Clinical Study Protocol

Title: An open-label, prospective, multicenter study investigating clinical efficacy, safety, and pharmacokinetic properties of the human normal immunoglobulin for intravenous administration BT595 as replacement therapy in patients with primary immunodeficiency disease (PID)

Clinical phase:	III Pivotal
Version incl. date:	Final 4.0 of 21-MAR-2018
EudraCT number/ IND number:	2015-003652-52/ 17046
Study no.:	991

Sponsor

Biotest AG
Department of Corporate Clinical Research & Development
Landsteinerstraße 5,
63303 Dreieich, Germany

[redacted]
Head Corporate Clinical Research & Development
[redacted]

[redacted]
Associate Director Corporate Clinical Research & Development
[redacted]

Coordinating Investigator

[redacted]

Overview of amendments integrated in the protocol text of version 1.0 of 14-MAR-2016:

Protocol #	Global/Local amendment	Date	Sections concerned	Rationale
2.0	**global**	**21 Oct 2016**	Flow chart, 9.2.1.4, 9.4	Additional blood sampling for Coombs test and serum haptoglobin for the first 10 patients and the first 2 infusions.
3.0	**global**	**02 Jun 2017**	Study synopsis, 7.1, 9.5.2	Allowance of homecare service for the pharmacokinetic sampling of pediatric subjects.
3.0	**global**	**02 Jun 2017**	Flowchart of study, 7.1	Further specification regarding vital sign assessments. In any case where the change in infusion rate is sooner than a 15 minutes interval, vital signs should be measured prior to the change.
3.0	**global**	**02 Jun 2017**	Study synopsis, 6.2	Clarification that every infusion should start at an initial rate of 0.3 mL/kg/h.
4.0	**global**	**21 Mar 2018**	Title, Header	Correction of IND Number from 128413 to 17046
4.0	**global**	**21 Mar 2018**	Synopsis, 3, 4.1, 10.9	Increase of study subjects from approximately 60 to approximately 70 for ensuring to have a sufficient number of paediatric subjects and to fullfil the requirements of the respective guidelines (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 Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). EMA/CHMP/BPWP/94033/2007 rev. 2; 22 July 2010.)
4.0	**global**	**21 Mar 2018**	Synopsis, 7.2	Change of last patient last visit from February 2018 to November 2019 due to shifted timelines

I. SIGNATURE PAGE

This clinical study is carried out in accordance with the international guidelines on Good Clinical Practice (ICH GCP) and in compliance with applicable Regulatory Authority requirements. It is confirmed that the clinical study will be carried out and documented in accordance with this study protocol.

Coordinating Investigator
[redacted]

11 Apr 2018 [redacted]
Date, signature

Head Corporate Clinical Research & Development
[redacted]

10. April 2018 [redacted]
Date, signature

Biostatistician [redacted]

11 APR 2018 [redacted]
Date, signature

I.I Signature Page for Investigators

Declaration of the Principal Investigator

I have read and understood this clinical study protocol and agree to the following:

- To adhere to the ethical and scientific principles of Good Clinical Practice, and the principles of the Declaration of Helsinki, the local laws and regulations, and the applicable regulatory requirements.
- To conduct the clinical study as set out in the protocol.
  This includes:
  - To wait until I have received approval from the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) before enrolling any subject in this study.
  - To obtain informed consent for all subjects prior to any study-related measure performed.
  - To permit study-related monitoring, audits, IEC/IRB review, and Regulatory Authority inspections.
  - To provide direct access to all study-related records, source documents, and subject files for the monitor, auditor, IEC/IRB, or Regulatory Authority upon request.
  - To use the investigational medicinal product (IMP) and all study materials only within the framework of this clinical study protocol.
  - To understand that changes to the clinical study protocol must be made in the form of an amendment that has the prior written approval of Biotest and, as applicable, of the appropriate IEC/IRB and Regulatory Authority.
  - To comply with the reporting obligations for all Adverse Events.

I understand that all documentation that has not been previously published will be kept in the strictest confidence. This documentation includes the clinical study protocol, Investigator's Brochure, case report forms, and other scientific data.

Principal Investigator
Name

Date, signature

Investigator stamp:

Please insert stamp of investigational site

II. STUDY SYNOPSIS

Title	An open-label, prospective, multicenter study investigating clinical efficacy, safety, and pharmacokinetic properties of the human normal immunoglobulin for intravenous administration BT595 as replacement therapy in patients with primary immunodeficiency disease (PID)
Clinical Phase	III Pivotal
Coordinating Investigator	[redacted]
Study Objectives	The primary objective of this study is to demonstrate that the rate of acute serious bacterial infections (i.e., the mean number of acute serious bacterial infections per subject-year) is less than 1.0 to provide substantial evidence of efficacy. The secondary objectives of this study, in addition to further efficacy assessments, are to evaluate the safety and pharmacokinetic characteristics of BT595.
Study Design	Open-label, prospective, multicenter, multinational.
Study Population	Male or female subjects (age: 2-75 years, inclusive) with PID. For those countries where local regulations permit enrolment of adult subjects only, subject recruitment will be restricted to those who are 18 through 75 years.
Inclusion Criteria	a) Written informed consent/assent obtained from subjects/subjects' 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. b) Male or female, aged 2 through 75 years. c) Diagnosis of PID with impaired antibody production, i.e.: - Diagnosis of common variable immunodeficiency (CVID) as defined by the European Society for Immunodeficiencies (ESID)/Pan American Group for Immunodeficiency (PAGID) diagnostic criteria. Or - X-linked agammaglobulinemia (XLA) as defined by ESID/PAGID diagnostic criteria. d) Established replacement therapy with any intravenous immunoglobulin (IVIg) reference preparation during the previous 6 months, including documentation of immunoglobulin G (IgG) trough levels. e) Established replacement therapy with a single IVIg reference preparation for at least 3 months prior to treatment start with BT595 at a 3- or 4-week schedule with a constant IVIg dose that did not change by ±20% of the mean dose, regular dosage intervals, and at least 1 IgG trough level of ≥5 g/L during the previous 3 months.

Exclusion Criteria	a) Pregnancy or unreliable contraceptive measures or lactation period (females only). b) Known intolerance to immunoglobulins or comparable substances (e.g., vaccination reaction). c) Known intolerance to proteins of human origin or known allergic reactions to components of the study product. d) Participation in another clinical study within 30 days before entering the study or during the study and/or previous participation in this study. e) Employee or direct relative of an employee of the Contract Research Organization, the study site, or Biotest. f) Acquired medical conditions known to cause secondary immune deficiency, such as chronic lymphatic leukemia, lymphoma, multiple myeloma, as well as protein losing enteropathies and hypoalbuminemia. g) Other medical condition, laboratory finding, or physical examination finding that precludes participation. h) Recent febrile illness that precludes or delays participation. i) Active infection and receiving antibiotic therapy for the treatment of this infection at the time of screening. Note: if the subject is deemed to be a screen failure due to a nonserious active infection requiring antibiotic therapy, the subject may be rescreened after the initial screening. j) Therapy with systemic steroids or other immunosuppressant drugs at the time of enrollment (current daily use of corticosteroids, i.e., >10 mg prednisone equivalent/day for >30 days. Intermittent corticosteroid use during the study is allowable, if medically necessary). k) History of thrombotic events (including myocardial infarction, cerebral vascular accident [including stroke], pulmonary embolism, and deep vein thrombosis) within the 6 months before treatment start with BT595 or the presence of significant risk factors for thrombotic events. l) Therapy with live-attenuated virus vaccines within 3 months before start of the study. m) Selective, absolute immunoglobulin A (IgA) deficiency or known antibodies to IgA. n) Positive diagnosis of hepatitis B or hepatitis C. o) Positive HIV test. p) History of drug or alcohol abuse within the 12 months before treatment start with BT595. q) Inability or lacking motivation to participate in the study.
Number of Subjects	At least 50 evaluable subjects. At least 20 subjects should be pediatric subjects (i.e., children [2-11 years, inclusive] or adolescents [12-17 years, inclusive]) with the age distribution representative of the PID patient population. At least 20 subjects should be adult subjects. Before any pediatric subjects begin the study, at least

	10 adult subjects will receive at least 2 BT595 infusions with no safety concerns (as reviewed by the Data and Safety Monitoring Board). About 70 subjects will have to be enrolled to account for drop-outs.
Countries/Number of Study Sites	About 25 sites in Europe and the United States.
Investigational Medicinal Product (IMP)	BT595: human normal IVIg for intravenous (iv) administration (10 g/100 mL).
Dosage and Mode of Administration	**Dosage:** Planned doses in a range of 0.2 to 0.8 g/kg body weight (bw) (2 to 8 mL/kg bw) as an iv infusion at 3- or 4-week intervals for a treatment period of approximately 12 months. The initial dose and dosage interval must be consistent with the subject's prestudy IVIg treatment and the initial dose and dosage interval will only be changed if medically indicated. This change will be at the investigator's discretion. **Infusion rate:** BT595 should be infused intravenously at an initial rate of 0.3 mL/kg/h for 30 minutes, to be increased to 1.4 mL/kg/h for a further 30 minutes. If well tolerated, the rate of administration may then be gradually increased to a maximum of 2.0 mL/kg/h for the remainder of the first infusion. From the second infusion, in subjects who have tolerated the infusion rate of 2.0 mL/kg/h well, the rate may be gradually increased to 4 mL/kg/h and, if still tolerated well, it may be further increased gradually to 6 mL/kg/h, and to a maximum of 8 mL/kg/h. In general, subjects' infusion rates will be individually tailored at the discretion of the investigator, but must always start again at an initial rate of 0.3 mL/kg/h.
Duration of Treatment	Approximately 12 months per subject.
Criteria for Evaluation ***- Efficacy***	**Primary Endpoint:** Rate of acute serious bacterial infections (i.e., the mean number of acute serious bacterial infections per subject-year). Acute serious bacterial infections include: • Bacteremia or sepsis • Bacterial meningitis • Osteomyelitis/septic arthritis • Bacterial pneumonia • Visceral abscess Specific diagnostic criteria for these infection types as given in the Food and Drug Administration (FDA) guidance will be used. **Secondary Endpoints:** • IgG trough levels (total IgG) before each infusion • Rate of any infections (number per year) • Rate of nonserious infections (number per year)

	• Time to resolution of infections • Antibiotic treatment (number of days antibiotic treatment received per month) • Rate of time lost from school/work due to infections (number of days per month) and their treatment (number of days treatment per month) • Hospitalization (number of days per month overall and due to infection) • Fever episodes (number of days per year) • Changes in health-related quality-of-life: Pediatric subjects (2-17 years, inclusive) will complete the Pediatric Quality of Life (Peds QL™) Measurement Model (child self-report and/or parent proxy-report). Additionally, all adult subjects will complete the EuroQol Five Dimension (EQ-5D-3L™) Health Questionnaire and pediatric subjects (4-17 years, inclusive) will complete the youth version of the EQ-5D™ (EQ-5D-Y™) Health Questionnaire (child self-report or proxy-report).
- Safety	Tolerability and safety of BT595: • Adverse events: - Number, severity, causality, and seriousness of adverse events (AEs) (including nonproduct related) temporally associated with the infusion (occurring during infusion or within 1, 24, and 72 hours after the end of infusion), defined as “infusional AEs”. Infusional AEs will be evaluated with regard to infusion rate and at which infusion (1st, 2nd, etc) they occurred. - Number of related infusional AEs occurring during infusion or within 1, 24, and 72 hours after the end of infusion. - Number and percentage of infusions temporally (within 72 hours) associated with 1 or more AEs. - Number, severity, causality, and seriousness of all AEs. - Number, severity, causality, and seriousness of all treatment-emergent AEs. - Number of noninfusional AEs (occurring more than 72 hours after the end of infusion). • Changes in safety laboratory parameters (including standard clinical chemistry, hematology, coagulation, urinalysis; outside reference range and clinically relevant). • Number of positive intravascular hemolysis test results (direct Coombs’ test, and other tests for detection/evaluation of intravascular hemolysis). • Changes in vital sign parameters (body temperature, blood pressure, pulse rate, respiratory rate). • Changes in physical examination parameters.

- Pharmacokinetics	Pharmacokinetic (PK) endpoints: • IgG trough levels (total IgG) before each administration. • IgG trough levels (subclasses 1-4) at baseline and before the 7th/5th infusion of the 3-week/4-week schedule, respectively (with the exception of pediatric subjects aged 2-5 years, inclusive). • IgG trough levels of specific antibody levels (anti-pneumococcal capsular polysaccharide, anti-hemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-HBs/hepatitis B) at baseline and before the 7th/5th infusion of the 3-week/4-week schedule, respectively (with the exception of pediatric subjects aged 2-11 years, inclusive). A homecare service is allowed for the PK sampling of pediatric subjects (2-17 years, inclusive). Subjects will complete serial blood sampling according to their age category. For adult subjects (18-75 years, inclusive) and pediatric subjects (6-17 years, inclusive), samples will be taken at a fixed series of time points after the 7th/5th infusion (according to treatment schedule). For pediatric subjects (2-5 years, inclusive), sparse sampling at flexible time points within specified time windows after the end of this infusion may be performed (note: these samples are optional). Evaluable data from at least 20 adult subjects and all available pediatric data will be included in the PK analysis. Analysis of the concentration-time profiles will be used to derive key PK parameters for total IgG, IgG subclasses 1-4, and IgG specific antibody levels following simple noncompartmental analysis or a more appropriate approach including population analysis. For pediatric subjects, analysis for total IgG will be from pediatric subjects aged 2 through 17 years, analysis for IgG subclasses 1-4 will be from pediatric subjects aged 6 through 17 years, and analysis for IgG specific antibody levels will be from pediatric subjects aged 12 through 17 years only. The following key PK parameters will be derived from the analysis: maximum concentration (C_{max}), time to reach maximum concentration (t_{max}), trough concentration (C_{trough}), area under the concentration-time curve (AUC) calculated from time zero to time t of the last measured concentration ($AUC_{(0-t)}$), area under the concentration-time curve calculated from start to end of the dosing interval (AUC_{tau}), steady-state clearance (CLss), volume of distribution at steady-state (Vss), %Fluctuation, and if data permit, terminal elimination half-life ($t_{1/2}$), area under the concentration-time curve calculated from time zero extrapolated to infinity ($AUC_{(0-inf)}$), mean residence time (MRT), and terminal elimination rate constant (λz).

	The efficacy, safety, and PK results of this study will be compared to historical data from previous PID studies with Intratect and Bivigam (already marketed 10% IVIgs), as well as to available data from literature.
Biostatistical Concept	A sample size of at least 50 evaluable subjects is considered a sufficient number to evaluate the primary study endpoint according to the relevant FDA and EMA guidelines. A sample size of at least 50 subjects will ensure a power of at least 80% to reject the null hypothesis of an acute serious bacterial infection 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 0.5 per year. The primary endpoint is the rate of acute serious bacterial infections (i.e., the mean number of acute serious bacterial infections per subject-year). The null hypothesis of 1 or more acute serious bacterial infections per subject-year will be tested against the 1-sided alternative hypothesis of less than 1 acute serious bacterial infection per subject-year at the 1% level of statistical significance. This 1-sided hypothesis test will utilize a Poisson model as used for the calculation of the upper confidence limit. Rejection of the null hypothesis of 1 or more acute serious bacterial infection per subject-year will result in the acceptance of the alternate hypothesis of less than 1 acute serious bacterial infection per subject-year. Secondary efficacy endpoints and safety endpoints will be analyzed descriptively. Exploratory 2-sided 90% confidence intervals will be calculated for the total incidence of AEs and of temporally associated AEs. Exploratory upper 1-sided 95% confidence limits will be calculated for the proportion of infusions temporally associated with 1 or more AE. Analyses of the IgG trough levels and PK parameters will be done descriptively and presented graphically, including a comparison of the IgG trough levels by analyte (total IgG, IgG subclasses, and IgG specific antibody levels), treatment schedule (3-week and 4-week schedule), and age category. Evaluation of total IgG trough levels will include the calculation of the proportion of subjects who failed to meet the target level (≥5 g/L) prior to dose adjustment, and an intra-individual comparison to trough levels of the former IVIg product (i.e., using prestudy data). No formal statistical test will be performed for these variables.
First Subject In *(planned)*	June 2016
Last Subject Last Visit *(planned)*	November 2019

Confidentiality Statement

III. FLOWCHART OF STUDY

3-Week and 4-Week Schedule

Study Schedule	**Visit** **3-week** **4-week**	**V1**	**V2 BL**	**V 3-19** **V 3-15**	**V 20** **V 16**
	Week **3-week** **4-week**	**W -4 to W 0**	**W 0**	**W 3-51** **W 4-52**	**Up to W 54** **Up to W 56**
	Day **3-week** **4-week**	**D -28 through D 0**	**D 1**	**Approx D 22-358** **D 29-365**	**Approx Up to D 379** **Up to D 393**
Assessments	**Periods**	**Screening**	**Treatment[a]**		**Closing (Follow-up)[a]**
Informed consent/assent		•			
Demographic data (incl. gender, date of birth, ethnic origin, height)		•			
Medical and surgical history (incl. drug history, previous medication, disease history)		•	•		
Eligibility criteria (inclusion/exclusion)		•	•		
Physical examination[b]		•	•	•	•
Vital signs (pulse, blood pressure, temperature, respiratory rate)		•	•[c]	•[c]	•
Body weight		•	•	•	
Pregnancy test[d]		•	•	•	•
Safety laboratory (hematology, coagulation, clinical chemistry, urinalysis)		•	•[e]	•	•
Intravascular hemolysis parameters (incl. Coombs test, haptoglobin, hemoglobin, hemosiderin)		•		•[i]	•
Viral safety (retention samples)		•			•
Virus serology (hepatitis B, hepatitis C, HIV)		•			
Infusion of BT595			•	•	
Immunoglobulin G trough levels (total IgG)		•	•[e]	•	•
Immunoglobulin G trough levels (subclasses 1-4)			•[f]	•[f]	
Specific antibody trough levels			•[g]	•[g]	
Subject diary (paper) dispensed			•	•	
Collection and review of subject diary (paper)				•	•
Health-related quality-of-life assessment			•	•	•
Concomitant medications		•	•		
Adverse events			•		
Pharmacokinetic parameters for total IgG, IgG subclasses, and IgG specific antibody levels				•[h]	

Approx = approximately; BL = baseline; D = day; incl = including; V = visit; W = week.

[a] A time window of ±2 days will be allowed for the treatment period visits and the closing (follow-up) visit; however, this time window will not apply for the PK assessments. Pharmacokinetic assessments will follow time point specific time windows.

[b] The physical examination will be followed-up with a verbal exchange (face-to-face) between the subject and the investigator 1 hour after the end of each infusion, and a verbal exchange (by telephone) 24 and 72 hours after the end of each infusion.

[c] Vital signs (pulse, blood pressure, respiratory rate) will be assessed within 30 minutes before each infusion, 15 to 30 minutes after the start of each infusion, 15 to 30 minutes after the end of each infusion, and 15 to 30 minutes after the start of any change in the infusion rate. In any case where the change in infusion rate is sooner than a 15 minute interval, vital signs should be measured prior to the change. The vital sign, temperature, will be recorded within 30 minutes before each infusion only.

[d] A pregnancy human chorionic gonadotropin test in serum will be taken for all female subjects ≥12 years of age or with presence of menstruation at screening. Urine pregnancy dipstick tests will be performed at all other study visits.

[e] Additional samples for safety laboratory assessments and total IgG will be taken at the end of the first BT595 infusion.

[f] Samples will be taken from subjects (6-75 years, inclusive) at baseline and before the 7th/5th infusion of the 3-week/4-week schedule, respectively (i.e., this sample is the same sample as the predose sample for PK analysis).

[g] Samples will be taken from subjects (12-75 years, inclusive) at baseline and before the 7th/5th infusion of the 3-week/4-week schedule, respectively (i.e., this sample is the same sample as the predose sample for PK analysis).

[h] At the 7th infusion (Week 18 [3-week schedule]) or 5th infusion (Week 16 [4-week schedule]), serum samples for the PK analysis of total IgG, IgG subclasses 1-4, and IgG specific antibody levels (anti-pneumococcal capsular polysaccharide, anti-hemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-HBs/hepatitis B) will be drawn from subjects (6-75 years, inclusive for total IgG and IgG subclasses 1-4; 12-75 years inclusive for IgG specific antibody levels) at the following time points: predose (i.e., 10 to 30 minutes before the infusion), 10 to 30 minutes postinfusion (end of infusion), 4 and 24 hours postinfusion; and 4, 7, 14, 21 days (for the 3-week and the 4-week treatment schedule), and 28 days postinfusion (4-week schedule only). For pediatric subjects (2-5 years, inclusive), sparse sampling for PK analysis of total IgG only may be performed at flexible time points within specified time windows after the end of the infusion (note: these samples are optional).

[i] For detecting any hemolytic outcome the first two infusions (V2, V3) should be followed up on the following visit (V3, V4) for the first 10 patients by analyzing Coombs test and test of haptoglobin.

IV. TABLE OF CONTENTS

V. LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AUC	area under the concentration-time curve
$AUC_{(0-\infty)}$	area under the concentration-time curve from time zero extrapolated to infinity
$AUC_{(0-t)}$	area under the concentration-time curve from time zero to time t of the last measured concentration
AUC_{tau}	area under the concentration-time curve calculated from start to end of the dosing interval
bw	body weight
CLss	steady-state clearance
C_{max}	maximum concentration
CRO	contract research organization
C_{trough}	trough concentration
CVID	common variable immunodeficiency
DEVP (Form)	Drug Exposure Via Parent Report (Form)
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EQ-5D™	EuroQol Five Dimension
EQ-5D-3L™	EuroQol Five Dimension (3 levels)
EQ-5D-Y™	EuroQol Five Dimension (youth version)
EQ VAS	EuroQol Visual Analog Scale
ESID	European Society for Immunodeficiencies
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
ICH	The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IMP	investigational medicinal product
IRB	Institutional Review Board
IRAE	immediately reportable adverse event
ITP	idiopathic thrombocytopenic purpura
iv	intravenous
IVIg/IGIV	intravenous immunoglobulin
Λz (lambda z)	terminal elimination rate constant

MedDRA®	Medical Dictionary for Regulatory Activities
MRT	mean residence time
n	number of observations
no.	number
PAGID	Pan American Group for Immunodeficiency
Peds QL™	Pediatric Quality of Life
PHI	protected health information
PID	primary immunodeficiency disease
PK	pharmacokinetic
PPS	Per-protocol Set
PRO	patient reported outcome
SAE	serious adverse event
SAF	Safety Set
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal elimination half-life
t_{max}	time to reach maximum concentration
TMF	Trial Master File
TRALI	transfusion-related acute lung injury
Vss	volume of distribution at steady-state
WHO-DD	World Health Organization Drug Dictionary
XLA	X-linked agammaglobulinemia

1 INTRODUCTION

Primary immunodeficiency diseases (PIDs) are a class of disorders in which there is an intrinsic defect in the human immune system. Since the original description of X-linked agammaglobulinemia (XLAs) in 1952, the number of independent PIDs has expanded to more than 100 entities.

Intravenous administration of immunoglobulins is a well-established therapy in patients with primary or secondary immune deficiencies and recurrent infections. The primary aim of therapy is to prevent infections by substituting missing antibodies. Moreover, immunoglobulins have a modulating effect on the immune system and may therefore also be helpful in the treatment of recurrent infections and autoimmune diseases (Björkander et al, 2006; Chapel et al, 2014; Imbach et al, 2010; Schwab and Nimmerjahn, 2013; Lünemann et al, 2015).

Immunoglobulin G Next Generation (BT595) is a normal immunoglobulin preparation manufactured from human plasma. BT595 is a sterile, highly purified solution of human normal immunoglobulin for intravenous administration (IVIg) containing, in concentrated form, all the immunoglobulin G (IgG) antibodies that regularly occur in the donor population. BT595 contains 100 mg human plasma protein per mL of solution (i.e., 10% ready-for-use solution).

Fundamental knowledge on the manufacturing conditions of the licensed IVIg products at Biotest AG formed the basis for the development of BT595. To optimize the production process, Biotest has established a new process aiming to produce an intravenously tolerated IgG preparation with a low content of polymers and high purity. The manufacturing process of BT595 ensures the required viral safety and provides a reproducible quality.

Further details on the manufacturing process are provided in the Investigator's Brochure.

To date, no clinical studies have previously been conducted with BT595 but pharmacokinetic (PK) properties and the efficacy and safety profile are expected to be comparable with other currently licensed immunoglobulin products, including Bivigam (Biotest's intravenous immunoglobulin [IGIV] 100 g/L; licensed in the United States) and Intratect, the IVIg preparation available in 2 strengths (50 g/L and 100 g/L) and marketed by Biotest in the EU and other international markets as a replacement therapy for patients with PID as well as for other antibody-deficiency/autoimmune diseases.

With Bivigam, 1 clinical study has been performed in 63 subjects with PID (Wasserman et al, 2012). These subjects received a total of 746 infusions over approximately 12 months. Forty subjects were reported with adverse events (AEs) that were related to the study product. The majority of the AEs were mild to moderate. The reported AEs were in the expected profile for IGIVs.

With Intratect (50 g/L), 3 clinical studies have been performed: 2 in subjects with PID (Study 941 [2002] and Study 957 [Kreuz et al, 2010]) and 1 in subjects with idiopathic

thrombocytopenic purpura (ITP; Study 942 [Colovic et al, 2003]). In the 2 PID studies, overall 68 subjects were treated over a period of 6 and 12 months, respectively.

With Intratect (100 g/L), 1 clinical study (Study 981 [Krivan et al, 2015]) has been performed over 3 to 6 months in 30 subjects with PID. These 30 subjects received a total of 165 infusions, where a total of 19 infusions (11.5%) were associated with adverse drug reactions (ADRs). The majority of these ADRs were mild to moderate and self-limiting. No serious ADR was observed during this study. The reported ADRs were consistent with the expected profile for IVIgs.

Study 981 demonstrated that the PK and safety profile of Intratect (100 g/L) is consistent with those of Intratect (50 g/L) and other IVIg products. Moreover, the data demonstrated that the escalation of infusion rates of Intratect (100 g/L) can lead to the identification of an individual's maximum tolerated infusion rate, which is well-tolerated and safe when administered at subsequent infusions.

The goal of the current clinical development plan is the parallel development of BT595 in European and United States' regulatory regions. Three studies are planned for the clinical development of BT595 which consider both European Medicines Agency (EMA/CHMP/BPWP/94033/2007 rev. 2, 2010) and Food and Drug Administration (FDA, 2008) guidelines for the PID and ITP indications, as well as recently-published and ongoing studies in the chronic inflammatory demyelinating polyneuropathy indication. The plan is to begin with a PID study in Europe and the United States to obtain PK data for BT595, as well as safety and efficacy data of long-term replacement therapy in this target indication in adult and pediatric subjects.

In the present study, subjects will receive intravenous infusions of BT595 at a dose and dosage interval consistent with their prestudy IVIg treatment. The planned schedule for the gradual increase of the infusion rate is based on the results of Clinical Study 981 (Krivan et al, 2015) which showed a good tolerability of Intratect (100 g/L); however, the infusion rate will be individualized for each subject.

In conclusion, due to comparable quality/biologic characteristics of BT595 and based on the clinical experience with the already-marketed Intratect, it is predicted that BT595 will have an acceptable safety profile, even at the scheduled increased infusion rate. The principal benefit for the participating PID subjects will be to receive their required immunoglobulin replacement therapy that will have the antiinfective effect already demonstrated for Intratect. Balancing the risk of a limited increase in frequency of maximally mild to moderate adverse reactions with the expected benefit for subjects and resource savings for the health care system, the expected benefits of the study clearly exceed the expected risks. Thus, the benefit-risk ratio of BT595 is considered favorable and the use of BT595 in this clinical study is justified.

2 STUDY OBJECTIVES

The main purpose of this study is to assess the efficacy, safety, and pharmacokinetics of BT595 in subjects with PID. The primary objective of this study is to demonstrate that the rate of acute serious bacterial infections (i.e., the mean number of acute serious bacterial infections per subject year) is less than 1.0 to provide substantial

evidence of efficacy. The secondary objectives of this study, in addition to further efficacy assessments, are to evaluate the safety and PK characteristics of BT595.

3 STUDY DESIGN

This is an open-label, prospective, uncontrolled, multicenter Phase III Pivotal study to evaluate the efficacy, safety, and pharmacokinetics of the human normal immunoglobulin for intravenous administration BT595 in subjects with PID.

The rate of acute serious bacterial infection – the primary efficacy endpoint - will also be compared to historical data from previous PID studies with Intratect and Bivigam (already marketed 10% IVIgs) as well as to available data from literature. These data will be provided by Biotest by the time of the analyses.

About 70 subjects will be enrolled to ensure data are available for at least 50 evaluable subjects. At least 20 subjects should be adult subjects (18-75 years, inclusive). At least 20 subjects should be pediatric subjects (i.e., children [2-11 years, inclusive] or adolescents [12-17 years, inclusive]), with the age distribution representative of the PID patient population. Age will be the age recorded at screening (initial visit). The same age will be used per subject during the entire study (i.e., if a subject's age changes from 17 years to 18 years during the study, the subject will remain in the age category of 12 through 17 years during the entire study).

A Data and Safety Monitoring Board (DSMB) will be used to monitor the safety data of at least 10 adult subjects (18-75 years, inclusive) (Section 9.4) before any pediatric subjects are enrolled to the study. The DSMB will review these data and provide recommendations on the suitability of the enrolment of pediatric subjects in the study. The final decision to enroll/not enroll pediatric subjects will be the responsibility of the sponsor.

Efficacy and safety will be assessed from baseline (Week 0) to the closing (follow-up) visit (Week 54 [3-week schedule]/Week 56 [4-week schedule]). For the baseline visit and the treatment period visits, subjects will remain at the site for at least 1 hour following the end of infusion and any new AEs will be reported to the investigator at the site. All changes in concomitant medications and any AEs following subject discharge from the site must be reported continuously (by subject diary) between site visits. The duration of treatment will be approximately 12 months per subject. In addition, all subjects will attend a closing (follow-up) visit up to 3 or 4 weeks (depending on the subject's treatment schedule) following the final treatment visit.

Serum samples for detailed PK analysis will be taken at a fixed series of time points after the 7th/5th infusion of the 3-week/4-week schedule, respectively, from at least 20 adult subjects (18-75 years, inclusive) and from pediatric subjects (6-17 years, inclusive). For pediatric subjects (2-5 years, inclusive), sparse sampling at flexible time points within specified time windows after the end of the infusion may be performed (note: these samples are optional). Evaluable data from at least 20 adult subjects and all available pediatric data will be included in the PK analysis. Analysis of the concentration-time profiles will be used to derive key PK parameters for total IgG, IgG subclasses 1-4, and IgG specific antibody levels (anti-pneumococcal capsular

polysaccharide, anti-hemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-HBs/hepatitis B).

Further details on the assessment schedule that will be used for the assessment of the efficacy, safety, and PK parameters in this study are presented in a flowchart in Section III.

The design of this study follows the EMA guidelines ("Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration [IVIg]"; EMA/CHMP/BPWP/94033/2007 rev. 2, 2010) and the FDA guidelines ("Guidance for Industry - Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous [Human] as Replacement Therapy for Primary Humoral Immunodeficiency"; FDA, 2008) applicable to the PID study type.

As the current regulatory goal is to receive marketing authorization in both the United States and European regions, this clinical study will be carried out in parallel in sites in the United States and Europe; thus, taking into account guidelines from both regions that provide specific recommendations on the general principles for the design of a clinical investigation of human normal immunoglobulin products for intravenous administration as replacement therapy in patients with PID. These guidelines also provide recommendations on the primary efficacy endpoint, secondary efficacy endpoints, and safety endpoints to be assessed in a study of this type. The present study will follow these guidelines to demonstrate clinical evidence of the efficacy and safety of BT595, and as such, the efficacy and safety endpoints used in this study are consistent with the recommendations made by both the EMA and the FDA. All safety signals, including short-term tolerance, will be closely monitored in this study. In addition, all PK parameters recommended by the EMA and FDA guidelines will be calculated to support the pharmacological activity and efficacy of BT595.

4 STUDY POPULATION

4.1 Study Population, Diagnosis, and Number of Subjects

It is planned to enroll about 70 male or female subjects (2-75 years, inclusive) with PID and established replacement therapy in approximately 25 sites in Europe and the United States, with about 2-3 subjects per site. For those countries where local regulations permit enrolment of adult subjects only, subject recruitment will be restricted to those who are 18 through 75 years. The goal is to have at least 50 evaluable subjects in this study. At least 20 of the evaluable subjects should be pediatric subjects (i.e., children [2-11 years, inclusive] or adolescents [12-17 years, inclusive]), with the age distribution representative of the PID patient population. At least 20 of the evaluable subjects should be adult subjects. Age will be the age recorded at screening (initial visit). The same age will be used per subject during the entire study. At least 10 adult subjects will receive at least 2 BT595 infusions with no safety concerns (as reviewed by the DSMB; Section 9.4) before any pediatric subjects begin the study.

4.1.1 Gender Distribution

The number of male and female subjects will not be predefined by the protocol.

4.2 Inclusion Criteria

Only subjects meeting all of the following inclusion criteria will be considered for study inclusion:

Inclusion Criteria	Rationale	Screening	Baseline
a) Written informed consent/assent obtained from subjects/subjects' 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	Administrative	X	
b) Male or female, aged 2 through 75 years	Administrative	X	
c) Diagnosis of PID with impaired antibody production, i.e.: - Diagnosis of common variable immunodeficiency (CVID) as defined by the European Society for Immunodeficiencies (ESID)[a]/Pan American Group for Immunodeficiency (PAGID)[b] diagnostic criteria Or - X-linked agammaglobulinemia (XLA) as defined by ESID/PAGID diagnostic criteria	Disease requirement	X	
d) Established replacement therapy with any IVIg reference preparation during the previous 6 months, including documentation of IgG trough levels	Pretreatment requirement	X	
e) Established replacement therapy with a single IVIg reference preparation for at least 3 months prior to treatment start with BT595 at a 3- or 4-week schedule with a constant IVIg dose that did not change by ±20% of the mean dose, regular dosage intervals, and at least 1 IgG trough level of ≥5 g/L during the previous 3 months	Pretreatment requirement	X	X

[a] ESID diagnostic criteria (European Society for Immunodeficiencies, 2006).
[b] PAGID diagnostic criteria (Conley et al, 1999).

4.3 Exclusion Criteria

Subjects having any of the following criteria, either at screening and/or baseline, will not be included in the study:

Exclusion Criteria	Rationale	Screening	Baseline
a) Pregnancy or unreliable contraceptive measures or lactation period (females only)	Lack of suitability for study due to safety reasons	X	X
b) Known intolerance to immunoglobulins or comparable substances (e.g., vaccination reaction)	Lack of suitability for study due to safety reasons	X	X
c) Known intolerance to proteins of human origin or known allergic reactions to components of the study product	Lack of suitability for study due to safety reasons	X	X
d) Participation in another clinical study within 30 days before entering the study or during the study and/or previous participation in this study	Lack of suitability for study	X	X
e) Employee or direct relative of an employee of the Contract Research Organization (CRO), the study site, or Biotest	Administrative	X	X

Exclusion Criteria	Rationale	Screening	Baseline
f) Acquired medical conditions known to cause secondary immune deficiency, such as chronic lymphatic leukemia, lymphoma, multiple myeloma, as well as protein losing enteropathies and hypoalbuminemia	Lack of suitability for study	X	X
g) Other medical condition, laboratory finding, or physical examination finding that precludes participation	Lack of suitability for study	X	X
h) Recent febrile illness that precludes or delays participation	Lack of suitability for study due to safety reasons	X	X
i) Active infection and receiving antibiotic therapy for the treatment of this infection at the time of screening. Note: if the subject is deemed to be a screen failure due to a nonserious active infection requiring antibiotic therapy, the subject may be rescreened after the initial screening	Lack of suitability for study	X	X
j) Therapy with systemic steroids or other immunosuppressant drugs at the time of enrollment (current daily use of corticosteroids, i.e., >10 mg prednisone equivalent/day for >30 days. Intermittent corticosteroid use during the study is allowable, if medically necessary)	Interference with study outcomes	X	
k) History of thrombotic events (including myocardial infarction, cerebral vascular accident [including stroke], pulmonary embolism, and deep vein thrombosis) within the 6 months before treatment start with BT595 or the presence of significant risk factors for thrombotic events	Lack of suitability for study due to safety reasons	X	X
l) Therapy with live-attenuated virus vaccines within 3 months before start of the study	Interference of IVIg with live-attenuated virus vaccines	X	
m) Selective, absolute immunoglobulin A (IgA) deficiency or known antibodies to IgA	Lack of suitability for study due to safety reasons	X	X
n) Positive diagnosis of hepatitis B or hepatitis C	Lack of suitability for study	X	X
o) Positive HIV test	Lack of suitability for study	X	X
p) History of drug or alcohol abuse within the 12 months before treatment start with BT595	Subject compliance	X	X
q) Inability or lacking motivation to participate in the study	Subject compliance	X	X

4.4 Subjects Withdrawal Criteria and Replacements

The participation of an individual subject may be terminated prematurely for reasons such as:

a. Withdrawal of written informed consent/assent
b. Study discontinuation due to subject's own request (e.g., personal reasons)
c. Required treatment with any medication known or suspected to interfere with the investigational medicinal product (IMP)
d. Any AE, laboratory abnormality, or other medical condition or situation occurs suggesting that continued participation in the study would not be in the best interest of the subject.
e. Protocol deviation requiring discontinuation of study treatment

f. Evidence of exclusion criteria
g. Lack of study compliance
h. Any of the following AEs occur: thromboembolic events (such as stroke, myocardial infarction, lung embolism) or hemolysis [Section 9.3.1 for further details]).

A subject and/or his/her parent(s) or legally acceptable representative is/are entitled to discontinue participation in the clinical study at their own request at any time without stating a reason.

The investigator can terminate a subject's participation in the study at any time if continuation could lead to disadvantages for the subject which cannot be justified by the investigator.

The participation of subjects may be stopped following guidance from the DSMB (Section 9.4).

The reason for withdrawal of the subject must be documented by the investigator together with all data collected until the day of premature study termination, including laboratory results and assessment of AEs. All examinations foreseen for the subject's last study visit (e.g., closing [follow-up] visit) should be performed.

In case a subject withdraws due to an AE or serious adverse event (SAE), please follow the instructions given in Appendix 2 of this protocol.

Withdrawn subjects will not be replaced.

4.5 Subjects' Information

The subject and/or - if applicable – his/her legally acceptable representative will be informed about the clinical study according to the requirements of Good Clinical Practice (GCP) and the legal requirements of the country in which the subject is recruited.

The clinical study, its objectives, possible benefits and risks, and its consequences will be verbally explained to the subject and/or his/her legally acceptable representative. Moreover, the subject and/or his/her legally acceptable representative is/are provided with written information about the clinical study. Sufficient time will be allowed for the information to be read and for questions to be asked. Attention should be paid to any signs of undue distress in pediatric subjects who are unable to clearly indicate their distress (ICH Harmonised Tripartite Guideline; E11 Step 4, 2000). The subject and/or his/her legally acceptable representative must be told that refusal to participate in the clinical study does not cause any disadvantages to their treatment; similarly, withdrawal of written informed consent/assent is possible at any time, without stating a reason, and without prejudice to further medical management.

Subjects and/or his/her legally acceptable representative should be informed and should agree that medical data may be reviewed by authorized persons during monitoring and during an audit or an inspection by the appointed Regulatory Authority or Ethics Committee, but that personal data will be treated with absolute confidentiality.

Upon request, the subject and/or his/her legally acceptable representative must be granted access to the insurance terms and conditions.

Any new and relevant information that evolves during the course of the clinical study concerning the IMP, alternative treatments, or the benefit/risk ratio will be communicated to the subject and/or his/her legally acceptable representative.

4.6 Declaration of Informed Consent/Assent

The subject and/or - if applicable – his/her legally acceptable representative must have given written consent/assent to participate in the clinical study by signing and personally dating the informed consent form. For pediatric subjects who can only be enrolled in the study with consent of their parent(s) or legally acceptable representative, the subject will be informed about the study to the extent compatible with their understanding and, if capable, the subject will assent, write their name when applicable, sign, and personally date the written informed consent. Separate assent and consent forms will be provided for pediatric subjects and their parent(s) or legally acceptable representative. Informed consent/assent to the proposed data handling and to data inspection must also be documented in written form. Written informed consent/assent must be obtained from each subject or legally acceptable representative before any study-related procedures are performed. The subject's and/or his/her legally acceptable representative's written informed consent/assent will be filed at the investigator's site.

A duplicate of the signed and dated written informed consent/assent form must be handed over to the subject and/or – if applicable – his/her legally acceptable representative.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Investigational Medicinal Product BT595

5.1.1 Description of Investigational Medicinal Product BT595

Substance code:	BT595
Active ingredients:	[redacted]
Composition:	[redacted]
	Excipients: [redacted]
	pH:
Dosage form:	Solution of 10 g human plasma protein per 100 mL for intravenous administration
Concentration:	100 mg/mL (10%) human plasma protein
Container:	Glass bottle (100 mL)
Manufacturer:	Biotest AG, 63303 Dreieich

Batch number(s) and expiry date(s) are given in the applicable certificates of analysis.

5.1.2 Formulation, Packaging, and Labelling

The dosage form of BT595 is a solution of 10 g human plasma proteins per 100 mL for intravenous administration in a 100 mL infusion bottle (glass).

The labelling of BT595 will be performed according to local requirements. A sample label will be contained in the Trial Master File (TMF).

Batch number(s) and bottle number(s) must be documented in the electronic case report form (eCRF) and the drug accountability log.

5.1.3 Storage Conditions and Stability

BT595 is to be stored in a cabinet or other enclosure which is security locked. Generally, access should be restricted to the investigator and authorized personnel.

BT595 is to be stored and transported at a temperature between 2°C to 8°C and documented on a temperature log. BT595 will have the following instructions: *Please keep in original packaging carton* and *Do not freeze*.

The expiry date for each batch will be given on the bottle label/outer carton and the Certificate of Analysis.

5.1.4 Preparation for Use

The product should be brought to room or body temperature before use (may take approximately 15 minutes). The solution should be administered immediately after opening the receptacle. The solution should be clear to slightly opalescent. Solutions that are cloudy or have deposits are not to be used. Bottles are for single use only. BT595 should not be mixed with any other product.

6 STUDY TREATMENT

6.1 Dosage Regimen

BT595 will be administered at 3- or 4-week intervals for a treatment period of approximately 12 months. The initial dose and dosage intervals must be consistent with the subject's prestudy IVIg treatment and the initial dose and dosage interval will only be changed if medically indicated. This change will be at the investigator's discretion.

6.2 Dosage and Administration

The planned dose of BT595 is 0.2 to 0.8 g/kg body weight (bw; 2 to 8 mL/kg) administered as intravenous infusions at 3- or 4-week intervals for a treatment period of approximately 12 months.

Infusion rate: BT595 should be infused intravenously at an initial rate of 0.3 mL/kg/h for 30 minutes, to be increased to 1.4 mL/kg/h for a further 30 minutes. If well tolerated, the rate of administration may then be gradually increased to a maximum of 2.0 mL/kg/h for the remainder of the first infusion. Every infusion must start again at an initial rate of 0.3 mL/kg/h. From the second infusion, in subjects who have tolerated the infusion rate of 2.0 mL/kg/h well, the rate may be gradually increased to 4 mL/kg/h, and

if still tolerated well, it may be further increased gradually to 6 mL/kg/h, and to a maximum of 8 mL/kg/h.

From the second infusion, subjects' infusion rates may be individually tailored (i.e., a certain infusion rate for a certain time period) at the discretion of the investigator, but must start again at an initial infusion rate of 0.3 mL/kg/h. This means that the 30 minute interval may be shortened to less than 30 minutes if deemed appropriate for the subject. Changes in infusion rates (increases and/or decreases) and the respective time of day must be documented.

In case of a decrease in infusion rate or an interruption of infusion as a consequence of an AE, all AE details must be recorded in the eCRF.

6.2.1 Dose Changes during the Study

The subject's total IgG trough levels from the previous infusion will be assessed at the local laboratory to allow dose adjustment at the next infusion if a subject's trough level was below 5 g/L. Serum trough levels of IgG ≥5 g/L must be met throughout the study. If a subject's IgG level changes to <5 g/L, the subject's dose must be adjusted to meet the target trough levels. Dose changes will be made at the investigator's discretion and must follow the dosage regimen detailed in Section 6.2 (i.e., 0.2 to 0.8 g/kg bw [2 to 8 mL/kg] administered as intravenous infusions at 3- or 4-week intervals).

Body weight will be assessed before each study infusion in order to calculate an accurate dose for each subject's dose infusion. The investigator will calculate the percentage change in the subject's body weight since the last assessment. If a subject's body weight changes by <5% from the weight used for the current dose, the total dose will remain the same as the current dose. If a subject's body weight changes by ≥5% from the weight used for the current dose, the total dose (g), but not the dose per weight (g/kg), will be adjusted accordingly to maintain a constant dose in g/kg/infusion during the study.

Any changes in dose and the reason for the change in dose will be recorded in the eCRF.

6.3 Compliance with Dosage Regimens

BT595 will be administered intravenously by the instructed study staff. If a subject's treatment deviates from the dosage regimen (e.g., a dosing interruption occurs due to the occurrence of an AE), this will be recorded in the eCRF (Section 6.2).

If a subject fails to comply with the dosage regimen (i.e., misses ≥1 dose[s] of BT595), the subject will be considered to be noncompliant and may be terminated prematurely from the study. The decision to terminate a subject from the study prematurely will be at the investigator's discretion after consultation with the sponsor. Details of any deviations from the dosage regimen will be recorded in the eCRF.

6.4 Dose Justification

The planned monthly dose of BT595 is in the range of 200 to 800 mg/kg bw (2 to 8 mL/kg bw) in 3- or 4-week intervals for a treatment period of approximately 12 months. This schedule follows the recommendation in the EU-Core Summary of Product Characteristics (SmPC) for human normal immunoglobulin for intravenous

administration as replacement therapy in subjects with PID (EMA/CHMP/BPWP/94038/2007 rev. 4, 2012).

Accordingly, the dose and dosage interval must be consistent with the subjects' prestudy standard IVIg treatment and only changed if medically indicated. The dose needs to be individualized for each subject depending on the subject's total IgG trough levels (the dose may need to be adjusted to meet target subject trough levels [measured before the next infusion] of ≥5 g/L).

The infusion rate is planned to be escalated from 0.3 mL/kg/h to a maximum of 8 mL/kg/h, initially at 30 minute intervals. Although no clinical studies have previously been conducted with BT595, it is expected from previous experience with Intratect that a relevant proportion of subjects will tolerate this escalation procedure up to an individually determined maximum tolerated infusion rate. The use of premedications to prevent AEs should be avoided in this study, if possible (Section 6.10).

In the clinical study conducted with Intratect at 100 g/L (Study 981; Krivan et al, 2015), subjects with PID received Intratect at the established dose and dosing interval of their previous reference IVIg therapy. The study was designed to gradually escalate infusion rates from 0.3 to 1.4 mL/kg/h to 2.0 mL/kg/h (in Part A; 30 subjects) to 0.3 to 1.4 mL/kg/h to 4.0 mL/kg/h to a maximum of 8.0 mL/kg/h (in Part B; 25 subjects). Of the 25 subjects treated in Part B, 16 subjects (64.0%) achieved an individual maximum tolerated infusion rate of 6.0 or 8.0 mL/kg/h at their 4th infusion and only 4 subjects (16%) had individual maximum tolerated rates of <4.0 mL/kg/h. The 30 subjects in the study (Part A and Part B) received a total of 165 infusions of Intratect, where a total of 19 infusions (11.5%) were associated with ADRs. Overall, 5 subjects (20%) in Part B experienced AEs limiting the infusion rate (all were nonserious). Three subjects reported SAEs in the study, but none were related to treatment with Intratect.

This study demonstrated that escalation of infusion rates leads to the identification of an individual's maximum tolerated infusion rate, which is well-tolerated and safe when administered at subsequent infusions. The identification of an individual's maximum tolerated infusion rate allows PID patients and their physicians to choose an infusion rate that shortens the duration of infusion (higher infusion rates reduce the time required for infusions). Shorter infusion times reduce the time PID patients spend receiving their IVIg treatment, reducing the burden of this condition on these chronically ill patients, and lowering the demand for healthcare resources.

Infusion rates of up to approximately 8.0 mL/kg/h have been shown to be tolerated for other 10% IVIgs: Bivigam (Wasserman et al, 2012), Gamunex (Gelfand and Hanna, 2006), Kiovig (Björkander et al, 2006), and Privigen (Stein et al, 2009).

Thus, the administration of BT595 at infusion rates currently recommended for Intratect is expected to demonstrate an acceptable tolerability compared to similar marketed IVIgs.

6.5 Treatment of Overdose

Based on the dosage recommendations in the EU-Core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/2007 rev. 4, 2012), an IVIg dose of more than 2 g/kg is considered to be an overdose in this

indication. However, within this PID study design, where doses of 0.2 to 0.8 g/kg are recommended for this indication, any dose ≥0.9 g/kg will be reported as an overdose.

BT595 will be administered intravenously by the instructed study staff; however, in the case of accidental overdose, subjects should be monitored closely for signs of adverse reactions. Overdose may lead to fluid overload and hyperviscosity, particularly in subjects at risk, including elderly subjects or subjects with renal impairment.

Any overdose event will be reported as an AE that must be reported to the sponsor within 24 hours of the study site being aware of the AE (i.e., overdose is an immediately reportable adverse event [IRAE]; Appendix 2).

6.6 Randomization Code

This is a nonrandomized, open-label clinical study; therefore, no randomization code is required.

6.7 Procedures for Emergency Unblinding

This is a nonrandomized, open-label clinical study; therefore, no procedure for unblinding is required.

6.8 Drug Accountability

The IMP will be supplied to the investigator at the time of site initiation under the assumption that all required regulatory documents are in place. The investigator or his/her designee should maintain records that document adequately that the subjects were provided the doses specified in the protocol and reconcile all IMPs received for the clinical study. The investigator has to ensure that consignments of IMPs are received correctly by a dedicated person (e.g., pharmacy) and that the IMP is safely and appropriately handled and stored.

The investigator or designee is obliged to keep sufficient documentation of the delivery, use, and destruction or return of unused, used, or partially used packages of IMP. The investigator must allow the monitor to perform drug reconciliation before any IMP is returned or destroyed. The documentation must include dates, quantities, subject numbers, batch numbers or other identification numbers, and expiry dates.

The entries in the eCRF as well as the documentation kept in the Investigator Site File will be compared with the returned and residual IMPs, with clarification of any discrepancies or inconsistencies.

6.9 Previous and Concomitant Medication or Treatment

6.9.1 Previous Medication or Treatment

Previous Established Replacement Therapy

Before the subject enters the study, the subject must have been on an established replacement therapy with any IVIg reference preparation for at least the previous 6 months. Before treatment starts with BT595 in a 3- or 4-week schedule, the subject must have been on an established replacement therapy with a single IVIg reference preparation for at least 3 months. The single IVIg reference preparation must have

been at a constant dose that did not change by ±20% of the mean dose, at regular dosage intervals. This information will be assessed at the initial visit and at the baseline visit (Day 1) to ensure the subject meets criteria for study entry and this information will be documented in the eCRF.

Other Previous Medications or Treatments
In case of blood-derived medications (i.e., administration of blood or blood products), documentation will be required for a period of 3 months before inclusion in the study.

Administration of all medication in the 4 weeks before enrollment will be documented in the eCRF.

6.9.2 Concomitant Medication or Treatment

Concomitant medication (other than immunoglobulins) may be taken as required. All routine concomitant medication should be given after information of/consultation with the investigator (i.e., the subject will be instructed to inform the investigator before taking any concomitant medications). In case of concomitant medication given for emergency reasons, the investigator should be informed as soon as possible.

Full details of any concomitant medication given during the study, including the time of its discontinuation, if applicable, will be documented in the eCRF. Changes of therapy (including changes in regimen) during the study will be recorded in the eCRF and in the subject's medical record.

For any concomitant medication (including any change in dose) given as treatment for a new or worsened condition after the first infusion of study treatment, the investigator will record the condition as an AE in the eCRF.

6.10 Prohibited Medication or Treatment

If not required by an emergency situation, passive or active immunizations, administration of plasma preparations, or administration of other immunoglobulins is not allowed during the study. In such instances, the subject will be withdrawn from the study.

Subjects who are prone to AEs occurring in conjunction with the infusion of IVIg products are often premedicated with antihistamines, antipyretics, and/or steroids. In this study, however, the use of premedications should be avoided (if possible), except in cases where such premedication is important to the safety of the study subject. The use of any premedication must be approved by the principal investigator before use and recorded in the concomitant medication record in the eCRF.

6.11 Warnings and Precautions

The safety profile of BT595 is expected to be comparable to Intratect (100 g/L; a 10% IVIg marketed in the EU and international markets), Bivigam (a 10% IGIV marketed in the United States), and other 10% IVIgs on the market. For further details, see the Investigator's Brochure.

Safety With Respect to Transmissible Agents
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma will include selection of donors, screening of individual donations and plasma pools for specific markers of infection, and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, hepatitis B virus, and hepatitis C virus (HCV). The measures taken may be of limited value against nonenveloped viruses such as hepatitis A virus and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety (EMA/CHMP/BPWP/94033/2007 rev. 2, 2010).

7 COURSE OF THE CLINICAL STUDY

7.1 Visit Schedule

Screening Visit (Visit 1, Week -4 to 0, Day -28 through Day 0)
All subjects will attend a screening visit up to 4 weeks before the first BT595 infusion, where the following procedures will be performed:

- Written informed consent/assent will be obtained.
- Demographic data (including gender, date of birth [for calculation of age; note: age will be the age recorded at screening], ethnic origin, height, and body weight) will be recorded.
- Medical and surgical history with regard to the subjects' drug history, previous medication, disease (i.e., PID) history, and other medical and surgical history will be recorded. Previous medication data up to 4 weeks before enrollment will be recorded, with the exception of data on the subject's established replacement therapy (at least 6 months before study enrollment) and data on blood-derived medication (i.e., administration of blood or blood products; at least 3 months before study enrollment). The type of previous medication, dose schedule, duration, and the indication the previous medication was given for will be documented. An x-ray may be performed at any time throughout the study to evaluate new observations against baseline findings, if medically indicated, and to confirm diagnostic criteria for acute serious bacterial infections. This is not applicable for Germany. (Note: if the subject has recently had an x-ray taken [i.e., within the last 3 months before study start], this result may be considered as baseline data).
- Eligibility to take part in the study will be assessed against the inclusion and exclusion criteria.
- A physical examination will be performed.
- Vital signs (pulse, blood pressure, temperature, respiratory rate) will be recorded.

- A serum pregnancy test (human chorionic gonadotropin) will be performed for all female subjects of child-bearing potential (≥12 years of age or presence of menstruation at screening).
- Samples for routine safety laboratory parameters (hematology, coagulation, clinical chemistry, urinalysis) will be taken.
- Samples for intravascular hemolysis laboratory parameters (including Coombs' test, haptoglobin, hemoglobin, hemosiderin) will be taken.
- Retention samples for viral safety laboratory parameters will be taken.
- Samples for virus serology laboratory parameters (hepatitis B, hepatitis C, HIV) will be taken.
- Samples for IgG trough levels (total IgG) will be taken.

Baseline Visit (Visit 2, Week 0, Day 1)

All subjects will attend a baseline visit on Day 1, where the following assessments will be performed 3 or 4 weeks (depending on the subject's treatment schedule) after the last infusion of the subject's previous IVIg replacement therapy and before the subject's first BT595 infusion (unless indicated):

- Any changes in medical and surgical history with regard to the subjects' drug history, previous medications, disease (i.e., PID) history, and other medical and surgical history since the screening visit will be recorded. The type of previous medication, dose schedule, duration, and the indication the previous medication was given for will be documented. (Note: if the subject has recently had an x-ray taken [i.e., within the last 3 months before study start], this result may be considered as baseline data).
- Eligibility to take part in the study will be confirmed against the inclusion and exclusion criteria, as appropriate (i.e., diagnostic tests will be repeated at the investigator's discretion).
- A physical examination will be performed.
- Vital signs (pulse, blood pressure, respiratory rate) will be recorded within 30 minutes before the infusion, 15-30 minutes after the start of infusion, 15-30 minutes after the end of infusion, and 15-30 minutes after the start of any change in the infusion rate. Temperature will only be recorded within 30 minutes before the infusion.
- Body weight will be recorded (to calculate subject dose).
- A urine pregnancy test (dipstick) will be performed for all female subjects of child-bearing potential (≥12 years of age or presence of menstruation at screening).
- Samples for routine safety laboratory parameters (hematology, coagulation, clinical chemistry, urinalysis) will be taken.
- An additional sample for routine safety laboratory parameters (hematology, coagulation, clinical chemistry, urinalysis) will be taken at the end of the first BT595 infusion.
- Samples for IgG trough levels (total IgG) will be taken.
- An additional sample for total IgG will be taken at the end of the first BT595 infusion.
- Samples for IgG trough levels (IgG subclasses 1-4) will be taken (with the exception of pediatric subjects [2-5 years, inclusive]).
- Samples for IgG trough levels (specific antibody levels) will be taken (with the exception of pediatric subjects [2-11 years, inclusive]).

- A subject diary (paper) will be dispensed. Full instructions on how to complete the paper diary (including information on how to identify and document AEs) will be given. Subject diaries will include a record of the following: occurrence of AEs (including infections), concomitant medication use (including antibiotic treatment), days lost from school/work due to infections and their treatment, any hospitalization, and the number of days in hospital.
- Health-related quality-of-life assessment will be performed.
- BT595 will be infused intravenously.
- Concomitant medications (including prohibited treatments) will be recorded. The type of concomitant medication, dose/schedule, duration, and the indication the concomitant medication was given for will be documented.
- Adverse events will be recorded.

Treatment Period Visits (Visit 3 through Visit 19, Week 3 through Week 51 [3-Week Schedule] or Visit 3 through Visit 15, Week 4 through Week 52 [4-Week Schedule])

Subjects will attend the study site for a further 17 visits (3-week schedule) or 13 visits (4-week schedule). All assessments will be carried out before BT595 infusion, unless indicated. The following procedures will be performed at each study site visit:

- A physical examination will be performed.
- Vital signs (pulse, blood pressure, respiratory rate) will be recorded within 30 minutes before each infusion, 15-30 minutes after the start of each infusion, 15-30 minutes after the end of each infusion, and 15-30 minutes after the start of any change in the infusion rate. In any case where the change in infusion rate is sooner than a 15 minute interval, vital signs should be measured prior to the change.
- The vital sign, temperature, will be recorded within 30 minutes before each infusion only.
- Body weight will be recorded (to calculate subject dose).
- A urine pregnancy test (dipstick) will be performed for all female subjects of child-bearing potential (≥12 years of age or presence of menstruation at screening).
- Samples for routine safety laboratory parameters (hematology, coagulation, clinical chemistry, urinalysis) will be taken.
- Samples for IgG trough levels (total IgG) will be taken. The subject‘s total IgG trough level result from the previous infusion will be made available before the infusion of BT595 to allow dose adjustment if a subject’s trough level was below 5 g/L.
- A subject diary (paper) will be collected and reviewed.
- A subject diary (paper) will be dispensed.
- Health-related quality-of-life assessment will be performed.
- Concomitant medications (including prohibited treatments) will be recorded. The content of the subjects’ diaries will be reviewed and the type of concomitant medication, dose/schedule, duration, and the indication the concomitant medication was given for will be documented.
- Adverse events will be recorded. The content of the subjects’ diaries will be reviewed and AEs will be documented.
- BT595 will be infused intravenously.

Pharmacokinetic Sampling (From Week 18 [3-Week Schedule] or From Week 16 [4-Week Schedule])

Serial sampling for PK analysis of total IgGs, IgG subclasses 1-4, and IgG specific antibody levels (anti-pneumococcal capsular polysaccharide, anti-hemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-HBs/hepatitis B) will be made at estimated steady-state after the 7th infusion of the 3-week schedule (Week 18) or after the 5th infusion of the 4-week schedule (Week 16). *The number of blood draws (and the amount of blood per sample) will be dependent on the subject's age category.*

For adult subjects (18-75 years, inclusive) and pediatric subjects (6-17 years, inclusive), samples will be taken at a fixed series of time points. Note: samples for IgG specific antibody levels will be taken from pediatric subjects aged 12 through 17 years only. Samples for all analytes will be taken as 1 aliquot. Subjects (6-75 years, inclusive) will have 8 or 9 PK blood samples taken (according to treatment schedule):

- 10 to 30 minutes before the infusion (note: this sample is the same sample as that taken for the trough levels of IgG subclasses 1-4 and IgG specific antibody levels before the 7th/5th infusion of the 3-week/4 week-schedule, respectively.)
- 10 to 30 minutes postinfusion (end of infusion sample)
- 4 hours (±1 hour) postinfusion
- 24 hours (±1 hour) postinfusion
- 4 days (±1 day) postinfusion
- 7 days (±1 day) postinfusion
- 14 days (±1 day) postinfusion
- 21 days (±1 day) postinfusion for trough IgG levels for all subjects (6-75 years, inclusive) both, in the 3-week treatment schedule and in the 4-week treatment schedule. This sample must be taken before the next infusion of BT595 for subjects in the 3-week treatment schedule.
- 28 days (±1 day) postinfusion for trough IgG levels for all subjects (6-75 years, inclusive) in the 4-week treatment schedule only. This sample must be taken before the next infusion of BT595.

For pediatric subjects (2-5 years, inclusive), sparse sampling for total IgG only may be performed at flexible time points within specified time windows after the end of this infusion. Pediatric subjects (2-5 years, inclusive) will have up to 5 PK blood samples taken (note: these samples are optional):

- 10 to 30 minutes before the infusion
- 10 to 30 minutes postinfusion (end of infusion sample)
- 6 hours (±1 hour) postinfusion or 24 hours (±1 hour) postinfusion
- 7 days (±1 day) postinfusion or 14 days (±1 day) postinfusion
- 21 days (±1 day) postinfusion for trough IgG levels for subjects in the 3-week treatment schedule only. This sample must be taken before the next infusion of BT595.
- 28 days (±1 day) postinfusion for trough IgG levels for subjects in the 4-week treatment schedule only. This sample must be taken before the next infusion of BT595.

A homecare service is allowed for the PK sampling of pediatric subjects (2-17 years, inclusive).

Closing (Follow-up) Visit (Visit 20, Week 54 [3-Week Schedule] or Visit 16, Week 56 [4-Week Schedule])

A closing (follow-up) visit will be performed 3 or 4 weeks after the last infusion, according to the subject's treatment schedule, and the following procedures will be performed:

- A physical examination will be performed.
- Vital signs (pulse, blood pressure, temperature, respiratory rate) will be recorded.
- A urine pregnancy test (dipstick) will be performed for all female subjects of child-bearing potential (≥12 years of age or presence of menstruation at screening).
- Samples for routine safety laboratory parameters (hematology, coagulation, clinical chemistry, urinalysis) will be taken.
- Samples for intravascular hemolysis laboratory parameters (including Coombs' test, haptoglobin, hemoglobin, hemosiderin) will be taken.
- Retention samples for viral safety laboratory parameters will be taken.
- Samples for IgG trough levels (total IgG) will be taken.
- A subject diary (paper) will be collected and reviewed.
- Health-related quality-of-life assessment will be performed.
- Concomitant medications (including prohibited treatments) will be recorded. The content of the subjects' diaries will be reviewed and the type of concomitant medication, dose/schedule, duration, and the indication the concomitant medication was given for will be documented.
- Adverse events will be recorded. The content of the subjects' diaries will be reviewed and AEs will be documented.

Further details on the visit schedule that will be used for the assessment of the efficacy, safety, and PK parameters in this study are presented in Section III, Flowchart of Study. A time window of ±2 days will be allowed for the treatment period visits and the closing (follow-up) visit; however, this time window will not apply for the PK assessments. Pharmacokinetic assessments will follow the time point specific time windows.

7.2 Duration of the Clinical Study

First Subject in *(planned)*	June 2016
Last Subject Last Visit *(planned)*	November 2019

Individual Subject

Each subject will be administered BT595 at 3- or 4-week intervals for a treatment period of approximately 12 months. In addition, each subject will attend a closing (follow-up) visit 3 or 4 weeks after the last BT595 infusion, according to the subject's treatment schedule.

A subject is considered to have completed the study when he/she is presumed to have followed the protocol (i.e., completed visits up to the end of Week 51 [3-week schedule] or up to the end of Week 52 [4-week schedule]). If for any reason, a subject discontinues involvement in the study early, every effort should be made to ensure the subject attends a closing (follow-up) visit (Section 4.4).

7.2.1 End of Study

The end of the clinical study will be defined as the Last Visit of the Last Subject.

7.3 Criteria for Premature Termination

7.3.1 Premature Termination of the Entire Clinical Study

The clinical study as a whole may be stopped by Biotest after consultation with the coordinating investigator if there are reasons for which continuation of the clinical study is no longer justified, such as:

a) Unacceptable delay of study completion
b) Low recruitment rate
c) A large number of subjects with premature termination
d) Changed benefit-risk ratio according to the efficacy and/or safety results from this or parallel studies
e) Lack of efficacy
f) Recently emerged information suggest that the study population can be offered a more advantageous study design

For sites in Europe, in case of premature termination of the entire clinical study, the sponsor has to notify the appropriate Regulatory Authorities within 15 days.

For sites in the US, in case of premature termination of the entire clinical study, the investigator has to notify the appropriate Regulatory Authorities promptly.

7.3.2 Premature Termination of an Individual Study Site

The clinical study may be stopped at an individual study site for reasons such as:

a) Determination of unexpected, significant, or unacceptable risk to subjects
b) Low recruitment rate
c) Lack of cooperation
d) Severe deviations from study protocol
e) Manipulation of study data
f) Violation of other ethical or legal principles

The participation of subjects may be stopped following guidance from the DSMB (Section 9.4). The DSMB Charter will include a description of stopping rules for the participation of subjects.

7.4 Treatment and Care after the End of the Study

For subjects who have finished the clinical study and for all subjects who drop out prematurely, it is the responsibility of the investigator to choose adequate therapeutic measurements.

8 BENEFIT-RISK EVALUATION

8.1 Benefit

The principal benefit for the participating PID subjects will be to receive the required immunoglobulin replacement therapy and thereby the antiinfective effect of BT595,

i.e. to prevent infections by substituting missing antibodies. Moreover, the participating PID subjects' quality of life will improve via the smaller infusion volume and shorter infusion duration feasible with BT595 (compared to a 5% IVIg), which will allow subjects to potentially experience a shorter stay in hospital or other health care facility.

Based on the extensive clinical experience with Intratect (50 g/L and 100 g/L) and the expected comparability of the safety profile between Intratect (100 g/L) and BT595, it is estimated that BT595 will show an acceptable safety profile even at the scheduled increased infusion rates.

8.2 Foreseeable Risk and Discomfort Related to BT595

Adverse Drug Reactions to be Expected with BT595

The identified risks for BT595 have been derived from the well-established safety profiles of Bivigam (licensed in the United States) and Intratect (50 g/L and 100 g/L; licensed in the EU and international markets); the EU-Core SmPC for IVIgs (EMA/CHMP/BPWP/94038/2007 rev. 4, 2012); and EMA guidance (EMA/CHMP/BPWP/94033/2007 rev. 2, 2010).

The following identified risks are considered to be expected ADRs for BT595 during the clinical study program:

- Thromboembolic events, including myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis;
- Hypersensitivity reactions (anaphylactoid and anaphylactic, including anaphylactic shock, chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure, and moderate low back pain; and transient cutaneous reactions);
- Aseptic meningitis;
- Hemolysis;
- Acute renal failure, increased serum creatinine;
- Leukopenia/neutropenia.

Foreseeable discomfort may result from blood samples taken from each subject during the course of the study for the assessment of exclusion criteria, laboratory parameters, viral safety (retention samples), immunoglobulin G trough levels, specific antibody trough levels, and PK parameters. The puncture of a vein and/or placement of indwelling catheters for blood withdrawal may cause pain and occasionally result in thrombosis or thrombophlebitis. Discomfort may also be caused by intravenous infusion of BT595.

8.3 Other Sources of Possible Risk and Discomfort

The following additional possible risks for BT595 have also been derived from the well-established safety profiles of Intratect (50 g/L and 100 g/L; licensed in the EU and international markets) and Bivigam (licensed in the United States); the EU-Core SmPC for IVIgs (EMA/CHMP/BPWP/94038/2007 rev. 4, 2012); and EMA guidance (EMA/CHMP/BPWP/94033/2007 rev. 2, 2010).

The following possible risks are considered relevant, but unexpected, for BT595 during this clinical study program:

- Suspected transmission of pathogen infection (infective agents)
- Interference of IVIg (interaction) with live-attenuated virus vaccines
- Transfusion-related acute lung injury (TRALI)
- Interference with serological testing by passively-transferred antibodies of IVIg.

To minimize the potential **risk of transmission of infective agents**, standard measures are established to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. These include the selection of donors, screening of individual donations and plasma pools for specific markers of infection, and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

Interference (interaction) of IVIgs with 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 medicinal 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, subjects receiving measles vaccine should have their antibody status checked. The foreign antibodies administered with IVIg could suppress a sufficient antibody induction by the live-attenuated virus vaccine in the subject.

Consequently, the above mentioned live-attenuated virus vaccines must not be administered during the respective time period.

Transfusion-related acute lung injury (TRALI) is a very rare and serious blood transfusion complication characterized by the acute onset of noncardiogenic pulmonary edema following transfusion of blood products. Transfusion-related acute lung injury is typically associated with products from SINGLE donors, such as fresh frozen plasma, or of packed red blood cells due to the residual plasma present in the unit. The American Association of Blood Banks recommended on 03 NOV 2006 (in Association Bulletin #06-07) that blood banks use high plasma volume components from female donors for further manufacturing instead of transfusion due to the higher risk of TRALI. In the company's opinion at present, no risk is seen for polyvalent immunoglobulins with manufacturing pool sized of more than 2000 donors. The reason for keeping it in this section is a class-label established in the United States.

Regarding the **interference with serological testing** by passively-transferred antibodies of IVIg, this risk can be considered in many cases as mild to moderate, and is spontaneously resolving.

8.4 Summary of Possible Risk and Discomfort

A single dose toxicity study is being performed in rats. The results are not yet available.

Of the possible risks associated with the administration of IVIgs in humans (Section 8.3), the risk of transmission of infective agents is considered to be controlled

by the manufacturing process, which includes several process-steps for the removal of bacteria, viruses, and other infective agents

The possible risk of interference (interaction) of IVIgs with live-attenuated virus vaccines will be prevented by the respective exclusion criterion (Section 4.3).

At present, there is considered to be no risk of TRALI in subjects with PID who are on a long-term low dose treatment regimen if the IVIg is manufactured from a sufficiently sized donor pool.

The possible risk of interference with serological testing by passively transferred antibodies of IVIg, if relevant, will be assessed by virus serology control.

No clinical studies in humans have previously been performed with BT595. However, BT595 as a 10% IVIg is expected to have a comparable safety profile to Intratect (100 g/L) and Bivigam, where favorable benefit-risk profiles have been established. In addition, the subjects eligible for this study will have been treated with an established replacement IVIg therapy for at least 6 months before inclusion in this study. So it is also predicted that similar ADRs will be observed under treatment with BT595 as with their previously established IVIg replacement therapy before study start.

This study will assess infusion rates ranging from 0.3 mL/kg/h to 8 mL/kg/h for BT595. As this is the same infusion rate range that is currently recommended for Intratect at 100 g/L, it is expected that BT595 at infusion rates up to 8 mL/kg/h will result in similar ADR frequencies and severities of ADRs as those observed with Intratect at 100 g/L. It is well known that the risk of hypersensitivity reactions, such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure, back pain, and transient cutaneous reactions increases with increased infusion rates (EMA/CHMP/BPWP/94033/2007 rev. 2, 2012), and as such, these types of anaphylactoid ADRs are expected in this study.

No change of the risk profile under treatment with BT595 is expected for subjects already being treated with other approved 10% polyvalent immunoglobulins at higher infusion rates. The occurrence of AEs which interfere significantly with the subjects' physical wellbeing or social activity during or after the testing period is not expected; however, cannot be excluded as a possibility.

The frequency, type, and severity of ADRs in the **pediatric population** are expected to be the same as in adults. A DSMB will be used to review the safety data of at least 10 adult subjects (18-75 years, inclusive) who have received at least 2 infusions with no safety concerns (Section 9.4), and will provide recommendations on the suitability of the enrollment of pediatric subjects into the study.

Although risks in general cannot be excluded entirely, the potential to occur can be minimized by the careful selection of subjects and by their close surveillance by experienced investigators who recognize safety issues early by carefully surveying warning signs and taking appropriate corrective action in case of AEs.

The potential risks and discomfort to the individual subject are reasonably balanced by the relevance of the study. Under the conditions of the study as described in the

present protocol, the coordinating investigator and the sponsor consider the benefit-risk ratio to be favorable.

9 ASSESSMENT OF OBJECTIVES/CRITERIA FOR EVALUATION

9.1 Efficacy

9.1.1 Specification of Efficacy Parameters

9.1.1.1 Primary Efficacy

The primary efficacy parameter is determined from the rate of acute serious bacterial infections per subject-year.

Data will be compared to historical data from previous PID studies with Intratect and Bivigam, as well as to available data from literature.

9.1.1.2 Secondary Efficacy

Secondary efficacy will be determined using the following:

- Immunoglobulin G trough levels (total IgG) before each infusion
- Infections (serious and nonserious, time to resolution of infections, antibiotic treatment for infections, and days lost from school/work due to infections and their treatment)
- Hospitalization
- Fever episodes
- Health-related quality-of-life

9.1.2 Methods for Assessing and Recording Efficacy Parameters

9.1.2.1 Primary Efficacy Parameter

The number and type of acute serious bacterial infections will be determined through review of data collected on infections. Infections will be reported as AEs which will be obtained by the investigator through observation of the subject (including examinations and investigations), from any information volunteered by the subject, and through active questioning. Subject diaries will be reviewed to check for instances where the AE occurs and the subject is not on a site visit. Subjects will receive instructions from the investigator on how to record this information in their subject diary (paper) in 'real time' from the time they leave their current site visit until the next site visit, what steps to take if an AE occurs, and the action to be taken if an infection is suspected. If a subject suspects they have an infection between visits, the subject must inform the investigator as soon as possible. If the investigator confirms/suspects the subject has an infection, the subject must attend the site to be examined by the investigator. Subjects will be instructed to bring their subject diary to each study visit. During each scheduled visit, subjects will be asked about AEs occurring since their last visit and subject diaries will be collected and reviewed for any signs of AEs (infections) occurring between visits before IMP administration. Specific diagnostic criteria, as recommended by the FDA guidance (Appendix 3), will be used by the investigator to define each type of serious infection included in the primary efficacy analysis.

Acute serious bacterial infections will include:

- Bacteremia or sepsis
- Bacterial meningitis
- Osteomyelitis/septic arthritis
- Bacterial pneumonia
- Visceral abscess

Essential diagnostic features are defined in the diagnostic criteria for acute serious bacterial infections recommended by the FDA guidance (Appendix 3). The infections must be documented by objective findings. If possible, blood for measurement of acute phase reactants should be obtained, but this is not an absolute requirement. If imaging procedures (i.e., x-rays) are taken to confirm diagnostic criteria for acute serious bacterial infections, data will be recorded in the eCRF.

The investigator will confirm the date of onset of an episode of acute serious bacterial infection and record this in the eCRF.

Details of all AEs defined as acute serious bacterial infections will be recorded in the subject's eCRF.

9.1.2.2 Secondary Efficacy Parameters

Immunoglobulin G Trough Levels (Total IgG)

Blood samples (approximately 7.5 mL) for the assessment of total IgG trough levels will be taken at the time points detailed in Section III, Flowchart of Study. Note: the approximate blood sample volumes are estimated, and as the samples will be tested by local laboratories, may differ from the approximate blood volumes detailed.

Before each infusion of BT595, blood samples will be taken for the assessment of total IgG trough levels. Samples will be analyzed at the local laboratory using standard assay methods. During the treatment period, the subject's total IgG trough level result from the previous infusion will be made available to the investigator before the next infusion of BT595. This is to allow dose adjustments to be made if the subject's trough level fell below the specified level of 5 g/L.

Infections and Infection-Related Events

All infections and episodes of fever will be reviewed and recorded as described in Section 9.1.2.1.

Infections (serious and nonserious) will be assigned using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA®) and using the coding levels of system organ class and preferred term. The investigator will confirm the date of onset of infection and record this in the eCRF. The time to resolution of infection will be recorded by the subject in the subject diary and verified by the investigator.

For each episode of infection, the subject must be examined by his/her investigator before initiation of antibiotic therapy. A record of antibiotic treatments will be reported in the subject's diary. If a subject's antibiotic treatment includes antipyretic treatment, the subject must also have their body temperature (before the antipyretic is taken) recorded in the subject diary.

A record of the number of days a subject is not able to attend school or work due to the infection and the treatment of the infection will be reported in the subject's diary. A record of any admission to hospital and the number of days in hospital will also be reported in the subject diaries. This record will include the hospitalization type (i.e., hospital admission or emergency room), the dates of the visit/admission, and the reason for the visit/admission.

Fever is defined as a body temperature ≥38°C (≥100.4°F). Fever which recurs after ≥3 days without fever will be counted as a new fever episode. The number of days of fever for a given fever episode is defined as the number of days from the first day of a body temperature ≥38°C (≥100.4°F) to the last day with a body temperature ≥38°C (≥100.4°F).

Details of all AEs defined as infections or episodes of fever will be recorded in the subject's eCRF.

Health-Related Quality-of-Life

The subjects' health-related quality-of-life will be assessed using 2 subject questionnaires (Peds QL™ [PedsQL™ Measurement Model] and EQ-5D™ [EuroQol Five Dimension Health Questionnaire, 2015]) collected as patient reported outcomes (PROs) while the subject attends the investigator site for a visit. For pediatric subjects, the PROs may be completed by proxy (i.e., by the subjects' parent[s] or legally acceptable representative).

All pediatric subjects (2-17 years, inclusive) will complete the 23-Item Pediatric Quality of Life (Peds QL™) Measurement Model (Version 4.0). The Peds QL™ Measurement Model consists of developmentally appropriate forms for children aged 2 through 4 years, 5 through 7 years, 8 through 12 years, and 13 through 18 years, and must include both child self-reports and parent proxy-reports, with the exception of children aged 2 through 4 years where only the parent proxy-report is required. The developmentally appropriate form will be selected based on the subject's age recorded at screening (initial visit). The same age will be used per subject during the entire study and the same developmentally appropriate form will be used per subject during the entire study, even if the subject's age indicates a change in form is required (i.e., if a subject's age changes from 7 to 8 years during the study, they must complete the form for children aged 5 through 7 years during the entire study). The person completing the parent proxy-report should be constant for the duration of the subject's study participation. The Peds QL™ Core Scales encompass the essential core domains for pediatric health-related quality-of-life measurement: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). In each domain, the person completing the form will be provided with a list of things which might be a problem for the subject and asked to respond with 'how much of a problem' each one is (i.e., 0 if it is never a problem, 1 if it is almost never a problem, 2 if it is sometimes a problem, 3 if it is often a problem, and 4 if it is almost always a problem).

All adult subjects will rate their quality of life by self-completing the EQ-5D™ Health Questionnaire (Version 1.0). The EQ-5D™ essentially consists of 2 pages: the EQ-5D™ descriptive system page and the EQ visual analog scale (EQ VAS) page. The EQ-5D™ descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each EQ-5D™ dimension has

3 levels (EQ-5D-3L™): no problems, some problems, extreme problems. The EQ-5D™ EQ VAS records the respondent's self-rated health on a vertical, visual analog scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'.

In addition to the Peds QL™ Measurement Model, pediatric subjects (4-17 years, inclusive) will rate their quality of life by completing the youth version of the EQ-5D™ (EQ-5D-Y™; child self-report or proxy-report). The EQ-5D-Y™ consists of the same 2 pages: the EQ-5D-Y™ descriptive system page and the EQ VAS page. The descriptive system comprises the same dimensions as the EQ-5D-3L™, but using child-friendly wording (mobility; looking after myself; doing usual activities; having pain or discomfort; and feeling worried, sad, or unhappy) and has 3 levels: no problems, some problems, and a lot of problems. The EQ VAS endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. A proxy version of the form will be used for children aged 4 through 7 years. All other pediatric subjects (8-17 years, inclusive) will self-complete the EQ-5D-Y™.

9.1.3 Specification of Efficacy Endpoints

9.1.3.1 Primary Efficacy

- Rate of acute serious bacterial infections (i.e., the mean number of acute serious bacterial infections per subject-year)

9.1.3.2 Secondary Efficacy

- IgG trough levels (total IgG) before each infusion
- Rate of any infections (number per year)
- Rate of nonserious infections (number per year)
- Time to resolution of infections
- Antibiotic treatment (number of days antibiotic treatment received per month)
- Rate of time lost from school/work due to infections (number of days per month) and their treatment (number of days treatment per month)
- Hospitalization (number of days per month overall and due to infection)
- Fever episodes (number of days per year)
- Changes in health-related quality-of-life parameters

9.2 Safety

9.2.1 Specification of Safety Parameters

Safety and tolerability in this clinical study will be addressed by the following safety parameters: AEs, laboratory parameters (routine and intravascular hemolysis), vital signs, and physical examination.

For the timing of individual safety parameters refer to Section III, Flowchart of Study. Any abnormal observation or finding detected during the screening procedures after subject's informed consent/assent that is considered clinically relevant must be documented as concomitant disease (ongoing medical history) or as past medical history. All medications other than the study medications should also be documented.

9.2.1.1 Adverse Events

Adverse event data are obtained by the investigator through observation of the subject (including examinations and investigations), from any information volunteered by the subject, and through active questioning. At each visit after informed consent/assent has been signed, subjects will be asked about AEs that occurred since the last visit, by questioning them with regard to their well-being by 'nonleading' questions. This includes AEs occurring during the administration of the study medication, as well as changes in concomitant diseases (i.e., ongoing medical history). The subject's diary (paper) is a source of collection of AE data that will be transcribed to the eCRF. Subject diaries will be reviewed for any signs of AEs occurring between visits.

Occurrence, frequency, nature, severity, causality, and seriousness of AEs will be recorded. This includes observations or abnormalities in physical examination, vital signs, laboratory, or other investigations reported as AEs. Any treatments for AEs will also be recorded. For further details regarding AEs including definitions and reporting procedures refer to Appendix 1 and Appendix 2.

9.2.1.2 Physical Examination

For each subject, a complete physical examination will be performed at the time points specified in Section III, Flowchart of Study. Physical examination includes inspection of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, vascular system, extremities, musculo-skeletal system, and nervous system. Clinical findings and existing diseases at screening are to be documented as medical history. A new appearance of an abnormal finding or worsening of a concomitant disease that is considered clinically significant and occurs after signature of informed consent/assent must be documented as an AE.

- Body weight is measured in kilograms (kg).
- Body height is measured in cm once at the screening visit for the purpose of calculation of body mass index.

The physical examination will be followed-up with a verbal exchange (face-to-face) between the subject and the investigator 1 hour after the end of each infusion, and a verbal exchange (by telephone) 24 and 72 hours after the end of each infusion. At each exchange, the subject will report any changes since the physical examination performed before the BT595 infusion. Any new physical examination finding will be documented as an AE.

9.2.1.3 Vital Signs

Vital signs are measured with the following methods/units:

- Blood pressure is measured in mmHg according to the Riva Rocci method while the subject has been resting in supine position for at least 15 minutes. The same arm should be used for blood pressure measurements throughout the study. The size of the cuff has to be chosen appropriately in relation to the subject's arm circumference.
- Pulse rate is measured in beats per minute either electronically and/or by palpation for 1 minute while the subject is supine and has been resting for at least 15 minutes. When pulse rate is of concern, cardiac monitors are used to determine not only rate, but also rhythm.

- Respiratory rate is measured in breaths per minute while the subject has been resting for at least 15 minutes.
- Body temperature is measured in degrees Centigrade or Fahrenheit using axillar measurements.

Measurements outside the normal range (according to the age and gender of the subject) or even values within the normal range showing a trend have to be assessed for clinical relevance by the investigator, and reported as AEs if considered to represent a clinically significant change as compared to screening values.

9.2.1.4 Laboratory Parameters

Routine Laboratory Parameters

All routine laboratory results have to be evaluated in the eCRF (by the investigator) according to the following pattern:

a) Within reference range (normal range)
b) Outside reference range but not clinically relevant (e.g., marginal deviation only, due to underlying diseases in the study population)
c) Outside reference range and clinically relevant

Laboratory values occurring (by date of blood sampling) after signature of informed consent/assent, which are outside the reference range and assessed as clinically relevant (as determined by investigator), have to be documented as AEs.

An abnormal laboratory value that is a sign of an AE (e.g., increased leukocytes due to bacterial infection) that has already been reported during the present clinical study, has to be stated but the respective abnormal laboratory value (e.g., increased leukocytes) does not constitute a separate AE.

For the routine laboratory parameters, the total volume of blood that will be drawn from a subject per visit will be approximately 13.5 mL.

The laboratory safety parameters to be assessed are summarized in Table 1.

Table 1: Laboratory Safety Parameters

Clinical Chemistry (Approximately 7.5 mL)
• Alanine aminotransferase • Aspartate aminotransferase • Gamma-glutamyltransferase • Alkaline phosphatase • Lactate dehydrogenase • Bilirubin (direct and indirect if total bilirubin is elevated) • Glucose • Total protein • Albumin • Creatinine • Blood urea nitrogen • Sodium • Chloride • Potassium • Calcium
Hematology (Approximately 3 mL)
• Hematocrit • Hemoglobin • Red blood cells

• White blood cells • Differential white blood cells • Platelets • Erythrocyte sedimentation rate • C-reactive protein
Coagulation (Approximately 3 mL)
• Fibrinogen • Prothrombin time, international normalized ratio • Partial prothrombin time
Urinalysis
• pH • Qualitative for blood • Leukocytes • Protein • Glucose • Ketone bodies • Bilirubin • Urobilinogen • Nitrites • Osmolality • Urine sediment microscopy

Note: the approximate blood sample volumes are estimated, and as the samples will be tested by local laboratories, volumes may differ from the approximate blood volumes detailed.

In addition, the following specific safety laboratory parameters will be assessed at the time points specified in Section III, Flowchart of Study:

Intravascular Hemolysis

The intravascular hemolysis tests will be performed at screening (initial visit) and the closing (follow-up) visit only, unless further tests are required. Tests for the detection of intravascular hemolysis will consist of a direct antiglobulin test (Coombs' test; approximately 7 mL blood sample) and the measurement of serum haptoglobin, plasma-free hemoglobin, and urine hemosiderin. If the Coombs' test result is positive, the test will be repeated and red blood cell count, hematocrit, hemoglobin, serum haptoglobin, bilirubin (total, direct, and indirect), lactate dehydrogenase, and urine hemosiderin tests will be performed within 2 to 5 days. If the hemoglobin level has dropped by ≥2.0 g/dL from the screening level, in conjunction with both a drop in serum haptoglobin to below the lower limit of normal and a rise in serum lactate dehydrogenase from the screening level, this will suggest intravascular hemolysis, and a repeat urine dipstick, micro-urinalysis, and assessment of hemoglobin levels will be obtained within 72 hours of being informed of the drop in hemoglobin levels.

For the first 10 patients and their first 2 infusions (V2 and V3) the results of the direct antiglobulin test (Coombs test) and the test of serum haptoglobin at the time points V3 and V4 are required as a prerequisite for the decision of the Data and Safety Monitoring Board. For those 10 patients approximately 7 mL of additional blood will be taken for each of the two visits (V3 + V4).

Note: the approximate blood sample volumes are estimated, and as the samples will be tested by local laboratories, volumes may differ from the approximate blood volumes detailed.

Virus Serology
The immunological status of viral infections will be assessed at screening (initial visit) for:

- HIV (anti-HIV1 and anti-HIV2)
- hepatitis B (total hepatitis B core antibody [anti-HBc], hepatitis B surface antibody [anti-HBs], hepatitis B surface antigen [HBsAg])
- hepatitis C (anti-HCV)

Pregnancy Test
In females of child-bearing potential (i.e., female subjects ≥12 years or with presence of menstruation at screening), a pregnancy human chorionic gonadotropin test in serum will be performed at screening (initial visit). Urine pregnancy dipstick tests will be performed at other time points in the clinical study as specified in Section III, Flowchart of Study.

The serum sample will be analyzed by the local laboratory using standard assay methods and the urine dipstick test will be analyzed at the study site.

9.2.1.5 Viral Safety (Retention Samples)

In order to respond rapidly to any reports on additional viral infections, a screening blood sample (5 mL) from each subject included in the study must be taken at the start of the study (screening [initial visit]) and stored at -70°C for possible future serum testing.

At the closing (follow-up) visit, an additional blood sample (5 mL) must be taken and stored up to 6 months after study end.

9.2.2 Methods for Assessing and Recording Safety Parameters

The following safety parameters are recorded in the eCRF: AEs (Section 9.3 for further details), physical examination findings, laboratory values (routine and intravascular hemolysis), virus serology, and vital signs.

All laboratory analyses will be performed by the local laboratory using standard assay methods and will be transcribed to the eCRF by the investigator in a timely manner.

9.2.3 Safety Endpoints

For each subject and for the study as a whole:

- Number, severity, causality, and seriousness of infusional AEs (including nonproduct related) temporally associated with the infusion (occurring during infusion or within 1, 24, and 72 hours after the end of infusion)
- Number of related infusional AEs (occurring during infusion or within 1, 24, and 72 hours after the end of infusion)
- Number and percentage of infusions temporally (within 72 hours) associated with 1 or more AEs
- Number, severity, causality, and seriousness of all AEs
- Number, severity, causality, and seriousness of all treatment-emergent AEs (TEAEs)
- Number of noninfusional AEs (occurring more than 72 hours after the end of infusion)

- Changes in safety laboratory parameters (outside reference range and clinically relevant)
- Number of positive intravascular hemolysis test results
- Changes in vital sign parameters
- Changes in physical examination parameters

For AEs that occur during an infusion, the following should be reported and analyzed: (1) the infusion rate in effect at the time of onset of the AE; (2) the time of onset of the AE; and (3) the time at which the AE changed materially in intensity and/or resolved. Listings of SAEs; AEs by severity; AEs by body system; and a determination of which AEs were product-related, and which were not, will be provided.

The mean number of AEs temporally associated with infusions per infusion will be calculated by (a)/(b) where: (a) equals the total number of AEs that occur during or within 72 hours of an infusion, and (b) equals the total number of infusions.

The proportion of infusions administered to subjects for which “infusional” AEs have been reported will be provided.

The proportion of subjects who experience 1 or more AEs at any time during the course of the study will be provided.

For each AE, it will be indicated which infusion of investigational product this occurred with or followed (i.e., 1st infusion, 2nd infusion, etc). The AE listings will include separate reports of all AEs and of AEs judged by investigators to be associated with the infusion of the product, even if the sponsor determines the AE not to be product-related.

Where appropriate, analyses of AEs should take into account the observed intra-subject correlation of the same type or any type of AE, as such within-subject events may not be independent. Methodology for these analyses will be described in the Statistical Analysis Plan (SAP).

9.3 Adverse Events

9.3.1 Definitions (also refer to Appendix 1)

- **Adverse Event (AE)**
  Any untoward medical occurrence in a patient or clinical study subject administered an investigational medicinal product (IMP) and which does not necessarily have a causal relationship with this treatment. An AE may be any aggravation or new unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

  Adverse Reaction (ADR) of an Investigational Medicinal Product:

  All untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs (= related AEs). The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal

relationship. This definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the IMP (Section 9.3.6).

- **Serious Adverse Event (SAE)**
  An SAE is any untoward medical occurrence or effect that at any dose*:
    - results in death
    - is life-threatening
    - requires hospitalization or prolongation of existing hospitalization
    - results in persistent or significant disability/incapacity
    - is a congenital anomaly/birth defect
    - is another important medical event

  * "At any dose" does not necessarily imply that the subject is receiving the study drug at the time of the event.

  Reporting requirements are detailed in Appendix 2.

- **Adverse Event of Special Interest (AESI)**
  An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's IMP or development program, for which ongoing monitoring and immediate communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Reporting requirements are detailed in Appendix 2.

  The following AEs have been defined as AESIs for this study:
    - Thromboembolic events (such as stroke, myocardial infarction, lung embolism)
    - Hemolysis
- **Immediately Reportable Adverse Event (IRAE)**
  An AE that must be reported to the sponsor **within 24 hours** of the study site being aware of the AE. Reporting requirements are detailed in Appendix 2.

  For this clinical study, IRAEs include:
    - All SAEs
    - All AESIs
    - All AEs that result in a subject's withdrawal from the study
    - Overdose
    - Pregnancy
- **Adverse Events Leading to Subject's Withdrawal from the Clinical Study**
  An AE, serious or nonserious, resulting in a subject's withdrawal from the clinical study, i.e. permanent treatment discontinuation. Reporting requirements by the investigator are detailed in Appendix 2.

  Mandatory Adverse Event Stopping Rules

  Subjects have to be withdrawn if any of the following AEs occur:
    - Thromboembolic events (such as stroke, myocardial infarction, lung embolism)
    - Hemolysis

9.3.2 Recording Adverse Events

All AEs, serious and nonserious, that occur during the period of observation defined for the clinical study (Section III, Flowchart of Study) have to be fully documented in the eCRF according to the provisions given in this section of the study protocol and CRF completion guidelines, as well as in the subject's source data. This applies also to AEs in subjects who signed the informed consent/assent but never received the study drug.

In addition, for a subset of AEs (SAEs, AESIs, AEs leading to withdrawal, overdose, and pregnancy), immediate reporting from the investigator to sponsor is required (IRAEs). This is further detailed in Appendix 2. The following information is necessary:

- **Diagnosis vs. Signs/Symptoms**

  The investigator should provide a diagnosis rather than individual signs and symptoms, wherever possible and appropriate. However, if there is not enough information to provide a diagnosis, individual signs and symptoms are to be recorded. If a diagnosis is accompanied by unusual symptoms, the diagnosis itself and the unusual symptoms have to be reported separately. For SAEs and other IRAEs, the investigator shall provide any other supporting information that may be required for the assessment of the events.

  A complication of an AE constitutes another AE. For example, in diarrhea leading to dehydration, diarrhea and dehydration would be captured as separate AEs.

  The eCRF provides for a number of items to be completed for each AE. This includes the onset date; end date; intensity/severity; seriousness; action taken with study medication; treatment for the AE; outcome; and causal relationship of the AE with the study medication, other drugs, or study procedures (Appendix 1).

  Severe vs. Serious: The severity is used to describe the intensity of an event. This is not the same as seriousness, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to subject's life or functioning. Seriousness, not severity, serves as the guide for defining regulatory reporting obligations.

- **Causal Relationship of the Adverse Event**

  The causal relationship with the study medication has to be reported for each AE. It refers to the presence or absence of a reasonable possibility of a causal relationship between the study medication and the AE.

  The investigator is asked to use medical judgment and take into account the nature of the AE; the subject's medical history; temporal relation; response to withdrawal or interruption of study drug (dechallenge); response to reintroduction of study drug (rechallenge); and any alternative explanations such as underlying or concomitant diseases, concomitant drugs, or study procedures.

  The following categories are used:

  - Related: There is a reasonable possibility of a causal relationship between the study medication and the AE.
  - Not related: There is no reasonable possibility of a causal relationship between the study medication and the AE.

For SAEs and other IRAEs, the investigator is asked to specify if there are alternative and/or additional explanations for the occurrence of the event (e.g., concomitant drugs, study procedures, or concomitant/underlying disease) and should provide this information already with the initial case report.

9.3.3 Period of Observation

The period of observation for collection of AEs extends from the time the subject signs the informed consent/assent form until the last study visit (closing [follow-up] visit), which is scheduled 3 or 4 weeks after the last dose of study medication (depending on the subject's treatment schedule).

Abnormal, clinically relevant findings or observations made prior to signature of informed consent/assent are to be recorded as medical history/concomitant disease, but not as AEs.

Adverse events occurring in the pretreatment period between signature of informed consent/assent until first administration of study medication are nontreatment emergent AEs.

Adverse events occurring from the first administration of study medication until the subject's last study visit are TEAEs.

If an SAE occurs in a subject after the period of observation, i.e., after the last study visit, which is considered by the investigator to be related to the study medication, this should be recorded as an SAE and should follow the immediate reporting process for SAEs as described in Appendix 2. If the eCRF has been closed for the subject, the investigator should contact the sponsor to determine how to report the SAE.

9.3.4 Assessment of Adverse Events

- **Responsibilities of Investigator**

  Adverse events are assessed by the investigator in a standardized manner including, but not limited to seriousness, severity, outcome, and causality. This has to be performed in line with the definitions and provisions given in Appendix 1.

  Laboratory values outside the reference range have to be assessed for clinical relevance taking into account the pretreatment values. For reporting of abnormal laboratory values as AEs, refer to Section 9.2.1.4.

  If an AE meets the definition of any of the mandatory AE related stopping rules (Section 9.3.1), the investigator must withdraw the subject and report the AE as an IRAE according to Appendix 2.

  For all AEs, the causality assessment has to be provided in the eCRF, even if based on preliminary data. Once more information is available, the investigator may change a preliminary causality assessment.

  During and after participation of a subject in a clinical study, the investigator/institution has to ensure that adequate medical care is provided to the subject for any ongoing AEs, including clinically significant abnormal laboratory values. The investigator has to inform the subject when medical care is needed for any intercurrent disease of which the investigator becomes aware.

- **Responsibilities of Sponsor**

  Adverse events are reviewed and assessed by the sponsor during ongoing safety monitoring activities throughout the study, as well as medical evaluation and regulatory assessment for reportability of SAEs and IRAEs. For the purpose of regulatory reporting, the causality assessment given by the investigator will not been downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, both the opinion of the investigator and the sponsor will be recorded.

  Regulatory assessment of an AE by the sponsor comprises the assessment of expectedness, which is based on Section 7 of the Investigator's Brochure for BT595.

- **Follow-up of Adverse Events**

  Adverse events should be followed up to determine the outcome.

  Adverse events that are serious or severe or considered related to the study medication or study procedures must be followed-up by the investigator until the AE is resolved or resolved with sequelae, and until all queries related to the AE have been clarified. If the subject had an AE with fatal outcome, an autopsy report should be provided, if possible.

  If AEs that are serious or severe or considered related to study medication or study procedures are ongoing at the time of the subject's last study visit, or if the subject has clinically relevant laboratory parameter abnormalities at the last study visit, one or more safety follow-up visit should be scheduled for those subjects. The investigator should set the interval to the additional Safety follow-up visit according to his/her medical judgment. Follow-up activities should be continued until the investigator considers it medically justifiable to stop further follow-up.

  All other AEs must be followed up by the investigator until the AE is resolved or resolved with sequelae or the end of the period of observation (i.e., last study visit), whichever comes first.

  The investigator should respond to any queries raised by the sponsor in relation to AEs, including provision of supporting documentation for SAEs or other IRAEs (e.g., electrocardiogram [ECG] data, laboratory results, hospital summary, autopsy report) within the requested timeline. In case of fatal or life-threatening SAEs, the sponsor may request urgent clarification within 1 calendar day. In general, if for AEs requiring immediate reporting from the investigator to sponsor (IRAEs/SAEs), follow-up information becomes available, this must be reported to the sponsor **within 24 hours** of becoming aware of this information (i.e., the same timeframe as for initial IRAE/SAE reports). Any supporting documents have to be identified by the subject identification, and personal data (e.g., subject name, address, or phone number) obliterated prior to sending to the sponsor. For details on reporting IRAEs/SAEs, see Appendix 2.

  Adverse event data in the eCRF must be updated accordingly when follow-up information is received.

  All efforts to collect follow-up information must be documented in the subject's source data.

Subjects who were treated with the study medication but did not complete the study as per protocol, should receive all the examinations and investigations scheduled for the last study visit. The investigator should make all efforts to contact subjects lost to follow-up and document the attempts in the subject's source data.

9.3.5 Immediate Reporting by Investigator to Sponsor

The reporting processes are outlined in detail in Appendix 2.

9.3.6 Use of Investigational Medicinal Product Outside the Specifications of the Clinical Study Protocol

Situations may occur where the IMP is used outside the specifications of the protocol, which may or may not be associated with an AE. These special situations comprise:

- Medication errors (including overdose)
- Abuse/misuse of the IMP

Such situations, whether or not associated with an AE, are documented in the eCRF on dedicated pages. Any AE that occurred in association with such a special situation has to be cross-referenced on the dedicated eCRF page. An IRAE/SAE occurring in conjunction with a medication error or abuse/misuse of the IMP has to follow the immediate reporting process for IRAE/SAE as described in Appendix 2 in addition to its documentation in the eCRF (also refer to Sections 9.3.1, 9.3.8, and 10.2).

9.3.7 Investigational Medicinal Product Complaints

Investigational medicinal product complaints must be recorded in the eCRF and in addition reported to the sponsor on the "Investigational Medicinal Product Complaint Report Form" **within 24 hours** of the investigator becoming aware of the IMP complaint. If the IMP complaint is associated with an AE, the AE must be entered in the eCRF also.

Any complaint samples should be provided to the sponsor upon request.

9.3.8 Special Situations Requiring Immediate Reporting

Special situations may occur that may or may not be associated with AEs. For these situations, special reporting provisions apply.

Special situations comprise:

- Pregnancy in a female study subject or the partner of a male study subject
- Investigational medicinal product complaint
- Use of IMP outside the specifications of the Clinical Study Protocol (e.g., medication errors, overdose, misuse and abuse; also refer to Section 9.3.6 and Section 10.2)
- Protocol deviations (refer to Section 10.2)

If such a situation occurs, the investigator should contact the sponsor immediately. A special paper report form has to always be completed in these situations and sent to the sponsor immediately, but not later **than 24 hours** after the investigator becoming aware of the situation.

9.3.8.1 Pregnancy

Pregnant women are excluded from the study, and female study subjects of child-bearing potential (≥12 years or presence of menstruation at screening) undergo pregnancy testing at screening and regularly during the study (Section III, Flowchart of Study). If pregnancy is suspected in a study subject during treatment with the IMP, the IMP must be immediately withheld until the result of a confirmatory test is available. If confirmed, the subject must be withdrawn from the study. Furthermore, the reason and the contraception methods may need to be reviewed and documented as a preventative measure for other participants.

Although not an AE per se, pregnancy in a female study subject or the partner of a male study subject must be recorded if it occurs during the period of observation of the study (see definition in Section 9.3.3). The investigator must contact the sponsor immediately in such a situation.

The pregnancy must be documented on a "Drug Exposure Via Parent Report Form" (DEVP Form) and reported to the sponsor **within 24 hours** of the investigator becoming aware of the pregnancy. If an AE occurs in relation to the pregnancy, it has to be noted on the DEVP Form and recorded in the eCRF. If an IRAE/SAE occurs in relation to the pregnancy, it has to be noted on the DEVP Form and recorded in the eCRF and follow the immediate reporting process for IRAE/SAE as described in Appendix 2.

The investigator must make all reasonable efforts to follow up the pregnancy until its end and will report all outcomes associated with the pregnancy to the sponsor. In the situation of pregnancy of the female partner of a male study subject, consent for the release of medical data should be obtained from the female partner to allow collection of information on the outcome of the pregnancy.

9.4 Data and Safety Monitoring Board

To monitor the safety data from adult subjects and provide advice and recommendations on the enrollment of pediatric subjects, a DSMB consisting of independent experts will be convened. The DSMB will review the safety data of at least 10 adult subjects (18-75 years, inclusive) who have received at least 2 BT595 infusions with no safety concerns and provide recommendations on the suitability of the enrollment of pediatric (2-17 years, inclusive) subjects into the study. In addition to the laboratory values already described and as a requirement from the DSMB the direct antiglobulin test (Coombs' test) and the test for serum haptoglobin for these 10 adult patients and their first two visits have to be performed on V3 and V4. The final decision to enroll/not enroll pediatric subjects will be the responsibility of the sponsor.

The specific responsibilities and composition of the DSMB are outlined in a separate document, the DSMB Charter, which will include a description of stopping rules for the participation of subjects. The DSMB Charter will also include details on the frequency of DSMB meetings and details of the information to be provided for the DSMB review.

9.5 Pharmacokinetics

9.5.1 Specification of Pharmacokinetic Parameters

Serial blood samples (approximately 7.5 mL) for the establishment of the PK characteristics of BT595 and the determination of PK parameters at steady-state for

total IgG, IgG subclasses 1-4, and IgG specific antibody levels (anti-pneumococcal capsular polysaccharide, anti-hemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-HBs/hepatitis B) will be obtained from at least 20 adult subjects (18-75 years, inclusive) and from pediatric subjects (6-17 years, inclusive). Note: samples for IgG specific antibody levels will be taken from pediatric subjects aged 12 through 17 years only.

Sufficient samples will be obtained to reconstruct a concentration-time curve and to derive key PK parameters for total IgG, IgG subclasses 1-4, and IgG specific antibody levels. The samples will be taken as 1 aliquot for all analytes.

Unused PK serum samples may be used to measure additional specific antibody levels/immunological variables of medical relevance as optional analytical variables which may be of importance with regard to efficacy of an IVIg in PID.

For pediatric subjects (2-5 years, inclusive), sparse sampling at flexible time points within specified time windows after the end of the infusion may be performed (note: these samples are optional; see Section 7.1). For pediatric subjects (2-5 years, inclusive), only total IgG kinetics at steady-state will be established; no samples for IgG trough levels of subclasses 1-4 and IgG trough levels of specific antibody levels will be taken.

9.5.2 Methods for Assessing and Recording Pharmacokinetic Parameters

Blood samples will be collected by health care professionals, with procedures adapted for each age category (i.e., pediatric tubes and plasma micro-sampling). A homecare service is allowed for the PK sampling of pediatric subjects (2-17 years, inclusive). Blood sampling will be performed with a very thin gauge needle to reduce discomfort as much as possible. Blood collection immediately and up to 6 hours after the infusion must not be performed from the subject's arm to which the infusion of study medication was administered; instead the contralateral arm must be used.

Blood samples will be taken at estimated steady-state after the 7th infusion of the 3-week schedule or after the 5th infusion of the 4-week schedule. Subjects will complete serial blood sampling according to their age category; therefore, the number of blood draws will depend on the subject's age category. For adult subjects (18-75 years, inclusive) and pediatric subjects (6-17 years, inclusive), samples will be taken at a fixed series of time points. For pediatric patients (2-5 years, inclusive), sparse sampling at flexible time points within specified time windows after the end of this infusion may be performed (note: these samples are optional).

The samples will be taken at the time points detailed in Section III, Flowchart of Study, and Section 7.1.

In total, 8 or 9 PK blood samples will be taken from adult subjects (18-75 years, inclusive) and pediatric subjects (6-17 years, inclusive) over a period of 3 or 4 weeks (according to the treatment schedule). The samples will be taken as 1 aliquot for all analytes. For pediatric subjects (2-5 years), up to 5 PK blood samples may be taken over a period of 3 or 4 weeks (according to the treatment schedule).

The blood samples taken for PK analysis will be analyzed by the central laboratory using standard assay methods, including the predose samples (trough levels) collected

for this purpose. An aliquot of each sample will be stored at -20ºC until the end of the study and centrally measured.

Pharmacokinetic data (including total IgG trough levels) will also be compared to historical data from previous PID studies with Intratect and Bivigam, as well as to available data from literature.

The statistical analysis of the PK data will be performed by [redacted].

9.5.3 Pharmacokinetic Endpoints

- IgG trough levels (total IgG) before each administration
- IgG trough levels (subclasses 1-4) at baseline and before the 7th/5th infusion of the 3-week/4-week schedule, respectively (with the exception of pediatric subjects aged 2-5 years, inclusive)
- IgG trough levels of specific antibody levels (anti-pneumococcal capsular polysaccharide, anti-hemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-HBs/hepatitis B) at baseline and before the 7th/5th infusion of the 3-week/4-week schedule, respectively (with the exception of pediatric subjects aged 2-11 years, inclusive)
- Pharmacokinetic parameters at steady-state: maximum concentration (C_{max}), time to reach maximum concentration (t_{max}), trough concentration (C_{trough}), area under the concentration-time curve calculated from start to end of the dosing interval (AUC_{tau}), steady-state clearance (CLss), %Fluctuation, and if possible, terminal elimination half-life ($t_{1/2}$), terminal elimination rate constant (λz), as well as other parameters described in greater detail in Section 10.10.

10 STATISTICS

The statistical planning and evaluation of the clinical study will be carried out by a qualified biostatistician in accordance with the ICH-guidelines and adequate biostatistical standard operating procedures. A SAP, providing details about the statistical methods for the analyses, will be finalized before the inclusion of the first subject in the study to avoid any data driven bias. This ensures that the integrity of the analyses is maintained.

Any deviations from the planned analyses will be described and justified in the clinical study report.

10.1 Analysis Sets

The following analysis sets will be defined:

All Subjects Enrolled Set:

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

Safety Set (SAF):

The SAF comprises all subjects who have received at least 1 dose of study medication. Subjects will be analyzed according to the treatment received.

Full Analysis Set (FAS):

The FAS includes all subjects following the principle of intention-to-treat. The FAS comprises all subjects who received at least 1 dose of study medication (i.e., there is no difference between the FAS and the SAF in this study).

Per-protocol Set (PPS):

The PPS includes all subjects who are compliant with the study protocol without any major protocol deviations. Classification of protocol deviations as major or minor will be agreed upon at the Data Review Meeting (DRM) prior to database lock. The decision to carry out any analysis based on the PPS will be evaluated at the DRM. Any analysis based on the PPS will be performed for the primary efficacy endpoint as an additional analysis.

Pharmacokinetic Trough Set:

The PK Trough Set includes all subjects following the principles of the SAF for whom at least 1 trough concentration of total IgG and/or subclass/specific IgG was available.

Dense Pharmacokinetic Subset:

The Dense PK Subset includes all subjects 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-hemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-HBs/hepatitis B), measured in the dense sampling period (i.e., after/at the 7th infusion of the 3-week schedule or after/at the 5th infusion of the 4-week schedule [depending on dosing schedule]) was available.

The FAS will be used for efficacy analyses. The safety analyses will be based on the SAF. All PK analyses involving trough concentrations will be conducted using the PK Trough Set. Pharmacokinetic parameter derivation will be done using the Dense PK Subset.

10.2 Protocol Deviations

Deviations from the protocol will be documented on an on-going 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. Protocol deviations will be collected and agreed in the DRM to find protocol deviations with major impact on subject safety or the validity of the study data. Subjects with major protocol deviations 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

10.3 General Considerations

Quantitative (continuous) data - absolute values and differences from baseline, where appropriate - will be summarized with number of observations (n), arithmetic mean, standard deviation, median, minimum, and maximum. Confidence intervals (95%, 2-sided) will be added where applicable.

Qualitative (categorical) data will be summarized using number of observations (n), and frequency and percentages of subjects. Unless stated otherwise, the calculation of percentages will be based on the total number of subjects in the population of interest. Thus counts of missing observations will be included in the denominator and presented as a separate category. Confidence intervals (95%, 2-sided) will be added, where applicable.

Definition of Baseline

In general, the last nonmissing valid observation before the first infusion will serve as the baseline measurement and may be measured at an unscheduled visit.

Missing Data Conventions

All available data will be included in the analyses and will be summarized as far as possible. Unless otherwise specified, there will be no substitution of missing data, i.e., missing data will not be replaced; missing data will be handled as 'missing' in the statistical evaluation.

A more detailed description of the handling of missing data will be provided in the SAP.

Pooling of Centers

As it is expected that the number of subjects within each center will be very small, summaries of data by center would be unlikely to be informative; data from all centers will be pooled.

Subgroups

Besides the analyses sets as described in Section 10.1, and the planned subgroup analyses for the PK parameters (see Section 10.10), subgroup analyses by age category are planned to be performed for the primary efficacy endpoints and for AEs (infusional AEs and TEAEs).

The age categories for the subgroup analyses will be children (2-11 years, inclusive), adolescents (12-17 years, inclusive), and adults (18-75 years, inclusive). The age categories will be consistent for all subgroup analyses, with the exception of PK where blood samples will be taken from all pediatric subjects aged 6 through 17 years and where PK blood samples are optional for pediatric subjects aged 2 through 5 years.

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

10.4 Efficacy Analyses

Analyses of the efficacy parameters will be based on the FAS and PPS as determined during the DRM. The analysis based on the FAS will be performed for the primary efficacy endpoint and the secondary efficacy endpoints, while the possible analysis based on the PPS will be carried out as an additional analysis for the primary efficacy endpoint only (see Section 10.1).

10.5 Primary Efficacy Analysis

The primary efficacy endpoint is the acute serious bacterial infection rate (i.e. the mean number of acute serious bacterial infections per subject-year).

The primary endpoint will be analyzed using the upper 1-sided 99% confidence limit for the acute serious bacterial infection rate, which will be calculated using a Poisson model accounting for the length of the observation period per subject.

A generalized linear model assuming the Poisson distribution for the number of acute serious bacterial infections with the logarithm as link function will be used. The Poisson model will include the natural logarithm of the length of the observation period in years as an offset to account for the (possibly) different lengths of the observation periods per subject.

To assess the primary outcome for efficacy, the null hypothesis of 1 or more acute serious bacterial infections per subject-year will be tested against the 1-sided alternative hypothesis of less than 1 acute serious bacterial infection per subject-year at the 1% level of statistical significance. This 1-sided hypothesis test will utilize the same Poisson model as used for the calculation of the upper confidence limit. Rejection of the null hypothesis if 1 or more acute serious bacterial infection per subject-year will result in the acceptance of the alternate hypothesis of less than 1 acute serious bacterial infection per subject-year.

If sensitivity analyses is to be carried out (the decision will be made during the DRM), this will be performed with the PPS.

10.6 Secondary Efficacy Analyses

The following secondary endpoints will be summarized descriptively:

- IgG trough levels (total IgG) before each infusion will be presented in tabulated statistical summaries of the raw data and absolute changes from baseline values by infusion schedule and overall (evaluation of IgG trough levels will include the calculation of the proportion of subjects who failed to meet the target level of ≥5 g/L).

- Rate of any infections: The annual rate of infection will be calculated as the mean number of all infections (serious plus nonserious) per subject-year. The point estimate will be the total number of infections in all subjects divided by the total duration expressed in years of the observation period of all subjects.

- Rate of nonserious infections: The annual rate of nonserious infection will be calculated as the mean number of nonserious infections per subject-year. The point estimate will be the total number of nonserious infections in all subjects

divided by the total duration expressed in years of the observation period of all subjects.

- Time to resolution of infections will be calculated as infection stop date – infection start date + 1. The presentation will be done by infusion schedule and overall and will include the frequencies of number of days until the resolution of infection. Kaplan-Meier plots will be generated for time to resolution of infection by infusion schedule and overall.

- Antibiotic treatment information will be collected via the subject diary: Monthly rates of days on antibiotic treatment will be calculated per subject-month. The point estimates will be the total number of days on antibiotics in all subjects divided by the total duration expressed in months (of 30 days) of the observation period of all subjects.

- Rate of time lost from school/work due to infections and their treatment: Monthly rates of the number of days not able to attend school/work due to infections and their treatment will be calculated per subject-month. The point estimates will be the total number of days off school/work due to infections and their treatment in all subjects divided by the total duration expressed in months (of 30 days) of the observation period of all subjects.

- Hospitalization: Monthly rates of the number of days of hospitalization (any hospitalization) will be calculated per subject-month. The point estimates will be the total number of days in hospital in all subjects divided by the total duration expressed in months (of 30 days) of the observation period of all subjects.

- Hospitalization due to infection: Monthly rates of the number of days of hospitalization due to infection will be calculated per subject-month. The point estimates will be divided by the total number of days in hospital due to infection in all subjects divided by the total duration expressed in months (of 30 days) of the observation period of all subjects.

- Fever episodes: The number of days with episodes of fever will be calculated as the mean number of fever episodes per subject-year. The point estimate will be the total number of days with episodes of fever in all subjects divided by the total duration expressed in years of the observation period of all subjects.

- The Peds QL™ questionnaire consists of 23 items. Scoring and handling of missing values will be done as recommended in the user manual. Three scores will be calculated: the Total Scale Score (all 23 items), the Physical Health Summary (8 items), and the Psychosocial Health Summary (15 items). The descriptive summary statistics for the total score and the single dimension scores will be provided by visit. In addition, changes from the baseline (Week 0) assessment to the posttreatment assessment will be determined.

- The EQ-5D™ questionnaire and the youth version of the EQ-5D™ (EQ-5D-Y™) questionnaire are 5 dimension instruments assessing quality of life. Scoring and handling of missing values will be done as recommended in the user manual. Descriptive summary statistics for the total score and the single dimension scores will be provided by visit. In addition, changes from baseline (Week 0) assessments to each posttreatment assessment will be determined.

10.7 Safety Analysis

The safety endpoints will be summarized descriptively.

Adverse events temporally associated with the infusion are AEs occurring during infusion or within 1, 24, and 72 hours after the end of infusion and will be defined as infusional AEs. Summaries of AEs will be based on TEAEs, defined as those events with onset date/time at or after the first infusion date/time. All AEs will be attributed to the most recently received infusion rate at the time of onset. Presentation for TEAEs will be done overall. The safety analysis has to consider the severity, causality, and seriousness of AEs.

Safety issues will mainly be addressed by measuring:

- The number of infusional AEs (including nonproduct related; occurring during infusion or within 1, 24, and 72 hours after the end of infusion).
- The number of related infusional AEs (occurring during infusion or within 1, 24, and 72 hours after the end of infusion).
- The number of infusional AEs (occurring during infusion or within 1, 24, and 72 hours after end of infusion) by infusion (e.g., 1st infusion, 2nd infusion, etc).
- The number of serious infusional AEs (occurring during infusion or within 1, 24, and 72 hours after the end of infusion).
- The number of nonserious infusional AEs (occurring during infusion or within 1, 24, or 72 hours after the end of infusion).
- The number of infusions temporally (within 72 hours) associated with 1 or more infusional AEs.
- The number of all AEs.
- The mean number of AEs temporally associated with infusions per infusion.
- The number of TEAEs (infusional and noninfusional).
- The number of TEAEs (noninfusional).
- The number of serious TEAEs (infusional and noninfusional).
- The number of serious TEAEs (infusional).
- The number of serious TEAEs (noninfusional).
- The number of related TEAEs (non infusional).
- The number of serious related TEAEs (noninfusional).
- The number of TEAEs by maximum severity (noninfusional).
- The number of TEAEs leading to study drug infusion interruption and/or study drug infusion stop.
- The number of TEAEs leading to premature withdrawals.
- The number of TEAEs of special interest.
- The number of ADRs.
- The number of expected/unexpected TEAEs or ADRs.
- Changes in safety laboratory parameters (outside reference range and clinically relevant).
- Results of intravascular hemolysis parameters (number of positive hemolysis test results).
- Changes in vital sign parameters.
- Changes in physical examination parameters.

Adverse events will be coded using the most current version of MedDRA. The version used will be defined in the SAP. Incidence rates (i.e., number and percentage of affected subjects) will be calculated for the coding levels *system organ class* and

preferred term. Further analyses of AEs will focus on seriousness, intensity, causal relationship to study medication, and outcome. Immediately reportable AEs (including SAEs etc) will be displayed in detail. Where appropriate, analyses of AEs will consider the observed intra-subject correlation of the same type or any type of AE, and as such within-subject events may not be independent. Methodology for these analyses is described in the SAP.

An exploratory 2-sided 90% confidence limit interval will be calculated for the total number of subjects with TEAEs and for the number of subjects with infusional AEs (i.e., AEs within 72 hours after the end of infusion).

An exploratory upper 1-sided 95% confidence limit will be calculated for the proportion of the infusions with 1 or more temporally-associated AE (including nonproduct related). The proportion will be calculated as the total number of infusions with infusional AEs (AEs occurring during or within 1, 24, and 72 hours after the end of an infusion) divided by the total number of infusions.

All AEs will be captured and registered (listed) and will include separate reports of all AEs and of all AEs judged by the investigator to be associated with the BT595 infusion, even if the sponsor determines the AE not to be product-related.

Safety laboratory assessments will be categorized with respect to the laboratory specific reference ranges as normal/abnormal. Abnormal values will be further classified with respect to clinical relevance. Changes over time will be described by means of “shift-tables”. The raw data will be listed. Values below or above the reference values in the data listings will be flagged. All laboratory values will be converted into common units for presentation reasons.

Intravascular hemolysis laboratory assessments will be summarized by the number and percentage of subjects and infusions with the given results at each visit. In case of positive Coombs’ test results, further evaluations and/or time points will be included in the summaries.

For the viral safety parameters (retention samples), the presentation of the data will be detailed in the SAP.

For vital sign parameters, absolute values and changes from baseline will be presented for each study visit using summary descriptive statistics.

Physical examination data will be summarized at each visit.

Safety analyses will be based on the SAF.

Data and Safety Monitoring Board

To monitor the safety data from adult subjects and provide advice and recommendations on the enrollment of pediatric subjects, a DSMB consisting of independent experts will be convened (see Section 9.4 for further details).

The DSMB Charter will include details of the outputs provided for the DSMB review.

10.8 Interim Analyses

No interim analysis is planned during the study.

10.9 Determination of Sample Size

A sample size of at least 50 subjects will ensure a power of at least 80% to reject the null hypothesis of an acute serious bacterial infection 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 0.5 per year. Thus, about 70 subjects will be enrolled to account for drop-outs.

The sample size will be at least 50 evaluable male or female subjects (2-75 years, inclusive), including at least 20 pediatric subjects (i.e., children [2-11 years, inclusive] or adolescents [12-17 years, inclusive]). Pharmacokinetic investigations will be carried out in at least 20 adult subjects and in pediatric subjects (6-17 years, inclusive).

The above sample size number (to obtain at least 50 subject–years) and inclusion of at least 20 pediatric (i.e., children [2-11 years, inclusive] or adolescent [12-17 years, inclusive]) subjects with the age distribution representative of the patient population follows the advice provided by both the EMA guidelines (EMA/CHMP/BPWP/94033/2007 rev. 2, 2010) and the FDA guidelines (FDA, 2008).

10.10 Pharmacokinetic Analyses

All PK data (IgG trough levels and PK parameters; as defined in Section 9.5.1) will be summarized by descriptive statistics by analyte (total IgG, IgG subclasses 1-4, and IgG specific antibody levels [anti-pneumococcal capsular polysaccharide, anti-hemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-HBs/hepatitis B]) for the study population as a whole, for each age category, for both treatment schedules (3-week and 4-week schedule) together, and treatment schedules separately. Similarly, data on dose levels and infusion rates will be summarized. Data from the different age categories will be compared descriptively. However, no formal statistical analysis will be performed.

Pharmacokinetic serum samples will be optionally analyzed to identify additional specific antibody levels/immunological variables of medical relevance which may be of importance with regard to efficacy of an IVIg in PID.

Graphical presentations will be provided for the IgG trough levels as well as for the PK time profiles for individual subjects and summarized by analyte (for subjects 6-75 years, inclusive), by schedule, and by age category (adult [18-75 years, inclusive] vs pediatric [6-17 years, inclusive for total IgG and IgG subclasses 1-4], [12-17 years, inclusive for IgG specific antibody levels], and [2-5 years, inclusive]).

The time-course of total IgG, IgG subclasses 1-4, and IgG specific antibody levels in adult subjects (18-75 years, inclusive) and pediatric subjects (6-17 years, inclusive for total IgG and IgG subclasses 1-4; 12-17 years inclusive for IgG specific antibody levels) will be analyzed by noncompartmental analysis. Key PK parameters will be derived from this analysis: maximum concentration (C_{max}), time to reach maximum concentration (t_{max}), trough concentration (C_{trough}), area under the concentration-time curve (AUC) calculated from time zero to time t of the last measured concentration ($AUC_{(0-t)}$), area under the concentration-time curve calculated from start to the end of

dosing interval (AUC_{tau}), steady-state clearance (CLss), volume of distribution at steady-state (Vss), %Fluctuation, and if data permit, terminal elimination half-life ($t_{1/2}$), area under the concentration-time curve calculated from time zero extrapolated to infinity ($AUC_{(0\text{-}inf)}$), mean residence time (MRT), and terminal elimination rate constant (λz).

A similar analytical approach might not be possible for pediatric subjects (2-5 years, inclusive) where only sparse sampling (total IgG only) is planned. Therefore, a population modelling approach will be proposed. First, a preliminary model based on prior PK data obtained with BT595 in adult subjects (18-75 years, inclusive) and pediatric subjects (6-17 years, inclusive) will be established. This model will be updated and used to reconstruct dense individual concentration-time profiles for all subjects, including the youngest pediatric subjects (2-5 years, inclusive), and to derive the different key PK parameters.

Finally, all data will be summarized by descriptive statistics for the study population as a whole, and for each age category. Data from the different age categories will be compared descriptively. However, no formal statistical analysis will be performed.

Evaluation of the total IgG trough levels will include the calculation of the proportion of subjects who failed to meet the target level (≥5 g/L) prior to dose adjustment. In addition, an intra-individual comparison to currently licensed IVIg products in the same subjects (i.e., using prestudy data) will be performed by suitable methods. No formal statistical test will be performed for these variables.

Pharmacokinetic data (including total IgG trough levels) will also be compared to historical data from previous PID studies with Intratect and Bivigam (already marketed 10% IVIgs) and to available data from literature.

11 DATA MANAGEMENT

11.1 Data Collection

Electronic Case Report Form (eCRF)

The eCRF is the primary data collection instrument for the clinical study. All data to be recorded according to this clinical study protocol must be documented. Entries in the eCRF must only be made by the investigator or persons authorized by the investigator. A list of all persons who are allowed to make entries in the eCRF must be available in each study site. Electronic case report form completion guidelines including e.g. handling of data corrections will be described in the Data Management Plan.

Clinical study data will be directly entered via the eCRF into the study database on a central server by the authorized investigator and/or study personnel.

According to the ICH GCP Guideline (Section 5.5), it is ensured that the electronic data capture system is built up with the following requirements: validated system, functionality of different user roles and access administration, password protection, given traceability, record keeping, and availability of audit trail functionality, and as well that appropriate standard operation procedures are maintained.

The investigator and/or assigned study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific eCRF. Subjects will be identified by a unique study specific number and/or code in any database. The subject's name and any other identifying detail will not be included in any study data-electronic file.

Laboratory samples (e.g., for IgG trough levels, specific antibody trough levels, safety laboratory levels, intravascular hemolysis levels, viral safety [retention samples], virus serology, PK, and any other study specific laboratory data) will be collected at each site.

Outcome measure data (e.g., the health-related quality-of-life questionnaire responses) will be collected by the investigator or assigned study personnel at each site to be further processed into the eCRF.

The complete data management activities (data capture, data entry, data validation, query handling, data editing after entry, coding, database closure, etc) will be defined in advance within a Data Management Plan together with a description of the personnel responsible for data entry/correction performance and controlling as well as specific data handling procedures.

MedDRA dictionary will be used for coding of AEs, concomitant diseases, and medical history. Concomitant medications will be coded of the **A**(natomical) **T**(herapeutical **C**(hemical)-code, level 2, using the Word Health Organization Drug Dictionary (WHO-DD).

11.2 Correction of Data

After data have been entered into the clinical study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis.

Queries are entered, tracked, and resolved through the electronic data capture system directly. If a correction is required for the eCRF, the time and date stamps tracking function creates an electronic audit trail for the person entering/updating the eCRF data.

11.3 Data Handling

The data will be entered into a validated database via the eCRF. The Data Management personnel will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted according to available ICH-GCP guidelines for the handling and analysis of data for clinical studies.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study Initiation Activities

The investigators are informed about objectives and methods of the study, the inclusion and exclusion criteria, the time-schedule, and the applied procedures by

means of a Prestudy Visit by the monitor (if necessary), an investigators' meeting prior to start of the study, and during the Site Initiation Visit by the monitor.

12.2 Training of Site Staff

The principal investigator needs to ensure that all persons assisting with the clinical study are adequately informed about the protocol, the investigational product, and their study-related duties and functions. Furthermore, the principal investigator is requested to maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.

12.3 Documentation and Filing

List of Subjects (Subject Identification Log)
The investigator is asked to keep a confidential list of names of all subjects participating in the study, giving reference to the subjects' records.

With the help of this list it must be possible to identify the subjects and their medical records. In addition, the investigator is asked to keep a list of all subjects screened on a screening log to document identification of subjects who entered prestudy screening. In case of noneligibility, a reason is to be provided.

Source Data
Source data are all the information in the original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subjects' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study). In this study, no data will be recorded directly on the eCRF and be considered as source data.

Investigator Site File/Regulatory Binder
Before site initiation, the CRO will provide an Investigator Site File/Regulatory Binder to each study site. The Investigator Site File will include essential documents as defined by the ICH-GCP guideline and applicable local requirements.

The investigator will be responsible for the continual update and maintenance of the Investigator Site File, which will be periodically reviewed by the monitor(s). In case of an audit by the sponsor or an inspection by the Regulatory Authorities, these documents will be reviewed.

All study-related documents are to be archived and stored according to legal requirements, but at **least for 15 years** after completion of the study.

Prior to destruction the investigator will contact Biotest AG for approval and conformation of such.

12.4 Monitoring

The monitor is responsible for checking the quality of data and adherence to the study protocol and to legal and ethical requirements according to local laws and GCP.

The interval between monitoring visits will be dependent on the recruitment rate and the complexity of the study.

Source data verification is an essential part of the monitoring process and the investigator must grant direct access to the subjects' source data.

The extent and nature of monitoring will be described in detail within the monitoring plan.

12.5 Audits and Inspections

Audits will be performed according to the corresponding audit program, including the possibility that a member of the sponsor's quality assurance function may arrange to visit the investigator in order to audit the performance of the study at the study site, as well as all study documents originating there. Audits may also be performed by contract auditors. In this case, the sponsor's quality assurance function will agree with the contract auditor regarding the timing and extent of the audit(s). In case of audits at the investigational site, the monitor, Project Manager CRO, or Clinical Manager, Biotest will usually accompany the auditor(s).

Inspections by Regulatory Authority representatives and IECs/IRBs are possible at any time, even after the end of study. The investigator has to notify the sponsor immediately of any such inspection. The investigator and institution will permit and support study-related monitoring, audits, reviews by the IEC/IRB and/or Regulatory Authorities, and will allow direct access to source data and source documents for monitoring, audits, and inspections. The principal investigator shall personally participate in all audits and inspections.

12.6 Archiving

After evaluation and reporting of the study data, all documents relating to the clinical study will be kept in the archives of the sponsor or of a contracted service provider and the study site(s) according to applicable regulatory requirements.

13 GENERAL REGULATIONS, AGREEMENTS, AND ORGANIZATIONAL PROCEDURES

13.1 Study Administrative Structure

Details for the study administrative structure are kept as a separate list filed in the TMF.

13.2 Ethical and Regulatory Considerations

This clinical study protocol and any amendments will be submitted to a properly constituted IEC/IRB and/or Regulatory Authorities, in agreement with applicable regulatory requirements, for formal approval of the study conduct. A copy of these

approvals must be submitted to Biotest before initiation of the clinical study and each site needs to keep a copy of these documents.

The clinical study will be performed according to the applicable regulatory requirements taking into account the principles of GCP and the latest version of the Declaration of Helsinki.

13.3 Committees/Monitoring Boards

Safety data from the clinical study (adult subjects only) will be evaluated by a DSMB at predetermined points in time, to ensure that the continuation of the study is appropriate and to make recommendations to the sponsor on the suitability of further conduct of the study in pediatric subjects. The DSMB will consist of permanent members who are not associated with the sponsor or with the operative conduct of the study. A description of the scope of work and operating procedures for the DSMB is provided in the DSMB Charter. The composition of the DSMB will also be outlined in the DSMB Charter.

13.4 Written Agreements

A written agreement will be set up between Biotest and each investigator setting out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters.

13.5 Insurance/Liability

In accordance with the relevant national regulations, the sponsor has taken out a subject liability insurance for all subjects who have given their consent to the clinical study. The subjects are insured against injury caused by study medication or participation. The subjects will be informed about the insurance and their own responsibilities and duties.

The insurance of this study will be outlined in a separate agreement between [redacted] and Biotest.

13.6 Investigator's Brochure

The investigator will be informed about current knowledge concerning the study medication through an Investigator's Brochure. All investigators will be informed immediately about relevant new information available.

13.7 Amendments to the Protocol

Changes to the clinical study protocol must be made in the form of a clinical study protocol amendment that has the prior written approval of Biotest. Substantial changes to the protocol need to be notified to/approved by IRB/IEC and/or Regulatory Authorities prior to implementation, as required by applicable regulations.

Amendments required in order to eliminate immediate hazard to subjects may be implemented before the approval of the IEC/IRB and/or Regulatory Authorities after consultation with Biotest.

In the event that a significant deviation from the protocol is anticipated based on the subjects' status, or occurs due to an accident or mistake, the investigator or his/her

designee must contact the CRO and then escalation will be made to Biotest, as appropriate, at the earliest possible time. This will allow an early joint decision to be made as to whether or not the subject should continue in the study. This decision will be documented by both the investigator and the CRO.

13.8 Confidentiality

The objectives and contents of this clinical study as well as its results are to be treated as confidential and may not be made accessible to third parties.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996. These regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

13.9 Final Report and Publication

For each study, an integrated final report according to ICH-requirements will be produced. At the end of the study, the sponsor will provide the Competent Authority and IEC/IRB with a summary of the clinical study report **within 6 months** after the end of the study (where required) or as agreed with the Competent Authorities.

It is generally recommended that the results of clinical studies be presented at congresses and symposia and/or published in scientific journals. Prior to their publication, all results of medical tests with the sponsor's products, and/or publications or lecture manuscripts concerning such results, are to be reviewed and discussed by the coordinating investigator and the sponsor by mutual agreement.

Each investigator is obligated to keep data pertaining to the study secret. He/she must consult with the sponsor before any study data are published.

The legitimate interests of the sponsor, such as acquiring optimum patent protection, coordinating submissions to the health authorities or coordination with other studies in the same field that are underway, protection of confidential data and information, etc. will be given due consideration by all partners involved.

14 LIST OF REFERENCES

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15 APPENDICES

Appendix 1: "Safety Definitions"

- **Adverse Event (AE)**

  Any untoward medical occurrence in a patient or clinical study subject administered an IMP and which does not necessarily have a causal relationship with this treatment. An AE may be any aggravation or new unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

  This includes abnormal laboratory and other investigation results which are considered clinically relevant by the investigator (unless already pre-existing at baseline). However, if an abnormal laboratory value is a sign of an already reported AE (e.g., infection), the respective abnormal laboratory value does not constitute a separate AE.

  A surgical or invasive procedure is not an AE in itself. Instead, the condition for which the surgical or invasive procedure is performed may be an AE. Planned or elective surgery or procedures (i.e., planned prior to signature of informed consent/assent) for a pre-existing condition and the pre-existing condition leading to surgery or procedure are not AEs. However, if the pre-existing condition worsened after signature of informed consent/assent, the worsening of the condition constitutes an AE.

  Worsening of the disease under study (underlying disease): This will be captured by efficacy parameters and should not usually be recorded as an AE, unless 1 or more of the following criteria are met:

  - The worsening of the disease under study constitutes a SAE
  - A deterioration exceeding the usual fluctuations of the disease under study has occurred in the opinion of the investigator
  - The worsening leads to discontinuation of the study medication
  - Additional treatment is required for the worsening, e.g., concomitant medication is added or changed.

  No causal relationship with the investigational drug, or comparator drug, or study procedures is implied by the use of the term “Adverse Event”.

- **Adverse Reaction (ADR) of an Investigational Medicinal Product:**

  All untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs (= related AEs). The expression reasonable causal relationship means to convey in general that there are facts, evidence, or arguments to suggest a causal relationship. This definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the IMP

- **Serious Adverse Event (SAE)**

  An SAE is any untoward medical occurrence or effect that at any dose*:

  - results in death

- *Death is an outcome of an AE and not an AE in itself. All deaths, regardless of cause or relationship must be reported for study subjects.*

- is life-threatening
  - *"Life-threatening" refers to an event in which the subject 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 were more severe.*
- requires hospitalization or prolongation of existing hospitalization
  - *In-subject hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time, which may or may not be overnight. It does not include presentation and care within an emergency department.*
  - *A complication that occurs during hospitalization and prolongs the existing hospitalization is an SAE. Complications that occur during hospitalization but do not prolong the existing hospitalization and do not meet any other seriousness criteria are nonserious AEs.*
  - *Elective or preplanned (prior to signature of informed consent/assent) hospitalization for investigations, medical or surgical treatment does not meet this seriousness criterion. However, if the underlying condition for which hospital treatment or surgery had been planned worsened during the study, the worsening of the condition is to be reported as an SAE.*
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is another important medical event
  - *Adverse events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above, should be reported as serious. Medical and scientific judgment must be exercised in deciding whether an event is serious.*

* "At any dose" does not necessarily imply that the subject is receiving the study drug at the time of the event.

- **Diagnosis vs Signs/Symptoms**

  The investigator should provide a diagnosis rather than individual signs and symptoms, wherever possible and appropriate. However, if there is not enough information to provide a diagnosis, individual signs and symptoms are to be recorded. If a diagnosis is accompanied by unusual symptoms, the diagnosis itself and the unusual symptoms have to be reported separately. For SAEs and other IRAEs, the investigator shall provide any other supporting information that may be required for the assessment of the events, specifically in the free text narrative description of the case. This is of particular importance in situations where a diagnosis cannot (yet) be made. Any subject identifying data on

supporting documents (e.g., name, address, phone number) have to be obliterated prior to sending them to the sponsor.

A complication of an AE constitutes another AE. For example in diarrhea leading to dehydration, diarrhea and dehydration would be captured as separate AEs.

The eCRF provides for a number of items to be completed for each AE. This includes the onset date, end date, intensity/severity, seriousness, action taken with study medication, treatment for the AE, outcome, and causal relationship of the AE with the study medication, other drugs, or study procedures.

- **Onset Date, End Date**

If an AE started during the study but did not end before the final closing (follow-up) visit, the investigator must make a reasonable effort to establish the outcome and the end date. If this is not possible, e.g., because the AE is still ongoing, or the subject is lost to follow-up, there will be no end date for the AE.

For all AEs that resolve, resolve with sequelae, or have a fatal outcome, an end date must be provided.

If an AE stops and restarts later, all occurrences have to be recorded separately.

If an AE starts as a nonserious AE and becomes serious at a later point in time, the following applies in regard to onset and end dates:

- **Intensity/Severity**

Refers to the extent to which an AE affects the subject's daily activities. Severity will be categorized according to the following criteria:

Table: Adverse Event Severity

Mild	The AE does not interfere with the subject's routine activities.
Moderate	The AE interferes with the subject's daily routine, but usual routine activities can still be carried out.
Severe	The AE results in inability to perform routine activities.

Severe vs Serious: The severity is used to describe the intensity of an event. This is not the same as seriousness, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to subject's life or functioning. Seriousness, not severity, serves as the guide for defining regulatory reporting obligations.

Example: While an event may be of "severe" intensity, it may be of relatively minor medical significance, such as severe headache. On the other hand, a myocardial infarction would be usually regarded as serious, even if its intensity is "mild".

Adverse events with changes in severity: If an AE changes in severity, this will be captured as 1 AE, with the highest severity grade recorded.

- **Seriousness**

  For definition of seriousness criteria refer to Section 9.3.1 For an SAE, all seriousness criteria that apply have to be reported. Reporting requirements by the investigator are detailed in Appendix 2.

- **Action Taken With Study Medication**

  The action taken with study medication as a result of the AE has to be documented. In the situation that the AE leads to permanent discontinuation of the study medication, this meets the definition of an AE leading to subject's withdrawal from the study, which is an IRAE. Reporting requirements by the investigator are detailed in Appendix 2.

- **Treatment for the Adverse Event**

  It has to be specified in the eCRF if counteractive treatment was given for the AE. Any treatment for an AE, whether pharmacological or other (e.g., surgical) treatment, has to be recorded in the eCRF.

- **Outcome**

  The following categories are used:

  - Resolved
    - Indicates that the event has fully resolved.
  - Resolving
    - Indicates that the event is in the process of recovery but has not yet fully resolved.
  - Not resolved
    - Indicates that the event is ongoing and there has been no recovery.
  - Resolved with sequelae
    - Indicates that there is a residual, possibly permanent consequence of the event (e.g., residual hemiparesis subsequent to stroke).
  - Fatal
    - Indicates that the subject died due to the event. The outcome "fatal" applies only to the event(s) that were the cause(s) of death. For other AEs that were ongoing at the time of death, the outcome must not be "fatal" but "not resolved".

- **Causal Relationship of Adverse Events**

  The causal relationship with the study medication has to be reported for each AE. It refers to the presence or absence of a reasonable possibility of a causal relationship between the study medication and the AE. The investigator is asked to use medical judgment and take into account the nature of the AE; subject's medical history; temporal relation; response to withdrawal or interruption of study drug (dechallenge); response to reintroduction of study drug (rechallenge); and any alternative explanations such as underlying or concomitant diseases, concomitant drugs, or study procedures.

The following categories are used:

- Related: There is a reasonable possibility of a causal relationship between the study medication and the AE.
- Not related: There is no reasonable possibility of a causal relationship between the study medication and the AE.

For SAEs and other IRAEs, the investigator is asked to specify if there are alternative and/or additional explanations for the occurrence of the event, e.g., concomitant drugs, study procedures, or concomitant/underlying disease, and should provide this information already with the initial case report.

Appendix 2: "Reporting Procedures"

Reporting Procedure:
All IRAE/SAEs have to be recorded in the eCRF immediately, but **not later than 24 hours**, after the investigational site becoming aware of the IRAE/SAE. In addition to the AE pages, the following eCRF pages have to be updated or completed at the same time as necessary: Subject accountability, study drug accountability, subject demographics, medical history, concomitant medication, and study completion/termination (in case of an AE leading to withdrawal).

The investigator must report the IRAE/SAE by means of a paper IRAE/SAE form **within 24 hours** of becoming aware of the event via fax or email to the following contact:

Biotest Corporate Drug Safety Email	[redacted]
Biotest Corporate Drug Safety Fax Number	[redacted]
[redacted] Email	[redacted]
[redacted] Fax Number	[redacted]

For questions regarding IRAE/SAEs or to notify the sponsor of an IRAE/SAE in the event of technical failure of the email or fax system, the investigator should contact Biotest CDS by phone under [redacted]

Once the eCRF is available again, the investigator has to record the IRAE/SAE and all additional information as required immediately (**within a maximum of 24 hours**).

Whenever follow-up information becomes available to a previously recorded IRAE/SAE, this has to be entered into the eCRF by the investigator immediately but not later than 24 hours after becoming aware of the follow-up information. In addition, any supporting documents (e.g., medical records, autopsy report, ECG, or laboratory reports) as part of the follow-up information to an IRAE/SAE must be sent accompanied by a cover page and provided via fax or email **within a maximum of 24 hours** of the investigator becoming aware of the information to the reporting contact above.

The investigator has to undertake active follow-up for subjects with IRAE/SAEs. The investigator shall respond to queries raised by the sponsor with regard to IRAE/SAEs within the timelines stipulated in the query, and provide all necessary information as requested. In case of a fatal or life-threatening SAE, the sponsor will contact the investigator urgently to obtain required additional information within 1 business day. If supporting documents are requested by the sponsor (e.g., copies of medical records, laboratory reports, ECG tracings, autopsy report), the investigator must ensure that subject identifying data are obliterated prior to sending to the sponsor. The supporting documents should carry the subject ID for identification.

If required the investigator is responsible to inform local IECs/IRBs of safety reports in compliance with applicable regulatory requirements. Copies of all correspondence relating to reporting of safety reports to IECs/IRBs should be maintained in the Investigator Site File/Regulatory Binder.

The sponsor is responsible for fulfilling all obligations regarding notification of Regulatory Authorities, ethics committees according to applicable regulatory requirements, in regard to expedited reporting (e.g., serious unexpected suspected adverse reactions) and periodic reporting (e.g., Development Safety Update Report). In addition, the sponsor is responsible for information of investigators according to the current legislation.

Appendix 3: "Diagnostic Criteria for Serious Infection Types"

Contains Nonbinding Recommendations

IV. APPENDIX Diagnostic Criteria for Serious Infection Types

Infection: Bacteremia/sepsis[a] ▪ *Symptoms:* chills, rigors ▪ *Physical findings:* fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure <90 mm Hg or a reduction of ≥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**[b], leukocytosis (white blood cell (WBC) count > 12,000/mm^3), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, 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[c], 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**

Note: Items in bold are considered essential diagnostic features.

[a] 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/min; respiratory rate >20 breaths/min, or $PaCO_2$ <32 mm Hg; WBC count >12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms (Ref. 14). For pediatric subjects, we recommend you employ the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis (Ref. 15).

[b] Indwelling catheter- or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IGIV replacement therapy. For subjects 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). Subjects 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 meningitides*, or *Haemophilus influenzae*, in combination with CSF leukocytosis and/or decrease in CSF glucose, can serve to confirm the diagnosis of acute bacterial meningitis (Ref. 16).

Contains Nonbinding Recommendations

Infection: Bacterial Pneumonia[d] ▪ *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, hypothermia (temperature < 36°C oral or < 37°C rectal) ▪ *Laboratory tests*: leukocytosis, differential WBC count of >10% band neutrophils, leukopenia, hypoxemia (PaO_2 < 60 mm Hg on room air), positive blood culture, Gram stain and culture of deep expectorated sputum[e], positive culture with or without positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with bronchoalveolar lavage (BAL) or protected brush sampling, ▪ *Imaging studies*: **Pulmonary infiltrate with consolidation on chest X-Ray (CXR)** (new in comparison with baseline CXR)
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**

Note: Items in bold are considered essential diagnostic features.

[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 IGIV, the finding of a new pulmonary infiltrate with consolidation on CXR 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, who tend to have a higher baseline temperature, 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^3 are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count <5000/mm^3 may be observed, usually associated with severe infection (Ref. 17).

[e] We recommend a deep expectorated sputum gram stain 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 (Ref. 17).

Source: Food and Drug Administration 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. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm078526.pdf.