Statistical Analysis Plan

[redacted]

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Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
1.0			Initial Release Version
1.2	08-NOV-2019	[redacted]	Definition of age classes. Stated “x to <y years”, instead of “x-y years, inclusive”. Definition of age classes different between EMA and FDA. Inclusion of FDA Guideline 2016 Deletion of SAS Code in the whole SAP text Section 3.4: Enrollment of about 70 subjects instead of 60 subjects Secondary efficacy endpoints: Include annual rates for Antibiotic treatment, Rate of time lost from school/work due to infections and Hospitalization
1.2	08-NOV-2019	[redacted]	Section 6.2: - Definition of baseline updated - Definition of infusional AEs included - Definition of Completion updated Section 6.3: Imputation rules updated Section 6.6: - Definition of subgroups revised - Definition of age groups for FDA and EMA included - Definition of pediatric population as subtotal

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1.2	08-NOV-2019	[redacted]	Section 8.1.1: Definition of serious bacterial infections revised Section 8.2.2: - Definition of infections revised - Categories updated Section 8.2.3: - Categories updated - Subgroup added for subjects that did not receive treatment for the full period of time, either by missing an infusion or discontinuing the study. Section 8.2.4 / 8.2.8: - Categories updated Section 8.2.5: - Categories updated - Annual rate added Section 8.2.6 / 8.2.7: - Categorization revised

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1.3	28-NOV-2019	[redacted]	Detailed information on the planned analyses added to Sections 8 and 11

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1.5	06-FEB-2020	[redacted]	Section 6.3: Clarification on Investigator comments for imputation of incomplete AE start dates and times Section 11.5: Delete outputs on abnormal findings in VS
1.6	17-MAR-2020	[redacted]	Updates for PK parts done

Version #	**Date** (dd-mmm-yyyy)	**Document Owner**	**Revision Summary**
Pre-final 2.0	02-APR-2020	[redacted]	Section 6.2: Update definition of Duration of concomitant antibiotic treatment Section 6.2: Update definition of Time to onset of AE since last infusion prior AE Include Appendix 2 for calculation of PedsQL scores Section 13 updated for changes to protocol added Mocks updated according to comments on dry-run deliveries Section 8.2.2 - Added that the annual rate of days with infections per subject will be the total number of days with infections of the subject divided by the total duration expressed in years of the observation period of the subject. - Tables will also be stratified by season (spring, summer, autumn, winter) using the calendar whereas e.g. spring starts on 01Mar. - In addition, summaries will be done for the subgroup of subjects that did not receive treatment for the full period of time, either by missing an infusion or discontinuing the study.
Final 2.0	24-APR-2020	[redacted]	Released version - WHO Drug B3 part updated

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

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ADaM	analysis dataset model
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
anti-HBs	hepatitis B surface antibody
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
$AUC_{(0\text{-inf})}$	area under the concentration-time curve from time zero extrapolated to infinity
AUC_{tau}	area under the concentration-time curve calculated from start to end of the dosing interval
BLQ	below limit of quantification
BMI	body mass index
C_{avg}	average concentration over dosing interval at steady state
CI	confidence interval
CL_{ss}	steady-state clearance
C_{max}	maximum concentration
CRO	contract research organization
CS	clinically significant
CSP	Clinical study protocol
CSR	clinical study report
C_{trough}	trough concentration
CV	coefficient of variation
CVID	common variable immunodeficiency
DRM	data review meeting
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
EMA	European Medicines Agency
EOI	end of infusion
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
ICH	The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgA	immunoglobulin A
IgG	immunoglobulin G
IMP	investigational medicinal product

Abbreviation	Description
iv	intravenous
IVIg	intravenous immunoglobulin
K_a	absorption constant
Λz (lambda z)	terminal elimination rate constant
Max	maximum
MedDRA®	Medical Dictionary for Regulatory Activities
Min	minimum
n	number of observations
NA	not applicable
NCA	noncompartmental analysis
NCS	not clinically significant
PAGID	Pan American Group for Immunodeficiency
Peds QL™	Pediatric Quality of Life
PID	primary immunodeficiency disease
PK	pharmacokinetic
PPS	per-protocol set
Q3W	dosing schedule for dose administration once per 3 weeks
Q4W	dosing schedule for dose administration once per 4 weeks
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SBI	serious bacterial infection
SD	standard deviation
SDTM	study data tabulation model
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TEE	thromboembolic event
TLF	table, listing, figure
$t_{1/2}$	terminal elimination half-life
t_{max}	time to reach maximum concentration
V	volume of distribution (compartmental)
VPC	visual predicted check
V_z	terminal volume of distribution (noncompartmental)
WHO-DD	World Health Organization Drug Dictionary
XLA	X-linked agammaglobulinemia

2. PURPOSE

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

2.1. RESPONSIBILITIES

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2. TIMINGS OF ANALYSES

The primary analysis of safety, efficacy, and pharmacokinetics (PK) is planned after all subjects complete the final study visit or terminate early from the study.

The efficacy, safety, and PK results of this study will be compared to historical data from previous primary immunodeficiency diseases (PID) studies with Intratect® (already marketed 10% IVIg from Biotest) and to available data from Bivigam® (a 10% IVIg, which was formerly developed by Biotest), as well as to available data from literature. These data will be provided by Biotest by the time of the analyses. This comparison will be described in the Clinical Study Report (CSR), but is not part of the SAP.

An independent Data and Safety Monitoring Board (DSMB) will review descriptive summaries of accumulating safety and subject disposition data on a regular basis. Further description of the DSMB timing can be found in the DSMB Data Monitoring Committee Charter Version 1.0. Outputs required for the DSMB meeting are described within the study SAP and shells.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

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.

3.2. SECONDARY OBJECTIVES

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

3.3. BRIEF DESCRIPTION

Study 991 is a Phase III pivotal, open-label, prospective, uncontrolled, multicenter study investigating clinical efficacy, safety, and PK properties of the human normal immunoglobulin BT595 for intravenous (iv) administration as replacement therapy in subjects with PID.

The study is planned to be conducted in about 25 sites in Europe (Germany, Spain, United Kingdom, Hungary and Russia) and in the United States.

The study population includes male and female subjects aged 2 through 75 years with PID. For those countries where local regulations permit enrolment of adult subjects only, subject recruitment is restricted to those who are 18 through 75 years.

About 70 subjects will be enrolled to ensure data are available for at least 50 evaluable subjects. Amongst those subjects at least 20 subjects are to be adults (17 resp. 18 to <76 years,) and at least 20 subjects are to be pediatric (i.e., young children [2 to <6 years], children [6 to <12 years] or adolescents [12 to <17 resp. <18 years]). The age distribution represents the PID patient population.

According to FDA advice from January 12, 2017 for Pediatric Study Plan, age groups are defined as stated in the FDA 2016 guideline for pediatric study plans differently for the US: The age group of adolescents for the US is restricted to 12 to <17 years and therefore only subjects 2 to <17 years can be enrolled into the group of pediatric subjects.

A DSMB is to be established in this study to monitor the safety data. At least 10 adult subjects (18 to <76 years) who have received at least 2 BT595 infusions will be reviewed by the DSMB before any pediatric subjects are enrolled to the study. The DSMB reviews the safety data and provides recommendations on the suitability of the enrolment of pediatric subjects in the study depending on the assessment of possible safety concerns. However, the final decision to enroll/not enroll pediatric subjects is the responsibility of the sponsor.

BT595 is administered at 3- or 4-week intervals for a treatment period of approximately 12 months. The initial dose and dosage intervals are chosen to be consistent with the

subject's prestudy IVIg treatment and the initial dose and dosage interval are only changed if medically indicated. This change will be at the investigator's discretion.

Efficacy and safety are 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 (Week 3/Week 4 until Week 51/Week 52, 3- or 4-week interval respectively), subjects remain at the site for at least 1 hour following the end of infusion and any new AEs are to be reported to the investigator at the site. 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.

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) and ("Guidance for Industry – Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans"; FDA, 2016) applicable to the PID study type. The present study follows 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.

The participation of an individual subject may be terminated prematurely at any time from the study for any of the following reasons:

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 adverse event (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.

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.

The reason for withdrawal of the subject is 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 closing (follow-up) visit should be performed. Withdrawn subjects will not be replaced.

3.4. SUBJECT SELECTION

It is planned to enroll (treat) about 70 male or female subjects (2 to <76 years) with PID and to establish replacement therapy with BT595 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., young children [2 to <6 years], children [6 to <12 years] or adolescents [12 to <17 resp. <18 years]), with the age distribution representative of the PID subject population. At least 20 of the evaluable subjects should be adult subjects.

According to FDA advice from January 12, 2017 for Pediatric Study Plan, age groups are defined as stated in the FDA 2016 guideline differently for the US: The age group of adolescents for the US is restricted to 12 to <17 years and therefore only subjects 2 to <17 years can be enrolled into the group of pediatric subjects (i.e., young children [2 to <6 years], children [6 to <12 years] or adolescents [12 to <17 years]). At least 10 adult subjects will receive at least 2 BT595 infusions with no safety concerns, as confirmed by the DSMB, before any pediatric subjects begin the study.

3.4.1. Inclusion Criteria

In order to be included in this study, subjects must meet the following criteria:

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, inclusive	Administrative	X	

Inclusion Criteria	Rationale	Screening	Baseline
c) Diagnosis of PID with impaired antibody production, i.e.: - Diagnosis of common variable immunodeficiency (CVID) as defined by the European Society for Immuno-deficiencies (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).

3.4.2. Exclusion Criteria

Subjects are excluded from this study if they meet any of the following criteria:

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

Exclusion Criteria	Rationale	Screening	Baseline
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
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	

Exclusion Criteria	Rationale	Screening	Baseline
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

3.5. DETERMINATION OF SAMPLE SIZE

A minimum sample size of 50 evaluable subjects was considered sufficient to 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. About 70 subjects will be enrolled (treated) to account for drop-outs.

The sample size contains at least 50 evaluable male or female subjects (2 to <76 years), including at least 20 pediatric subjects (i.e., young children [2 to <6 years], children [6 to <12 years] or adolescents [12 to < 17 resp. <18 years]) and at least 20 adult subjects.

According to FDA advice from January 12, 2017 for Pediatric Study Plan, age groups are defined as stated in the FDA 2016 guideline differently for the US: The age group of adolescents for the US is restricted to 12 to <17 years and therefore only subjects 2 to <17 years can be enrolled into the group of pediatric subjects (i.e., young children [2 to <6 years], children [6 to <12 years] or adolescents [12 to <17 years]).

The above sample size number (to obtain at least 50 subject–years) and inclusion of at least 20 pediatric subjects with the age distribution representative of the subject population follows the advice provided by the EMA (EMA/CHMP/BPWP/94033/2007 rev. 2, 2010) and FDA (FDA, 2008) and FDA (FDA, 2016).

Full pharmacokinetic (PK) characterization at steady state is to be carried out in at least 20 adult subjects and all consenting pediatric subjects (EMA: 6 to <18 years; FDA: 6 to <17 years). Optional sparse sampling will be taken for young children (2 to <6 years).

3.6. TREATMENT ASSIGNMENT & BLINDING

All subjects receive BT595 infusions on dosage intervals of 3– or of 4– weeks. The initial dose and dosage intervals are consistent with the subject's prestudy IVIg treatment and the

initial dose and dosage interval are only changed if medically indicated. The change is at the investigator's discretion. This is an open-label study; therefore; there is no blinding.

3.7. ADMINISTRATION OF STUDY MEDICATION

The planned dose of BT595 is 0.2 to 0.8 g/kg body weight (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 is infused intravenously at an initial rate of 0.3 mL/kg/h for 30 minutes, and increased to 1.4 mL/kg/h for a further 30 minutes. If well tolerated, the rate of administration is then 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.

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 could 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 are to be documented.

3.7.1. Dose Changes during the Study

The subject's total immunoglobulin G (IgG) trough levels are assessed prior to each infusion at the local laboratory to allow immediate dose adjustment if a subject's trough level was below 5 g/L. Serum trough levels of total 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 had to be adjusted to meet the target trough levels. Dose changes are made at the investigator's discretion and are following the dosage regimen detailed in Section 6.2 of the clinical study protocol (CSP).

Body weight is assessed before each study infusion in order to calculate an accurate dose for each subject's dose infusion. The investigator calculates the percentage change in the subject's body weight since the last assessment. If a subject's body weight changed by <5% from the weight used for the current dose, the total dose remains the same as the current dose. If a subject's body weight changed by ≥5% from the weight used for the current dose, the total dose (g), but not the dose per weight (g/kg), is 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 are recorded in the electronic Case Report Form (eCRF).

3.8. STUDY PROCEDURES AND FLOWCHART

For an overview of the timing of the clinical and laboratory measurements see the Flowchart of the Study below.

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)		•			•
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 antigen specific IgG 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. 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 to <76 years) 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 to <76 years) 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 antigen specific IgG 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 to <76 years for total IgG and IgG subclasses 1-4; 12 to <76 years for antigen specific IgG 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 to <6 years),

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).

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the 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 FDA guidance (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) are used.

4.2. SECONDARY EFFICACY ENDPOINTS

- IgG trough levels (total IgG) before each infusion
- Rate of any infections (number per year)
- Rate of nonserious infections (number per year), defined as all infections not fulfilling the FDA-guidance “Diagnostic criteria for serious infection types” (as defined under 4.1)
- Time to resolution of infections
- Antibiotic treatment (number of days antibiotic treatment received per month and per year)
- Rate of time lost from school/work due to infections (number of days per month and per year) and their treatment (number of days treatment per month and per year)
- Hospitalization (number of days per month and per year overall and number of days per month and per year due to infection)
- Fever episodes (number of days per year)

4.3. EXPLORATORY EFFICACY ENDPOINTS

- Changes in health-related quality-of-life parameters:

  a) Pediatric subjects (2 to <18 years) complete the Pediatric Quality of Life (Peds QL™) Measurement Model (child self-report and/or parent proxy-report).

  b) all adult subjects complete the EuroQol Five Dimension (EQ-5D-3L™) Health Questionnaire

  c) pediatric subjects (4 to <18 years) complete the youth version of the EQ-5D™ (EQ-5D-Y™) Health Questionnaire (child self-report or proxy-report). (Note for the US only: The age group of adolescents for the US is restricted to 12 to

<17 years and therefore only subjects 2 to <17 years can be enrolled into the group of pediatric subjects.)

4.4. 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 to <6 years).
- 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 to <12 years).
- Pharmacokinetic parameters at steady-state for: a) total IgG (2 to <76 years), b) antigen-specific IgG (12 to <76 years), and c) IgG subclasses (6 to <76 years).

4.5. SAFETY ENDPOINTS

Tolerability and safety of BT595 will be evaluated by:

- Adverse events.
- 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.

5. ANALYSIS SETS

5.1. ALL SUBJECTS ENROLLED SET

The All Subjects Enrolled Set includes all subjects who have given informed consent/assent to this study. Listings will be based on this set.

5.2. SAFETY SET

The Safety Set (SAF) comprises all subjects who have received at least 1 dose of study medication. Subjects will be analyzed according to the treatment received. The SAF will be used for all analyses of safety endpoints.

5.3. FULL ANALYSIS SET

The Full Analysis Set (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). Subjects will be analyzed according to the treatment planned. FAS will be used for all analyses of efficacy endpoints.

5.4. PER-PROTOCOL SET

The Per-protocol Set (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. Subjects will be analyzed according to treatment received.

5.5. PK 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 in the age group 2 to <76 years and/or subclass IgG in the age group 6 to <76 years (measured in local laboratory) is available. All PK analyses involving trough concentrations will be conducted using the PK Trough Set.

The total IgG PK concentrations measured at the end of 1st infusion by local labs will be also presented for the PK Trough Set, but not used for the calculation of summary statistics of the trough concentration of total IgG.

Additional trough samples for the 5th/7th infusion measured centrally via separate analytical method for the dense PK characterization and used for the Dense PK Subset data will not be included in the PK trough set.

Upon review, complete profiles or only certain time points may be excluded from the summary of trough concentrations from subjects who did not receive proper study medication dosing or had out-of-window sampling.

5.6. SPECIFIC IGG TROUGH PK SET

The Specific IgG Trough PK Set includes all subjects in the age group 12 to <76 years following the principles of the SAF for whom at least 1 trough concentration of at least one specific IgG (measured at the central lab) is available. All PK analyses involving specific IgG trough concentrations will be conducted using the Specific IgG Trough PK Set.

Upon review, complete profiles or only certain time points may be excluded from summary of trough concentrations if they have not received proper study medication dosing or had out-of-window sampling.

5.7. DENSE PK SUBSET

The Dense PK Subset includes all subjects who received planned doses following the principles of the FAS and for whom at least 1 concentration of total IgGs, IgG subclasses 1-4, or antigen specific IgG 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, including the predose concentrations) at the central lab will be available. Pharmacokinetic parameter derivation will be done using the Dense PK Subset.

Upon evaluation, subjects may be excluded from the Dense PK Subset if they have not received the required number of study medication doses to achieve steady-state. In other cases, if the number of PK samples is not sufficient to derive PK parameters from standard analytical methods (non-compartmental analysis), an alternative approach (population modelling analysis) may be undertaken.

5.8. PROTOCOL DEVIATIONS

Protocol deviations are collected and agreed in the DRM to evaluate protocol deviations considered to have 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. In some circumstances protocol deviations may result in subject's exclusion from other sets.

Major protocol deviations may include, but not necessarily limited to, the following categories:

- Deviation from Inclusion/Exclusion criteria
- Deviations in study medication administration
- Missed sampling required for dose adjustment
- Use of prohibited medications or treatments
- No diary data collected

- Diary data not reliable

All protocol deviations will be reviewed and decided for major or minor on a regular basis by the Regular Joint Deviation Review Meeting. In case of frequent major protocol deviations according to GCP that may critically compromise the data integrity of the study, the sponsor may also temporally stop the study.

All protocol deviations are reviewed at the DRM with regard to analysis.

All major protocol deviations will be presented in a summary table by protocol deviation category.

A listing of all protocol deviations including major and minor will be also presented and those subjects excluded from analysis sets will be identified in the listing.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

Data from all subjects collected in this study will be documented with the help of subject data listings. Summary tables will be provided for all patients, except screen failures.

Generally, descriptive statistics will be provided by treatment schedule (3- or 4- week) and overall. Additionally by dosage and by observation time (visit), if applicable. Only scheduled visits/time points will be presented in summary tables. Data from unscheduled visits will be listed only.

Quantitative (continuous) data - absolute values and changes from baseline, where appropriate - will be summarized with number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Confidence intervals, 25th percentile and 75th percentile 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 set of interest. Thus, counts of missing observations will be included in the denominator and presented as a separate category. Confidence intervals will be added, where applicable.

All data will be listed for the All Subjects Enrolled Set, sorted by subject number and time of occurrence (visit, start of event) whereas treated subjects will be sorted above screening failures.

Shells for summary tables, figures, and subject listings are described in a separate document, which is seen as an Appendix to the SAP. Templates for each unique table, figure, and listing are provided. These provide only a draft indication of the content and appearance of the tables, figures, and listings, and the final output may vary in appearance from these templates.

6.2. KEY DEFINITIONS

Age

Age at screening is entered by site and this value will be used in all analyses.

Body Mass Index (BMI)

The BMI of a patient will be calculated in kg/m²:
BMI = body weight [kg] / (height [m])²

Absolute Change from Baseline

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

Relative change from baseline:

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

Definition of Baseline

Baseline will be defined as the last available value before the first infusion of study medication and may be any visit between screening and day 1 (including the baseline visit [V2]) and unscheduled visit.

Duration of concomitant antibiotic treatment

If medication starts before date of first infusion (Visit 2, Day 1):
Duration of concomitant antibiotic treatment [days] = Date of stop of antibiotic treatment – Date of first infusion +1.

If medication starts at/after date of first infusion (Visit 2, Day 1):

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

Duration of infusional AE

Duration of AE [hours] = (Date/time of stop of AE – Date/time of start of AE)

Duration of noninfusional AE

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

Time to onset of AE since last infusion prior AE

- For infusional AE: Time to onset of AE [hours] = Date/time of start of AE – Date/time of start of last infusion prior AE
- For non-infusional AE: Time to onset of AE [days] = Date/time of start of AE – Date/time of start of last infusion prior AE

Time to onset of AE since the first infusion

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

Infusional AE

Adverse events temporally associated with the infusion are AEs occurring during intravenous administration or within 1, 24, and 72 hours after the end of infusion.

Start Day of previous/concomitant medication
If medication starts before date of first infusion (Visit 2, Day 1):

Start Day of Medication = Date of start of medication – Date of first infusion

If medication starts at/after date of first infusion (Visit 2, Day 1):
Start Day of Medication = Date of start of medication – Date of first infusion + 1
Incomplete start dates of medication will not be imputed. Start day of medication will be missing.

Day of Study Termination
Day of study termination = Date of termination – Date of first infusion + 1

Definition of Completion
A subject will be defined as "completed" if s/he completes the Follow-up period of the study. Termination at a different time point will be considered as discontinuation.

PID Diagnosis
Time since diagnosis [months] = ((Date of Informed Consent – Date of diagnosis)+1)/30

6.3. MISSING DATA

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.

Incomplete/missing start and stop date/time for AEs/antibiotic treatments will be handled as follow:

Start date will be imputed

- Missing start day with the day of first drug administration within that month. If no drug was administered then with '01'.
- Missing start day and month with the 1st of January. If the AE/antibiotic treatment start year = year of the first drug administration then with the date of the first drug administration.
- Missing start year with the date of the first drug administration
- In case an Investigator comment is available, imputation will take this into account:
    - AE started before the day of a drug administration: missing start day with '01'
    - AE started after the day of a drug administration: missing start day with one day after the day of drug administration
    - AE started at least 72 hours after the day of a drug administration: missing start day with four days after the day of drug administration

Stop date will be imputed

- Missing stop day with last day (28/29/30/31) of the month.
- Missing stop day and month with 31st of December.
- Missing stop year with the date of study termination.

- Incomplete AE stop dates will only be imputed in case of the AE is not ongoing.

Missing start time of AE

In case, AE can be assumed as infusional AE (started on the date of infusion or within 72 hours after last infusion), time will be imputed as 00:00. If date of AE start = Date of infusion start, date/time of AE start will be assumed as the date/time of the infusion start.

In case an Investigator comment is available for the assumed infusional AE, imputation will take this into account:

- AE started before treatment: time will be imputed as 00:00
- AE started during treatment: time will be imputed as start time of infusion
- AE started after treatment: time will be imputed as one minute after end of infusion

Missing stop time of AE:

In case, AE can be assumed as infusional AE (started on the date of infusion or within 72 hours after last infusion, missing stop time will be imputed with end of day: 23:59

Incomplete PID diagnosis date will be imputed

Missing start day with '15'.

Missing start day and month with the '15' of July.

Incomplete severity / seriousness and/or relationship:

In situations where an AE has a missing severity / seriousness and/or relationship, a worst-case scenario will be applied. That is, missing severities will be imputed as 'severe', missing seriousness will be imputed as serious, while missing relationships will be imputed as 'related'. 'Related' relationship will be only be imputed after start of first drug administration. During screening phase the relationship will be not related.

Missing body weight assessment:

In case body weight assessment is missing at any visit the last available body weight assessment of the subject will be used for the calculation of the actual dose.

6.4. VISIT WINDOWS

A tolerance for the visit day of ±2 days will be allowed for the treatment visits and closing (follow-up) visit; however, all visits will be summarized according to the nominal visit. Different rules may apply for the analysis of pharmacokinetics.

6.5. POOLING OF CENTERS

Data from all centers will be pooled together. Serum concentrations estimated in the course of the study for dosing decisions (by local laboratories) may be separated from the serum concentrations estimated by central laboratories for formal the PK analyses.

6.6. SUBGROUPS

There are 4 defined subgroups: age, gender, race and region (US vs. Europe vs. Asia).

Two age categories for the subgroup analyses are defined:

1) Age category according to FDA
   young children (2 to <6 years),
   children (6 to <12 years)
   adolescents (12 to <17 years)
   adults (17 to <76 years)
   geriatric (>=65 years)

2) Age category according to EMA
   young children (2 to <6 years),
   children (6 to <12 years)
   adolescents (12 to <18 years)
   adults (18 to <76 years)
   geriatric (>=65 years)

The pediatric population (young children, children and adolescents) will be presented as a subtotal.

Age is the age recorded at screening (initial visit) by the investigator. The same age is 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 remains in the age category of 12 through 17 years during the entire study).

The subgroup analysis will be performed within the treatment schedule (3-week and 4-week) and overall, if not stated otherwise, for:

- All demographics, other baseline characteristics and medication (section 7)
- All efficacy endpoints (primary and secondary) (section 8)
- All safety parameters (section 11)
- All PK parameters (section 9)

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

The summary statistics will be based on the FAS and will be done by treatment schedule (3- or 4- week) and overall, if not stated otherwise.

In addition, all Demographic, other baseline characteristics and medication will be summarized descriptively stratified by age categories, gender, race and region as defined in Section 6.6. Age classes will be presented separately by FDA and by EMA criteria. The pediatric population (young children, children and adolescents) will be presented as a subtotal.

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition will be summarized by presenting the number and percentage of subjects eligible for the study, treated with study medication and completed or discontinued from the study together with the primary reason for premature termination.

Major protocol deviations will be summarized for subjects in FAS.

A further summary table will be presented detailing the number of subjects in each analysis set. Furthermore, the number of subjects excluded from each analysis set will be summarized by reason for exclusion and will also be stratified by age groups.

All data will be summarized and listed.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic (age, gender, height, weight, BMI and race) and baseline characteristics (e.g. child-bearing potential status, IgG trough level at screening, IgG trough level at baseline, IgG trough levels of specific antibody levels at baseline, IgG trough levels (subclasses 1-4)) will be presented in a summary table and a listing.

The summary table will be based on the FAS, PK Trough set, Specific IgG Trough PK set, Dense PK Subset and PPS, if applicable.

Age will be summarized as both a continuous variable and using the subgroup categories defined in Section 6.6.

All data will be listed.

Viral serology data (HIV, hepatitis B and hepatitis C) collected at screening (initial visit) will be listed only.

7.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

Medical history terms, including surgeries, will be coded using MedDRA version 19.0 to give a preferred term and a system organ class (SOC) term for each medical history term. At the end of the study, prior to database closure, medical history will be recoded applying the latest available MedDRA version available at this time point.

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

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

All data will be summarized and listed.

7.4. OTHER BASELINE CHARACTERISTICS

Previous established replacement therapy will be coded using the WHO Drug Dictionary (WHO-DD B3), March 2018. The number and percentage of subjects who used different established replacement therapies will be presented by A(natomical) T(herapeutical) C(hemical) Levels 2 and 4, and the investigator term.

Duration of the intake of an established replacement therapy with any IVIg reference preparation and with a single IVIg reference preparation will be summarized overall. 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.

Primary immunodeficiency disease history will be summarized by presenting the type of disease and time since disease diagnosis. Time since disease diagnosis will be presented by means of descriptive statistics. These summaries will also be stratified by age groups.

The summary table will be based on the FAS.

All data will be listed.

7.5. MEDICATION

All medications will be coded using WHO Drug Dictionary (WHO-DD B3), March 2018.

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

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

The number and percentage of subjects taking previous and concomitant antibiotic medications will be summarized overall and for each treatment schedule by ATC Levels 2 and 3.

Concomitant antibiotic medication is one of the secondary efficacy endpoints and is described in the Section 8.2.5.

The number and percentage of subjects taking prohibited medication or treatment during the study will be summarized overall and for each treatment schedule by ATC Levels 2 and 3. Prohibited medication or treatment includes passive or active immunizations, administration of plasma preparations, or administration of other immunoglobulins and will be identified by a review of the coded medications.

The number and percentage of subjects taking rescue medication during the study will be summarized overall and for each treatment schedule by ATC Levels 2 and 3. Medication will be ticked as rescue medication by the investigator on the eCRF.

All presentations will be done based on the FAS.

7.5.1. Previous Medication

Medications stopped prior to first infusion will be summarized as 'Previous' medications. Separate outputs will be generated for previous other medication, previous established replacement therapy (IVIg) and previous antibiotic medication (in addition stratified by route of administration). If subject has taken a previous medication more than once, the subject will be counted only once in the respective total (overall).

7.5.2. Concomitant Medication

Medications taken at/after first infusion will be summarized as 'Concomitant' medications. Premedications taken to avoid AEs will be classified as concomitant medication, even if administered prior to the first BT595 infusion. Separate outputs will be generated for other concomitant medication, premedication, prohibited medication or treatment and rescue medication (added or changed concomitant medication due to the worsening of underlying disease). If subject has taken a concomitant medication more than once, the subject will be counted only once in the respective total (overall).

8. EFFICACY ANALYSIS

Efficacy endpoints are based on data from the eCRF. Data from subject paper diary and questionnaires are transferred into the eCRF.

The summary statistics will be based on the FAS and will be done by treatment schedule (3- or 4- week) and overall, if not stated otherwise.

In addition, all efficacy endpoints will be summarized descriptively stratified by age categories, gender, race and region as defined in Section 6.6. Age classes will be presented separately by FDA and by EMA criteria. The pediatric population (young children, children and adolescents) will be presented as a subtotal.

The primary efficacy endpoint, the number and type of acute serious bacterial infections, is determined through review of data collected on infections. Infections are reported as AEs which 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. Subject diaries are reviewed to check for instances where the AE occurs and the subject is not on a site visit. 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 are instructed to bring their subject diary to each study visit. During each scheduled visit, subjects are asked about AEs occurring since their last visit and subject diaries are collected and reviewed for any signs of AEs (infections) occurring between visits before IMP administration. Specific diagnostic criteria, as recommended by the FDA guidance (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), are used by the investigator to define each type of serious infection included in the primary efficacy analysis.

In addition to the primary efficacy endpoint, the following secondary efficacy parameters will be determined by the review of diary data: any infections, nonserious infections, time to resolution of infections, antibiotic treatment, number of days a subject was not able to attend school or work due to the infection and the treatment of the infection, information regarding hospitalization and fever episodes.

Immunoglobulin G trough level (total IgG) data are collected before each infusion and are recorded on the eCRF. An additional sample is taken after first BT595 infusion. The subject's total IgG trough levels are assessed at the local laboratory. The subject's total IgG trough level results from the previous infusion are made available to the investigator before the next infusion to allow dose adjustment if a subject's trough levels fall below 5 g/L.

Health-related quality-of-life data will be considered as exploratory efficacy parameters. Health-related quality-of-life data are collected using 2 subject questionnaires: Peds QL™ [PedsQL™ Measurement Model] and EQ-5D™ [EuroQol Five Dimension Health Questionnaire, 2015]. For pediatric subjects, the questionnaires may be completed by proxy reports (i.e., by the subjects' parent[s] or legally acceptable representative).

All pediatric subjects complete the 23-Item Pediatric Quality of Life (Peds QL™) Measurement Model (Version 4.0), consisting 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 includes 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 is selected based on the subject's age recorded at screening (initial visit). 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 is 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 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 labeled 'Best imaginable health state' and 'Worst imaginable health state'.

In addition to the Peds QL™ Measurement Model, pediatric subjects 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 labeled 'The best health you can imagine' and 'The worst health you can imagine'. A proxy version of the form is used for children aged 4 through 7 years. All other pediatric subjects (8 through 17 years) self-complete the EQ-5D-Y™.

(Note for the US only: The age group of adolescents for the US is restricted to 12 to <17 years and therefore only subjects 2 to <17 years can be enrolled into the group of pediatric subjects.)

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

8.1.1. Primary Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the rate of acute serious bacterial infections (i.e., the mean number of acute serious bacterial infections per subject-year) and will be based on the total of all of the following events as defined by the FDA: bacteremia or sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess.

Serious bacterial infections are identified by the following criteria:

- Any AE leading to the following MedDRA PTs: sepsis, bacterial sepsis, bacteremia, meningitis bacterial, osteomyelitis bacterial, arthritis bacterial, pneumonia bacterial, abdominal abscess.

- All AEs leading to any other PT are reviewed by the sponsor for a possible relationship to the primary endpoint (e.g. AEs including one of the following words: bacteremia, sepsis, meningitis, osteomyelitis, arthritis, pneumonia, and abscess). Identified AEs possibly related to the primary endpoint are queried to the investigator to clarify if the AE fulfils the FDA criteria for acute serious bacterial infections. The investigator transfers his decision to the eCRF (AE term).

The date of onset of an episode of acute serious bacterial infections is the day the diagnosis made.

For each subject, the study duration (days) will be calculated as:

(date of last visit) – (date of first infusion) + 1

The number of subject years will be calculated by summing the total subject days and dividing by 365. An estimate of the acute serious bacterial infection rate for BT595 will be obtained by dividing the total number of acute serious bacterial infections by the total number of subject years.

Any intra-subjects correlations of acute serious bacterial infections are not considered to follow a conservative approach for the infection rates.

For the primary efficacy analysis, the acute serious bacterial infection rate for BT595 and the upper 1-sided 99% CI will be estimated by 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 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.

The primary efficacy analysis will be tested overall, e.g., without separation by treatment schedule.

Frequency tables presenting the number of subjects with number of experienced serious infections (total and by kind of infection) will be presented.

In addition frequency tables presenting the number of subjects with number of experienced serious infections (total and by kind of infection) for the subgroup of subjects that did not receive treatment for the full period of time, either by missing an infusion or discontinuing the study, will be presented.

A description of each serious bacterial infection will be provided in respective section.

Rate of acute serious bacterial infection will also be compared to relevant historical data from previous PID studies with Intratect® (already marketed 10% IVIg from Biotest) and to available data from Bivigam® (a 10% IVIg, which was formerly developed by Biotest), as well as to available data from the literature. These data will be provided by Biotest by the time of the analyses. The comparison to literature and discussion thereof will be part of the CSR.

8.1.2. Sensitivity Analysis of Primary Efficacy Endpoint

The same analysis as described in Section 8.1.1 will be performed based on the PPS. The decision regarding this analysis will be made during the DRM.

8.2. SECONDARY EFFICACY ENDPOINTS AND ANALYSES

8.2.1. Immunoglobulin G Trough Levels (Total IgG)

Trough levels of total IgG before each infusion will be presented in tabulated statistical summaries of the raw data, absolute and relative changes from baseline values by infusion schedule for all subjects together.

In addition, 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 at a given visit.

8.2.2. Rate of Any Infections

Infections are identified by the following criteria:

- Any AE leading to the MedDRA SOC „infections and infestation".

- All AEs leading to any other SOC are reviewed by the sponsor for possible relation to an infection (e.g. pyrexia leading to SOC General disorders and administration site conditions). Identified AEs possibly related to this endpoint are queried to the investigator. The investigator transfers his decision to the eCRF (AE term).

The annual rate of infections will be calculated as the mean number of all infections (serious plus nonserious) per subject-year as described in Section 8.1.1. The annual rate per subject will be the total number of infections of the subject divided by the total duration expressed in years of the observation period of the subject. Summaries will be as for a continuous variable and by categorizing the number of any infections per subject according to the following categories:

- 0
- 1
- 2
- 3 to <5
- 5 to <10
- ≥10

The annual rate of days with infections per subject will be the total number of days with infections of the subject divided by the total duration expressed in years of the observation period of the subject.

Frequency tables presenting the number (%) of subjects with infections, the number of days with any infections and the total number of infections will be done.

Tables will also be stratified by season (spring, summer, autumn, winter) using the calendar whereas e.g. spring starts on 01Mar.

In addition, summaries will be done for the subgroup of subjects that did not receive treatment for the full period of time, either by missing an infusion or discontinuing the study.

8.2.3. Rate of Nonserious Infections

The annual rate of nonserious infections will be calculated as the mean number of nonserious infections per subject-year as described in Section 8.1.1. The annual rate per subject will be the total number of nonserious infections of the subject divided by the total duration expressed in years of the observation period of the subject. Summaries will be as for a continuous variable and by categorizing the number of any nonserious infections per subject according to the following categories:

- 0
- 1
- 2

- 3 to < 5
- 5 to <10
- ≥10

The annual rate of days with nonserious infections per subject will be the total number of days with nonserious infections of the subject divided by the total duration expressed in years of the observation period of the subject.

Frequency tables presenting the number (%) of subjects with infections, the number (%) of days with any infections and the total number (%) of infections will be done.

In addition, summaries will be done for the subgroup of subjects that did not receive treatment for the full period of time, either by missing an infusion or discontinuing the study.

8.2.4. Time to Resolution of Infections

Time to resolution of infections (days) will be calculated as infection stop date – infection start date + 1. For the imputation rules of incomplete start/stop dates refer to Section 6.3. The presentation will include the continuous variable and also by categorizing the number of days until the resolution of infection the data according to the following categories:

- 1 to <3
- 3 to <5
- 5 to <8
- 8 to <10
- 10 to <14
- ≥14

Time to resolution will be presented for any infections, serious infections and nonserious infections.

Kaplan-Meier plots will be generated for time to resolution of infection by infusion schedule and overall.

8.2.5. Antibiotic Treatment Information

Monthly rates of days on concomitant antibiotic treatment will be calculated per subject-month. The monthly rate per subject will be the total number of days on antibiotics of the subject divided by the total duration expressed in months (of 30 days) of the observation period of the subject. For the imputation rules of incomplete start/stop dates refer to Section 6.3. Summaries will be as for a continuous variable.

Annual rates of days on concomitant antibiotic treatment will be calculated per subject-year. The annual rate per subject will be the total number of days on antibiotics of the subject divided by the total duration expressed in years (of 365 days) of the observation period of the subject. For the imputation rules of incomplete start/stop dates refer to Section 6.23.

Summaries will be as for a continuous variable and also by categorizing the number of days on antibiotic treatment according to the following categories:

- 0
- >0 to <7
- 7 to <14
- 14 to <21
- 21 to <35
- 35 to <70
- >=70

Summaries will be done for the number of subjects requiring treatment with antibiotics and the number of days on antibiotic treatment.

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

8.2.6. Rate of Time Lost from School/Work due to Infections and their Treatment

Monthly rates of the number of days subjects are not able to attend school/work due to infections and their treatment will be calculated per subject-month. The monthly rate per subject will be the total number of days off school/work due to infections and their treatment of the subject divided by the total duration expressed in months (of 30 days) of the observation period of the subject. Summaries will be as for a continuous variable.

Annual rates of the number of days subjects are not able to attend school/work due to infections and their treatment will be calculated per subject-year. The annual rate per subject will be the total number of days off school/work due to infections and their treatment of the subject divided by the total duration expressed in years (a) of 365 school/work days and b) of 220 school/working days) of the observation period of the subject.

Summaries will be as for a continuous variable and also by categorizing the number of days lost from school/work according to the following categories:

- 0
- >0 to <7
- 7 to <14
- 14 to <21
- 21 to <35
- 35 to <70
- >=70

Summaries will be done for the number of subjects, total number of subject days during study, and the number of days losing school/work due to infections.

8.2.7. Hospitalization / Hospitalization due to Infection

Monthly rates of the number of days of hospitalization (any hospitalization/ hospitalization due to infection) will be calculated per subject-month. The monthly rate will be the total number of days in hospital of the subject divided by the total duration expressed in months (of 30 days) of the observation period of the subject. Summaries will be as for a continuous variable.

Annual rates of the number of days of hospitalization (any hospitalization/ hospitalization due to infection) will be calculated per subject-year. The annual rate will be the total number of days in hospital of the subject divided by the total duration expressed in years (of 365 days) of the observation period of the subject.

Summaries will be as for a continuous variable and also by categorizing the number of days of hospitalization according to the following categories:

- 0
- >0 to <7
- 7 to <14
- 14 to <21
- 21 to <35
- 35 to <70
- >=70

Summaries will be done for number of subjects (%) with hospitalization and the number of days of hospitalization.

Separate calculation will be generated for hospitalization due to serious bacterial infections (SBI).

8.2.8. Fever Episodes

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) including gaps between days with fever <3 days.

The number of days with episodes of fever will be calculated as the mean number of fever episodes per subject-year as described in Section 8.1.1. The annual rate per subject will be the total number of days with episodes of fever of the subject divided by the total duration expressed in years of the observation period of the subject.

Summaries will be as for a continuous variable and also by categorizing the data according to the categories:

- 0
- 1 to <=2
- 3 to <5
- 5 to <8
- 8 to <10
- 10 to <14
- ≥14

Summaries will be done for number (%) of subjects with fever episodes and total number of days with episodes of fever.

8.3. EXPLORATORY EFFICACY ENDPOINTS AND ANALYSES

8.3.1. The Peds QL™ Questionnaire

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 parent proxy-report for children aged 2-4 years consists of 21 items. See Appendix 2 for calculation of scores. 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 post treatment assessment will be determined. The Peds QL will be presented for each age category separately. The questionnaire was designed for: aged 2 through 4 years, 5 through 7 years, 8 through 12 years, and 13 through 18 years. Both child self-reports and parent proxy-reports will be presented, if applicable.

8.3.2. The EQ-5D™ Questionnaire

Scoring and handling of missing values will be done as recommended in the user manual. Descriptive summary statistics for the single dimension scores “Mobility”, “Self-Care”, “Usual Activities”, “Pain/Discomfort” and “Anxiety/Depression” will be provided by visit. The VAS question ‘Your own health state today’ will be analyzed by means of descriptive statistics. In addition, changes from VAS baseline (Week 0) assessments to each posttreatment assessment will be determined. The EQ-5D will be presented for each age category separately. The questionnaire was designed for: children 4 to <18 years and adults ≥ 18 years. Both child self-reports and parent proxy-reports will be presented, if applicable.

9. ANALYSIS OF PHARMACOKINETICS

The summary statistics will be based on according analysis sets and will be done by treatment schedule (3- or 4- week) and overall, if not stated otherwise.

In addition, all PK parameters will be summarized descriptively stratified by age categories, gender, race and region as defined in Section 6.6. Age classes will be presented separately by FDA and by EMA criteria. The pediatric population (young children, children and adolescents) will be presented as a subtotal.

9.1. MEASUREMENTS

Pharmacokinetic endpoints can be found in Section 4.4 of this SAP.

Serum concentrations will be determined for different types of IgG: total IgG, subclass of IgG, and IgG directed against specific antigens, namely, pneumococcal capsular polysaccharide, hemophilus influenzae type B, measles, tetanus toxoid, anti-cytomegalovirus, and hepatitis B antigens.

PK results of this study will be compared to relevant historical data from previous PID studies with Intratect® (already marketed 10% IVIg from Biotest) and to available data from Bivigam® (a 10% IVIg, which was formerly developed by Biotest)), as well as to available data from the literature.

9.2. HANDLING OF DROPOUTS, MISSING DATA OR DATA BELOW THE LOWER LIMIT OF QUANTIFICATION, OUTLIERS

If the actual time of sampling is missing, the planned time may be used after visual check of the data and adequacy with the rest of the concentration-time profile.

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

The "PK concentrations" of samples taken outside the permitted time window will be listed and presented graphically on the individual plots using actual time. These data will be also used for PK parameters derivation using actual time. However, concentrations from samples taken outside the permitted sampling windows (mostly trough levels) may be excluded from summary statistics; this will be determined during DRM.

All below limit of quantification (BLQ) values for the serum concentration will be listed in concentration listings and will be set to missing for PK parameters derivation; % of BLQ values will be summarized for each time point within each age category/dosing interval combination.

For the individual PK profiles of serum concentration and for summary statistics of PK concentrations including generation of mean concentration versus time plots the following rules will apply: first BLQ value after quantifiable concentration as well as BLQ values

flanked by two quantifiable concentrations will be set to LLOQ/2, further values below BLQ will be set to zero unless deemed as outliers.

Obvious outliers will be considered as missing data. The outliers may be defined based on data review and comparison with typical values such as unexpected occurrence of BLQ results at the end of infusion, or significantly higher result than the typical max range of concentrations, etc. Data will be listed, but not included in summary statistics.

9.3. SAMPLING SCHEDULE FOR TROUGH LEVELS AND DENSE PHARMACOKINETICS

Venous blood samples with corresponding times for each analyte are shown in Table 1 below.

Table 1. Schedule of IgG type analysis by dosing schedule, age category, type of PK analysis, and time points

Dosing Schedule	Age (years)	PK Set	Time point (week)	Total IgG[1]	IgG subclasses[2]	Specific IgG[3]
Q3W	2 to <6	PK Trough	Baseline Post-1st EOI[4] Predose for all infusions (total IgG)	+ + +	- - -	- - -
		Dense PK	Infusion 7 (week 18): optional, sparse sampling at flexible time points[5]	+	-	-
	6 to <12	PK Trough	Baseline Post-1st EOI[4] Predose for all infusions (total IgG) Only baseline and predose (before 7th infusion)	+ + + -	+ - - +	- - - -
		Dense PK	Infusion 7 (week 18): Predose, EOI[4], 4h, 24h, 4d, 7d, 14d, 21d	+	+	-
	12 to <76	PK Trough	Baseline Post-1st EOI[4] Predose for all infusions (total IgG), Only baseline and predose (before 7th infusion)	+ + + -	+ - - +	+ - - -
		Specific Trough PK	Only baseline and predose (before 7th infusion)	-	-	+
		Dense PK	Infusion 7 (week 18): Predose, EOI[4], 4h, 24h, 4d, 7d, 14d, 21d	+	+	+
Q4W	2 to <6	PK Trough	Baseline Post-1st EOI[4] Predose for all infusions for total IgG	+ + +	- - -	- - -
		Dense PK	Infusion 5 (week 16): optional, sparse sampling at flexible time points[5]	+	-	-
	6 to <12	PK Trough	Baseline Post-1st EOI[4] Predose for all infusions (total IgG) Only baseline and predose (before 5th infusion)	+ + + -	+ - - +	- - - -

Dosing Schedule	Age (years)	PK Set	Time point (week)	Total IgG[1]	IgG subclasses[2]	Specific IgG[3]
		Dense PK	Infusion 5 (week 16): Predose, post-EOI[4], 4h, 24h, 4d, 7d, 14d, 21d, 28d	+	+	-
	12 to <76	PK Trough	Baseline Post-1st EOI[4] Predose for all infusions (total IgG) Only baseline and predose (before 5th infusion)	+ + + -	+ - - +	+ - - -
		Specific Trough PK	Only baseline and predose (before 5th infusion)	-	-	+
		Dense PK	Infusion 5 (week 16): Predose, EOI[4], 4h, 24h, 4d, 7d, 14d, 21d, 28d	+	+	+

EOI – end of infusion
Q3W – dosing schedule for dose administration once per 3 weeks
Q4W – dosing schedule for dose administration once per 4 weeks

[1] Total IgGs will be measured as trough concentrations prior each infusion in local laboratory, and in central lab for samples collected for the dense PK sampling
[2] Subclasses of IgGs will be measured as trough concentrations at baseline and prior to 7th/5th infusion for 3 or 4 –week schedule respectively in local laboratory, and in central lab for samples collected for the dense PK sampling.
[3] Anti-pneumococcal capsular polysaccharide, anti-hemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-HBs/hepatitis B concentrations will be measured at central lab (Biotest). This analysis is planned only for subjects 12 years and older.
[4] Pre-dose samples collected within 10-30 min before the start of infusion. Post-infusion (EOI) samples collected within 10-30 min window from the end of infusion, PK sampling windows for 4 and 24 hrs post-infusion - ±1 h; for 7, 14, 21 and 28 days - ±1 d
[5] For pediatric subjects (2 to <6 years), 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)

9.4. ANALYSIS OF SERUM CONCENTRATIONS

9.4.1. Summary of Trough Concentrations for Total IgG, and IgG Subclasses 1-4 (PK Trough Set).

Trough concentrations measured by local lab (Total IgG) and by central lab (IgG subclasses) will be summarized for each type of analyte (total IgG, subclasses of IgG) by dosing regimen (Q3W, Q4W), whole population, each age category, and visits, combining all dose levels including baseline values for prior IVIG formulations used by subjects before start of treatment with BT595 to study. Additional summaries will also be provided by dose level divided into 3 bins (0.2-<0.4, 0.4-<0.6, 0.6-0.8 g/kg dose bins) according to dosing regimen. Based on the number of subjects per age category the summaries by dose level may combine all or specific age categories, e.g., pediatric vs adult to have sufficient number of data for descriptive statistics.

Age categories are based on FDA (FDA, 2016) and EMA (EMA/CHMP/BPWP/94033/2007 rev. 2) guidance for IVIG. Additionally FDA and EMA guidance on pediatric studies and PK in pediatric studies were taken into consideration for planning of PK analyses [Food and Drug Administration (FDA) Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. December 2014. Available from: http://www.fdanews.com/ext/resources/files/12-14/12-08-14-pediatricguidance.pdf?1418077303; European Medicines Agency Guideline ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population. January 2001. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf; European Medicines Agency Guideline On The Role Of Pharmacokinetics In The Development Of Medicinal Products In The Paediatric Population. June 2006. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003066.pdf].

Summary statistics will not be presented if 50% or more of the actual values for the PK sets at any 1 time point or bin are BLQ or missing or less than 3 values are available. The reporting will be limited to median value for n=1 and to median, min and max values for 1<n≤2.

In addition, for the IgG subclasses, each individual concentrations (g/L) will be transformed to relative proportion of the total of the 4 subclasses (percent of the total). Individual percentage will be listed in same table reporting the concentrations (g(L) and summarized separately for the Q3W and Q4W regimen (all subjects and all dose together).

Evaluation of total IgG trough levels will include the calculation of the proportion of subjects who failed to meet the total IgG target level (≥5 g/L) prior to dose adjustment (Section 8.2.1), and an intra individual comparison to trough levels of the former IVIg product (i.e., using baseline data before 1st infusion of BT595, see Section 9.7).

Additionally, trough concentrations measured by local lab (Total IgG) and central lab (IgG subclasses) will be summarized by age categories based on FDA and EMA requirements:

Analyte	**Schedule**	**Age category (years)**	**Visit**
Total IgG	Q3W Q4W	2 to <6 (EMA, FDA) 6 to <12 (EMA, FDA) 12 to <17 (FDA) 12 to <18 (EMA) 2 to <17 (FDA) 2 to <18 (EMA) 17 to <76 (FDA) 18 to <76 (EMA) 17 to <65 (FDA) 18 to <65 (EMA) >=65 (EMA, FDA) Overall: 2 to <76	V1 to V20 according to dosing schedule
IgG subclasses	Q3W Q4W	6 to <12 (EMA, FDA) 12 to <17 (FDA) 12 to <18 (EMA) 6 to <17 (FDA) 6 to <18 (EMA) 17 to <76 (FDA) 18 to <76 (EMA) 17 to <65 (FDA) 18 to <65 (EMA) >=65 (EMA, FDA) Overall: 6 to <76	V1 (baseline) and V7/V5 (before the 7^{th}/5^{th} infusion)

Finally, trough concentrations measured by local lab (Total IgG) and central lab (IgG subclasses) will be summarized by dose level for last infusion:

Analyte	Schedule	Age category	Visit	Dose levels
Total IgG	-Q3W -Q4W -Combined	All: 2 to <76 **Pediatric vs adult:** 2 to <17 and 17 to <76 (FDA) 2 to <17 and 17 to <65 (FDA) 2 to <18 and 18 to <76 (EMA) 2 to <18 and 18 to <65 (EMA)	V1 to V20 according to dosing schedule	0.2-<0.4 0.4-<0.6 0.6-0.8
IgG subclasses	Q3W Q4W	All: 6 to <76 **Pediatric vs adult:** 6 to <17 and 17 to <76 (FDA) 6 to <17 and 17 to <65 (FDA) 6 to <18 and 18 to <76 (EMA) 6 to <18 and 18 to <65 (EMA)	V1 (baseline) and V7/V5 (before the 7th/5th infusion)	0.2-<0.4 0.4-<0.6 0.6-0.8

9.4.2. Antigen Specific IgG Trough Concentrations (Specific IgG Trough PK Set)

Trough concentrations for antigen-specific IgG measured only at the central laboratory will be summarized in the same manner as described for the PK Trough Set in Section 9.4.1. Separate listings and summary tables will be provided for this data set.

Summary statistics will not be presented if 50% or more of the actual values for the PK sets at any 1 time point or bin are BLQ or missing or less than 3 values are available. The reporting will be limited to median value for n=1 and to median, min and max values for 1<n≤2.

Additionally, trough concentrations for antigen-specific IgG measured only at the central laboratory will be summarized by dose level and antigen-specificity:

Analyte	Schedule	Age category (years)	Visit	Dose levels
Specific	Q3W Q4W	12 to <17 (FDA) 12 to <18 (EMA) 17 to <76 (FDA) 18 to <76 (EMA) 17 to <65 (FDA) 18 to <65 (EMA) >=65 (EMA, FDA) Overall: 12 to <76	V1 (baseline) and V7/V5 (before the 7^{th}/5^{th} infusion)	All dose combined Bins: 0.2-<0.4 0.4-<0.6 0.6-0.8

9.4.3. Steady State Trough Concentrations (Multiple PK Sets)

For comparison purpose, steady state trough concentrations (C_{ss}), defined as the trough concentration prior to infusion 7 for Q3W schedule and infusion 5 for Q4W, and measured both at local lab and at central lab (Biotest), will be listed for each subject. The steady state trough concentrations will be summarized separately for PK Trough set (local lab) for all subjects and for the Dense PK Subset (central lab) only for subjects participating to steady state PK study combined by age and dosing regimen (Q3W or Q4W). The comparison between local lab and central lab measurements will be done graphically for the subjects in Dense PK Subset as described in Section 9.6.3.

Antigen-specific IgGs will be summarized in a separate table for Specific IgG Trough PK Set.

In addition, steady-state trough concentrations C_{ss} of total IgG normalized by dose level i.e. divided by actual administered dose will also be calculated. Latest dose level before measurement will be used for dose normalization.

9.4.4. Summary of all Dense PK Serum Concentrations (Dense PK Subset)

Similar to the trough concentrations, summary of all serum concentrations of the Dense PK Subset measured in central lab (including the trough concentrations for the dense PK sampling period measured at central lab) will be done by analyte, whole population, age

category, treatment schedule (Q3W/Q4W) and by dosing regimen combining all dose levels. An additional summary will include the split by dose level for the last dose before sampling for dense PK, as presented above with 3 dose ranges (0.2-<0.4, 0.4-<0.6, 0.6-0.8 g/kg). For the summaries based on dosing bins, results for subjects with changes to dose level will be combined after dose adjustment based on dose history. Dose history will include the starting dose level and the adjusted dose level as well as the time of adjustment. If the dose adjustment was done close to the measurement of C_{ss} the resulting concentration may be excluded from the summary due to insufficient time to reach steady state at the adjusted dose level.

Nominal time points will be used for all summary statistics of PK concentrations. Summaries by age categories (based on the availability of pediatric subjects) will include the Dense PK Subset data for total IgG, IgG subclasses, and antigen-specific IgG. Data will be presented in separate table for each analyte.

Summary statistics will not be presented if 50% or more of the actual values for the Dense PK Subset at any time point are BLQ or missing or if less than 3 values are available. The reporting will be limited to median value for n=1 and to median, min and max values for 1<n≤2.

All total IgG concentrations measured in the Dense PK Subset will also be presented as change from "baseline" concentrations with "baseline" defined in this case as a predose concentration before the start of dense PK sampling period. Change from baseline total IgG concentrations will be used in an additional PK analysis. (This definition of this "baseline" concentration will be indicated in appropriate tables, listings, and figures when relevant).

9.5. DENSE PK ANALYSIS

9.5.1. Noncompartmental PK Analysis and Pharmacokinetic Parameters

Pharmacokinetic parameters (see list below) will be primarily derived by noncompartmental analysis (NCA) using actual sampling times for each subject (as data allow). This analysis will be performed for total IgG, IgG subclasses, and antigen-specific IgG whenever data from dense PK sampling are available (see Table 1, Section 9.2).

Concentrations of IgG analytes will be presented as originally measured values and as change from "baseline" values to derive two sets of PK parameters. The set of PK parameters derived using change from "baseline" in concentration will be presented separately and will have flag CFB (change from "baseline") added to all resulting PK parameters. For the purposes of the change from "baseline" analysis the baseline in this case is defined as a pre-dose concentration before the start of dense PK sampling period.

In addition, to evaluate the effect of reduced PK sampling, a NCA analysis for total IgG will be performed with a reduced PK dataset obtained from the Dense PK Subset for the age category 6 to <76 years. This "in silico" reduced PK datasets will be constructed by removing PK time points at either 4 or 24 hours, 7 or 14 days using random combinations of available concentrations. The reduced datasets will contain the following time points:

Set	Timepoint			
Reduced set 1	Predose=0h	4h	7d	21d or 28d
Reduced set 2	Predose=0h	24h	7d	21d or 28d
Reduced set 3	Predose=0h	4h	14d	21d or 28d
Reduced set 4	Predose=0h	24h	14d	21d or 28d

The resulting datasets will be analyzed using the same NCA analysis as defined for the complete Dense PK Subset. Data will be presented in separate listings and tables. The exploratory comparison between complete dataset and reduced datasets will be performed using an ANOVA as described in Section 9.9.

Alternative PK analysis through population PK modeling is described in Section 9.10.

The following PK parameters will be derived and listed for each subject:

C_{max}	Maximum observed serum concentration over dosing interval following infusion 7 (Q3W)/ 5 (Q4W) dosing interval
C_{max}/D	C_{max} normalized by dose level*
t_{max}	Time to reach C_{max}
C_{trough}	Trough concentration
AUC_{0-t}	Area under concentration-time curve calculated from time zero to time t after the last measured concentration
AUC_{0-t}/D	AUC_{0-t} normalized by dose level
AUC_{tau}	Area under the serum concentration-time curve from time of dosing (infusion 7(Q3W) or 5 (Q4W)) to the end of dosing interval
AUC_{tau}/D	AUC_{tau} normalized by dose level
MRT	Mean residence time
C_{avg}	Average serum concentration over the dosing interval following infusion 7 (Q3W) or 5 (Q4W) calculated by dividing AUC_{tau} over dosing interval (tau)
C_{ss}	Steady-state trough concentrations measured prior to infusion 7 (Q3W)/ 5 (Q4W) dosing interval
C_{ss} /D	Steady-state trough concentrations measured prior to infusion 7 (Q3W)/ 5 (Q4W) dosing interval normalized by dose level
% Fluctuation	% fluctuation is computed as $100*(C_{max}-C_{min})/C_{avg}$, where Cmin and C_{max} measured over dosing interval following infusion 7 (Q3W)/ 5 (Q4W) dosing interval
CL_{ss}	An estimate of the total body clearance = Dose/AUCtau
V_{ss}	Volume of distribution at steady-state
AUC_{0-inf}	Area under the concentration-time curve from time of dosing (infusion 7(Q3W)/ 5 (Q4W) extrapolated to infinity
AUC_{0-inf}/D	AUC_{0-inf} normalized by dose level
$t_{1/2}$	Serum terminal elimination half-life (time to reduce concentration by half during the terminal phase of the profile)
λ_z	terminal elimination rate constant

Clast	Last measured quantifiable concentration
tlast	Time point for the last measured quantifiable concentration

The noncompartmental analysis will be performed using an appropriate software solution. For the derivation of the PK parameters, the sampling time of pre-dose samples relative to dosing will be treated as time zero, using days as time units.

The PK parameters will be estimated as follows:

- The apparent C_{max} and the corresponding t_{max} will be read directly from the concentration-time plot of the observed data (not predicted data by the software);

- AUCs will be calculated using the linear/log trapezoidal rule.

- The terminal elimination rate constant (λ_z) will be generally determined by log-linear regression obtained using the 3 last quantifiable concentrations and will not include C_{max}. The adjusted square of the correlation coefficient (Rsquare adjusted) for the goodness of fit of the regression line through the data points must be at least 0.8500 for the λ_z value to be considered adequately reliable.

  For sparse PK sampling for age category 2-5 years the 2 time points within the expected terminal phase time window may be used for calculation of λz. The resulting data will be flagged as "sparse data" and will not be summarized.

- $t_{1/2}$ is calculated by the software as $\ln 2/\lambda_z$.

- If the time interval between the lower and upper time points used for the regression spans less than the derived half-life itself then λ_z and the associated $t_{1/2}$ will be flagged as “calculation interval shorter than resulting elimination half-life”. Summaries for the elimination parameters will be duplicated with all parameters available as well as flagged parameters excluded.

- The AUC from 0 to infinity is calculated by the program as: $AUC_{inf} = AUC_{last} + AUC_{last\text{-}inf}$ where last is the sampling time point of the last measurable concentration (t_{last}). $AUC_{last\text{-}inf}$ is calculated by the program as: C_{last}/λ_z, where C_{last} is the observed concentration at time t_{last} and λ_z is the elimination rate constant during the apparent terminal elimination phase; all AUC_{inf} will be presented in the listings of PK parameters.

- Secondary PK parameters such as Rsquare adjusted, interval for λ_z calculation, number of points excluding Cmax to calculate λ_z, AUC_{extrap}% will be listed separately for each subject.

- The AUC extrapolation to infinity must be ≤25% of the total area for AUC_{inf} to be considered reliable.

- For subjects with PK parameter which do not meet acceptance criteria (i.e., Rsquare adjusted <0.8500, interval for λ_z calculation shorter than $t_{1/2}$, number of points excluding

Cmax to calculate λ_z <3), λ_z, $t_{1/2}$, AUC_{inf} will be flagged based on the specific criteria in the individual data listings.

- CL_{ss} is calculated by program as (Dose/AUC_{tau}).
- For subjects with unreliable AUC_{inf} (because of extrapolation >25%), AUC_{inf} will be reported, but flagged in the individual data.

All PK parameters will be estimated both by baseline corrected and baseline uncorrected.

Flagged PK parameters will only be included in summarization and statistical analyses after careful consideration.

The PK parameters derivation will be based on data availability for analytes total IgG, or total IgG and IgG subclasses, and antigen-specific IgG by different age categories. Data for different analytes will be summarized in separate tables.

9.5.2. Summary of PK Parameters

Individual PK parameters for original concentration values and for change from "baseline" from complete and reduced data sets will be all listed for each subject when available. PK parameters for original concentration values and for change from baseline will be summarized similarly to the serum concentrations based on data availability (see Section 9.3) for different age categories, by age category and dose levels, individually for the two dosing regimen (Q3W and Q4W), as described in Section 9.4.1 for trough levels. Briefly, PK parameters will be summarized by analyte, and age category combining all dose levels. Additional summaries will include the split by dose level for the latest dose before sampling, as presented above with 3 dose ranges (0.2-<0.4, 0.4-<0.6, 0.6-0.8 g/kg). Comparison between complete PK parameters derived from the full dataset and the "in silico" reduced datasets is further described in Section 9.9.

The following descriptive statistics will be provided:

Variable	**Summarized with:**
AUC_{0-t}, AUC_{0-t}/D, AUC_{tau}, AUC_{tau}/D, AUC_{0-inf}, AUC_{0-inf}/D, C_{max}, C_{avg}, C_{ss}, , CL_{ss}, C_{max}/D, C_{ss}/D, C_{trough}, C_{last}, MRT, %Fluctuation, V_{ss}	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean, and geometric CV%
$t_{1/2}$, and λ_Z	n, arithmetic mean, SD, CV%, minimum, median, and maximum
t_{max} (actual time), t_{last}	n, minimum,Q1, median, Q3, and maximum

Note: CV% = SD/mean in %.

%BLQ = 100 * (total number of subjects who have BLQ values/total number of subjects within each cohort at each time point)

The following conventions will be used for the presentation of the descriptive statistics of PK parameters and of serum concentrations:

PK Reporting Precision

Statistics	Degree of Precision
Minimum, Maximum	3 significant digits or as needed based on actual measured values (for example PK concentrations)
Mean (arithmetic and geometric), Median	4 significant digits or as needed based on actual measured values (for example PK concentrations)
Standard deviation	5 significant digits or as needed based on actual measured values (for example PK concentrations)
CV% and Geometric CV%	1 decimal point or as needed based on actual measured values (for example PK concentrations)

9.6. DATA PRESENTATION FOR TOTAL IGG, IGG SUBCLASSES AND SPECIFIC IGG ANTIBODY LEVELS (PK TROUGH SET, SPECIFIC IGG TROUGH PK SET AND DENSE PK SUBSET)

9.6.1. Listings and Summary Tables

The actual sampling time of blood sample collection for determination of serum concentrations of total IgG, IgG subclasses or antigen-specific IgG will be listed for each infusion schedule for all subjects, and will include the deviation from scheduled sampling time relative to sampling time window described in protocol and in the footnote to Table 1.

All individual serum IgG concentrations (g/L) will be listed by subject, time point and dosing interval (Q3/Q4W), together with body weight, and body weight adjusted dose and actual total dose for each infusion. Concentrations will be summarized for each nominal time point and specific analyte by infusion schedule, age category and dose range level for latest dose before sampling as described in Section 9.4.

Individual PK parameters will be listed for the Dense PK Subset (total IgG/IgG subclasses and antigen-specific IgGs) in a table by subject for each analyte (total IgG, IgG subclasses, antigen-specific IgG) and will be summarized, by infusion schedule, age category and dose level as described in Section 9.4. Unreliable PK parameters will be listed and flagged in the listing, but potentially excluded from the summary.

Pharmacokinetic parameters of secondary interest for all analytes – total IgG, IgG subclasses and specific IgGs, namely R-square adjusted, the number of data points used for estimating λ_z, the upper and lower time point used for estimation of λ_z (h) compared to $t_{1/2z}$ (h), and the % AUC extrapolation from t_{last} to infinity will be listed by subject with the resulting flags for the primary PK parameters.

The summaries will be calculated based on dose adjustment as described above in Section 9.4.

Key PK parameters derived from the "in silico" reduced data set will be listed separately and labeled "CFB" (change from baseline).

In addition, for the IgG subclasses, each individual concentration (g/L) will be transformed to the relative proportion of the total of the 4 subclasses (percent of the total). Individual percentages will be listed in same table reporting the concentrations (g/L) and summarized separately for the Q3W and Q4W regimen (all subjects and all doses together).

9.6.2. Figures for Trough Total IgG Concentrations

The following mean trough concentration profiles will be produced for total IgG measured for all subjects, vs infusion number from 1st dose of BT595.

1. Mean ± SD (all subjects, all doses together) of serum trough total IgG concentration at each infusion number will be presented vs infusion number/day of treatment combining curves for Q3W and Q4W dosing interval on the same plot together. Separate plots will be generated with the y-axis as (i) linear and (ii) logarithmic y-axis.

2. Mean ± SD (all subjects) serum trough total IgG concentration vs infusion number profiles for each dose range level (0.2-<0.4; 0.4-<0.6; and 0.6-0.8) will be presented combining the curves within the same figure, on linear y-axis scale separately for each infusion schedule. A second plot will be generated with logarithmic y-axis scale.

3. Mean ± SD serum trough total IgG concentration vs infusion number profiles will be presented for each age category separately for each dosing interval. Separate plots will be generated with the y-axis using a (i) linear and (ii) logarithmic scale.

4. Individual profile of serum trough total IgG concentration vs infusion number will be presented on the same plot, separately for each dosing interval (Q3W / Q4W) and age category. Subjects with changes to the dose levels will be identified in the footnotes to the figures including time of dose adjustment and level of adjusted dose. Separate plots will be generated with the y-axis as (i) linear and (ii) logarithmic y-axis.

5. Figures 1.-3. (Mean ± SD) and Figure 4. (individual) will additionally be generated with the x-axis being actual time relative to the start of the first infusion (= time 0) with time in days or weeks as appropriate. Separate plots will be generated with the y-axis as (i) linear and (ii) logarithmic y-axis.

Figures presenting data for the different age categories will be produced for FDA and EMA categories separately. The number of subjects in each age category will be given in the legend. A horizontal reference line of the targeted minimal trough level of 5 g/L will be displayed in all figures as dotted line.

9.6.3. Figures for Baseline and Steady State Trough Levels

Steady state trough concentrations will be measured for all subjects for total IgG, and predefined age categories for the IgG subclasses (6 to <76 years) and antigen-specific IgG (12 to<76 years). Total IgG and IgG subclasses trough concentrations for baseline and pre-dose for 7th/5th infusion (Q3W / Q4W) will be available from (Total IgG) and central (IgG subclasses) lab for all subjects in all age categories. Trough concentrations obtained as a

part of Dense PK sampling will not be included in the figures. All antigen-specific IgG trough concentrations for the Specific IgG Trough PK Set will be only available from central lab (Biotest).

Data will be presented by Box-whisker plots for the 2 time points. A first set of figures will present baseline (which is the trough concentration of a similar product used by subjects previously to the study) and steady state data for all subjects together, and Q3W and Q4W separately on the same graph (6 boxes). Separate figures will be provided for each of the IgG variable (total IgG, 4 subclasses, and 6 antigen-specific IgGs).

A similar set of figures will present baseline and steady state levels for each age categories (FDA, EMEA categories on separate graphs) for each dosing interval and for each IgG variables on separate figures (total IgG, 4 subclasses, and 6 antigen-specific IgG).

Additionally, figures for different age categories will be produced for dose-normalized steady-state concentration C_{ss}/D for total IgG, IgG subclasses, and specific IgGs after the 7th BT595 infusion for Q3W schedule or the 5th infusion for Q4W schedule by age category on the same box plot.

Finally, a figure representing only the steady state concentrations of total IgG measured once in local lab and once in central lab for the subjects participating to the PK dense sampling will be presented by Box-whisker plots for the 2 measurement methods, see Section 9.4.3 (Multiple PK set).

9.6.4. Figures for Dense PK Sampling

PK profiles of total IgG, IgG subclasses, and antigen-specific IgG will be presented using data for all subjects participating to the dense PK sampling at steady state (at least 20 adults and voluntary pediatric patients) in the same way, on different plots unless otherwise indicated. The concentration data will be presented as original values and as change from baseline. The X-axis will indicate the time since last infusion (5th/7th infusion) in days. For the mean plots the nominal time will be used. All graphs will be provided with the y-axis as linear scale and as log-linear scale. Groups corresponding to infusion intervals, and age categories will be presented. Mean concentrations will be presented for all dose levels combined, without binning into separate dose ranges.

1. Mean ± SD (all subjects, all doses together) of concentration at each nominal time point elapsed from the current infusion will be presented combining curves for the Q3W and Q4W schedules within the same figure on a linear and log-linear scale for total IgG, IgG subclasses, and antigen-specific IgG on separate plots.

2. Mean ± SD (all doses together) concentrations at each nominal time point elapsed from the current infusion will be presented within the same figure on a linear and log-linear scale combining curves for each age category, separately for the Q3W and Q4W schedules. The plots will be produced for the FDA and EMEA defined categories.

Individual serum concentration-time profiles will be presented separately for each subject combining all analytes - total IgG, 4 IgG subclasses and 6 antigen-specific IgG on a linear and log-linear scale. The values of specific IgGs will be presented using Y2 scale to accommodate the use of different units – U/mL for specific IgGs vs g/L for all other IgG analytes.

In addition, overlay graphs of individual concentration-time profiles will be provided, separately for each dosing interval and each IgG variable (total, subclasses, antigen-specific) on linear and log-linear scale for each age category separately. The plots will be produced for the FDA and EMEA defined categories.

9.6.5. Figures for PK Parameters

PK parameters will be presented on box plots for total IgG, 4 IgG subclasses, and 6 different antigen-specific IgG for each PK parameter individually (C_{max}/D, AUC_{tau}/D and $AUC_{0\text{-}inf}$/D, and $t_{1/2z}$). Data will be reported separately for each dosing interval (Q3W and Q4W) and age category (FDA and EMA separately).

Box plots comparing PK parameters (C_{max}, T_{max}, AUC_{tau}, $AUC_{0\text{-}inf}$, $t_{1/2z}$) from complete and "in silico" reduced data sets will be presented by dosing schedule pooling together all subjects (6-75 years) and all dose levels.

9.7. EXPLORATORY COMPARISON OF STEADY-STATE TROUGH CONCENTRATIONS FOR TOTAL IGG, IGG SUBCLASSES, AND SPECIFIC IGGS WITH PREVIOUS IGG FORMULATION

Exploratory comparison of C_{ss} and dose-normalized C_{ss}/D between BT595 and similar products (IVIG products) will be performed for age categories and overall by ANOVA. The data for PK Trough Set and Specific IgG Trough PK Set will be used.

Log-transformed parameters Css/D for total IgG, IgG subclasses and specific IgGswill be compared separately by dosing interval and by age category where possible with treatment as fixed effect and subject as random effect based on existing guidance on bioequivalence from EMA (European Medicines Agency Questions and Answers: positions on specific questions addressed to Pharmacokinetics and FDA (Food and Drug Administration (FDA) Guidance for Industry). The following hypotheses will be tested for C_{ss} values:

H_{01}: $\mu_T/\mu_R \leq 80\%$ vs. H_{A1}: $\mu_T/\mu_R > 80\%$ and H_{02}: $\mu_T/\mu_R \geq 125\%$ vs. H_{A2}: $\mu_T/\mu_R < 125\%$

The same model will also be repeated for dose normalized trough concentration.

If the 90% CI for the geometric mean ratio (GMR) is within (80% – 125%) for any of the contrasts for the parameters C_{ss}/D, the null hypotheses, that is H_{01} and H_{02}, will be rejected with conclusion that the administration with BT595 (T=Test) is equivalent to administration of the previous IgG formulation (R=Reference).

The following contrasts will be explored (total IgG and IgG subclasses 1-4):

Q3W schedule - Css/D for 7th infusion vs baseline

Q4W schedule - C_{ss}/D for 5th infusion vs baseline

The formula for calculation of the estimated ratio between the test and reference and the (1-2*α)*100 % CI of the ratio is given below.

Difference = Estimate of difference between test and reference least square means

$$Ratio = 100 \times e^{Difference}$$

(1-2*α)*100% CIs for the Ratio:

$$Lower = 100 \times e^{(LowerBound\,(1\text{-}2*\alpha)\%CIs\ for\ the Difference)}$$

$$Upper = 100 \times e^{(UpperBound\,(1\text{-}2*\alpha)\%CIs\ for\ the Difference)}$$

Comparison between BT595 and previous IVIG products will also be explored graphically with box plots of C_{ss}/D as described in Section 9.6.5**Fehler! Verweisquelle konnte nicht gefunden werden.** of the SAP.

9.8. EXPLORATORY COMPARISON OF STEADY-STATE PK PARAMETERS FOR TOTAL IGG, IGG SUBCLASSES AND SPECIFIC IGGS BETWEEN AGE CATEGORIES

Exploratory comparison of CL_{ss}, not dose-normalized and dose-normalized, C_{max}/D, AUC_{tau}/D and if available $AUC_{0\text{-}inf}$/D using Dense PK Subset and C_{ss} and C_{ss}/D separately using the PK Trough set and the Specific IgG Trough PK set for the Q3W schedule and the 5th infusion for the Q4W schedule between age categories will be performed for total IgG, IgG subclasses and antigen specific IgGs by ANOVA approach as described above. Only subgroups with at least n=3 subjects will be retained for the comparison test.

Dense PK Subset will be used for the comparison of PK parameters. The PK Trough set and Specific IgG Trough PK set will be used for comparison of trough concentrations at steady state.

Log-transformed parameters for total IgG, IgG subclasses and specific IgGs will be compared separately by infusion schedule between age categories.

The same model will be repeated for dose normalized trough concentration and CL_{ss}.

The following contrasts will be explored:

Total IgG:

Regulatory agency	Age category 1 for comparison*	Age category 2 for comparison*
FDA	2 to <6**	6 to <12
	6 to <12	12 to <17
	12 to <17	17 to <76
	12 to <17	17 to <65
	17 to <65	>=65
EMA	2 to <6**	6 to <12
	6 to <12	12 to <18
	12 to <18	18 to <76
	12 to <18	18 to <65
	18 to <65	>=65

* if data from at least n=3 subjects available

** comparison with 2 to <6 years old category will be done only for C_{ss} and C_{ss}/D parameters due to differences in PK sampling schedule with other age categories

IgG subclasses (each subclass individually):

Regulatory agency	Age category 1 for comparison	Age category 2 for comparison
FDA	6 to <12	12 to <17
	12 to <17	17 to <76
	12 to <17	17 to <65
	17 to <65	>=65
EMA	6 to <12	12 to <18
	12 to <18	18 to <76
	12 to <18	18 to <65
	18 to <65	>=65

Specific IgGs:

Regulatory agency	Age category 1 for comparison	Age category 2 for comparison
FDA	12 to <17	17 to <76
	12 to <17	17 to <65
	17 to <65	>=65
EMA	12 to <18	18 to <76
	12 to <18	18 to <65
	18 to <65	>=65

9.9. EXPLORATORY COMPARISONS BETWEEN PK PARAMETERS DERIVED FROM COMPLETE AND REDUCED DATASETS

9.9.1. Exploratory Comparisons between Continuous PK Parameters Derived from Complete and Reduced Datasets

PK parameters derived from complete and reduced datasets for total IgG as described in Section 9.5.1 will be compared using the ANOVA approach described in Section 9.7.

The endpoints for comparison will be C_{max}, AUC_{tau}, AUC_{inf}, C_{max}/D, AUC_{tau}/D, $AUC_{0\text{-}inf}/D$ derived from both complete and reduced datasets.

The following contrasts will be explored
Full dataset vs reduced set 1
Full dataset vs reduced set 2
Full dataset vs reduced set 3
Full dataset vs reduced set 4
Reduced set 2 vs reduced set 1
Reduced set 3 vs reduced set 1
Reduced set 4 vs reduced set 1
Reduced set 3 vs reduced set 2
Reduced set 4 vs reduced set 2
Reduced set 4 vs reduced set 3

9.9.2. Exploratory Comparisons between Tmax Derived from Complete and Reduced Datasets

T_{max} parameter derived from complete and reduced datasets for total IgG as described in Section 9.5.1 will be compared using the Friedman approach.

T_{max} comparisons between reduced and full PK sets for total IgG using Dense PK Subset for ages 6 to <76 years old will be analyzed using Friedman's test. Pairwise treatment comparisons will be assessed using the Wilcoxon sign-rank test on the within-subject differences. The model will include only type of the sets.

The following contrasts will explored
Full dataset vs reduced set 1
Full dataset vs reduced set 2
Full dataset vs reduced set 3
Full dataset vs reduced set 4
Reduced set 2 vs reduced set 1
Reduced set 3 vs reduced set 1
Reduced set 4 vs reduced set 1
Reduced set 3 vs reduced set 2
Reduced set 4 vs reduced set 2
Reduced set 4 vs reduced set 3

9.10. POPULATION PK ANALYSIS

Population PK analysis is planned to obtain further information for the sparse PK sampling data from subjects in the age category 2 to <6 years. The decision to proceed with population PK analysis will be made as soon as all PK data are collected; results of the exploration using "in silico" reduced data set (Section 9.9) may also be taken into consideration, if available.

The population PK analysis will be performed according to the regulations from FDA and EMA for population PK analysis [Food and Drug Administration (FDA) Guidance for Industry: Population Pharmacokinetics. February 1999. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf, European Medicines Agency Guideline On Reporting The Results Of Population Pharmacokinetic analyses. June 2007. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003067.pdf].

The population PK model will be developed using dense PK sampling, for all available subjects in the study from age categories 6 to <76 years as well as the sparse sampling from the 2 to <6 years pediatrics subjects.

Covariates of interest will be evaluated for their effect on pediatric PK (e.g. age, and weight). Allometric scaling of the centered covariates (weight) will be tested.

The best population PK model will be evaluated using visual predictive checks and bootstrap approach.

The details of the population PK analysis as well as the acceptance criteria for the visual predicted check (VPC), terms of model evaluation and quality procedures for population PK output will be further described in a separate population PK analysis plan.

10. ANALYSIS OF PHARMACODYNAMICS

Pharmacodynamic analysis is described as efficacy analysis based on the secondary efficacy endpoint of trough concentrations of total IgG as described in Section 8.2.1 of the SAP.

Additionally to the analyses described above the changes in dosing levels due to values of secondary endpoints of total IgG trough concentrations below the target levels will be summarized based on the starting dose level for each subject.

Frequency of dose adjustments by treatment schedule, age category, starting dose, time of adjustment (infusion number) and overall will be presented in summary table.

11. SAFETY

All analyses described in this section will be performed using the SAF and will be presented by treatment schedule (3- or 4 week) and overall, if not stated otherwise. The results will be descriptive in nature. All data will be summarized and listed.

In addition, all safety parameters will be presented stratified by age categories, gender, race and region as defined in Section 6.6. Age classes will be presented separately by FDA and by EMA criteria. The pediatric population (young children, children and adolescents) will be presented as a subtotal.

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

11.1. EXTENT OF EXPOSURE

The duration of exposure will be expressed as the time in days from the first infusion of BT595 through to the last visit (inclusive). Summaries will be for a continuous variable and also by categorizing the data according to the following categories:

≤ 1 month
>1 - ≤ 2 months
>2 - ≤ 3 months
etc.

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

1 - ≤ 2 infusions
3 - ≤ 4 infusions
5 - ≤ 7 infusions
8 - ≤ 11 infusions
>11 infusions

The actual calculated dose in g/kg, based on the total dose administered and body weight at a given visit, will also be calculated at each infusion.

The following will be summarized:

- The actual dose in g/kg,
- The actual dose in g and ml for each infusion
- Number of subjects with dose modification or dose interruption for each infusion together with the reason for changes in the dose.
- Changes of planned infusion rate [ml/kg/h] during any infusion and the reason for change.

- Maximal administered infusion rate [ml/kg/h] in categories: ≤0.3, >0.3 - ≤1.4; >1.4 - ≤2; >2 - ≤4; >4 - ≤6; >6

- The total dose administered in g and ml across all infusions.
- Duration of infusion in min for each infusion.

Additionally, extent of exposure will be presented for PK Trough Set and age categories defined in the Section 6.6.

11.2. TREATMENT COMPLIANCE

BT595 is 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.

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.

11.3. ADVERSE EVENTS

Adverse events (AEs) will be coded using MedDRA, version 19.0, to give a preferred term and a SOC term for each event. At the end of the study, prior to database closure, AEs will be recoded applying the latest available MedDRA version available at this time point.

Adverse events temporally associated with the infusion are AEs occurring during infusion or within 1, 24, and 72 hours after the end of infusion and are defined as infusional AEs.

Summary tables will be based on treatment-emergent adverse events (TEAEs), defined as those events with onset date/time at or after the first BT595 infusion until the subject's last study visit. All tables will be displayed for overall AEs and for each treatment schedule.

Thromboembolic events ([TEEs], such as stroke, myocardial infarction, lung embolism) and **hemolysis** are defined as adverse events of special interest (AESIs) in this study.

The above mentioned AESIs will be retrieved from the database by the investigator assessment and by use of the following MedDRA Standard Queries (SMQ), separately:

-TEEs:	(1) MedDRA SMQ Embolic and thrombotic events (2) MedDRA SMQ Thrombophlebitis
-Hemolysis	MedDRA SMQ Haemolytic disorders

Adverse drug reactions (ADR) of an IMP are 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).

Tables will be presented overall and stratified by age categories defined in the Section 6.6., as listed below:

An overall summary of AEs will show the number and percentage of subjects (and the corresponding number of AEs) who report

- any AEs,
- any TEAEs (overall, infusional and noninfusional),
- any related TEAEs (overall, infusional and noninfusional),
- any TEAEs by maximum severity (overall, infusional and noninfusional),
- any serious TEAEs (overall, infusional and noninfusional),
- any nonserious TEAEs (overall, infusional and noninfusional),
- any serious related TEAEs (overall, infusional and noninfusional),
- any nonserious related TEAEs (overall, infusional and noninfusional),
- any TEAEs leading to study drug infusion interruption,
- any TEAEs leading to study drug dose reduction
- any TEAEs leading to study discontinuation / withdrawal,
- any TEAEs of special interest (investigator assessment / SMQ information, separately for TEE and Hemolysis),
- any TEAEs not caused by infection or infestation (defined by SOC),
- any TEAEs leading to death

The exploratory 2-sided 90% exact confidence limit interval will be calculated for the total number of subjects with TEAEs expressed as a percentage and the corresponding number of noninfusional TEAEs and corresponding to this for the infusional TEAEs.

The incidence of AEs and TEAEs (number and percentage of subjects reporting an event, and the number of events) will be summarized by SOC and preferred term.

Treatment emergent adverse events will be listed separately for two categories: with and without infections. In addition, the infections will be listed separately within the efficacy section. Additionally, summary by SOC and preferred term will be provided for infections.

The number and percentage of subjects with related TEAEs, and the number of related TEAEs will be summarized by SOC and preferred term.
If counted per subject and if more than 1 related TEAE is recorded for a subject within any SOC or preferred term, the subject will be counted only once.

The number and percentage of subjects with TEAEs and the number of preferred terms per MedDRA SOC will be summarized by maximum severity. If counted per subject and if more than 1 TEAE is recorded for a subject within any SOC or preferred term, the subject will be counted only once at the worst severity.

The number and percentage of subjects with noninfusional TEAEs and the number of preferred terms per MedDRA SOC will be summarized by maximum severity. If counted per

subject and if more than 1 TEAE is recorded for a subject within any SOC or preferred term, the subject will be counted only once at the worst severity.

The number and percentage of subjects with serious TEAEs and related serious TEAEs will be summarized by SOC and preferred term.

The number and percentage of subjects with TEAEs of special interest (separated by investigator assessment and SMQ information) and ADRs will be summarized by SOC and preferred term.

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

- any infusional AEs,
- any serious infusional AEs,
- any nonserious infusional AEs,
- any related infusional AEs,
- any related infusional AEs by infusion,
- any serious related infusional AEs
- any infusional AEs by maximum severity
- any infusional AEs by infusion

The number and percentage of infusions temporally associated with 1 or more AEs that began during an infusion or up to 72 hours after the completion of the infusion will be displayed. This summary will be repeated for infusional ADRs.

The number and percentage of infusional AEs and of subjects with infusional AEs at each infusion (e.g. 1st infusion, 2nd infusion) will be presented for each infusion schedule. 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.

An exploratory upper 1-sided 95% exact confidence limit will be calculated for the proportion of the infusions with 1 or more infusional AEs (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. The upper 95% CI limit should be less than 0.4 to meet the FDA recommendation (FDA Guideline for industry 2008).

The number and percentage of subjects with AEs that occur during an infusion will be summarized by the infusion rate at which the AEs are reported. Further parameters will be time to onset (for infusional AEs), action taken, duration, outcome, severity, seriousness, and investigator causality.

In addition, the number and percentage of subjects with AEs occurring during infusion or within 1, 24 and 72 hours after infusion completion will also be summarized by SOC and preferred term. The same summary will be repeated for product related events (ADRs).

Listings will be provided for all AEs, AEs temporally associated with infusion (events beginning during the infusion or up to 72 hours after the completion of the infusion), severe AEs, product related AEs, serious adverse events, serious related adverse events, deaths, AEs resulting in discontinuation, AEs of special interest,. Details regarding severity, product relation, time to onset and stop of AE, information regarding infusion (e.g. infusion number, infusion rate and respective change) and AE outcome will be included as a minimum.

AEs of the same type and of any type shall be presented per subject to elucidate a possible intra subject correlation:

- One table shall enlist AEs by frequency in the following order 1. PT and 2. subject. The number and percentage of the following additional parameters shall be displayed: Seriousness, Severity, Investigator Causality, Infusional AE, Noninfusional AE,

- One table shall enlist AEs by frequency in the following order 1. per subject, 2. per SOC and 3. per PT The number of the following additional parameters shall be displayed: Seriousness, Severity, Investigator Causality, Infusional AE, Noninfusional AE.

The same shall be applied for Infections as defined in 8.2.2

FDA Specified AE Table: The AE table as specified below will also be presented.

Adverse reactions (FDA specification) are defined as treatment emergent adverse events, which meet any of the following criteria:

(a) Infusional AE: Adverse events temporally associated with the infusion are adverse events occurring during intravenous administration or within 72 hours after the end of infusion.

(b) Adverse events considered by the investigator to be related to administration of BT595.

(c) Adverse events for which the investigator's causality assessment was missing a worst-case scenario will be applied: The missing relationships will be imputed as 'related'.

The above defined Adverse reactions (FDA Specification), sorted by MedDRA SOC and PT, will be displayed in two columns:

- Number and percent of subjects experiencing the Adverse reaction (FDA Specification) using total number of subject as denominator.

- Number and percent of Adverse reaction (FDA Specification) using total number of infusion as denominator.

11.4. LABORATORY EVALUATIONS

All laboratory analyses are performed by the local laboratory using standard assay methods. Laboratory evaluation includes clinical chemistry, hematology, coagulation, urinalysis and urine sediment microscopy and the hemolysis parameters.

Clinical Chemistry
• 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/ Urea • Sodium • Chloride • Potassium • Calcium
Hematology
• Hematocrit • Hemoglobin • Red blood cells • White blood cells • Differential white blood cells (Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils) • Platelets • Erythrocyte sedimentation rate • C-reactive protein
Coagulation
• 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 (Erythrocyte casts, Hemoglobin urinary casts, leukocyte urinary casts, epithelial urinary casts (tubular urinary casts) , granular urinary casts) • Hematuria
Hemolysis parameter
• Coombs test • serum haptoglobin • plasma-free hemoglobin • urine hemosiderin

Safety laboratory assessments will be categorized with respect to the local laboratory specific reference ranges as normal/abnormal. Abnormal values will be further classified with respect to clinical relevance: not clinically significant (NCS) high or low or clinically significant (CS) high or low. All laboratory results will be listed with International System of Units (SI). The number and proportion of subjects with at least 1 CS abnormal value and the number of CS abnormal values will be summarized by laboratory test categories: clinical chemistry, hematology, coagulation, urinalysis by baseline and all post-baseline visits. Changes over time will be described by means of “shift-tables”, comparing the post-baseline values versus baseline value. The data will be listed. Values below or above the reference values in the data listings will be flagged. All laboratory values will be converted into standard units (SI units, if applicable) for evaluation and presentation reasons. Presentations will be done by scheduled visits as described in the flow chart, Section 3.8.

For the definition of baseline value refer to Section 6.2.

All data including pregnancy test results will be listed.

11.5. VITAL SIGNS

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate and respiratory rate) are assessed at all visits at the following time points: 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.

Body temperature is collected at all visits during the treatment period within 30 minutes before each infusion only.

For vital sign parameters, absolute values and changes from baseline will be presented for each study visit and where available at the time points 30 minutes before each infusion, 15 to 30 minutes after the start of each infusion, 15 to 30 minutes after the start of any change in the infusion rate and 15 to 30 minutes after the end of each infusion using summary descriptive statistics.

In addition changes from infusion start (30 minutes before each infusion) will be presented for each infusion at the time points 15 to 30 minutes after the start of each infusion, 15 to 30 minutes after the start of any change in the infusion rate and 15 to 30 minutes after the end of each infusion using summary descriptive statistics.

Absolute values and changes from baseline will be presented for each scheduled study visit for body temperature and weight.

For the definition of baseline value refer to Section 6.2.

All data will be listed.

11.6. PHYSICAL EXAMINATION

For each subject, a complete physical examination is performed at each visit as described in the Flowchart, Section 3.8.. The physical examination includes an 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 is 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 reports any changes since the physical examination performed before the BT595 infusion. Any new physical examination findings are documented as AEs.

The number and percentage of subjects with assessments of normal, abnormal NCS, abnormal CS or Not Done at all scheduled visits (prior to infusion during the treatment period) will be displayed in a summary table for each body system.

The number and proportion of subjects with at least 1 CS abnormal value and the number of CS abnormal values will be summarized by the different categories.

Changes over time will be described by means of “shift-tables”, comparing the post baseline values versus baseline value. Percentages will be calculated from the number of subjects with the given result at baseline. For the definition of baseline value refer to Section 6.2.

All data will be listed.

11.7. OTHER SAFETY

11.7.1. Intravascular Hemolysis

The intravascular hemolysis tests are performed at screening (initial visit) and the closing (follow-up) visit only, unless further tests are required. Tests for the detection of intravascular hemolysis consist of a direct antiglobulin test (Coombs test) and the measurement of serum haptoglobin, plasma-free hemoglobin, and urine hemosiderin.

For the first 10 patients, additional data are available for their first 2 infusions (V2 and V3) on direct antiglobulin test (Coombs test) and the test of serum haptoglobin at the time points V3 and V4, as those data had been required by the Data and Safety Monitoring Board.

If the Coombs test result is positive, the test will be repeated and red blood cell count, hematocrit, hemoglobin (including plasma-free), 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.

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

In addition, summaries will be presented in case of drop in hemoglobin level ≥ 1.0 g/dL in conjunction with a drop in serum haptoglobin to below the lower limit of normal and rise of serum lactate dehydrogenase compared to screening level.

11.7.2. Viral Safety (Retention Samples)

In order to respond rapidly to any reports on additional viral infections, a screening blood sample from each subject included in the study is taken at the screening (initial) visit and stored at -70°C for possible future serum testing. At the closing (follow-up) visit, an additional blood sample is taken and stored up to 6 months after study end.

The analysis of viral safety samples will be decided on a case-by-case basis depending on the need for further data investigations for a subject. If viral safety samples are analyzed for any subject, data will be listed only.

12. INTERIM ANALYSES

No interim analysis of data from this trial is planned.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

13.1.1. Specific IgG Trough PK Set

Specific IgG Trough PK Set was added to the definition of PK Sets to distinguish between trough concentration for Specific IgG measured at central lab unlike trough concentrations for total IgG and IgG subtypes measured at local labs.

13.1.2. Dense PK Subset

The protocol definition “The Dense PK Set includes all subjects following the principles of the SAF for whom at least 1 concentration of total IgGs […]” was adjusted to “The Dense PK Set includes all subjects who received all planned doses and for whom at least 1 concentration of total IgGs […]”.

13.1.3. Rate of Any Infections

According to the protocol: 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. This is specified in the SAP “The annual rate per subject will be the total number of infections of the subject divided by the total duration expressed in years of the observation period of the subject”

13.1.4. Rate of Nonserious Infections

According to the protocol: 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. This is specified in the SAP as “The annual rate per subject will be the total number of nonserious infections of the subject divided by the total duration expressed in years of the observation period of the subject.”

13.1.5. Time to Resolution of Infections

According to the protocol: The presentation will be done by infusion schedule and overall and will include the frequencies of number of days until the resolution of infection. To be consistent with the analysis of all other efficacy endpoints, analysis will be done overall only.

13.1.6. Antibiotic Treatment Information

According to the protocol: Antibiotic treatment (number of days antibiotic treatment received per month). This is specified in the SAP as “Antibiotic treatment (number of days antibiotic treatment received per month and per year).

According to the protocol: 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. This is specified in the SAP as “The monthly rate per subject will be the total number of days on antibiotics of the subject divided by the total duration expressed in months (of 30 days) of the observation period of the subject.”

13.1.7. Rate of Time Lost from School/Work due to Infections and their Treatment

According to the protocol: Rate of time lost from school/work due to infections (number of days per month) and their treatment (number of days treatment per month). This is specified in the SAP as “Rate of time lost from school/work due to infections (number of days per month and per year) and their treatment (number of days treatment per month and per year)”

According to the protocol: 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. This is specified in the SAP as “The monthly rate per subject will be the total number of days off school/work due to infections and their treatment of the subject divided by the total duration expressed in months (of 30 days) of the observation period of the subject.”

13.1.8. Hospitalization/ Hospitalization due to Infection

According to the protocol: Hospitalization (number of days per month overall and due to infection). This is stated in the SAP as “Hospitalization (number of days per month and per year overall and number of days per month and per year due to infection)”

According to the protocol: 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. This is specified in the SAP as “The monthly rate will be the total number of days in hospital of the subject divided by the total duration expressed in months (of 30 days) of the observation period of the subject.”

13.1.9. Fever Episodes

According to the protocol: 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. This was specified in the SAP as “The annual rate per subject will be the total number of days with episodes of fever of the subject divided by the total duration expressed in years of the observation period of the subject.”

13.1.10. Subgroup Analysis

According to the protocol: “The age categories for the subgroup analyses will be children (2 to <12 years), adolescents (12 to < 17 resp. <18 years), and adults (17 resp. 18 to <76 years). 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”. The decision was revised to support the FDA and EMA guidelines on the subgroup analysis. Analysis will be performed for two age categories:

1) Age category according to FDA
   young children (2 to <6 years),
   children (6 to <12 years)
   adolescents (12 to <17 years)

adults (17 to <76 years)
geriatric (>= 65 years)

2) Age category according to EMA
young children (2 to <6 years),
children (6 to <12 years)
adolescents (12 to <18 years)
adults (18 to <76 years)
geriatric (>= 65 years)

The pediatric population (young children, children and adolescents) will be presented as a subtotal.

Analysis will be performed for additional subgroups, which were not defined in the protocol: region (United States vs Europe vs Asia), race categories and gender.

13.1.11. Definition of Completion

According to the protocol: 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]). The definition was modified to “A subject will be defined as “completed” if s/he completes the Follow-up period of the study. Termination at a different time point will be considered as discontinuation”.

13.1.12. Health-related quality-of-life

According to the protocol, health-related quality-of-life questionnaires are secondary efficacy endpoints. These endpoints are defined as exploratory efficacy endpoints in this SAP, which follows the FDA advice to consider the endpoints as exploratory rather than as secondary.

13.1.13. The Peds QL™ Questionnaire

According to the protocol, the age group of adolescents for the US is restricted to 12 to <17 years and therefore only subjects 2 to <17 years can be enrolled into the group of pediatric subjects. However, the Peds questionnaire is analysed based on the given age classed from the questionnaire.

13.1.14. The EQ-5D™ Questionnaire

According to the protocol, the age group of adolescents for the US is restricted to 12 to <17 years and therefore only subjects 2 to <17 years can be enrolled into the group of pediatric subjects. However, the EQ-5D questionnaire is analysed based on the given age classed from the questionnaire.

13.1.15. Expected/unexpected TEAEs or ADRs

According to the protocol: The number of expected/unexpected TEAEs or ADRs should be taken into account for the analysis. This analysis was not included into the SAP as the definition of expected/unexpected TEAEs would be based on subjective opinion.

14. REFERENCE LIST

1. ICH (1996): Note for Guidance on Structure and Content of Clinical Study Reports. ICH Topic E3 (CPMP/ICH/137/95)
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3. CDISC: Study Data Tabulation Model (SDTM) Implementation Guide: Human Clinical Trials (V3.2), dated November 26, 2013
4. CDISC: Analysis Data Model (ADaM), Final Version 2.1, dated December 17, 2009
5. CDISC: Analysis Data Model (ADaM) Implementation Guide, Final Version 1.1, dated February 12, 2016
6. European Society for Immunodeficiencies [Internet]. [Place unknown], [Publisher unknown]; 10 May 2006. Available from: http://esid.org/Working-Parties/Clinical/Resources/Diagnostic-criteria-for-PID2#tophttp://esid.
7. Conley ME, Notarangelo LD, Etzioni A (1999). Diagnostic criteria for primary immunodeficiencies. Clin Immunol., 93(3):190-7.
8. 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. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004766.pdf.
9. 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. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm078526.pdf.
10. Food and Drug Administration (FDA) Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Mended Initial Pediatric Study March 2016. Available from: http://www.fda.gov/media/86340/download
11. The PedsQL™ Measurement Model for the Pediatric Quality of Life Inventory™ [Internet]. [Place unknown], [Publisher unknown]; [Date Unknown]. Available from: http://www.pedsql.org/index.html.
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14. Food and Drug Administration (FDA) Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. January 2001. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070244.pdf
15. Food and Drug Administration (FDA) Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. December 2014. Available from: http://www.fdanews.com/ext/resources/files/12-14/12-08-14-pediatricguidance.pdf?1418077303
16. European Medicines Agency Guideline ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population. January 2001. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf
17. European Medicines Agency Guideline On The Role Of Pharmacokinetics In The Development Of Medicinal Products In The Paediatric Population. June 2006. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003066.pdf
18. Food and Drug Administration (FDA) Guidance for Industry: Population Pharmacokinetics. February 1999. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf
19. European Medicines Agency Guideline On Reporting The Results Of Population Pharmacokinetic analyses. June 2007. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003067.pdf
20. Biotest_991_Data Monitoring Committee Charter_Final

15. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures, and statistical analyses will be generated using SAS® for Windows, Release 9.4 or higher (SAS® Institute Inc., Cary, NC, USA. Computer-generated table, listing, and figure output will adhere to the following specifications.

PK concentration data will be evaluated using Phoenix WinNonLin 6.3 or higher on Windows 7 platform.

15.1. CDISC

All tables, listings and figures (TLFs) will be provided based on ADaM (Analysis Dataset Model) datasets. The only data sources for generating ADaM datasets are SDTM datasets. The structure of SDTM datasets is created based on the following documents: Study Data Tabulation Model (SDTM), Final Version 1.4, Study Data Tabulation Model (SDTM) Implementation Guide, Final Version 3.2. ADaM datasets will be created according to the Analysis Data Model (ADaM), Final Version 2.1, Analysis Data Model (ADaM) Implementation Guide, Final Version 1.1. Detailed metadata will be provided for SDTM and ADaM datasets.

15.2. GENERAL CONSIDERATIONS

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in pdf format.
- Numbering of TLFs will follow ICH E3 guidance.

15.3. TABLE, LISTING, AND FIGURE FORMAT

15.3.1. General

- All TLFs will be produced in A4 landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 9.
- The data displays for all TLFs will have a 2.54-cm (1-inch) blank margin on all sides.
- Headers and footers for figures will be in Courier New font, size 9.
- TLFs will be in black and white (no color).
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TLFs. Special characters, such as nonprintable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer supplied formats, as appropriate.

15.3.2. Headers

- All outputs will have the following header at the top left of each page:
- Biotest AG Protocol 991 ([redacted] number [redacted])

15.3.3. Display Titles

- Each TLF will be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering will be applied for the current study.

15.3.4. Body of the Data Display

15.3.4.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

15.3.4.2. Table Conventions

- Units will be included where available.
- A missing category will be added to any parameter for which information is not available for 1 or more subjects.
- Percentage values will be printed to one decimal place. If a value rounds down to 0.0 then display as '<0.1'. Unless otherwise noted, for all percentages, the number of subjects in the analysis set will be the denominator. Percentages equating to 100% will be presented as 100%, without any decimal places. Zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).
- Unless otherwise specified, mean, median, and percentile values will be presented with one decimal more than the original value, SD will be displayed with two decimals more than the original value and minimum/maximum values will have the same number of decimals as the original value.
- P-values will be output in the format: “0.xxxx”, where xxxx is the value rounded to 4 decimal places. Any p-value less than 0.0001 will be presented as <0.0001. If the p-value is returned as >0.9999 then present as >0.9999.
- Missing descriptive statistics or p-values which cannot be estimated will be reported as “-”.

15.3.4.3. Listing Conventions

- Listings will be sorted for presentation by subject number and occurrence.
- Dates will be presented as “DD-MMM-YYYY”, e.g., 01-NOV-2012. Missing portions of dates will not be presented e.g. –NOV-2012.

- All observed time values will be presented using a 24-hour clock HH:MM format (e.g., 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

15.3.4.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., mean value) values will be displayed on the Y-axis.

15.3.4.5. Footnotes

- All footnotes will be left justified.
- Each new footnote will start on a new line where possible.
- If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- Each table will include a reference to the source listing.
- The last line of the footnote section will be a standard source line that indicates:
    - left justified: date/time the program was ran
    - centered: the name of the program used to produce the data display
    - right justified: the pagination

16. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, or statistical analyses. An overview of the development of programs is detailed in [redacted] SOP Developing Statistical Programs (3907).

[redacted] SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency, and commenting and by review of the produced output.

17. APPENDICES

Appendix 1: “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.

Appendix 2: PedsQL™ Scoring

The Parent Report for Toddlers (ages 2-4) of the **PedsQL™** 4.0 Generic Core Scales is composed of 21 items comprising 4 dimensions.

DESCRIPTION OF THE QUESTIONNAIRE:

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Physical Functioning	8	1-8	1-8	Higher scores indicate better HRQOL.
Emotional Functioning	5	1-5	1-5	
Social Functioning	5	1-5	1-5	
School Functioning	3	1-3	1-3	

SCORING OF DIMENSIONS:

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always)
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100.
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. **Step 2: Calculate Scores** Score by Dimensions: • If more than 50% of the items in the scale are missing, the scale scores should not be computed. • Mean score = Sum of the items over the number of items answered. Psychosocial Health Summary Score = Sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. Physical Health Summary Score = Physical Functioning Scale Score

	Total Score: Sum of all the items over the number of items answered on all the Scales.
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

The **Child and Parent Reports** of the **PedsQL™** 4.0 Generic Core Scales for:

- Young Children (ages 5-7),
- Children (ages 8-12),
- And Teens (ages 13-18),

are composed of 23 items comprising 4 dimensions.

DESCRIPTION OF THE QUESTIONNAIRE:

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Physical Functioning	8	1-8	1-8	Higher scores indicate better HRQOL.
Emotional Functioning	5	1-5	1-5	
Social Functioning	5	1-5	1-5	
School Functioning	5	1-5	1-5	

SCORING OF DIMENSIONS:

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always) 3-point scale: 0 (Not at all), 2 (Sometimes) and 4 (A lot) for the Young Child (ages 5-7) child report
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100.
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. **Step 2: Calculate Scores** <u>Score by Dimensions</u>: • If more than 50% of the items in the scale are missing, the scale scores should not be computed. • Mean score = Sum of the items over the number of items answered.

	Psychosocial Health Summary Score = Sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. Physical Health Summary Score = Physical Functioning Scale Score **Total Score**: Sum of all the items over the number of items answered on all the Scales.
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.