and urinalysis).

- The proportion and number of patients with a positive Coomb's test following the 5<sup>th</sup> infusion for the 28-day infusion schedule and the 7<sup>th</sup> infusion for the 21-day infusion schedule.
- The proportion and number of patients with a positive urine hemosiderin test following the 5<sup>th</sup> infusion for the 28-day infusion schedule and the 7<sup>th</sup> infusion for the 21-day infusion schedule.
- Plasma-free hemoglobin level following the 5<sup>th</sup> infusion for the 28-day infusion schedule and the 7<sup>th</sup> infusion for the 21-day infusion schedule.
- Serum haptoglobin level following the 5<sup>th</sup> infusion for the 28-day infusion schedule and the 7<sup>th</sup> infusion for the 21-day infusion schedule.

**Pharmacokinetics Endpoints (evaluated on approximately 24 adult patients in order to collect data on 20 evaluable patients):**

- Total IgG levels, IgG subclasses levels, and selected specific antibody levels before and after the 5<sup>th</sup> infusion for the 28-day infusion schedule and before and after the 7<sup>th</sup> infusion for the 21-day infusion schedule.
- Pharmacokinetic parameters of total IgG and specific antibodies before and after the 5<sup>th</sup> infusion for the 28-day infusion schedule and before and after the 7<sup>th</sup> infusion for the 21-day infusion schedule (i.e., concentration-time curve, half-life, area-under-the-curve [AUC<sub>0-t</sub>; AUC<sub>0-in</sub>]), volume of distribution, concentration maximum [C<sub>max</sub>], T<sub>max</sub>, elimination rate constant).

**Statistical Analyses:**

A detailed statistical analysis plan (SAP) is provided with IND/CTA submission. Protocol deviations will be defined at the beginning, and data will be checked throughout the study on a regular basis (ICH E6 [R2] addendum). Protocol deviations will be described in the SAP.

The following populations are defined: The Full Analysis Set (FAS) comprises all patients who have received at least 1 dose of study medication. Safety Analysis Set (SAF) is coincident with FAS. Other populations will be defined. Efficacy end points will be analyzed on the FAS while safety endpoints will be analyzed on the SAF unless specified differently. The PK Evaluation Set will include all adult patients who consented to this part of the protocol and had PK analysis performed before and after the 5<sup>th</sup> infusion for the 28-day infusion schedule (or before and after the 7<sup>th</sup> infusion for the 21-day infusion schedule).

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 per patient in

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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. Supportive and sensitivity analyses will be performed as appropriate. Secondary and exploratory efficacy endpoints will be summarized using descriptive statistics.

Secondary safety endpoints will be summarized using descriptive statistics.

Additionally, 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 CI. An analysis of variance method will be used to calculate the Intra Cluster Correlation Coefficient (Wu, 2012). For this analysis, safety will be declared if the upper 1-sided 95% confidence is less than **CCI**. Other methods that take in account the clustered nature of the data could be performed (e.g., Generalized Estimating Equation).

Further details will be provided in the SAP.

Pharmacokinetic analysis of total IgG, IgG subclasses, and selected specific IgG antibody levels will be done by non-compartmental analysis. Pharmacokinetic parameters will be derived from serum IgG levels and summarized descriptively, taking into account doses of the drug. Trough levels for all patients will be summarized relative to dosing interval and age category. The frequency of patients with trough concentrations < 6 g/L will be estimated for each infusion number, dose level, and age category, as well as overall. All other data will be reported descriptively. Trough concentrations for total IgG at steady state achieved by the study drug will be compared to IVIg trough concentrations prior to the study entry using statistical model.

Interim PK analysis will be performed when approximately **CCI** adult patients (in order to have 20 evaluable patients) complete intense PK sampling before and after infusion 5 for the 28-day schedule and infusion 7 for the 21-day schedule.

**Data Safety Monitoring Board:**

A Data Safety Monitoring Board (DSMB) will be established for this study. The DSMB will be independent from Sponsor and Investigators. The primary responsibilities of the DSMB are to periodically monitor, review and evaluate the safety and infection data collected during study conduct.

The DSMB will be asked to 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 3 infusions (i.e., 3 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).



<b>Kedrion S.p.A.</b>	<b>Protocol Code KIG10_US3_PID01</b>
<b>Version 4, 30-November-2020 Amendment 2 to Version 2, 17-January-2019</b>	<b>Confidential</b>

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DSMB will also review data that are indicative of intravascular hemolysis.	

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

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



Study Week	Screening	1 (Day 1)	4	8	12	16	20	24	28	32	36	40	44	48	52
		Baseline Visit 1	Treatment Visits												
Visit Number			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	
<b>STUDY EVENT</b>															
Patient Diary reviewed and data collected <sup>7</sup>			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
<b>Efficacy</b>															
Assess serious bacterial infections		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fever episodes <sup>8</sup>		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 <sup>3</sup>	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 <sup>9</sup> levels (Pre-infusion)		X				X				X				X	
PK parameters of total IgG and specific antibodies (Pre and post infusion) <sup>9</sup>						X									
Quality of life questionnaires <sup>10</sup>		X							X						X
Health care utilization		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Week	Screening	1 (Day 1)	4	8	12	16	20	24	28	32	36	40	44	48	52
		Baseline Visit 1	Treatment Visits												
Visit Number			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	
<b>STUDY EVENT</b>															
Patient satisfaction questionnaire <sup>11</sup>								X							
<b>Study completion procedures</b>															
Study termination <sup>12</sup>															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 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 infusion 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	
Visit Number	Screening	Baseline Visit 1	Treatment Visits																Study Termination Visit	
			2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		
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	+3
Infusion Number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		
<b>STUDY EVENT</b>																				
<b>Study Treatment</b>																				
IVIg infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Screening and safety</b>																				
Informed Consent <sup>1</sup>	X																			
Medical History	X																			
Demography	X																			
Physical Examination <sup>2</sup>	X	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	X
Blood chemistry <sup>3</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology <sup>3</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intravascular hemolysis testing <sup>4</sup>	X	X						X												X
Chest X-ray <sup>5</sup>	X																			
Urinalysis <sup>3</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X																			

Study Week		1 (Day 1)	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	
	Visit Number	Screening	Treatment Visits																Study Termination Visit	
Visit Window (Days)	-21 to 0	n/a	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>	<u>+3</u>
Infusion Number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		
<b>STUDY EVENT</b>																				
Exclusion/Inclusion Criteria	X																			
Retention sample blood drawn <sup>6</sup>	X																			X
Patient Diary reviewed and data collected <sup>7</sup>			X	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	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Efficacy</b>																				
Assess serious bacterial infections		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fever episodes <sup>8</sup>		X	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	X
IgG levels <sup>3</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgG subclasses (Pre-infusion)		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	
Visit Number	Screening	Baseline Visit 1	Treatment Visits																Study Termination Visit	
	-21 to 0	n/a	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	±3	
Visit Window (Days)			±3	±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		
<b>STUDY EVENT</b>																				
Ab anti-measles and specific antibodies (Pre-infusion) <sup>9</sup>		X						X				X						X		
PK parameters of total IgG and specific antibodies (Pre and post-infusion) <sup>9</sup>								X												
Quality of life questionnaires <sup>10</sup>		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 <sup>11</sup>										X										
<b>Study completion procedures</b>																				
Study termination <sup>12</sup>																			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 infusion 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  $\geq 38^{\circ}\text{C}$  ( $\geq 100.4^{\circ}\text{F}$ ).
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.

## 1. LIST OF ABBREVIATIONS

<b>AE(s)/ADR(s)</b>	Adverse event(s)/adverse drug reaction(s)
<b>ALT</b>	Alanine aminotransferase
<b>AMS</b>	Aseptic meningitis syndrome
<b>AST</b>	Aspartate aminotransferase
<b>AIDS</b>	Acquired Immunodeficiency Syndrome
<b>CFR</b>	Code of Federal Regulations
<b>eCRF(s)</b>	Electronic case report form(s)
<b>CSF</b>	Cerebrospinal fluid
<b>CVID</b>	Common variable immunodeficiency
<b>CRO</b>	Clinical research organization
<b>CT</b>	Computerized tomography
<b>DSMB</b>	Data Safety Monitoring Board
<b>EDC</b>	Electronic data capture
<b>EMA</b>	European Medicines Agency
<b>IRB(s)/IEC(s)</b>	Institutional Review Board(s)/Independent Ethics Committee(s)
<b>FAS</b>	Full Analysis Set
<b>FDA</b>	Food and Drug Administration
<b>GCP</b>	Good Clinical Practice
<b>ICH</b>	International Council for Harmonization
<b>ICF</b>	Informed consent form
<b>ID</b>	Identification
<b>Ig(s)</b>	Immunoglobulin(s)
<b>IMP</b>	Investigational medicinal product
<b>IUIS</b>	International Union of Immunological Societies
<b>IVIg</b>	Intravenous immunoglobulin
<b>Kg</b>	Kilograms
<b>KIg10</b>	Kedrion intravenous immunoglobulin 10%
<b>MedDRA</b>	Medical Dictionary for Drug Regulatory Activities
<b>mg</b>	Milligram

<b>ml</b>	Milliliter
<b>mm Hg</b>	Millimeter of mercury
<b>MRI</b>	Magnetic resonance imaging
<b>CCI</b>	
<b>PedsQL™</b>	Pediatric Quality of Life Inventory™
<b>PID(s)</b>	Primary immunodeficiency disease(s)
<b>PK</b>	Pharmacokinetic(s)
<b>PPS</b>	Per-Protocol Set
<b>QoL</b>	Quality of Life
<b>RBC(s)</b>	Red blood cell(s)
<b>SAE(s)/SADR(s)</b>	Serious adverse event(s)/serious adverse drug reaction(s)
<b>SAF</b>	Safety Set
<b>SAP</b>	Statistical analysis plan
<b>SCIG</b>	Subcutaneous immunoglobulin
<b>SOPs</b>	Standard operative procedures
<b>TRALI</b>	Transfusion-related acute lung injury
<b>US</b>	United States
<b>WBC(s)</b>	White blood cell(s)



## 2. BACKGROUND AND RATIONALE

This study aims to evaluate the efficacy, safety, and pharmacokinetics (PK) of the Kedrion 10% immunoglobulin preparation for intravenous administration (hereafter Klg10) in patients with primary immunodeficiency disease (PID), in accordance with Food and Drug Administration (FDA) guideline “Guidance for Industry: Safety, Efficacy and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency; June 2008” and European Medicines Agency (EMA) guidelines “Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg); EMA/CHMP/BPWP/94033/2007 rev. 3” and “Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg); EMA/CHMP/BPWP/94038/2007 Rev. 5.”

Klg10 is a ready-to-use liquid normal immunoglobulin (Ig, 100 mg/mL) developed by Kedrion S.p.A. from source plasma obtained in the United States (US). The Klg10 manufacturing process includes 4 manufacturing steps, which are effective for viral removal/inactivation. The quality attributes, biological characteristics, and biological activity of the Klg10 product meet requirements of both US and European pharmacopoeias. In addition to the release testing, process intermediates, drug substance, and drug product are further characterized by physicochemical standpoint.

### 2.1 BACKGROUND

Primary immunodeficiency disease occurs in individuals with a genetic defect in the immune system. As a consequence, patients are affected by recurrent protozoal, bacterial, fungal, and viral infections (Picard C, 2015). Antibody deficiencies, also referred to as B-cell or humoral immunodeficiencies, comprise the largest group of PIDs. This is a group of disorders characterized by an impaired ability to produce specific antibodies in response to antigen. 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. Still, the molecular basis of most cases remains unknown.

The first antibody deficiency and best studied is X-linked agammaglobulinemia, which is caused by mutations in the Bruton tyrosine kinase (Bruton OC, 1952; Bonilla FA, 2003). Loss-of-function mutations in this gene lead to a block in B-cell maturation, a near-total absence of B-cells in the periphery, and panagammaglobulinemia. Other autosomal recessive gene defects may lead to similar phenotype. Patients with agammaglobulinemia typically present with symptoms in early childhood but are usually well for the first 9 to 12 months of life because they are passively protected by transplacentally acquired IgG from their mothers. When symptoms present, they commonly appear as recurrent pyogenic infections such as otitis media, sinusitis, meningitis, conjunctivitis, pneumonia, and pyoderma mainly caused by *Haemophilus influenzae* and *Streptococcus pneumoniae*

(Rosen FS, 1995). Infrequently enteroviral infections with a chronic meningoencephalitis and a syndrome resembling dermatomyositis are present. Patients are also prone to *Mycoplasma pneumoniae* infections.

The largest group of patients with antibody deficiency are classified as common variable immunodeficiency (CVID) with an estimated prevalence of 1 in 50,000. Diagnosis of CVID is based on the exclusion of other known causes of humoral immune defects (Resnick ES, 2012). It is defined principally as low IgG (often with low IgA) together with a significant impairment of specific antibody production in response to bacterial vaccine or natural infectious challenge (Conley ME, 1999; Cunningham-Rundles C, 1999). Males and females are equally affected, and presentation is most common at the ages of 20 to 40 with only about 20% of patients diagnosed in childhood. While some genetic defects have been shown to cause CVID, in most patients the molecular defect remains unknown. Signs and symptoms of CVID are generally that of recurrent pyogenic sino-pulmonary infections. The patients are also prone to infection with enteric pathogens, such as *Giardia lamblia* infection, and a variety of autoimmune disorders (Resnick ES, 2012). A number of studies have demonstrated the steadily decreasing incidence of infection with increasing frequency of IVIg administration in CVID patients.

In PID diseases with primary antibody deficiency and bacterial infections, lifelong replacement therapy with IgG is required and necessary to reduce incidence (frequency) and severity of infections and prevent long-term deterioration principally in pulmonary functions. Treatment recommendation is that patients with primary antibody deficiency should be treated with IVIg at a starting dose of 400-600 mg/kg every 3 to 4 weeks (Jolles S, 2015). Less frequent treatment, or use of lower doses, is not substantiated by clinical data. Each patient may demonstrate his or her own individual response to therapy, and experience dramatic differences in the frequency and severity of infections with moderate changes in the dose of IVIg (Shapiro RS, 2017). Patients suffering from a serious acute infection often benefit from booster doses of IVIg. Ultimately, IVIg dosage must be individualized based upon the response of the patient (frequency of infection episodes) and potential serious complication of the primary disease (e.g., bronchiectases).

### Quality of Life

The direction of healthcare is moving toward patient satisfaction scores and perception of health. Quality of life (QoL) assessment is valued not only by patients, as they are able to directly contribute to the evolution of their care, but is also considered a measure of efficacy. Quality of life data are used to provide evidence to be used in making critical clinical decisions; it influences managed care, formulary, and purchasing decisions; and positively contributes to the body of scientific knowledge. Contemporary studies of IVIG in treatment of PID patients need to address QoL as an outcome measure to provide information to providers, patients, and payers (Routes J, 2016). The Pediatric Quality of Life

Inventory™ (PedsQL™) is a self-rated and proxy-rated questionnaire, and both versions include 23 items (Varnj JW, 2005).

## 2.2 RATIONALE

Polyclonal Ig preparations of human origin, including IVIg products, have historically been used as replacement therapy to reduce the frequency and severity of serious bacterial infections in patients with PID. Prior to the introduction of IVIg therapy, patients suffering from hypogammaglobulinemia and agammaglobulinemia due to PID experienced approximately 4 or more serious acute bacterial infections each year. However, maintenance of a trough serum level of  $\geq 5$  g IgG/L controls most recurrent infections and their chronic complications, improving the patients' quality of life (Roifman 2008).

With this clinical trial, Kedrion provides more treatment choice in the area of IgG therapy for PID patients and new insight regarding QoL prior to initiation of treatment compared to QoL following the initiation of Klg10. After performing the clinical trial and successive authorization of Klg10 in PID, Kedrion will take a part in stability for IVIg market's supply and will confirm tolerability of IgG therapy as *state of art* treatment of these patients. Performing this clinical trial, Kedrion makes a higher scientific guarantee for using IgG in PID patients and at the same time provides the availability on various IgG production lines, allowing selection between different IgG products as to which is the most suitable (Feldmeyer L, 2010).

This study is being conducted to evaluate the efficacy, safety, and PK of Klg10 in PID patients. Furthermore this study will, for the first time, assess QoL and health care utilization data in PID patients.

The results obtained from this study will support the licensure of the product for the treatment of adult patients affected by PID.

## 2.3 BENEFITS AND RISKS

Replacement Ig therapy is standard practice for patients with PID. Most patients receive IVIg infusions at intervals of 3 or 4 weeks. Reductions in hospitalization and infection rates have been well documented in patients receiving high dose ( $> 400$  mg/kg every 3 weeks) IVIg, and maintaining trough levels of IVIg above 5 g/L is considered a reasonable standard of care (Roifman CM, 2008).

The main goal of replacement therapy in PID is to provide sufficient level of missing Ig to fight against common bacterial agents. To provide quantitative data about sufficient levels of IgG in PID patients during the clinical trial with Klg10, PK sampling will be performed. Determination of Ig levels through the PK parameters in PID patients is desirable for several important reasons. First, performing PK assessment in PID patients provides data about biological integrity of IVIg, measuring total IgG level. Assessment of PID PK parameters equips clinicians with the tools to rationally design IVIg therapeutic regimens (dosing) in order to maximize clinical benefits. Second, PK profile of specific immunoglobulins (Igs) (e.g., antibodies against bacterial antigens (as H. influenzae and toxins), provides indirect proof that the IVIg administered in the study contains sufficient level of specific antibodies against the most common bacterial antigens which cause damage to the organs (primarily the lungs).

The expected adverse events (AEs) occurring with IVIg treatment have been described in the "Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg), EMA/CHMP/BPWP/94038/2007 Rev. 5", in literature, and in clinical trials with PID patients (Schroeder HW, 2012). The incidence of AEs considered to be related to the study IVIg in earlier PID trials ranged from 5-27.6 % (Schroeder HW, 2012).

Safety monitoring during this trial will be managed through different levels of caution.

After all screening procedures have been conducted and reviewed by the site principal investigator, the patient's eligibility assessment will be carried out by the CRO's Medical Monitor, who will consult the study principal investigator for confirmation as needed, based on key protocol inclusion and exclusion criteria to promote appropriate patient enrollment and data quality. Sites should submit specific Screening information as soon as possible after the Screening Visit, but only when all required information is available, for review by the Medical Monitor prior to proceeding to the Baseline visit. Patients who are deemed eligible by the Medical Monitor will be allowed to proceed in the study.

Initially the trial will include adult PID patients and adolescents in whom data will be collected. The data of at least 10 patients with at least 3 infusions (i.e., 3 months of exposure) will be reviewed by a Data Safety Monitoring Board (DSMB), and after positive evaluation, Kedrion intends to continue studying the efficacy and safety of Klg10 in the young age group of PID patients (children < 12 years of age).

There is no risk to the patient in completing QoL questionnaires and self-reported health care utilization. Completion of questionnaires and reporting of data could be beneficial in determining the continuous utilization of IVIg in the treatment of PID.

The selected study centers are highly specialized centers with previous experience in the treatment of PID patients with IVIg as well as with experience in clinical trials. Patients will have diaries, and local medical staff will contact them to check on their well-being when they

are not at a regular site-scheduled visit. All patients will have the first infusion of IgG at a lower infusion speed which may be gradually increased based on individual experience and tolerance. Higher infusion speed might play an important role in determining the safety profile of the product (Cherin P, 2016).

The following adverse reactions are known occasionally to be associated with IVIg products: chills, headache (which is the most frequent AE described in previous clinical trials with IVIg in PID patients, range 22-52% of patients) (Schroeder HW, 2012), dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure, and moderate low back pain.

Rarely, Ig therapy may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis (Schroeder HW, 2012), and rare cases of transient cutaneous reactions (including cutaneous lupus erythematosus – frequency unknown) have been observed with human normal Ig. Reversible hemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB. Rarely, haemolytic anemia requiring transfusion may develop after high dose IVIg treatment. A specific test for early detection of hemolysis will be performed during this clinical trial (see Section 8.2.3, Clinical Laboratory Analysis). The appearance of Coombs positivity after infusion of the study IVIGs occurred in few clinical trials. The proportion of patients that became Coombs-positive after infusion varied from 8.5 to 47%. However, none of the patients in any of earlier trials developed evidence of hemolysis or anemia (Schroeder HW, 2012).

Increase in serum creatinine level and/or acute renal failure have been observed (in most patients with pretreatment known damage of kidney function). Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis have been observed. In previous clinical trials with PID patients only 1 serious AE (SAE) of thrombosis was reported (Moy JN, 2010). If thrombosis occurs, arterial thrombosis is present in about 80% of all patients after using IVIg, and venous thrombosis is seen in the remaining number of patients. There are different risk factors which could play an important role in developing this SAE after IVIg administration. Risk factors connected directly with patient characteristics are advanced age, pre-existing vascular risk factor in general, immobilization, or hereditary hypercoagulability conditions. Some co-medications and risk factors directly related to IVIg product and method of administration for the first ever infusion of IVIg are large dose, high infusion rate, and presence of contaminants in IVIg product such as activated factor XI, factor XII or pre-kallicrein activator (Cherin P, 2016). The careful monitoring of patients treated with IVIg for thrombosis is necessary, even if the risk for thrombosis is small, not only in the first few days after the infusion of IVIg, but also several weeks later (Sentinel Blood SCAN study, 2017). Very rarely, cases of Transfusion



Related Acute Lung Injury (TRALI) have been reported in patients administered IVIg products.

### 3. OBJECTIVES

The purpose of this study is to evaluate the efficacy, safety, and PK of Klg10 in patients with PID in accordance both with FDA and EMA guidelines as specified previously.

#### 3.1 PRIMARY OBJECTIVES

##### Primary Efficacy Objective

To assess the efficacy of Klg10 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.

##### Safety Objective

To assess the safety of Klg10 in the overall study population from day 1 to week 51/52.

##### Pharmacokinetic Objectives

To assess the distribution, metabolism, and elimination of Klg10, 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 OBJECTIVES

##### Secondary Efficacy Objectives

To assess the efficacy of Klg10 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.

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## 4. STUDY DESIGN

### 4.1 OVERVIEW OF STUDY DESIGN

This is a phase III, open-label, prospective, single arm, historically controlled, multicenter study to evaluate efficacy, safety and PK of Klg10 in patients, aged 2 to 70 years at the time of screening and affected by PID.

However, enrollment of the 2 to 11 year-old pediatric patients will be delayed until acceptable safety and efficacy of Klg10 for the PID treatment of adolescents (age 12 to 17) or adults are demonstrated.

All patients will receive an intravenous infusion of Klg10 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 Klg10 will mark the beginning of the investigation period and enrollment, which is further described in Section 6.4. Visits will be performed every 21 ( $\pm$  3) days or 28 ( $\pm$  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).

<b>Procedure 28-day regimen (21-day regimen in parentheses)</b>	<b>Timing</b>	<b>Comments</b>
Screening	Day -28 to day 0 (Day -21 to day 0)	Up to 3 to 4 weeks prior to the first infusion
Infusion 1	Week 1, Day 1 Baseline	Enrollment
Infusion 2 to 4 (Infusion 2 to 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 3 to 4 weeks after the last study infusion

After obtaining a signed informed consent form (ICF), assent form (as applicable), and authorization to access personal health information, the screening procedures will be performed. Screening will include documentation of diagnosis by the site Investigator.

A Patient Diary will be 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.

General and specific disease state questionnaires will be administered to patients to evaluate QoL.

Health care utilization data will also be collected during the study.

Patient personal satisfaction with participation and treatment during the study will be assessed.

The study design is in compliance with both FDA and EMA guidance as specified previously, except for the pediatric enrollment being lower than that required by FDA and EMA for market approval.

## **4.2 STUDY PERIOD**

Each patient should expect to participate in the study for approximately 13 months from the time of signing informed consent through the last study visit, including a 21- or 28-day screening period, a 48-week treatment period, and 3- or 4-week study termination visit (depending on the treatment regimen).

## **4.3 BLINDING AND RANDOMIZATION PROCEDURES**

This is an open-label study; no blinding and randomization procedures will be applied.

## **4.4 DATA COLLECTION**

### **4.4.1 DATA COLLECTED FROM PATIENTS**

The following data will be collected from each patient during their study participation:

- Medical history, including infections history, tolerance of previous IgG treatment, antibody response to pneumococcal vaccination (when available), and documentation of the last 3 commercially available IVIg infusions before the study entry.

NOTE that any potential undesirable effect from screening to infusion 1 will be reported as medical history. Those effects considered serious and related to prior IVIg, will also be notified to the marketing authorization holder.

- Demographic information including date of birth, gender, and ethnicity.
- Physical examination (evaluation of all body systems and body weight).
- Vital signs (blood pressure, heart rate, and temperature).
- Adverse events.
- Relevant prior and concomitant medications, including antibiotic treatment.
- Days missed from work/school/other major activities due to an infection.
- Fever episodes.
- Hospitalizations.
- Chest X-ray obtained within 6 months prior to enrollment.
- Laboratory analysis including hematology, blood chemistry, urinalysis, and intravascular hemolysis testing.
- Pregnancy test on urine (only for females of childbearing age).
- IgG levels throughout the study, and 2 documented IgG levels within 12 months (1 being within 6 months) prior to enrollment.
- IgG subclasses levels (IgG1, IgG2, IgG3, IgG4).
- Specific antibodies levels (anti-tetanus toxoid, anti-pneumococcal polysaccharide, anti-measles, and anti-haemophilus influenza).
- PK parameters of total IgG and specific antibodies (anti-tetanus toxoid, anti-pneumococcal polysaccharide, and anti-haemophilus influenza) (PK Evaluation Set only).
- QoL questionnaires (PedsQL™ and CCI ).
- Health care utilization data as measured by the need for any care in addition to the protocol-defined standard of care visits and items listed in the Schedule of Events (e.g., additional visits to health clinic, doctor office, urgent care center, hospital; additional prescription medications; additional therapies, etc).
- Study-specific questionnaire to evaluate patient satisfaction with participation and treatment during the study (Appendix A).

#### 4.4.2 TOOLS USED FOR DATA COLLECTION

Data will be recorded in medical records and Patient Diary, and collected on electronic case report form (eCRF).

##### **Patient Diary**

Patients, and/or patient's parent(s)/legal guardian(s), will be given a Patient Diary at each infusion visit. The Investigator will explain that the diary is a very important study document and that entries should be made daily in order to collect all safety and efficacy data. The Investigator will train the patient and/or patient's parent(s)/legal guardian(s) on how to complete the Patient Diary, starting at the first infusion visit. The Patient Diary will be collected at the following visit, data will be reviewed by the Investigator, and a new Patient Diary provided to patients at every visit. The patient/patient's parent(s)/legal guardian(s) will enter the following information in the diary:

- All AEs that occurred since the previous study infusion with special emphasis on AEs during the first 24 and 72 hours after infusion, and infections of any type as diagnosed by a physician or other qualified personnel.

NOTE: Infusion AEs during the infusion and within 1 hour after the infusion will be collected at the site, not at home with the Patient Diary.

- Any medication taken, prescription and non-prescription, including antibiotic treatment.
- Days missed from work/school/other major activities due to an infection.
- Fever episodes.
- Days of hospitalization.

The Patient Diary will be collected and reviewed by the Investigator at the clinic visit. Any additional information will be recorded on the source document and collected in the eCRF.

The following additional rules apply to documentation of safety information collected in the Patient Diary:

1. No corrections or additions to the Patient Diary will be allowed after it is reviewed by the site study staff.
2. Any blank or illegible fields on the Patient Diary must be described as missing in the eCRF.

3. Any corrections to the Patient Diary must be performed by the person completing the Patient Diary and should include a single strike through line through the incorrect value or text with a brief explanation for each change, the initials of that person, and date of correction.

### Case Report Forms

This study utilizes eCRFs to collect study-related data from each patient. A qualified and trained site staff member(s) is required to enter patient data in the eCRFs based on the medical information available in each patient's source record.

The following additional rules apply to documentation of Patient Diary information collected in the eCRFs:

1. The site must enter all readable entries in the Patient Diary into the eCRF.
2. Any illegible or implausible data (e.g., those values that may be biologically implausible - body temperature: 400°C) should be reviewed with the patient and parent(s)/legal guardian(s). If an AE is described upon review with the patient, this should be described in the source document and in the eCRF (e.g., if the patient above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Patient Diary, this fever of 40°C should be recorded in the AE eCRF).
3. Any newly described safety information must not be written into the Patient Diary and must be described in the source document as a verbally reported AE. Any AE reported in this fashion must be entered on the eCRF.
4. Data should be entered into the eCRF within 72 hours following each patient's clinic visit or study procedure. Each patient's eCRF casebook will be compared with the patient's source records by a Sponsor-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

## Quality of Life Questionnaires

1. PedsQL™: The PedsQL™ Measurement Model is a modular approach to measuring health-related QoL in healthy children and adolescents and those with acute and chronic health conditions. The 23-item PedsQL™ Generic Core Scales were designed to measure the core dimension of health as delineated by the World Health Organization, as well as role (school) functioning ([www.pedsq.org](http://www.pedsq.org)). This tool can be used across different countries and ages, including adults.

### Scales

Physical Functioning (8 items)  
Emotional Functioning (5 items)  
Social Functioning (5 items)  
School Functioning (5 items)

### Summary Scores

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

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## 4.5 COLLECTION OF CLINICAL SPECIMENS

Blood and urine clinical specimens will be collected from each patient. Processing of each specimen is to be completed by a qualified site member and in accordance with the study-specific Clinical Specimen Laboratory Manual. Testing of clinical specimens will be performed by a designated laboratory.

Refer to the study-specific Clinical Specimen Laboratory Manual for additional details.

### Blood Specimens

A total of approximately 25 to 35 mL of blood will be drawn from all patients at screening, baseline, Study Visits 11 and 17 (for 21-day infusion patients), Study Visits 9 and 13 (for 28-day infusion patients, and at the study termination visit (Week 51/52). At each PK time point (Visit 4 for 21-day infusion patients and Visit 7 for 28-day infusion patients, approximately 20 to 25 mL of blood will be drawn. At all other visits, approximately 10 mL of blood will be drawn. In addition, a pretreatment serum sample at the screening visit and a serum sample at the study termination visit (retention samples) from each patient will be taken and stored at a temperature  $\leq -70^{\circ}\text{C}$  at the central laboratory for at least 2 years following study closure (last patient last visit), for viral safety and possible future viral testing.

The blood samples collected from young/small children enrolled in this study will not exceed the recommended safety limits based on child's size (Toronto Hospital for Sick Children Research Ethics Board) to avoid placing children at unreasonable risk of severe anemia and its complications (Howie SRC, 2011). Existing guidelines for blood sample volume limits (ranging from 1 to 5% of total blood volume within 24 hours and up to 10% of total blood volume over 8 weeks) are consistent with the limited evidence available on "minimal risk" to children. This specification is met if children are over 12.2 kg and should be fulfilled for children  $\geq 2$  years of age.

### Urine Specimens

Urine will be collected for pregnancy testing in females of child bearing potential at screening. In addition, urinalysis will be performed in all patients at each visit, including the screening visit and the study termination visit (week 51/52).

NOTE: If clinical specimens other than those listed above are to be collected, specific purpose, date of collection and amount of sample, must be recorded in the source document and in the eCRF (as unscheduled visits).

#### 4.6 STOPPING/PAUSING GUIDELINES

Investigational New Drug Safety Reports will be submitted to the FDA according to 21 Code of Federal Regulations (CFR) 312.32 requirements and submitted to Health Canada.

If safety concerns arise during the study that indicate the study should be stopped, the Sponsor will terminate the study (21CFR 312.56[d]).

Safety concerns that will be evaluated by the Sponsor and the DSMB will include the following:

- Serious or life-threatening adverse drug experiences that are clearly related to the investigational product.
- Unexpected adverse drug experience related to treatment with the investigational product.
- Suspected thrombotic events.

In addition, conditions that may warrant study termination at a particular site, include, but are not limited to, the following (21CFR 312.56[b]):

- The discovery of unexpected and significant or unacceptable risks for the patients in the study, usually arising due to Good Clinical Practice (GCP) violations.
- A decision of the sponsor to suspend or terminate enrollment at a site due to low/no recruitment, noncompliance, or GCP issues.

If the trial is prematurely terminated or suspended, the Sponsor will inform the investigators, the Institutional Review Boards (IRBs) and the FDA promptly of the termination or suspension and the reason(s) for the termination or suspension.

Patients may be withdrawn from the study according to Investigator discretion as described in Section 4.8, Premature Withdrawal from Study.

#### 4.7 DATA MONITORING COMMITTEE

The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DSMB will provide recommendations about continuing or terminating the trial on ethical grounds.



The DSMB will be advisory to the Sponsor clinical trial team. The sponsor clinical trial team will be responsible for promptly reviewing the DSMB recommendations, to decide whether to continue or terminate the trial and to determine whether amendments to the protocol or changes in study conduct are required.

The DSMB will be asked to review the full documentation for specific AEs and determine whether they meet the criteria for acute serious bacterial infections (as described in Section 8.1.1, Serious Bacterial Infections), defining the study's primary endpoint. Furthermore, the DSMB will be asked to review safety and efficacy data (in terms of IgG trough levels) on at least 10 adolescent or adult patients with 3 infusions (i.e., 3 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 < 12 years of age).

DSMB will also review data that are indicative of intravascular hemolysis.

The DSMB will be independent from Sponsor and Investigators providing their expertise and recommendations. Functions and organization of DSMB are described in the DSMB Charter.

#### **4.8 PREMATURE WITHDRAWAL FROM STUDY**

Patients may withdraw or parent/legal guardian may withdraw a child at any time, without any prejudice or negative impact on the patient's further treatment. The patient or parent should contact the Investigator immediately and notify him/her that they are leaving the study. If possible, the reason for withdrawal for all patients who do not complete the 12-month treatment period, including those who are withdrawn after screening but prior to their first infusion, will be recorded in the source documentation.

For details regarding withdrawals due to infusion AEs, refer to Section 7.1.1, Method of Administration.

The Investigator may withdraw a patient from the study in the following cases:

- For safety reasons, such as a severe AE or SAE, that does not justify continuation in the study in the opinion of the investigator.
- For a protocol violation that jeopardizes performance of the study.
- The patient does not comply with the protocol.
- Continued participation will pose a risk to the patient.
- Pregnancy.

- Use of other IgG products.

In the event of patient withdrawal, site personnel should attempt to collect the patient study diary (completed through the day of withdrawal, if available).

The Investigator or study coordinator must notify the Sponsor/clinical research organization (CRO) immediately when a patient has been withdrawn.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The Investigator should make every attempt to evaluate the patient's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a patient wants to withdraw from the study before all doses are administered or prior to the last planned study visit, the patient will be asked to be followed for safety for the duration of the study. When a patient withdraws, or is withdrawn, from the study, the procedures described in this section should be completed if possible.

The reasons for premature withdrawal from the study include: AE, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

#### **4.8.1 ADVERSE EVENT**

For any patient withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the AE eCRF page by indicating "Withdrawn from study due to AE." Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Patients who develop an SAE judged to be possibly or probably related to the study product should not receive subsequent treatment.

#### **4.8.2 DEATH**

For any patient withdrawn from study participation due to death, this should be noted on the Study Termination eCRF page, and the associated SAE that led to the death must be reported.

#### **4.8.3 WITHDRAWAL OF CONSENT**

The patient and/or parent(s)/legal guardian(s) can withdraw consent for participation in the study at any time without penalty or loss of benefit to which

the patient is otherwise entitled. Reason for early termination should be deemed as “withdrawal of consent” if the patient withdraws from participation due to a non-medical reason (i.e., reason other than AE).

#### **4.8.4 LOST TO FOLLOW-UP**

For patients who fail to show up for final clinic visits, or for 3 consecutive clinic visits, study staff are encouraged to make at least 3 documented attempts to contact the patient/patient’s parent(s)/legal guardian(s) by telephone and at least 1 documented written attempt to contact the patient/parent(s)/legal guardian(s) to encourage the completion of study termination procedures. These efforts to contact the patient should be recorded in the source document.

#### **4.8.5 ADMINISTRATIVE REASON**

Examples for patients withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, patient meeting a pre-specified withdrawal criterion, patient discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Termination eCRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the Investigator has to promptly inform the study patients and local Independent Ethics Committee (IEC)/IRB and should assure appropriate therapy and follow up for the patients. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/devices, etc) must be returned to the Sponsor or its designee (See Section 7.4, Destruction of Used [or Partially Used] and Unused Study Drug).

#### **4.8.6 PROTOCOL COMPLIANCE**

Protocol compliance is the adherence to all the trial-related requirements, GCP, and the applicable regulatory requirements.

Investigators will apply due diligence to avoid protocol noncompliance. Under no circumstances should the Investigator contact the Sponsor or its designee, if any, monitoring the study to request approval of a protocol noncompliance, as no authorized deviations are permitted. If the Investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IEC and health authorities it cannot be implemented (see Section 15.5, Protocol Amendments).

#### 4.9 END OF STUDY

A patient is considered to have completed the study when he/she has:

1. Received all intended doses of Klg10; and
2. Completed the 3 or 4 weeks (according to the treatment regimen) safety study termination visit after the last dose of Klg10.

#### 5. SELECTION OF STUDY POPULATION

The study will entail the evaluation of approximately 50 patients selected in accordance with both the FDA and EMA guidelines stated previously, except for the pediatric enrollment being lower than that required by FDA and EMA for market approval.

Patients with a confirmed diagnosis of PID will be selected for the study. Confirmation of PID diagnosis will include a review of infections history, trough IgG serum concentration within 12 months (at least 2 documented IgG trough levels, 1 must be within 6 months), and previous IVIg treatment data (last 3 commercially available IVIg infusions administered before study entry).

Up to 12 pediatric patients (2 to 17 years old) may be enrolled among the 50 patients to gain primary data for the full pediatric study which is deferred after Biologic License Application approval of the PID adult population. In the meantime, enrollment of the 2 to 11 year old pediatric patients in this study will be delayed until acceptable safety and efficacy of Klg10 for the PID treatment of adolescent or adult patients are demonstrated.

Patients who have an acute infection at the time of screening (exclusion criterion #8) may be rescreened at the investigator's discretion as long as the infection is not serious and is resolved by the time of rescreening.

#### 5.1 INCLUSION CRITERIA

Patients must meet the following inclusion criteria to be enrolled into the study:

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 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.  
(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  $\geq 6$  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 for at least 3 infusion cycles (21 or 28 days) prior to screening.

## 5.2 EXCLUSION CRITERIA

Patients must not meet any of the exclusion criteria to be enrolled into this study:

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 [ $CD3^+ < 300 \text{ cell/mm}^3$ ] 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  $\geq 38^{\circ}\text{C}$  ( $\geq 100.4^{\circ}\text{F}$ ) within 7 days prior to screening.
9. Acquired immunodeficiency syndrome (AIDS) and/or hepatitis B/C active disease 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 ( $\leq 1000$  neutrophils per  $\text{mm}^3$ ) 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  $\mu\text{mol/L}$  or 0.51 - 0.95 mg/dl; b) Male (18+ years): 59 - 103  $\mu\text{mol/L}$  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 prior to 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  $\geq 0.15$  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.

## 6. STUDY PROCEDURES

The sections below provide an overview of the procedures that are to be followed in enrolling, evaluating, and following up the patients who participate in this clinical study. The timing of study procedures is summarized in Table 1.1, Time and Events Table for 28-day Infusion Schedule and Table 1.2, Time and Events Table for 21-day Infusion Schedule.

### 6.1 INFORMED CONSENT/ASSENT/ AUTHORIZATION TO ACCESS PERSONAL HEALTH INFORMATION

*"Informed consent"* is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

*"Assent"* is a term used to express willingness to participate in research by persons who are by definition too young to give informed consent but who are old enough to understand the proposed research in general, its expected risks and possible benefits, and the activities expected of them as patients. Assent by itself is not sufficient, however. If assent is given, informed consent must still be obtained from the patient's parent(s) or legal guardian(s). Local laws define who constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a protocol.

*"Authorization to access personal health information"* is the voluntary authorization of an individual or his/her legal guardian(s) to individual's personal data (related to the clinical trial) processing by the Sponsor, the Investigator or their delegates.

*"Processing"* means any operation or set of operations, which is performed on personal data or on sets of personal data, whether or not by automated means, such as collection, recording, organization, structuring, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, restriction, erasure or destruction.

Informed consent of the patient or of the parent(s)/legal guardian(s), assent of patient and authorization to access personal health information (i.e. Health Insurance Portability and Accountability Act for US and Personal Information Protection and Electronic Documents Act for Canada) following local IRB/IEC guidance **must** be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent, assent and



authorization to access personal health information should be documented in the patient source document.

The signed and dated informed consent, assent, and authorization to access personal health information (personally signed and dated by the patient/parent/legal guardian and by the Investigator) must be retained by the Investigator as part of the study records in the patient source document. A copy of the signed and dated informed consent, assent, and authorization to access personal health information will be given to the patient or patient's legally authorized representative.

Additional specifics regarding the informed consent, assent, and authorization to access personal health information processes are located in Section 15.2, Informed Consent Procedures.

If the patient/parent(s)/legal guardian(s) is unable to read, an impartial witness should be present during the entire informed consent, assent, and authorization to access personal health information discussion. An impartial witness is defined as a person who is independent from study conduct, who cannot be unfairly influenced by those involved with the study, who attends the informed consent process if the patient or the patient's legally acceptable representative cannot read, and who reads the ICF and any other written information supplied to the patient. After the written ICF and any other written information to be provided to patients, is read and explained to the patient/parent(s)/legal guardian(s) and after the patient/parent(s)/legal guardian(s) has verbally consented to the patient's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the patient/parent(s)/legal guardian(s) and that informed consent was freely given by patient/parent(s)/legal guardian(s).

## **6.2 SCREENING VISIT**

Once the informed consent/assent form(s) and authorization to access personal health information have been signed and dated by the patient/parent/legal guardian and by the Investigator (Section 15.2, Informed Consent Procedures), for those patients who meet enrollment criteria, the following procedures will be performed at the screening visit.

1. Medical history including infections history, tolerance of previous IgG treatment, antibody response to pneumococcal vaccination (when available), documented last 3 commercially available IVIg infusions before the study entry.
2. Collection of prior medications.

3. Baseline IgG levels and 2 documented IgG trough levels within 12 months (1 being within 6 months) prior to screening.
4. Demography information including date of birth, gender, race, and ethnicity.
5. Physical examination (evaluation of all body systems and body weight) with an evaluation of vital signs (blood pressure, heart rate, and temperature).
6. Collection of blood samples for IgG levels, hematology, blood chemistry, and intravascular hemolysis testing (see Section 8.2.3, Clinical laboratory Analysis).
7. Collection of urine samples for urinalysis and pregnancy test (for patients of childbearing age).
8. Chest X-ray (if an X-ray performed within 6 months prior to ICF signature is not available).
9. Collection of blood for a retention serum sample, for viral safety and possible future testing.

All screening procedures should be performed within 3 or 4 weeks (depending on treatment regimen) of the first KIG10 infusion.

### **6.3 PATIENT IDENTIFICATION**

Patients who consent to participate in the study will be assigned a unique Patient identification (ID) number. The Patient ID will be in the format xx-yy composed of the study center number (xx) and patient number (yy). The center number will be assigned by the Sponsor. The patient number will be assigned sequentially by the Investigator beginning with 01 at each site.

The study center is responsible for recording all the different codes assigned to the patients in order to avoid errors such as missing subsequent numbers or assigning identical codes to different patients. The patient's ID number must be included in all study documents (e.g., on the eCRF, on the sample containers, on the card where the administration of the medicinal product is recorded, etc.).

The Investigator is responsible for keeping the patient register up to date, in order to avoid the erroneous attribution of numbers (repetitions, skips). The ID number should be used to identify a given patient in all study documents (e.g., eCRFs, documents for submission of trial material, accounting records for the drug, etc.).

## 6.4 ENROLLMENT

Each patient who meets the following criteria will be enrolled in the study and will start the treatment:

1. Has a confirmed PID diagnosis as defined by IUIS Phenotypic Classification for Primary Immunodeficiencies (Bousfiha A, 2018);
2. Satisfies the inclusion and exclusion criteria;
3. Has supplied signed and dated informed consent, assent (as applicable) and authorization to access personal health information; and
4. Has completed all screening activities.

All patients in the study will be treated for a period of 48 weeks according to the dose and schedules reported in sections below.

Patient enrollment will be considered complete with the completion of the Study Eligibility Form in the eCRF.

## 6.5 TREATMENT REGIMEN

All patients will receive an intravenous infusion of Klg10 at the same dose and interval as used for their previous IVIg maintenance therapy. Klg10 will be administered every 21 or 28 days for a period of 48 weeks (depending on the treatment regimen).

The dosage should be calculated so that the amount administered should match the patient's previously individualized dosing regimen, to maintain a trough level of  $\geq 6$  g/L (200 to 800 mg/kg of body weight), in accordance with "Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg); EMA/CHMP/BPWP/94038/2007 Rev. 5." The first infusion of Klg10 will be based on the patient's baseline weight.

The patient's weight will be measured and recorded at screening, baseline and before every infusion at clinic visit for pediatric patients, and at screening, baseline and weeks 12, 24, 36, and 48 for adults, to determine if a dose adjustment is required. Variations in body weight of up to  $\pm 10\%$  will not require a dose adjustment. Variations in excess of  $\pm 10\%$  may require a dose adjustment at the discretion of the Investigator, providing a rationale for his/her choice. In any case, dosage adjustment should be maintained within the standard dosage regimen, unless clinically required otherwise.

Patients will be treated at the site for each infusion (see Table 1.1, Time and Events Table for 28-day Infusion Schedule and Table 1.2, Time and Events Table for 21-day Infusion Schedule).

Details regarding investigational product and treatment of patients are provided in Section 7, Treatment of Patients. Additional information about the investigational product is provided in the Investigator's Brochure.

## 6.6 BASELINE VISIT (Day 1, WEEK 1)

The day of the first Klg10 administration will be considered the baseline visit (day 1, week 1).

Each patient will undergo the following tests and procedures:

- A physical examination (evaluation of all body systems and body weight) with an evaluation of vital signs (blood pressure, heart rate, and temperature).
- Collection of blood (pre-infusion) to measure IgG levels, IgG subclasses (IgG1, IgG2, IgG3, IgG4) and specific antibodies (anti-Haemophilus influenza type b, anti-Tetanus toxoid, anti-pneumococcal polysaccharide, and anti-measles) levels.
- Collection of blood samples (pre-infusion) for hematology and blood chemistry.
- Collection of urine samples (pre-infusion) for urinalysis.
- Collection of blood and urine samples for intravascular hemolysis testing (post-infusion).
- Recording of all AEs and SAEs, including any infections, fever episodes, and hospitalization.
- Recording of all prior and concomitant medication, including use of antibiotics for any kind of infection.
- Training and dispensing of Patient Diary.
- Recording of Klg10 administration information (batch number, dosage, amount of product infused, infusion start and end time, infusion rate).
- Recording days off work/school/other major activities due to infections.
- Completion of QoL questionnaires (PedsQL™ and CCI [REDACTED]).
- Other health care utilization information.

## 6.7 TREATMENT VISITS

Patients will be required to return to the study site for each visit every 21 ( $\pm$  3) days or every 28 ( $\pm$  4) days depending on treatment regimen for a period of 48 weeks – see

Table 1.1, Time and Events Table for 28-day Infusion Schedule and Table 1.2, Time and Events Table for 21-day Infusion Schedule.

Each patient will be treated with Klg10 as reported in the Section 6.5, Treatment Regimen, and undergo the following tests and procedures:

- A physical examination (evaluation of all body systems) with an evaluation of vital signs (blood pressure, heart rate, and temperature); body weight will be collected at each visit for pediatric patients and at weeks 12, 24, 36, and 48 for adults.
- Collection of blood (pre-infusion) to measure IgG levels
- Collection of blood (pre-infusion) to measure IgG subclasses (IgG1, IgG2, IgG3 and IgG4) and specific antibodies (anti-Haemophilus influenza type b, anti-Tetanus toxoid, anti-pneumococcal polysaccharide and anti-measles) at infusions 5, 9, and 13 for the 28-day infusion schedule and at infusions 7, 11, and 17 for the 21-day infusion schedule.
- Collection of blood samples (pre-infusion) for hematology and chemistry.
- Collection of urine samples (pre-infusion) for urinalysis.
- Collection of blood and urine samples for intravascular hemolysis testing (post-infusion).(at infusion 5 for the 28-day infusion schedule or at infusion 7 for the 21-day infusion schedule).
- Recording of all AEs and SAEs, including any infections, fever episodes, and hospitalization.
- Recording of all concomitant medication, including use of antibiotics for any kind of infection.
- Review of Patient Diary (with data collection) and dispensing.
- Record Klg10 administration information (batch number, dosage, amount of product infused, infusion start and end time, infusion rate).
- Record days off work/school/other major activities due to infections.
- At infusion 5 (28-day infusion schedule) or at infusion 7 (21-week infusion schedule), only for those patients that consent to the PK portion of the study (PK Evaluation Set), additional blood samples will be collected for evaluating total IgG levels, IgG subclasses, and specific antibodies, at the time points as described at Section 8.4 Pharmacokinetic (PK) Assessment (PK Evaluation Set):
  - Total IgG levels, IgG subclasses and selected specific antibody levels before (as for all patients) and after infusion 5 (28-day infusion schedule) or infusion 7 (21-day infusion schedule).

- PK parameters<sup>1</sup> of total IgG pre- and post-infusion 5 (28-day infusion schedule) or pre- and post-infusion 7 (21-day infusion schedule).
- PK parameters<sup>1</sup> of specific IgG antibodies pre- and post-infusion 5 (28-day infusion schedule) or pre- and post-infusion 7 (21-day infusion schedule):
  - a. anti-Haemophilus influenza type b
  - b. anti-Tetanus toxoid
  - c. anti-pneumococcal polysaccharide

<sup>1</sup> Plasma concentration-time curve, half-life, area under the curve ( $AUC_{0-t}$ ;  $AUC_{0-inf}$ ), volume of distribution, concentration maximum ( $C_{max}$ ),  $T_{max}$ , elimination rate constant.

- At infusion 7 (for 28-day schedule) or at infusion 9 (for 21-day schedule) completion of QoL questionnaires (PedsQL™, and CCI).
- Collection of other health care utilization information.
- Collection of study-specific questionnaire to evaluate patient satisfaction with participation and treatment during the study at week 24 (infusion 7 for the 28-day schedule or infusion 9 for the 21-day schedule).

## 6.8 REMINDER PHONE CALLS

Reminder calls will be performed on day 2 or 3 after each scheduled infusion. The purpose of this call is to remind the patient/parent(s)/legal guardian(s) about completion of the Patient Diary. The call follows the reminder telephone call script provided to the site, and it is not intended to be an interview for collection of safety data. If the patient/parent(s)/legal guardian(s) wishes to describe safety information, this information should only be collected by a healthcare professional at the site, and the safety data described must be written down in the patient's source document. The patient/parent(s)/legal guardian(s) should be reminded to write the information down in the Patient Diary and to contact the site via the telephone number provided in the informed consent to discuss medical questions.

## 6.9 UNSCHEDULED VISITS

During all the study periods, an unscheduled visit (non-routine study visit triggered by a specific event or for repetition of tests, e.g. Direct Coombs) may occur at Investigator's discretion and will be recorded in the source document and in eCRF.

## 6.10 STUDY TERMINATION VISIT

The study termination visit will occur at week 51/52 (depending on treatment regimen). The termination visit is a clinic visit. The date of termination is the date of

the last contact in which the patients' health status is assessed or, in case where the patient does not agree to any further follow up, it is the date the consent is withdrawn. This date should be recorded on the termination CRF page.

Each patient will undergo the following tests and procedures:

- A physical examination (evaluation of all body systems and body weight) with an evaluation of vital signs (blood pressure, heart rate, and temperature).
- Collection of blood to measure IgG levels.
- Collection of blood samples for hematology, blood chemistry, and intravascular hemolysis testing.
- Collection of urine sample for urinalysis and intravascular hemolysis testing (urine hemosiderin).
- Collection of blood for a retention serum sample, for viral safety and possible future testing.
- Recording of all AEs and SAEs, including any infections, fever episodes, and hospitalization.
- Recording of concomitant medication, including use of antibiotics for any kind of infection.
- Review Patient Diary (with data collection).
- Record days off work/school/other major activities due to infections.
- Completion of QoL questionnaires (PedsQL™, and CCI [REDACTED]).
- Collection of other health care utilization information.

### 6.11 EARLY TERMINATION VISIT

When a patient is withdrawn from treatment or withdraws from the study (Section 4.8, Premature Withdrawal From the Study), the Investigator will notify the Sponsor and, when possible, will perform the procedures listed in Section 6.10, Study Termination Visit. The reason(s) for the early termination will be included in the patient's source documentation. If the Early Termination Visit is a telephone call, as much information as possible will be collected.

## 7. TREATMENT OF PATIENTS

The study drug used in this study must be stored separately from other drugs and medications in a secure location under appropriate storage conditions with temperature monitoring. **All Klg10 vials must be checked for expiration date prior to use. Expired drug must not be administered to patients.**

### 7.1 INVESTIGATIONAL MEDICINAL PRODUCT

Immune Globulin Intravenous (Human) 10% solution will be administered. 1 mL of solution for infusion contains:

Human plasma proteins mg 100 of which immunoglobulin G (IgG) at least 96%.

For details on product composition please refer to the Investigator's Brochure.

The solution is filled into 50 mL type II glass vials.

All study product shall be properly packaged for the clinical study and provided by the Sponsor in compliance with the arrangements made with the Investigator.

#### 7.1.1 METHOD OF ADMINISTRATION

Before administration, the solution must be allowed to reach room temperature. The average time to reach room temperature after storage at <sup>CCI</sup> C is approximately <sup>CCI</sup> hours. Once a vial has been put outside the refrigerator must be used within the same day. Once opened the product must be used immediately.

<sup>CCI</sup>

The study drug will be administered intravenously. Prior to infusion of Klg10, 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.



CCI

### 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 (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.
- 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 (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.

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 Klg10 over the course of the 48-week treatment period. Different lots may not be mixed for a single infusion.

#### **7.1.2 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the investigational product that may impact

patient participation is provided in the Investigator's Brochure.

For intravenous application only.

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human normal Ig by initially injecting the product slowly (with regards to the infusion rate, relevant section of the study protocol must be strictly followed);
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal Ig, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored at the hospital during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

In all patients, IVIg administration requires:

- adequate hydration prior to the initiation of the infusion of IVIg;
- monitoring of urine output;
- monitoring of serum creatinine levels;
- avoidance of concomitant use of loop diuretics.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

#### Infusion reaction

Certain severe adverse drug reactions (ADRs) (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) may be related to the rate of infusion.

The recommended infusion rate given in the study protocols must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Adverse reactions may occur more frequently:

- in patients who receive human normal Ig for the first time or, in rare cases,

when the human normal Ig product is switched or when there has been a long interval since the previous infusion;

- in patients with an untreated infection or underlying chronic inflammation.

### Hypersensitivity

Hypersensitivity reactions are defined according to Gell and Coomb's classification which categorizes hypersensitivity reactions into four subtypes (Uzzaman A, 2012).

Hypersensitivity reactions are rare.

Anaphylaxis can develop in patients who had tolerated previous treatment with human normal immunoglobulin.

In case of shock, standard medical treatment for shock should be implemented.

### Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism, and deep vein thrombosis which is assumed to be related to a relative increase in blood viscosity through the high influx of Ig in at-risk patients.

Acute myocardial infarction (MI) is defined as an acute myocardial injury with clinical evidence of acute myocardial ischemia and detection of a rise and/or fall of cTn values with at least 1 value above the 99<sup>th</sup> percentile upper reference limit and at least 1 of the following (Thygesen K, 2018):

- Symptoms of myocardial ischemia
- New ischemic ECG changes
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs)

Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders,

patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases that increase blood viscosity).

In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

#### Acute renal failure

Acute renal failure is defined according to AKIN/KDIGO criteria (Thomas ME, 2015). Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered.

While reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain these excipients may be considered.

#### Aseptic meningitis syndrome

Aseptic meningitis syndrome (AMS) is defined as meningeal inflammation - i.e. cerebrospinal fluid (CSF) pleocytosis  $\geq 5$  cells/mm<sup>3</sup> - not related to an infectious process (Tattevin P, 2019). Aseptic meningitis syndrome (AMS) has been reported to occur in association with IVIg treatment. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm<sup>3</sup>, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL.

AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

#### Haemolytic anaemia

IVIg products can contain blood group antibodies that may act as hemolysins and induce in vivo coating of red blood cells (RBCs) with Ig, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, hemolysis. Hemolytic anaemia can develop subsequent to IVIg therapy due to enhanced RBC sequestration. IVIg recipients should be monitored for clinical signs and symptoms of hemolysis.

#### Neutropenia

A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIGs. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

#### Transfusion related acute lung injury (TRALI)

In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema TRALI. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1-2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

#### Interference with serological testing

After the administration of Ig the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

### 7.1.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Hypersensitivity to human Igs, especially in patient with antibodies against IgA.

### 7.1.4 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

#### Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

#### Loop diuretics

The use of loop diuretics should be avoided.

### 7.1.5 UNDESIRABLE EFFECTS

Adverse reactions caused by human normal Ig (in decreasing frequency) encompass:

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure, and moderate low back pain;
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion;
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration;
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus – frequency unknown);
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis;
- cases of reversible aseptic meningitis;

- cases of increased serum creatinine level and/or acute renal failure;
- cases of TRALI.

Frequencies have been evaluated according to the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data).

#### 7.1.6 INSTRUCTIONS FOR USE

The product should be brought to room temperature before use.

The solution should be clear or slightly opalescent and colourless or pale yellow. Do not use solutions that are cloudy or have deposits.

Solution should be inspected visually for particulate matter and discoloration prior to administration. Any unused product or waste material should be disposed of in accordance with local requirements.

#### 7.1.7 EXPIRY AND STORAGE

Data as collected from the stability studies support a shelf life of **CCI** when the drug product is stored at temperature of **CCI**. The product must be stored at a temperature of  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ , away from the light. Do not freeze Klg10.

## 7.2 LABEL

Klg10 will be supplied open-label.

### Vial Label text fac – simile (English and French)

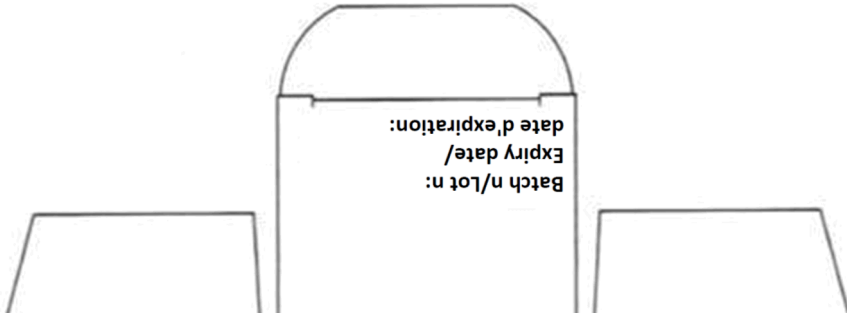
<p><b>Sponsor:</b> Kedrion S.p.A. Loc. ai Conti 55051 – Castelvecchio Pascoli - Barga (LU) Italy <b>Study Code/ étude Clinique:</b> KIG10_US3_PID01 <b>Center number n./Site n.:</b> __ __ <b>Patient/ Sujet n.:</b> __ __ <b>Investigator/ Expérimentateur:</b> _____ <b>IMP:</b> Immune Globulin Intravenous (Human) 10% solution <b>ME:</b> Immunoglobuline Intraveineuse (Humaine) solution à 10 % <b>Dosage:</b> See study protocol/ Voir l'étude clinique <b>Volume:</b> 50 ml <b>Potency/ Puissance:</b> 10 g/100 ml <b>Pharmaceutical form/ Forme pharmaceutique:</b> solution for infusion/ solution pour perfusion <b>Instruction for use/Des instructions pour l'utilisation:</b> See study protocol/ Voir l'étude clinique <b>Route of administration/ Procédé d'administration:</b> intravenous/ intraveineuse <b>Storage condition/Préservation:</b> CCI <b>Caution:</b> New drug - Limited by Federal law to investigational use by a qualified Investigator <b>Attention:</b> Un nouveau médicament - Limité par la loi Fédérale à un usage expérimental on par un chercheur qualifié</p>	<b>Batch n/Lot n:</b>
---	-----------------------

### Package Label Text fac – simile

Number of treatment

XXXXXX





Sponsor: Kedrion S.p.A. Loc. al Conti 55051 - Castelvecchio Pascoli -  
Barga (LU) Italy  
Study Code: KIG10\_US3\_PID01  
Center number: \_\_\_\_\_ Patient number: \_\_\_\_\_  
Investigator: \_\_\_\_\_  
IMP: Immune Globulin Intravenous (Human) 10% solution  
Volume: 50 ml Potency: 10 g/100 ml  
Dosage: See study protocol  
Pharmaceutical form: solution for infusion  
Instruction for use: See study protocol  
Route of administration: Intravenous  
Storage condition: \_\_\_\_\_  
**Caution: New drug - Limited by Federal law to investigational use by a qualified investigator**

**KEDRION**  
BIOPHARMA

Sponsor: Kedrion S.p.A. Loc. al Conti 55051 - Castelvecchio Pascoli -  
Barga (LU) Italy  
étude Clinique: KIG10\_US3\_PID01  
Site n: \_\_\_\_\_ Sujet n: \_\_\_\_\_  
Expérimentateur: \_\_\_\_\_  
ME: Immunoglobuline intraveineuse (Humaine) solution à 10 %  
Volume: 50 ml Puissance: 10 g/100 ml  
Dosage: Voir l'étude clinique  
Forme pharmaceutique: solution pour perfusion  
Des instructions pour l'utilisation: Voir l'étude clinique  
Procédé d'administration: intraveineuse  
Préservation: \_\_\_\_\_  
**Attention: Un nouveau médicament - Limité par la loi Federale à un usage expérimentation par un chercheur qualifié**

**KEDRION**  
BIOPHARMA

### 7.3 INVESTIGATIONAL PRODUCT ACCOUNTABILITY AND DOCUMENTATION

The investigational product will be stored and administered at the investigational site by trained personnel. Each vial will have a lot number and a serial number. Klg10 vials will arrive from the distributor in boxes containing multiple vials. These boxes can be discarded confidentially or destroyed upon receipt and reconciliation of Klg10 vials contained within.

An Investigational Product Accountability Record for Klg10 used for this study must be kept current by the clinical site and must contain:

- Dates, quantities, expiration date(s) and lot number(s) of all investigational product received;
- Dates, quantities, serial number(s) and lot number(s) of investigational product dispensed for each infusion for each patient;
- Patient ID;
- Initials of the staff person dispensing the product.

The Investigator must account for all product and supplies used in the study. Investigators must complete and return the Investigational Product Form together with the unused vials of Klg10. At the end of the study, a final investigational product reconciliation statement must be completed by each site and provided to the Sponsor/CRO representative.

Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to Regulatory Authority inspection or Sponsor/CRO inspection.

The Sponsor/CRO and the pharmacist (or otherwise dedicated person) must keep records regarding shipment, receipt, storage temperature logs, distribution, drug accountability and destruction of the study medication.

### 7.4 DESTRUCTION OF USED (OR PARTIALLY USED) AND UNUSED STUDY DRUG

During the study, the used (or partially used) vials must not be destroyed until Klg10 files have been checked by the monitor. After verification of Klg10 inventory documentation, the monitor will inform the pharmacist (or designated person) to destroy the used (or partially used) vials at the site.

At the end of the study:

- any remaining used (or partially used) vials will be destroyed at site in accordance with local requirements;
- the unused vials should return to the Investigational Product distribution vendor for the destruction.

The Sponsor/CRO and the pharmacist (or designated person) must keep records regarding shipment, receipt, distribution, drug accountability and destruction of the study medication.

## 7.5 CONCOMITANT MEDICATIONS

Concomitant medications are those administered from the first Klg10 infusion until the study termination visit.

Patients who are prone to AEs associated with Ig infusions are frequently pre-medicated with antihistamines, antipyretics, and/or steroids. Premedication intended to prevent AEs associated with infusion of Klg10 should be avoided in this study and may be used if considered necessary by the Investigator.

The rationale to initiate premedication to prevent re-occurrence of AEs will be recorded.

Any medication(s) (excluding biologics or chemotherapy agents) that is (are) not intended for the primary purpose of masking signs of adverse reactions to the infusions, and is (are) taken by the patient on a regular basis may be continued. In particular, daily low dose ( $\leq 100$  mg) aspirin, non-steroidal anti-inflammatory drugs medications, and salicylates for inflammatory bowel disease may be continued.

Concomitant medications (including over-the-counter medications) **with start and stop dates** must be recorded in the source documentation at the study site and collected in the eCRF. The indication for treatment must be recorded, including drug name, route, and duration of drug administration.

Concomitant medications will be recorded during all study periods.

## 7.6 PROHIBITED MEDICATIONS

The use of other polyclonal IgG (SCIG or IVIg) will be prohibited between the first infusion of Klg10 and the study termination visit. High dose steroids (oral and parenteral, daily  $\geq 0.15$  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.

After Klg10 administration, a time interval of at least 3 months must pass before use of a live attenuated virus vaccine.

## **7.7 MISUSE OF STUDY DRUG**

Misuse is defined as administration of wrong dosage and any use not in accordance with IMP instructions. Any misuse must be reported to the Sponsor as such within 24 hours.

## 8. EFFICACY PHARMACOKINETIC, AND SAFETY VARIABLES

### 8.1 EFFICACY VARIABLES

#### 8.1.1 SERIOUS BACTERIAL INFECTIONS

If an acute serious bacterial infection is suspected, the patient must be evaluated for the infection according to the methods described in the *FDA Guidance for Industry: "Safety, Efficacy and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency; June 2008,"* as defined below.

Items in **bold** are considered essential diagnostic features.

The DSMB will be responsible for review the full documentation for specific AEs and determine whether they meet criteria for acute serious bacterial infections. The procedure to complete this activity will be detailed in the DSMB Charter.

All acute serious bacterial infections will be recorded in the eCRF.

#### **Infection:** Bacteremia/sepsis<sup>a</sup>

- *Symptoms:* chills, rigors
- *Physical findings-* fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure < 90 mm Hg or a reduction of  $\geq 40$  mm Hg from baseline in the absence of other causes of hypotension), altered mental status, petechiae, purpura, oligouria, cutaneous vasodilation/vasoconstriction
- *Laboratory tests:* **positive blood culture<sup>b</sup>**, leukocytosis (white blood cell count [WBC] > 12,000/mm<sup>3</sup>), differential WBC count demonstrating > 10% immature (band) neutrophils, leukopenia (defined as < 3000 WBC/ $\mu$ l), thrombocytopenia, coagulopathy, lactic acidosis

#### **Infection:** Bacterial meningitis

- *Symptoms:* headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea/vomiting, rigors, seizures
- *Physical findings:* Kernig's sign, Brudzinski's sign, meningococcal rash, fever of > 38 °C oral or > 39°C rectal
- *Laboratory tests:* **positive cerebrospinal fluid (CSF) Gram stain and/or culture and/or positive CSF bacterial antigen assay**, positive blood culture<sup>c</sup>, CSF leukocytosis with neutrophil predominance, decrease in CSF glucose

**Infection:** Osteomyelitis/Septic arthritis

- *Symptoms:* pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (Local inflammatory symptoms/signs may be lacking in adults.)
- *Physical findings:* evidence of soft tissue infection adjacent to the involved bone/joint; drainage from sinus tract from involved bone; fever of > 38°C oral or > 39°C rectal
- *Laboratory tests:* positive blood culture, positive probe to bone, positive bone aspirate culture, positive bone biopsy culture, positive bone histopathology, positive joint fluid Gram stain and culture
- *Imaging studies:* **positive X-ray, nuclear medicine bone scan, magnetic resonance imaging (MRI) scan, or computed tomography (CT) scan showing bony destruction with radiolucent areas; for chronic osteomyelitis: sequestra, involucra**

**Infection:** Bacterial pneumonia<sup>d</sup>

- *Symptoms:* productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgias
- *Physical findings:* rales; pulmonary consolidation as reflected by: dullness on percussion, bronchial breath sounds, egophony; fever (> 38°C oral or > 39°C rectal), or < 36 °C, or hypothermia (temperature < 36°C oral or < 37°C rectal)
- *Laboratory tests:* leukocytosis; differential WBC count of > 10% band neutrophils; leukopenia (defined as < 3000 WBC/μl); hypoxemia (PaO<sub>2</sub> < 60 mm Hg on room air); positive blood culture; Gram stain and culture of deep expectorated sputum<sup>e</sup>, positive culture with or without positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with bronchoalveolar or protected brush sampling,
- *Imaging studies:* **Pulmonary infiltrate with consolidation on chest X-Ray (new in comparison with baseline chest X-Ray)**

**Infection:** Visceral abscess

- *Symptoms:* abdominal pain, anorexia, weight loss, cough/pleuritic chest pain (hepatic abscess), rigors (seldom present)
- *Physical findings:* intermittent fevers (temperature > 38°C oral or > 39°C rectal); abdominal tenderness; palpable mass; hepatomegaly; jaundice
- *Laboratory tests:* **positive Gram stain and/or culture from the infected site, with isolation of an appropriate pathogen;** positive blood culture; leukocytosis with accompanying left shift; differential WBC count of > 10% immature (band) neutrophils, elevated serum amylase concentration (pancreatic abscess); elevated alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess
- *Imaging studies:* **typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan**

<sup>a</sup> Two of the following should be present to make the diagnosis of sepsis in adults: temperature > 38°C oral/ > 39°C rectal or < 36°C oral or < 37°C rectal; heart rate > 90 beats/minute; respiratory rate > 20 breaths/minute, or PaCO<sub>2</sub> < 32 mm Hg; WBC count > 12,000/mm<sup>3</sup>, < 4,000/mm<sup>3</sup>, or > 10% immature (band) forms. For pediatric patients, the definition of sepsis using age-specific criteria is recommended by the International Consensus Conference on Pediatric Sepsis (Pediatric Crit Care Med 2005; 6(1):2-8).

<sup>b</sup> Indwelling catheter or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IVIg replacement therapy. For patients without indwelling catheters or vascular access devices, a single blood culture positive for a pathogenic organism will meet the diagnostic criteria

for bacteremia (multiple blood cultures are typically obtained in cases of suspected bacteremia/sepsis, as per standard medical practice, and the finding of a single positive culture should prompt additional confirmatory cultures). Patients meeting criteria for positive blood culture but without 2 or more of the sepsis criteria listed above will be classified as having bacteremia.

- c A blood culture positive for growth of *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae*, in combination with CSF leukocytosis and/or glycorrhachia, can serve to confirm the diagnosis of acute bacterial meningitis.
- d For the diagnosis of pneumonia in adults, commonly at least 2 of the listed symptoms and/or signs should be present in conjunction with at least one laboratory and one imaging studies diagnostic element. However, for the purposes of counting serious infection episodes in a clinical trial of IVIg, the finding of a new pulmonary infiltrate with consolidation on chest x-ray is considered sufficient. To establish the diagnosis of bacterial pneumonia for pediatric patients, most of the same diagnostic criteria listed may be used, with the following exceptions: Because pediatric patients may not produce a sputum specimen for culture, blood cultures or serology may be substituted to identify the etiologic bacterial pathogen. In infants age 3 to 24 months, fever is defined as a rectal temperature > 38.3°C (101°F). In children > 2 years, fever is more commonly defined as a rectal temperature > 38°C (100.4°F). In pediatric patients, elevations of WBC counts > 15,000/mm<sup>3</sup> are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count < 5000/mm<sup>3</sup> may be observed, usually associated with severe infection.
- e A deep expectorated sputum gram stain is recommended to demonstrate the presence of microorganisms on examination of 10-20 oil immersion microscopic fields and < 10 squamous epithelial cells and > 25 polymorphonuclear leukocytes at 10X low power magnification to determine suitability of sputum culture.

### 8.1.2 IgG LEVELS

During the clinic visit the pre-infusion IgG levels will be evaluated.

During study treatment, a blood sample for the evaluation of IgG levels (pre-infusion) will be taken before each infusion, every 21 or 28 days during all study period depending on the patient's infusion schedule, and at the study termination visit.

Information about the IgG levels will be recorded in the source documentation at the study site and collected in eCRF.

### 8.1.3 IgG SUBCLASSES/SPECIFIC ANTIBODIES LEVELS

A blood sample for IgG subclasses (IgG1, IgG2, IgG3, IgG4) and the quantitative evaluation of the anti-Tetanus toxoid, anti-pneumococcal capsular polysaccharide, anti-Haemophilus influenza type B and anti-measles antibodies levels will be taken before the following infusions:

- 21-day infusion schedule: at infusions 1, 7, 11, and 17
- 28-day infusion schedule: at infusions 1, 5, 9, and 13

Information about the above IgG subclasses and specific antibodies levels will be recorded in the source documentation at the study site and collected in eCRF.

#### **8.1.4 DAYS MISSED FROM WORK, SCHOOL, OTHER MAJOR ACTIVITIES DUE TO INFECTIONS**

The patient/patients' parent(s)/legal guardian(s) will provide the following information in a Patient Diary that will be provided starting from the first infusion visit: days missed from work/school/other major activities due to infections.

The information entered in the diary since the previous visit will be reviewed at the following visit and collected in the visit specific eCRF pages.

#### **8.1.5 INFECTIONS OTHER THAN SERIOUS ACUTE BACTERIAL INFECTIONS**

All the information regarding infections (other than serious acute bacterial infections), including the number of days for resolution, collected by the patient/patient's parent(s)/legal guardian(s) in the Patient Diary or during clinic visit will be recorded in the specific eCRF pages.

Information entered in the diary since the previous visit will be reviewed at every visit.

#### **8.1.6 FEVER EPISODES**

All the information regarding fever episodes, including the number of days for resolution, collected by the patient/patient's parent(s)/legal guardian(s) in the Patient Diary or during clinic visit will be recorded in the specific eCRF pages.

The definition of fever for all patients participating in the study will be defined as any temperature  $\geq 38^{\circ}\text{C}$  ( $\geq 100.4^{\circ}\text{F}$ ).

Information entered in the diary since the previous visit will be reviewed at every visit.

##### **8.1.6.1 DAYS OF HOSPITALIZATIONS**

The patient/patients' parent(s)/legal guardian(s) will also provide the information regarding the overall hospitalization days and days of hospitalizations due to infection in the Patient Diary that will be provided starting from the first infusion visit.

Information entered in the diary since the previous visit will be reviewed at the following visit and collected in the specific eCRF page.



### 8.1.6.2 USE OF THERAPEUTIC ANTIBIOTICS

The patient/patients' parent(s)/legal guardian(s) will also provide the information regarding the use of therapeutic antibiotics, including the duration of patient on antibiotics, for the treatment of any kind of infections in the Patient Diary that will be provided starting from the first infusion visit.

Information entered in the diary since the previous visit will be reviewed at the following visit and collected in the specific eCRF page.

Start dates and stop dates of antibiotic treatment will be collected to determine the number of days on therapeutic antibiotics.

### 8.1.7 HEALTH CARE UTILIZATION

Health care utilization will be collected during the study as part of self-reported AEs and/or ADRs. These events may be collected from different sources by study personnel assessment during routine study visits, patient diary, or by other notification such as an AE. The health economic data will include only *additional* utilization of health care.

### 8.1.8 QUALITY OF LIFE

#### 8.1.8.1 Pediatric Quality of Life Inventory™

The total score of PedsQL™, and scores in different domains will be computed at baseline, week 24, and at study termination visit, and will be collected in the specific eCRF page.

CCI



## 8.2 SAFETY VARIABLES

The safety assessment will be performed during all study periods.

Starting at the first infusion visit, a Patient Diary will be used to collect and document any AEs. The patient/patients parent(s)/guardian(s) will be trained to complete the Patient Diary.

### 8.2.1 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 vital sign measurements will have an allowable window of  $\pm 5$  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.

### 8.2.2 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 at weeks 12, 24, 36, and 48 for adults.

Information about the physical examination will be recorded in the source documentation at the study site and in the eCRF.

### 8.2.3 CLINICAL LABORATORY ANALYSIS

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.

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

Intravascular hemolysis testing will be performed at the screening visit, after the first study infusion, after the 5<sup>th</sup> infusion for the 28-day infusion schedule or the 7<sup>th</sup> 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.

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 result.

Information about the clinical laboratory analysis will be recorded in the source documentation at the study site and in the eCRF.

Refer to the study-specific Clinical Specimen Laboratory Manual for additional details.

#### **8.2.4 RETENTION OF SAMPLES FOR VIRAL SAFETY AND ANY FUTURE VIRAL TESTING**

In compliance with the “*Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)*” (EMA/CHMP/BPWP/94033/2007 rev.3), a serum sample before treatment at the screening visit and a serum sample at the study termination visit CCI must be drawn from each patient and stored for at least 2 years, following study closure (last patient last visit), at  $\leq -70^{\circ}\text{C}$  temperature for viral safety and any future viral testing at the central laboratory. At the end of that period, the samples should be destroyed.

#### **8.2.5 ADVERSE EVENT**

All serious and non-serious AEs, will be collected for all study periods, evaluated with regard to the infusion rate, and recorded as indicated in the Section 9, Safety Reporting Rules.

In particular, infusion AEs will be collected, defined as AEs occurring during or within 1 hour, 24 hours, and 72 hours following each infusion.

Severity and causality correlation to the therapy will be evaluated. Definition and reporting for event and collection of AEs are described in Section 9, Safety Reporting Rules.

Note that any potential undesirable effect from screening to infusion 1 will be reported as medical history. Those effects considered serious and related to prior IVIg, will also be notified to the marketing authorization holder.

### Medical Events of Interest

For this study, the following will be considered medical events of interest (see Section 7.1.2):

- Thrombotic events
- Hemolysis
- Transfusion-related acute lung injury (see Section 7.1.1, Method of Administration)
- Aseptic meningitis
- Acute renal failure
- Neutropenia
- Hypersensitivity reactions (including anaphylaxis)

Anaphylaxis, defined according to NIAID/FAAN clinical criteria (Shaker MS, 2020), is highly likely when any one (1) of the following three (3) criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg generalized hives, pruritus or flushing, swollen lips-tongue-uvula)  
AND AT LEAST 1 OF THE FOLLOWING:
  - a. Respiratory compromise (eg dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
  - b. Reduced Blood Pressure (BP) or associated symptoms (eg hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after the exposure to a likely allergen for that patient (minutes to several hours):
  - a. Involvement of the skin-mucosal tissue (eg generalized hives, itch-flush, swollen lips-tongue-uvula)
  - b. Respiratory compromise (eg dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
  - c. Reduced Blood Pressure (BP) or associated symptoms (eg hypotonia [collapse], syncope, incontinence)
  - d. Persistent gastrointestinal symptoms (eg crampy abdominal pain,

- vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

### 8.3 DEMOGRAPHIC ASSESSMENT

#### 8.3.1 MEDICAL HISTORY AND DEMOGRAPHIC INFORMATION

The following demographic information, including date of birth, gender and ethnicity, and a complete medical history, will be collected at the screening visit and recorded directly in the eCRF:

- infections history;
- tolerance of previous IgG treatment;
- antibody response to pneumococcal vaccination (when available);
- documented last 3 commercially available IVIg infusions before the study entry;
- baseline IgG levels;
- 2 documented IgG trough levels of  $\geq 6$  g/L within 12 months (1 being within 6 months) prior to enrollment.

In particular, history results relevant to the confirmation of PID diagnosis must be collected. Patients must have a documented history of stable commercially available IVIg therapy at approximately 21- or 28-day intervals for at least 3 infusion cycles prior to receiving Klg10. There must also be documentation of at least 2 trough serum levels of  $\geq 6$  g/L during the previous 6 and 12 months.

#### 8.3.2 CONCOMITANT MEDICATIONS

All medications, drugs and blood products taken or received by the patient starting on the day of the first Klg10 infusion until the study termination visit are to be collected into the e-CRF (see Section 7.5, Concomitant Medications).

#### 8.3.3 CHEST X-RAY

A chest x-ray will be performed at the screening visit if a chest x-ray is not available within last 6 months prior to the ICF signature.

## 8.4 PHARMACOKINETIC ASSESSMENT (PK EVALUATION SET)

Pharmacokinetic assessments will be performed in approximately 24 adult patients in order to have 20 evaluable patients before and after the 5<sup>th</sup> study infusion (28-day infusion schedule) or the 7<sup>th</sup> 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 24 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:

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

Information about the PK assessment will be recorded in the source documentation at the study site and in the eCRF.

### 8.4.1 PK PARAMETERS OF TOTAL IgG

Blood samples for the analysis of PK parameters for total IgG will be taken before and after infusion 5 for the 28-day infusion schedule or infusion 7 for the 21-day infusion schedule, and at the time points indicated above in Section 8.4, Pharmacokinetic Assessment.

Total IgG levels and the following PK parameters will be evaluated. The PK parameters are also described in Section 10.4.4.

Plasma concentration-time curve, half-life,  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , volume of distribution,  $C_{max}$ ,  $T_{max}$ , and elimination rate constant.  $AUC_{0-inf}$  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.

Data about the above total IgG levels will be recorded in the source documentation at the study site and in the eCRF.

#### **8.4.2 IgG SUBCLASSES 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 8.4, Pharmacokinetic Assessment.

IgG subclasses levels will be recorded in the source documentation at the study site and in the eCRF.

#### **8.4.3 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 8.4, Pharmacokinetic Assessment.

Specific antibodies levels and the following PK parameters will be evaluated. The PK endpoints are also described in Section 10.4.4.

Plasma concentration-time curve, half-life,  $AUC_{0-t}$ , volume of distribution,  $C_{max}$ ,  $T_{max}$ , and elimination rate constant.  $AUC_{0-inf}$  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.

Data about the above specific IgG antibodies will be recorded in the source documentation at the study site and in the eCRF.

## 9. SAFETY REPORTING RULES

### 9.1 DEFINITIONS

#### 9.1.1 ADVERSE EVENT/ADVERSE DRUG REACTION

An AE is “any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment” Directive 2001/20/EC.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An ADR is “any untoward and unintended responses to an IMP related to any dose administered.” The definition of ADR covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The definition implies a reasonable possibility of a causal relationship between the event and Klg10. This means that there are facts (evidence) or arguments to suggest a causal relationship.

#### 9.1.2 SERIOUS ADVERSE EVENTS

A SAE is “any AE that, at any dose:

- results in death,
- is life threatening,
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect.”

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it was more severe.

Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to as ‘important medical events’) should also be considered as ‘serious’ in accordance with the definition.



A **non-serious AE** is an AE that does not meet the above criteria.

### 9.1.3 UNEXPECTED ADVERSE DRUG REACTIONS

An unexpected adverse reaction is an “adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator’s brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).”

Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

### 9.1.4 CAUSALITY CORRELATION

The Investigator should evaluate the association between the AE and the on-going treatment using information found in the Investigator’s Brochure in conjunction with the patient’s pre-existing medical conditions and concomitant medications and the timing of the AE relative to the administration of Klg10. Any AE will be reported as “Related” or “Not Related” to Klg10 in accordance with the following definitions, elaborated from those of the World Health Organization:

#### Related:

**Any event which falls into one of the below definitions (certain, probable or possible), it should be considered as “Related” to study drug.**

#### Certainly Related

A clinical event (including laboratory test abnormalities):

- occurring in a plausible time relationship to drug administration;
- which cannot be explained by concurrent disease or other drugs;
- which response to withdrawal of the drug (de-challenge) is clinically plausible;
- which must be definitively associated pharmacologically or phenomenologically, using a satisfactory “re-challenge” procedure, if necessary.

Probably related:

A clinical event (including laboratory test abnormalities):

- with reasonable time sequence to administration of the drug;
- unlikely to be attributed to concurrent disease or other drugs or chemicals;
- which follows a clinically reasonable response on withdrawal (de-challenge);
- “re-challenge” information is not required to fulfil this definition.

Possibly related:

A clinical event (including laboratory test abnormalities):

- with a reasonable time sequence to administration of the drug;
- which could also be explained by concurrent disease or other drugs or chemicals;
- information on drug withdrawal may be lacking or unclear.

Not related:

An event for which sufficient information exists to conclude that the etiology of the event is unrelated to Klg10.

Please note that this definition is intended to be used when the exclusion of drug causality of a clinical event is supported by the existence of an alternative cause (e.g., concomitant medications, medical history, concomitant diseases, disease under study, or other) which should be clearly specified with additional details.

If a possible correlation cannot be excluded, the definition to be used is “Related.”

## 9.2 REPORTING METHODS

**Any serious and non-serious AE** must be communicated to Kedrion or its designee. An eCRF will be used for this study. All serious AEs will be communicated to Kedrion/designee as noted in Section 9.2.1.

### 9.2.1 SERIOUS ADVERSE EVENT/SERIOUS ADVERSE DRUG REACTIONS

All SAEs/serious adverse drug reactions (SADRs) must be reported by the Investigator to the Sponsor or its designee by entering all information relevant to the event in the appropriate "Serious Adverse Event(SAE)/Medical Event of Interest Report Form" **immediately** and, in any case, **no later than 24 hours** following the receipt of this information. A detailed report (**follow-up**) on the case should be supplied by the Investigator within the **subsequent 3 calendar days**, using the same form.

In the case of a SAE with a **fatal** outcome, the Investigator must notify not only the Sponsor/designee but also the local IEC/IRB and must provide any additional required information.

### 9.2.2 NON-SERIOUS ADVERSE EVENTS

The Investigator is required to notify the Sponsor/designee of all non-serious AEs. This information should be reported by the Investigator to the Sponsor/designee by updating the eCRF "Adverse Event Report Form" following the receipt of this information.

### 9.2.3 ABNORMALITIES IN LABORATORY PARAMETERS

The Investigator must evaluate the clinical significance of all abnormal laboratory values based on standard laboratory reference values. Any clinically significant abnormality must be fully investigated. The term "clinically significant" refers to any abnormal value that, according to the Investigator, represents an important clinical problem that requires the intervention of a physician or that otherwise may fall within the definition of a "serious" AE. When clinical significance is indicated, further analysis or other assessments must be obtained in order to determine the significance or cause of an abnormal result, or to monitor the course of an AE. Any persistently abnormal value must be monitored at the Investigator's discretion. Clinically significant abnormal results shall be documented in the appropriate eCRF.

Pregnancy test will be performed locally at each site. Hematology, chemistry, urinalysis, IgG levels, subclasses, specific antibodies, and intravascular hemolysis testing will be analyzed centrally. Direct Coombs and urine hemosiderin can be tested either centrally or at site level. For centralized tests, Investigators will receive the results and the reference normal ranges for patient monitoring.

#### **9.2.4 PRE-EXISTING AND CONCOMITANT DISEASES**

Pre-existing diseases that are present prior to the study entry before the ICF signature up to the first Klg10 infusion must be reported in the appropriate eCRF (Medical History). Please note that signs/symptoms of a pre-existing disease that occur with the same severity, frequency or duration after the administration of Klg10 will be considered as Medical History.

Concomitant diseases that occur following the first Klg10 infusion until the study termination visit or cases that show an increase in the severity or the duration of a pre-existing disease must be reported as AEs.

#### **9.2.5 PREGNANCIES**

To ensure patients' safety, each pregnancy in a patient after study drug administration must be reported to the Sponsor within 24 hours of the site learning of its occurrence. If the patient agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy and Breastfeeding Exposure Report form and reported to the Sponsor/designee. Follow-up reports will be submitted on the same form. Instructions and contact details for submitting the Pregnancy and Breastfeeding Exposure Report will be provided to the Investigator.

#### **9.2.6 INSTRUCTIONS FOR THE STUDY PERSONNEL REGARDING CLINICAL SIGNS AND SYMPTOMS**

Patients/patient's parent(s)/legal guardian(s) will be instructed to call specified study personnel if any clinical sign or symptom appears after treatment. Patients who develop severe systemic events should be examined, if possible, at the treating facility at the time of the maximal symptoms and clinically monitored until their resolution.

Any event causing the withdrawal of the patient from the study shall be reported in the appropriate eCRF section. All AEs shall be followed until recovery and/or diagnosis. If an AE is not resolved by the end of the study, the Investigator shall determine whether to authorize a follow-up. All drugs administered during the

study to treat either AEs or previously diagnosed conditions shall be recorded in the appropriate eCRF.

Where a diagnosis is possible, it is preferable to report this rather than a series of terms relating to the diagnosis itself. When a syndrome is reported, the associated signs and symptoms must be documented as part of the syndrome and not as separate events.

Any patient reporting an AE shall be examined by a physician as soon as possible. The physician must do whatever is necessary for the safety and welfare of the patient. All these events shall be monitored until recovery or clinical stabilization.

The AE shall be described in the eCRF using standard terminology (MedDRA) to avoid the use of vague, ambiguous, or colloquial expressions. The Investigator shall evaluate the severity of all AEs and their correlation with the study drug and shall report the result of the analysis and the necessary actions to be taken.

## 10. STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan (SAP) is provided with IND/CTA submission. Protocol deviations will be defined at the beginning and data will be checked throughout the study on a regular basis (International Council for Harmonization [ICH] E6 [R2] addendum). Protocol deviations will be described in the SAP.

### 10.1 ANALYSIS SETS

The efficacy and safety analyses will be based, respectively on the Full Analysis Set (FAS) and the Safety Set (SAF) unless stated otherwise. All PK analyses will be done on the PK Evaluation Set.

The following analysis sets will be defined:

#### 10.1.1 ALL PATIENTS ENROLLED SET

The All Patients Enrolled Set includes all patients who have given informed consent/assent to this study.

#### 10.1.2 FULL ANALYSIS SET

The FAS comprises all patients who have received at least 1 dose of study medication.

#### 10.1.3 SAFETY SET

The 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.

#### 10.1.4 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. Any analysis based on the PPS will be performed for the primary efficacy endpoint as an additional supportive analysis.

#### 10.1.5 PHARMACOKINETIC 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 5<sup>th</sup> infusion (28-day infusion schedule) or the 7<sup>th</sup> 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-pneumococcal capsular polysaccharide, anti-haemophilus influenzae type B, anti-tetanus toxoid), measured in the dense sampling period (i.e., before and after the 5<sup>th</sup> infusion of the 28-day infusion schedule and before and after the 7<sup>th</sup> infusion for the 21-day infusion schedule).

## 10.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be summarized on the FAS using descriptive statistics.

## 10.3 PRIMARY ENDPOINT

### 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 pre-specified criteria).

### 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 per patient. The estimate and 1-sided 99% upper confidence limit will be reported. Efficacy will be claimed if this limit is less than 1.0.

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## 10.4 SECONDARY ENDPOINTS

### 10.4.1 SECONDARY EFFICACY ENDPOINTS

#### Definitions

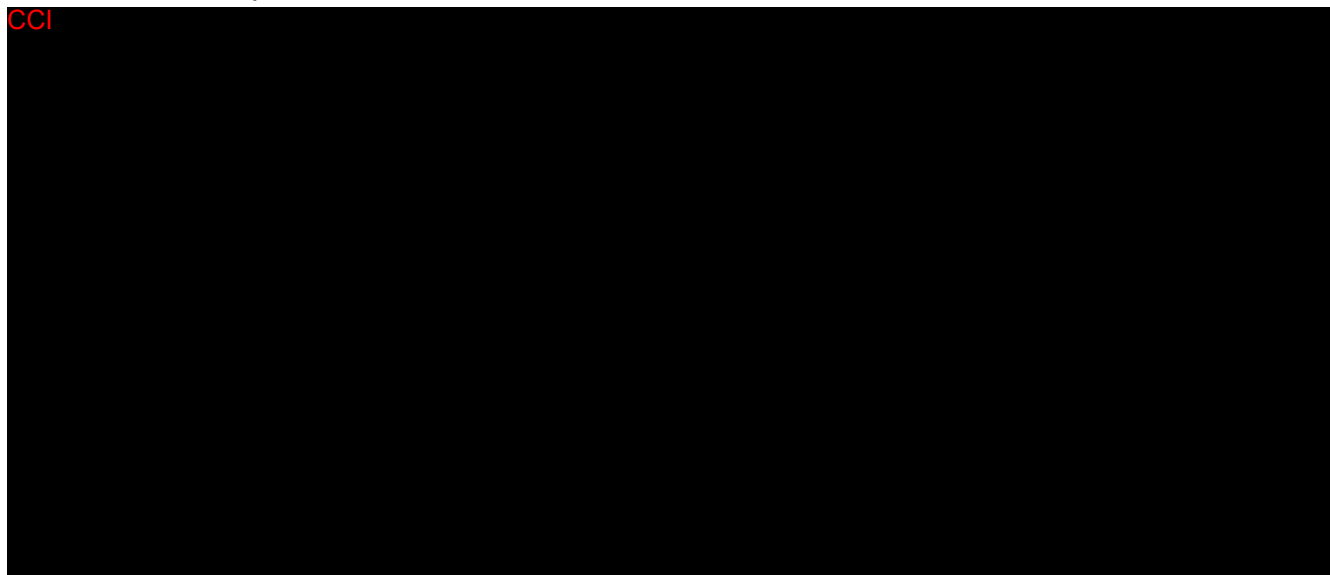
1. Serum IgG trough levels before each infusion of Klg10 and at the study termination visit (week 51/52).
2. IgG subclasses levels (IgG1, IgG2, IgG3, IgG4) before infusions 1, 5, 9, and 13 for the 28-day infusion schedule, and before infusions 1, 7, 11, and 17 for the 21-day infusion schedule.
3. Frequency 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-Haemophilus 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 patient 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, and study termination visit.

### **Analysis**

Secondary efficacy endpoints will be summarized using descriptive statistics. Further details will be provided in the SAP.



### **10.4.3 SAFETY ENDPOINTS**

#### **Definition**

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 Klg10 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 5<sup>th</sup> infusion for the 28-day infusion schedule and the 7<sup>th</sup> infusion for the 21-day infusion schedule.
8. The proportion and number of patients with a positive urine hemosiderin test following the 5<sup>th</sup> infusion for the 28-day infusion schedule and the 7<sup>th</sup> infusion for the 21-day infusion schedule.
9. Plasma-free hemoglobin level following the 5<sup>th</sup> infusion for the 28-day infusion schedule and the 7<sup>th</sup> infusion for the 21-day infusion schedule.
10. Serum haptoglobin level following the 5<sup>th</sup> infusion for the 28-day infusion schedule and the 7<sup>th</sup> infusion for the 21-day infusion schedule.

### **Analysis**

Secondary safety endpoints will be summarized using descriptive statistics. Additionally, a 1-sided 95% 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 (Wu, 2012). For this analysis, safety will be declared if the upper 1-sided 95% confidence is less than 0.4. Other methods that take in account the clustered nature of the data could be performed (e.g., Generalized Estimating Equation). Additionally, a 2-way table will summarize the frequency and proportion of infusion related AE by speed of infusion category. 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).

Further details will be provided in the SAP.

#### **10.4.4 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 5<sup>th</sup> infusion (28-day infusion schedule) or 7<sup>th</sup> infusion (21-day infusion schedule).
2. PK parameters of total IgG before and after the 5<sup>th</sup> infusion (28-day infusion schedule) or 7<sup>th</sup> infusion (21-day infusion schedule).
3. PK parameters of specific IgG antibodies before and after the 5<sup>th</sup> infusion (28-day infusion schedule) or 7<sup>th</sup> 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. The details will be further described in the SAP.

## 10.5 SCHEDULE OF ANALYSES

### 10.5.1 INTERIM PK ANALYSIS

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. The data for total IgG, IgG subclasses and specific IgGs will be received from the bioanalytical laboratory for PK analysis and reconciled by data management to format interim PK datasets. Planned and additional PK parameters as data allow will be derived by the PK scientist using professional PK software and formatted as interim PK analysis TLFs in SAS. Interim PK report will be produced by the study PK scientist.

**10.5.2 DSMB Reviews** Safety and efficacy data recorded during the study period will be reviewed by an independent DSMB at specific intervals. The timing of the DSMB reviews will be described in the DSMB charter.

## 10.6 SUBGROUPS

Subgroup analyses are planned to be performed for the primary and secondary efficacy endpoints and for safety endpoints, including AEs (infusional AEs and treatment-emergent AEs).

### 10.6.1 AGE

The age categories for the subgroup analyses will be children (2 to 11 years, inclusive), adolescents (12 to 17 years, inclusive), and 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).

### 10.6.2 TREATMENT SCHEDULE

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

## 10.7 HANDLING OF MISSING DATA

Missing data will not be an issue on primary efficacy analysis as, in the worst case scenario, a patient will contribute with no person year to analysis. For other data, further details will be provided in the SAP.

## 10.8 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, 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 under the assumption that the deviation may have an impact on the efficacy analysis.

The investigator should not implement any deviation from, or changes of the protocol, without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, 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.

**10.9 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 and EMA 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]

[REDACTED]

[REDACTED]

[REDACTED]

## 11 SOURCE DOCUMENTATION, STUDY MONITORING, AND AUDITING

In order to ensure consistency across sites, study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated CRO standard operating procedures (SOPs) and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrollment of the first study patient, the Sponsor or its delegate will train Investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. eCRFs supplied by the Sponsor must be completed for each enrolled patient. All patients' documentation, including screened but not enrolled patients, must be maintained at the site and made available for review by the site monitor. Data and documents will be checked by the Sponsor and/or monitor.

### 11.1 SOURCE DOCUMENTATION

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The list of documents that will serve as source documents will be agreed between Sponsor (or its designee) and Investigator and study staff prior to patient enrollment.

In addition, source documentation **must** include all of the following: patient ID number, eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of AEs, documentation of prior/concomitant medication/drugs, study drug receipt/dispensing/return records, study drug administration information, any data collected during the visits and by a telephone conversation with the patient and/or parent(s)/legal guardian(s), and date of completion and reason.

The patient and/or parent(s)/legal guardian(s) must also allow access to the patient's medical records. Each patient and/or the parent(s)/legal guardian(s) must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by patients must be collected down in source documents prior to entry of the data into eCRFs. If there are multiple sources of information (e.g., verbal report of the patient, telephone contact details) supporting the diagnosis of an AE, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in eCRF. The eCRF must also capture which source(s) of information were used to determine the AE (e.g., patient recall, medical chart, Patient Diary).

## 11.2 STUDY MONITORING, AUDITING, AND SOURCE DATA VERIFICATION

Study progress will be monitored by the Sponsor or its designee as frequently as necessary to ensure:

- that the rights, safety and well-being of human patients are protected;
- the reported study data are accurate, complete, and verifiable from the source documents; and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the Sponsor or its designee involved in study monitoring will be provided to the Investigator. Study data recorded on eCRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol.

Additional documents such as the Investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The Investigator and/or site staff must make source documents of patients enrolled in this study available for inspection by Sponsor or its representative at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA, and others) and/or IECs. The Investigator and study site staff must comply with applicable privacy, data protection, and medical confidentiality laws for use and disclosure of information related to the study and enrolled patients.

## 11.3 QUALITY ASSURANCE PROCEDURES AND AUDITING

The competent authorities or the Sponsor, may decide to audit the study in order to ensure its compliance with the Protocol, with SOPs, GCP and all applicable regulations. The Investigator shall ensure that the inspectors/auditors have access to the patients' medical records and to all study documents. The Investigator and his/her staff shall also be available to discuss any issues that may arise with the inspectors.

Sponsor and/or its designee, in particular, may carry out periodic audits at the trial centers, laboratories and CROs/other vendors involved in the study.



The patient or the patient's parents or legally acceptable representative(s) must also allow access to the patient's medical records. Each patient, or the patient's parent(s) or legally acceptable representative(s), should be informed of this prior to the start of the study.



## 12 DATA MANAGEMENT

### 12.1 DATA ENTRY AND MANAGEMENT

All clinical data will be entered onto eCRFs in 72 hours by the Investigator and/or the Investigator's dedicated site staff. The data collected on this secure website are assimilated into an electronic data capture (EDC) system. The data system includes password protection and internal quality checks. The Investigator or designated delegate must review data entered and electronically sign the eCRFs to verify their accuracy.

Access to the EDC for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

### 12.2 DATA CLARIFICATION

The Investigator must review and electronically sign the eCRFs to verify their accuracy. Correction to data on eCRFs will be tracked via an audit trail within the web based EDC system. Each correction will be identified by the person making the change and will include time, date, and reason for change. If corrections are made to a previously and electronically signed eCRF, the Investigator must confirm and endorse the changes.

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed eCRF, the Investigator must confirm and endorse the changes.

### 12.3 DATA PROTECTION

Sponsor and its designee respect the patients' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

### 13 RECORD RETENTION

The Investigator is responsible for maintaining all records pertaining to the clinical trial and for ensuring complete and accurate documentation.

The Investigator is responsible for maintaining a patient ID log. This confidential patient ID code provides the link between named patient source records in the patient file and anonymous CRF data provided to Sponsor.

The Sponsor requires that each Investigator retain all study related documents for a minimum of 25 years after the study completion (last patient last visit) in alignment with the current applicable guidelines. If the study is discontinued, or if no application/license is to be filed or if the application/license is not approved for such indication, records should be retained for 25 years after the investigation is discontinued or as per local regulations, whichever is longer.

The Investigator could be relieved of this responsibility by transferring the documentation custody to another person who is a member of the trial center and who will accept the conservation responsibility. In this case the Sponsor should be informed about the custody transfer, preferably within 10 days from the date of transfer.

It is prohibited for study documents to be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator wish to assign the study records to another party, or move them to another location, the Sponsor must be notified in writing.

## 14 PROPERTY OF DATA AND PUBLICATION

The Investigator is informed that the information produced in such study will be used by the Sponsor in relationship with the product development and, therefore, may be widespread to the governmental agencies in various countries. To enable the use of data, the Investigator should supply the Sponsor with the complete results of the tests, all the study data and the access to all study documents.

As the exclusive owner of the results obtained, the Sponsor acknowledges the importance of the diffusion of medical data and, therefore, encourages their publication on reputed scientific journals and the diffusion during seminars and conferences.

The Investigator may publish the trial results only following the relative authorization from the Sponsor. The eventual absence of the Sponsor authorization should be adequately motivated.

Any results of the medical research on Kedrion's products and/or the publication/oral diffusion/relevant manuscripts will be examined and discussed by the Investigator and Kedrion representative 60 days before the submission for the publication or presentation during a conference. The due diligence should be offered to the Sponsor's legitimate interests, or the paternity of the manuscript, obtaining an excellent patent protection, coordinating and keeping the exclusive nature of the submission to the health authorities, coordinating with other studies on-going in the same area, and protecting the confidential data and information.

The Sponsor should receive the copy of each publication proposed. Kedrion's comments should be issued without any exceeding delay and not beyond 60 days. In case of publication or presentation of the material of multicentre clinical trials, Kedrion should act as a coordinator and referee. The individual Investigators of a multicentre trial cannot publish or submit data which are considered to be common to such a study without the consent of the other Investigators and the previous review of Kedrion.

In the case of a disagreement between the participants in the multicentre trial, Kedrion will be the final arbiter. Kedrion's comments should be issued with no extra delays. Whenever they are not accepted, the senior author of the manuscript and the Kedrion's representatives should meet to discuss and find a common position for the final written text and/or the character of the publication. The above mentioned procedure also applies to data pertaining to prematurely discontinued or not completed studies.

The results of the Investigators can be divulged to third parties from the trial team only with the paper version and only after Kedrion's approval. Kedrion will not mention the data of Investigators' publications in its scientific information and/or promotional material without the complete acknowledgment of the sources (namely author and references).

## 15 ETHICS

### 15.1 REGULATORY AND ETHICAL COMPLIANCE

International Council for Harmonization E6 GCP Guidelines require that Independent IRB/IEC oversees all investigational drug studies. This committee, the makeup of which must conform to applicable regulations and guidelines, will approve all aspects of the study, including said protocol, written ICF, and any patient information sheets to be used, prior to initiation of the study. The Investigator will provide the Sponsor with a copy of the communication from the committee to the Investigator indicating approval of the protocol and consent form/information sheets. All amendments to the protocol must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human patients.

The Investigator will be responsible for obtaining annual IRB/IEC renewal and submitting SAE reports to the IRB/IEC for the duration of the study (as per IRB/IEC policies and procedures). Copies of the Investigator's report and/or copies of the IRB/IEC extension approval must be sent to the Sponsor.

Protocol deviations and violations will be submitted to IRB/IEC according to the requirements of each of these institutions.

### 15.2 INFORMED CONSENT PROCEDURES

Eligible patients may only be included in the study after providing written ICF, assent and authorization to Access Personal Health Information, in compliance with the GCP and local regulation, as described in Section 6.1, Informed Consent/Assent/Authorization to Access Personal Health Information. Before the start of the study, the Investigator will have the informed consent, assent, authorization to access personal health information and any other materials that will be provided to the patients and parent(s)/legal guardian(s) reviewed and approved by the IRB/IEC. This review and approval will be documented and archived with other study documents.

The Investigator or designee must fully inform the patient and parent(s)/legal guardian of all pertinent aspects of the study. A copy of the written ICF, assent and authorization to access personal health information will be given to the patient or the designee. The patient/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The patient and/or legal guardian(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. If the patient and/or legal guardian(s) is unable to read and write, a witness must be present during the informed consent discussion and at the time of ICF signature. Adult patients

who lack the capacity to provide consent will not be allowed to enroll in the protocol through the use of a legally authorized representative.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements indicated in the protocol for the duration of the study. In case of doubts on the ability of a patient to adhere to these requirements, that patient should not be allowed in the study.

In addition, the Investigator or designee should explain pertinent aspects of the study in an age appropriate manner to pediatric patients who are eligible for informed assent in accordance with local policies.

### **15.3 RESPONSIBILITIES OF THE INVESTIGATOR AND IRB/IEC**

The protocol and the proposed informed consent/assent/authorization to access personal health information forms must be reviewed and approved by a properly constituted IRB/IEC before study start. Properly constituted IEC is defined in ICH Guideline for GCP E6 (R1), Section 3 (ICH, 1997). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to the Sponsor before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the Sponsor's monitors, auditors, and Clinical Quality Assurance representatives, designated agents of the Sponsor, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform the Sponsor immediately that this request has been made.

The Investigator is also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the Investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable patients within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.

- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions.
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of patients experiencing any AE related to the study.
- If permission to do so is given by the patient and parent(s)/legal guardian(s), ensuring that the patient's primary healthcare provider is informed of the patient's participation in the study.

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

The Investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to study patients without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- (a) to the IRB/EC for review and approval/favorable opinion;
- (b) to the Sponsor for agreement and, if required;
- (c) to the regulatory authority(ies).

### **Liabilities and Insurance**

The study sponsor, Kedrion S.p.A. will pay for all study-related costs. A separate financial agreement will be made (as appropriate) with the Investigator and/or institutions.

In case of any damage or injury occurring to a patient in association with the investigational product or participation in the study, the manufacturer of Klg10 has a policy with an insurance company.

### **15.4 CONFIDENTIALITY**

The Investigator will ensure that the patients' confidentiality will be maintained on the eCRF or other documents submitted to the Sponsor or its designee. Patients will not be

identified by their names, but by a unique Patient ID number, (see Section 6.3, Patient Identification). Documents not for submission to the Sponsor or its designee (e.g., the site confidential patient enrollment log, original ICF, assent form, and authorization to access personal health information), will be maintained by the Investigator in strict confidence.

## 15.5 PROTOCOL AMENDMENTS

An amendment is a written description of change(s) to or formal clarification of a study protocol, which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects.

The changes to the protocol may be performed only after consultation and agreement with the Sponsor and the Investigator. The only exception is when the Investigator deems that the patients' safety may be impaired without an immediate action. In these cases, the immediate approval of the IRB/IEC should be required and the Investigator should inform the Sponsor and the Competent Authority within 5 working days after the occurrence of the emergence. All the changes that have an impact on the risk of the patients or on the objectives of the study or require a change of the Informed Consent should receive the approval of the IRB/IEC before their implementation.

An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on patient safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by the Sponsor, health authorities where required, and the IRB/IEC.

## 16 REFERENCE LIST

- Bonilla FA, Geha RS. Primary immunodeficiency diseases. *J Allergy Clin Immunol*, 2003. 111(2 Suppl): S571-581.
- Bousfiha A, Jeddane L, Al-Herz W, et al., The 2015 IUIS Phenotypic Classification for Primary Immunodeficiencies *J Clin Immunol* 2018, 38(1): 129-143.
- Bruton OC. Agammaglobulinemia. *Pediatrics*. 1952;9:722-728.
- Cherin P, Marie I, Michallet M, et al. Management of adverse events in the treatment of patients with immunoglobulin therapy: A review of evidence. *Autoimmun Rev*. 2016 Jan; 15(1):71-81.
- Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). *Clin Immunol*, 1999;93(3):190-197.
- Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol*, 1999;92(1):34-48.
- Directive 2001/20/EC of the European parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
- 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.
- 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.
- 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.
- Feldmeyer L, Benden C, Haile SR, et al. Not all intravenous immunoglobulin preparations are equally well tolerated. *Acta Derm Venereol*. 2010 Sep;90(5):494-497.



- Goldstein B, Giroir B, Randolph A. International pediatric consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005 Jan;6(1):2-8.
- Howie SRC. Blood sample volumes in child health research: review of safe limits. *Bull World Health Organ* 2011; 89:46–53.
- ICH Guidance E6 – Guidelines for Good Clinical Practice: Consolidated Guideline. ICH Harmonised Tripartite Guideline, ICH Secretariat, May 1996.
- Jolles S, Orange JS, Gardulf A, et al. Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodeficiency disease. *Clinical Exp Immunol* 2015; 179: 146–160.
- Moy JN, Scharenberg AM, Stein MR, et al. Efficacy and safety of a new immunoglobulin G product, Gammaplex<sup>®</sup>, in primary immunodeficiency diseases. *Clin Exp Immunol*. 2010 Dec;162(3):510-515.
- Picard C, Al-Herz W, Bousfiha A, et al. Primary Immunodeficiency Diseases: an Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. *J Clin Immunol*. 2015 Nov;35(8):696-726.
- Resnick ES, Cunningham-Rundles C. The many faces of the clinical picture of common variable immune deficiency. *Curr Opin Allergy Clin Immunol*. 2012 Dec; 12(6):595-601.
- Roifman CM, Berger M, Notarangelo LD. Management of primary antibody deficiency with replacement therapy: summary of guidelines. *Immunol Allergy Clin North Am*. 2008 Nov; 28(4):875-876.
- Rosen FS, Cooper MD, Wedgwood RJ. The primary immunodeficiencies. *N Engl J Med*, 1995. 333(7): p. 431-440.
- Routes J, Tavares Costa-Carvalho B, Grimbacher B, et al. Health related quality of life and health resource utilization in patients with primary immunodeficiency disease prior to and following 12 months of immunoglobulin G treatment. *J Clin Immunol* 2016; 36:450–461.
- Schroeder HW Jr, Dougherty CJ. Review of intravenous immunoglobulin replacement therapy trials for primary humoral immunodeficiency patients. *Infection*. 2012 Dec; 40(6):601-611.

- Sentinel Blood SCAN study, 2017  
([https://www.sentinelinitiative.org/sites/default/files/PRISM/Sentinel\\_Product\\_Assessment\\_Evaluation\\_of\\_the\\_Risk\\_of\\_TEE\\_after\\_IG\\_Administration\\_Report\\_20170713.pdf](https://www.sentinelinitiative.org/sites/default/files/PRISM/Sentinel_Product_Assessment_Evaluation_of_the_Risk_of_TEE_after_IG_Administration_Report_20170713.pdf)).
- Shapiro RS, Wasserman RL, Bonagura V, et al. Emerging Paradigm of Primary Immunodeficiency Disease: Individualizing Immunoglobulin Dose and Delivery to Enhance Outcomes. *Clin Immunol*. 2017 Feb;37(2):190-196. doi: 10.1007/s10875-014-9990-x. Epub 2014 Jan 30.
- Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. *J Allergy Clin Immunol*. 2020 Jan 28. pii: S0091-6749(20)30105-6. doi: 10.1016/j.jaci.2020.01.017 .
- Tattevin P, Tchamgoué S, Belem A, Bénézit F, Pronier C, Revest M. Aseptic meningitis. *Rev Neurol (Paris)*. 2019 Sep - Oct;175(7-8):475-480. doi: 10.1016/j.neurol.2019.07.005 .
- Thomas ME, Blaine C, Dawnay A, Devonald MA, Ftouh S, Laing C, et al. The definition of acute kidney injury and its use in practice. *Kidney Int*. 2015 Jan;87(1):62-73. doi: 10.1038/ki.2014.328 .
- Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation*. 2018;138(20):e618–e651. <https://doi.org/10.1161/CIR.0000000000000617> .
- Uzzaman A, Cho SH. Chapter 28: Classification of hypersensitivity reactions. *Allergy Asthma Proc*. 2012 May-Jun;33 Suppl 1:96-99. doi: 10.2500/aap.2012.33.3561 .
- Varni JW, Burwinkle TM, Seid M. The PedsQL as a pediatric patient-reported outcome: reliability and validity of the PedsQL Measurement Model in 25,000 children. *Expert Rev Pharmacoecon Outcomes Res*. 2005;5:705–719.
- 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):869-880.

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## APPENDIX A

## STUDY-SPECIFIC QUESTIONNAIRE

## Additional questions for PID patients

## in the context of the Kedrion IVIG clinical study

1.	How satisfied you were with your <i>previous</i> IVIG treatment <b>before</b> entering in this clinical study?
	<input type="checkbox"/> unsatisfied <input type="checkbox"/> rather unsatisfied <input type="checkbox"/> neither unsatisfied nor satisfied <input type="checkbox"/> rather satisfied <input type="checkbox"/> satisfied
2.	How satisfied you are with your <i>current</i> IVIG treatment <b>during</b> this clinical study?
	<input type="checkbox"/> unsatisfied <input type="checkbox"/> rather unsatisfied <input type="checkbox"/> neither unsatisfied nor satisfied <input type="checkbox"/> rather satisfied <input type="checkbox"/> satisfied
3.	Is there something that disturbs or bothers you with your <i>current</i> IVIG treatment <b>during</b> this clinical study?
	<hr/> <hr/> <hr/> <hr/>
4.	What was your motivation to participate in this clinical study?
	<hr/> <hr/> <hr/>
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?
	<div style="display: flex; justify-content: space-between; align-items: center;"> <div style="text-align: center;"> <p>0</p> <p> </p> <p>not at all</p> </div> <div style="flex-grow: 1; border-top: 1px solid black; position: relative;"> <div style="position: absolute; top: -5px; left: 50%; transform: translate(-50%, -50%);">—————</div> </div> <div style="text-align: center;"> <p>100</p> <p> </p> <p>completely</p> </div> </div>