Clinical Pharmacology BLA Review
Division of Clinical Evaluation General Medicine
Office of Clinical Evaluation
Office of Therapeutic Products

BLA	125810/0
Product	Immune Globulin Intravenous Human, 10% Liquid, IgG Next Generation (BT595)
Sponsor	Biotest AG
Indication	For primary humoral immunodeficiency in patients 2 years of age and older
Date Received	June 30, 2023
Reviewer	Yang Chang, PhD, PharmD
RPM	Mona Badawy
Through	
	Lola Fashoyin-Aje, MD, MPH
	Director, Office of Clinical Evaluation

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1   EXECUTIVE SUMMARY

Biotest AG submitted a Biologic License Application (BLA) STN125810/0 on June 30, 2024, requesting approval for Human Immune Globulin product YIMMUGO for the treatment of patients with primary humoral immunodeficiency (PI) 2 years of age and older. The product is also referred to as BT595 in this review.

The clinical pharmacology evaluation of this BLA is based on the results of Study 991, a Phase III clinical study evaluating the efficacy, safety, and pharmacokinetics (PK) of BT595 in 49 adults (20 to 74 years of age) and 18 children (2 to 16 years of age). All 67 patients enrolled in Study 991 received ≥1 dose of BT595 according to the following dosage: 12 patients received BT595 on a 3-week treatment schedule (Q3W) and 55 patients received BT595 on a 4-week treatment schedule (Q4W).

The mean total immunoglobulin G (IgG) trough levels at steady state were above the acceptable minimal trough level of 5 g/L and generally remained constant after reaching steady state. Overall, the mean total IgG trough levels at steady state following administration of BT595 were comparable to levels observed in recipients of reference intravenous immunoglobulin (IVIG) therapy across the relevant age groups. The PK profiles of patients 6 to <76 years of age were characterized by non-compartmental analyses (NCA). The Applicant conducted population PK analysis to characterize the PK of BT595 total IgG in adult and pediatric patients aged 2 to 76 years and assess potential effects of the intrinsic and extrinsic factors on total IgG PK. No relationship between PK parameters and age and sex were identified in the covariate analysis, although subgroup analyses may be limited due to the small sample size.

As described in the clinical review memo, the proposed dosing regimen of BT595 administered by intravenous (IV) infusion has demonstrated clinical efficacy with a tolerable safety profile. From a clinical pharmacology standpoint, the BLA is acceptable to support approval.

2   INTRODUCTION

BT595 is a highly purified, sterile, non-pyrogenic, ready-to-use 10% liquid preparation of concentrated polyclonal human IgG antibodies for IV administration. The product is a clear to slightly opalescent liquid, which is colorless to pale yellow. The active ingredient is human IgG purified from human source plasma and processed using a combination of cold ethanol fractionation, caprylic acid precipitation, as well as anion and cation exchange chromatography.

3   SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

- The mean total IgG trough levels at steady state following administration of BT595 were comparable with patients' baseline total IgG levels. The trough levels did not differ notably between levels observed in patients who received reference IVIG therapy.

- The PK profile of total IgG at steady state showed that mean total IgG concentrations remained above 5 g/L at all time points assessed in both dosing schedules and across age subgroups.
- During the study, 10 patients required a dose adjustment (increase) due to low IgG levels, including 5 patients with low baseline levels (below 5 g/L)who received treatment Q4W.
- The difference of the PK parameters between the Q3W and Q4W was due to the 7-day shorter dosing interval.
- The steady state trough levels for IgG subclasses 1-4 followed the same pattern as observed for total IgG.
- The trough levels of the six analyzed antigen-specific IgGs at steady state were comparable to levels in patients who received reference IVIG therapy.
- Per the pharmacometrics consult review, the Applicant's population PK analysis is considered acceptable for the purpose of predicting the PK and exposure parameters of total IgG in adult and pediatric patients with primary immunodeficiency disease (PID). No relationship between PK parameters and age and sex were identified in the covariate analysis. However, it is important to note that the prediction of PK parameters of total IgG in children 2 to <6 years of age may carry some uncertainty due to the small sample size in this population group.

4   LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125810/0 and finds it acceptable pending the following revisions shown below. The reviewer verified the patient number and revised PK parameters in Table 4 based on ADPC and ADPP datasets.

5   CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
YIMMUGO provides a broad spectrum of opsonizing and neutralizing immune globulin G (IgG) antibodies against a wide variety of pathogens and their toxins, which helps to avoid recurrent serious opportunistic infections. The mechanism of action has not been fully elucidated but may include immunomodulatory effects.

12.2 Pharmacodynamics
YIMMUGO contains mainly IgG with a broad spectrum of antibodies against various infectious agents, reflecting the IgG activity found in the donor population. YIMMUGO which is prepared from pooled plasma from not less than 1,000 donors, has an IgG subclass distribution similar to that of native human plasma. Adequate doses of IGIV can restore an abnormally low IgG level to the normal range. Standard pharmacodynamics studies were not performed.

12.3 Pharmacokinetics
The pharmacokinetic parameters for YIMMUGO were determined in an open-label, prospective, multicenter, multinational clinical trial in 57 patients with PI *[see Clinical Studies (see Clinical Studies (14)]*. IgG levels for determination of PK parameters were

measured after the 7th (3-week schedule, n=10) or 5th infusion (4-week schedule, n=47) in 57 patients (6 to <76 years of age). Patients for whom PK data was available received doses of YIMMUGO between 280 mg/kg to 800 mg/kg. The mean half-life of YIMMUGO for adults was 24.8 to 29.9 days depending on the treatment schedule (see Table 4). PK parameters did not indicate any clinically relevant differences between the 3-week and 4-week schedule.

Table 4: Pharmacokinetic Parameters of YIMMUGO in PI Patients at Steady State

a) PK Parameters: 3 Week Schedule - Mean (SD)

Parameter	6-<12 Years	12-<17 Years	17-<76 Years
N^*	2	1	7
C_{max} (mg/mL)	19.6 (3.9)	34.8	32.3 (6.3)
C_{trough} (mg/mL)	8.2 (0.2)	13	10.4 (2.4)
AUC_{tau} (day × g/L)	238.7 (5.9)	477	398.4 (99)
CL_{ss} (mL/day/kg)	2 (0.3)	1.2	1.4 (0.3)
V_{ss} (mL/kg)	69.4 (23)	27	53.5 (15.7)
Half-life (days)	29.5, n=1	15.5	24.8 (5.1), n=5

b) PK Parameters: 4 Week Schedule - Mean (SD)

Parameter	6-<12 Years	12-<17 Years	17-<76 Years
N[*]	3	5	39
C_{max} (mg/mL)	24.7 (1.2), n=2	22.2 (2.3), n=4	27.1 (6.3)
C_{trough} (mg/mL)	7.1 (1.2), n=3	9.1 (1.7), n=5	8.1 (2.5)
AUC_{tau} (day × g/L)	392.1 (19.7), n=2	415.1 (94.9), n=4	397 (103.6), n=36
CL_{ss} (mL/day/kg)	1 (0.1), n=2	0.9 (0.3), n=4	1.3 (0.5), n=36
V_{ss} (mL/kg)	74.6 (7.2), n=2	56.5 (12.8), n=4	61.8 (39.1), n=35
Half-life (days)	57.5, n=1	31.7 (3), n=2	29.9 (12.4), n=22

[*] Divergent number of patients for individual PK parameters are indicated behind values. Abbreviations: AUC_{tau} = area under the concentration-time curve calculated from start to end of the dosing interval; CL_{ss} = clearance at steady state; C_{max} = maximum serum concentration; C_{trough} = trough concentration at steady state; n = number of patients with data; SD = standard deviation; V_{ss} = volume of distribution at steady state

Although no systematic study was conducted to evaluate the effect of sex on the pharmacokinetics of YIMMUGO, subgroup analysis between males (n=37) and females (n=30) revealed no clinically relevant differences in exposure and IgG trough levels.

6   RECOMMENDATIONS

The clinical pharmacology information in this BLA is acceptable provided that satisfactory agreement is reached between the Applicant and the FDA regarding the language in Section 12 of the package insert. Please refer to Section 4 for detailed Labeling Recommendations.

7   COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

7.1   Study 991

Title: An open-label, prospective, multicenter study investigating clinical efficacy, safety, and pharmacokinetic properties of the human normal immunoglobulin for IV administration BT595 as replacement therapy in patients with PI.

Study Number: 991

Investigational Product: BT595

Clinical Phase: III Pivotal

Study Objectives:
The main purpose of this study was to assess the efficacy, safety, and PK characteristics of BT595 in pediatric and adult patients with PI.

The primary objective was to demonstrate that the rate of acute serious bacterial infections (SBIs) is less than 1.0, to provide substantial evidence of efficacy.

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

PK Endpoints:
- IgG trough levels (total IgG) before each administration (secondary efficacy endpoint).
- IgG trough levels (subclasses 1-4) at baseline and before the 7th/5th infusion of the Q3W or Q4W schedule, respectively (except for pediatric patients 2 to <6 years of age).
- IgG trough levels of specific antibody levels (anti-pneumococcal capsular polysaccharide, anti-haemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus, and anti-HBs/hepatitis B) at baseline and before the 7th/5th infusion of the Q3W or Q4W schedule, respectively (except for pediatric patients 2 to <12 years of age).
- PK parameters at steady state for:
  a) Total IgG (patients 2 to <76 years of age)
  b) IgG subclasses 1-4 (patients 6 to <76 years of age)
  c) 6 antigen-specific IgG (patients 12 to <76 years of age)

Dosage and Administration:
Patients were assigned to receive BT595 at doses between 0.2 and 0.8 g per kg body weight (bw) (2 to 8 mL/kg bw), either at a Q3W or Q4W schedule, for a treatment period of approximately 12 months. The initial dose and dosage interval had to be consistent with the patient's pre-study IVIG treatment and was only to be changed if medically indicated (if a patient's IgG trough level before infusion decreased to <5 g/L), at the investigator's discretion.

There were 14 infusions for the Q4W regimen and 18 infusions for the Q3W regiment in a treatment period of approximately 12 months. Trough IgG levels were measured prior to each study drug infusion. and the steady state trough levels were measured before the 7th infusion of the Q3W schedule (Week 18) or the 5th infusion of the Q4W schedule (Week 16).

PK Sampling Time:
Serial sampling for PK analysis of total IgG, IgG subclasses 1-4, and IgG specific antibody levels was done at estimated steady state after the 7th infusion of the Q3W schedule (Week 18) or after the 5th infusion of the Q4W schedule (Week 16). The number of blood draws (and the amount of blood per sample) were dependent on the patient's age category. For adult patients (18 to 75 years, inclusive) and pediatric patients (6 to 17 years, inclusive), samples were taken at a fixed series of time points: pre-dose, End of Infusion (EOI), 4h, 24h, 4d, 7d, 14d, 21d, and 28d (in the Q4W schedule only). For young children (2 to <6 years of age), only sparse sampling for steady-state PK parameters was performed.

PK Dataset:
Eighty-one patients were screened and enrolled, and 67 patients were eligible for the study. The numbers of patients across the PK analysis sets are summarized in Table 1.

Table 1. Pharmacokinetic Dataset and Patient Numbers

Analysis Set	Adults	Pediatric Patients 2 to <6 Years of Age	Pediatric Patients 6 to <12 Years of Age	Pediatric Patients 12 to <17 Years of Age	Overall
PK trough set for total IgG	49	3	9	6	67
PK trough set for IgG subclasses 1-4	49	0	9	6	64
Dense PK subset	46	0	5	6	57
Specific IgG trough PK set	48	0	0	6	54

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: IgG, immunoglobulin G; PK, pharmacokinetics.

PK Analyses:
The time-course of total IgG, IgG subclasses 1-4, and IgG specific antibody levels in adult patients (18 to <76 years of age) and pediatric patients (6 to <18 years of age for total IgG and IgG subclasses 1-4; 12 to <18 years of age for IgG-specific antibody levels) were analyzed by noncompartmental analysis. The population PK modeling approach was used for the PK analyses of pediatric patients (2 to <6 years of age) as only sparse samples (total IgG only) were collected.

The adjusted square of the correlation coefficient (R^2 adjusted) of the goodness of fit of the regression line through the data points was required to be ≥0.85 for the λz value of a given patient to be considered adequately reliable.

7.2   General Pharmacology and Pharmacokinetic Characteristics

7.2.1   Immunoglobulin G Trough Levels at Steady State

7.2.1.1   Total Immunoglobulin G

The mean total IgG trough levels at steady state following administration of BT595 were comparable with patients' baseline total IgG levels. At steady state, the mean (SD) trough concentrations for BT595 (Q3W: 10.03 [2.28] g/L; Q4W: 8.63 [3.50] g/L) were similar to those for the previous IVIG reference therapy (Q3W: 10.26 [2.72] g/L; Q4W: 7.82 [2.77] g/L), as shown in Table 2. The mean trough levels remained constant after the 7th infusion of the Q3W schedule (Week 18) or after the 5th infusion of the Q4W schedule (Week 16). The trough levels did not differ notably between BT595 and patients' previous IVIG reference therapy in different age groups (Table 2 and Figure 1, Figure 2, and Figure 3).

The mean total IgG trough levels at steady state were above the targeted minimal trough level of 5 g/L. During the study, 10 patients required a dose adjustment (increase) due to low IgG levels (including seven patients in whom the levels went below the target trough level of <5 g/L). Five patients, all in the Q4W schedule group, had total IgG trough levels <5 g/L at baseline, including 4 patients treated in Russia (site 0704) with very low baseline levels of 3.76 g/L, 3.52 g/L, 0.90 g/L and 0.58 g/L each. Patients (b) (6) had dose increase at infusion 2 and/or 3. The observed trough levels were either within (b) (6) or very close to (b) (6) the steady state trough range (infusions 6 to 14). Patient (b) (6) was withdrawn due to personal reason after infusion 5. Only the observed Cmax and Tmax were included for PK analysis. This patient was not included for the analysis of Vss, CLss, AUCtau, and half-life. Based on the protocol and observed values, the 5 patients are acceptable to be included in the pk datasets.

Additionally, two patients required dose adjustment (increase) due to infections, and one patient required a dose reduction due to an adverse reaction (worsening of fatigue).

Table 2. Summary of Steady State Trough Concentrations for Total IgG [g/L] by Treatment Schedule and Age Category

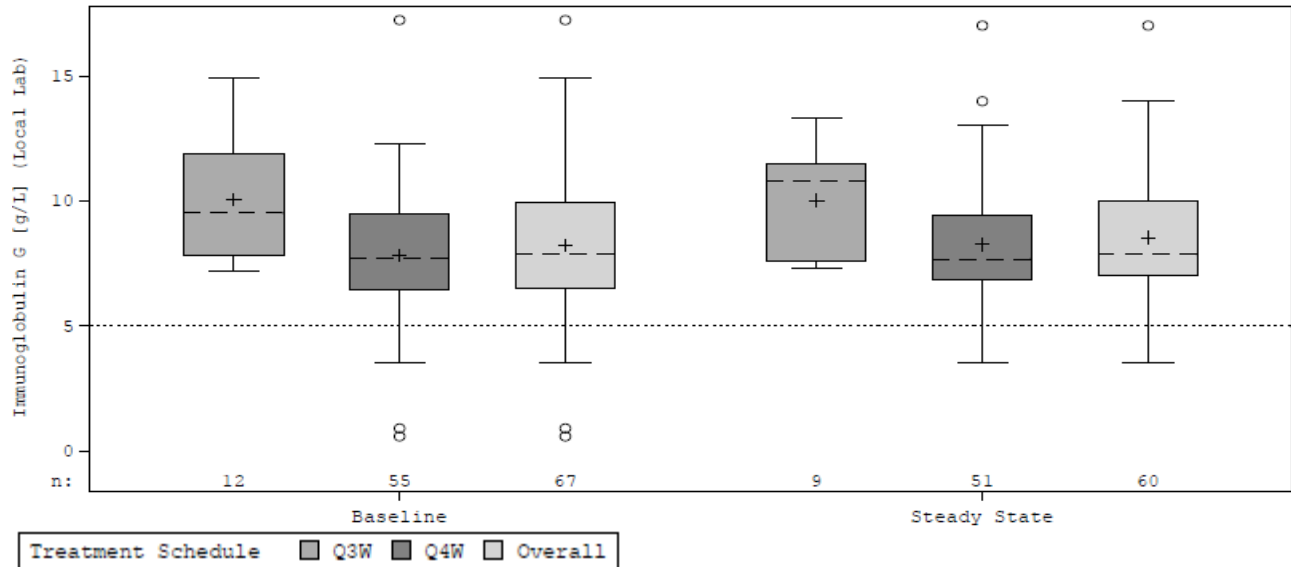| Years of Age	Q3W, n[a]	Q3W, Mean (g/L)	Q3W, SD	Q4W, n[a]	Q4W, Mean (g/L)	Q4W, SD
Baseline	11	10.26	2.72	55	7.82	2.77
Overall, SS[b]	9	10.03	2.28	52	8.63	3.50
Adults (17 to <76)	6	10.65	2.18	39	8.51	3.97
12 to <17	1	11.47	-	5	9.03	1.63
6 to <12	2	7.46	0.18	6	8.53	1.15
2 to <6				2	10.39	0.72

Source: Reviewer's analysis
a. Number of observations contributing to statistic.
b. Steady state before the 7th infusion of the Q3W schedule (Week 18) or the 5th infusion of the Q4W schedule (Week 16).
Abbreviations: g, grams; IgG, immunoglobulin G; L, liter; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks; SD, standard deviation.
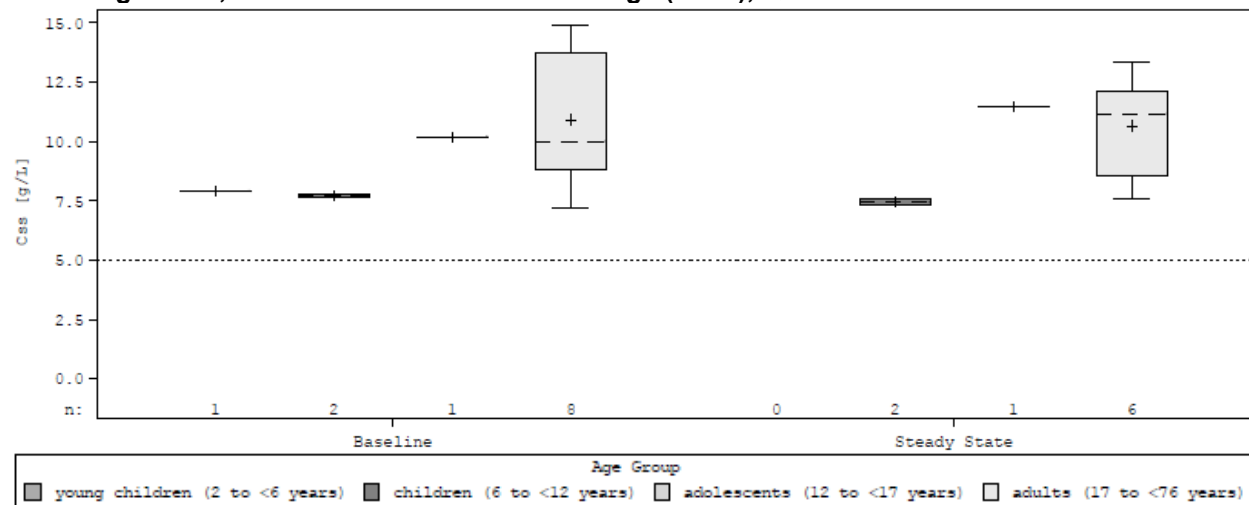
Figure 1. Trough Levels of Total IgG (Box Plots) at Steady State for BT595 and Previous Immunoglobulin, All Patients, N=67, Age 2 to <76 Years of Age

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: g, grams; L, liter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks
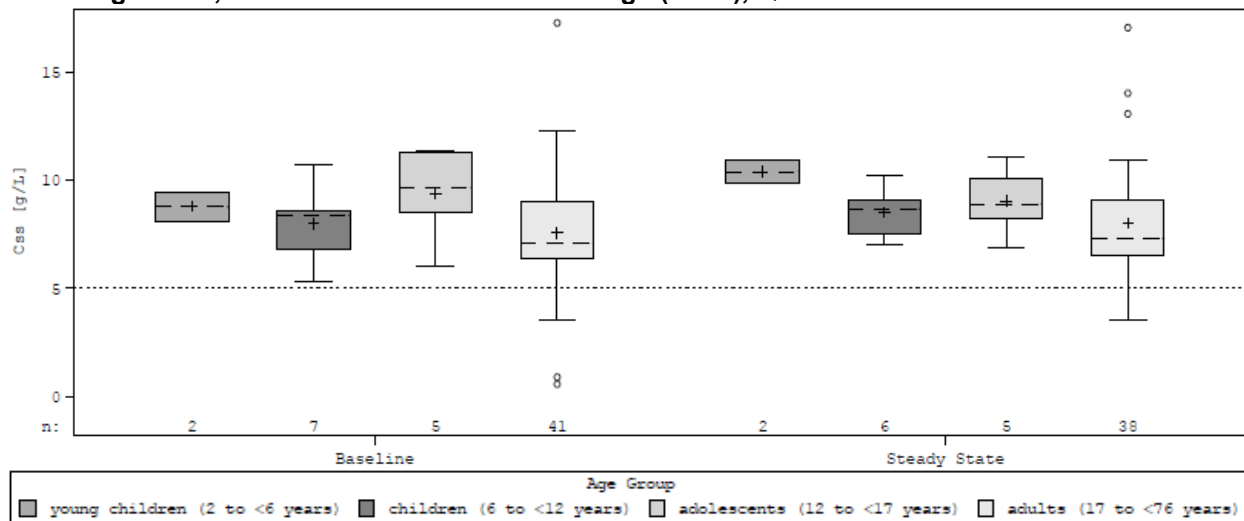
Figure 2. Trough Levels of Total IgG (Box Plots) at Steady State for BT595 and Previous Immunoglobulin, All Patients 2 to <76 Years of Age (N=12), Q3W Schedule

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: Css, steady state concentration; g, grams; L, liter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks

Figure 3. Trough Levels of Total IgG (Box Plots) at Steady State for BT595 and Previous Immunoglobulin, All Patients 2 to <76 Years of Age (N=55), Q4W Schedule
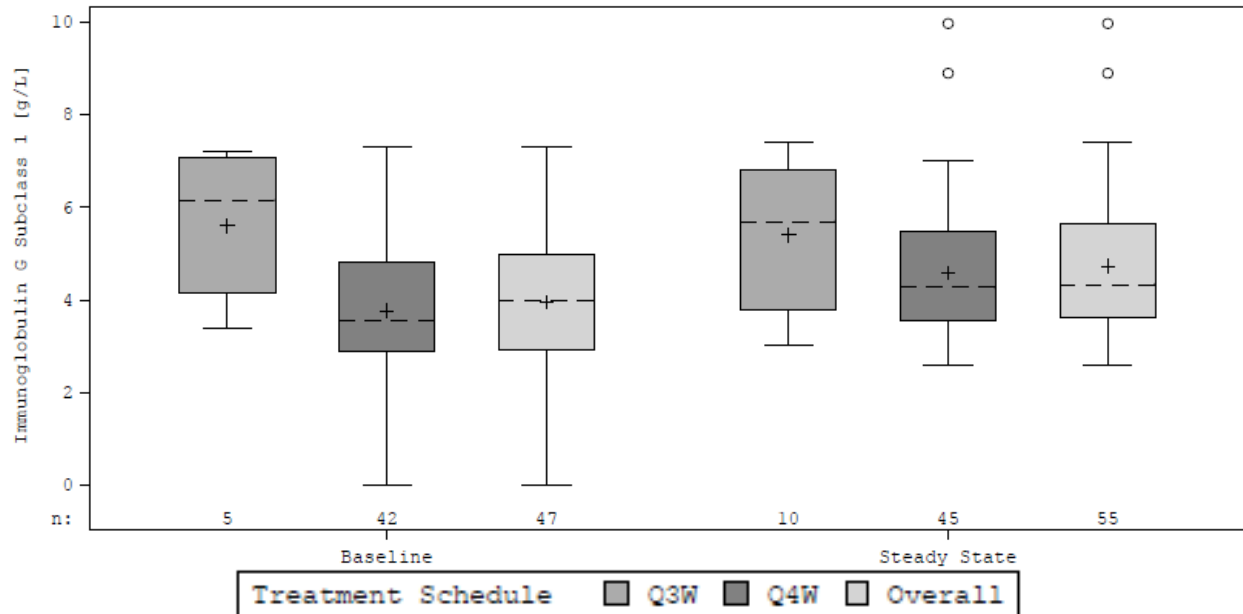

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: Css, steady state concentration; g, grams; L, liter; N, number of patients in specified population; n, number of observations contributing to statistic; Q4W, every 4 weeks

7.2.1.2 Immunoglobulin G Subclasses 1-4

The steady state trough levels for IgG subclasses 1-4 followed the same pattern as observed for total IgG. The trough levels of IgG subclasses 1-4 at steady state did not differ notably between BT595 and patients' previous IVIG reference therapy in different dosing regimens and age groups, as shown by box plot presentations of the data from 64 patients in the Q3W and Q4W schedule groups (Figure 4, Figure 5, Figure 6, and Figure 7). No obvious differences of the steady state IgG subclass trough levels between BT595 and patients' previous IVIG reference therapy were observed in the different age groups (Table 3). There were no obvious differences in the relative percentage of IgG subclasses 1-4 in trough levels between baseline and BT595 steady state for all patients ≥6 years of age in either treatment schedule. Overall, IgG subclasses 1 and 2 were the most abundant (accounting for >50% and >30% of the total IgG sample, respectively), whereas IgG subclasses 3 and 4 each accounted for <5% of the total IgG.
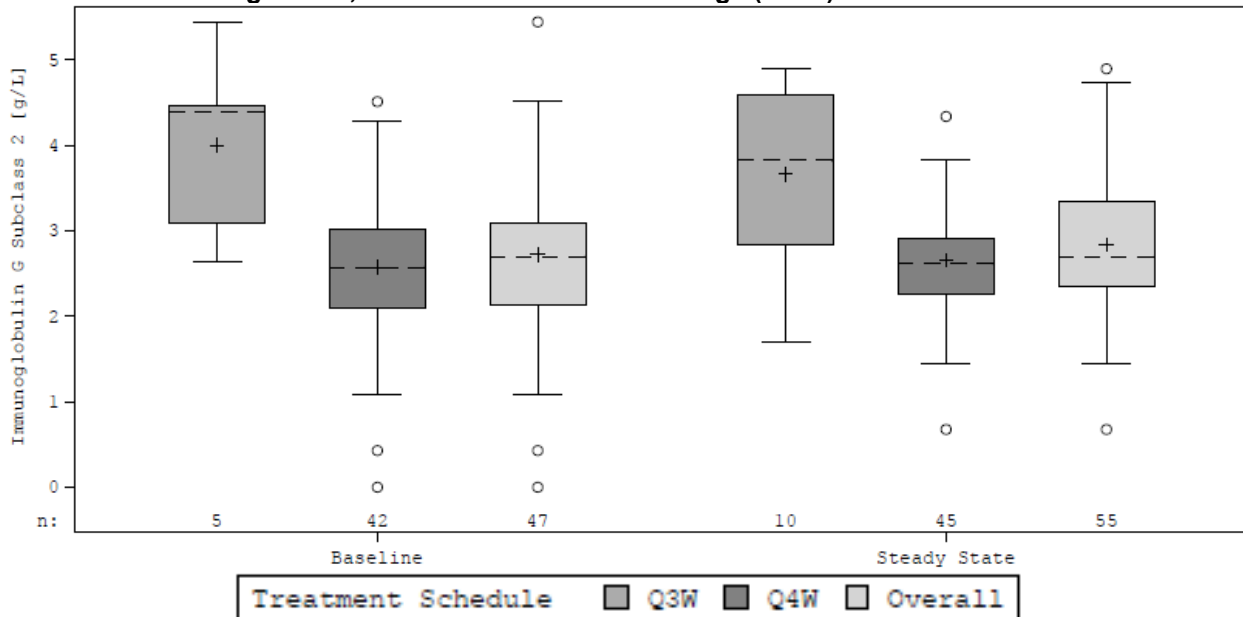
Figure 4. Trough Levels of IgG Subclasses 1 (Box Plots) at Steady State for BT595 and Previous Reference Immunoglobulin, Patients 6 to <76 Years of Age (N=64)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: g, grams; IgG, immunoglobulin G; L, liter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks

Figure 5. Trough Levels of IgG Subclass 2 (Box Plots) at Steady State for BT595 and Previous Reference Immunoglobulin, Patients 6 to <76 Years of Age (N=64)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: g, grams; IgG, immunoglobulin G; L, liter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks

Figure 6. Trough Levels of IgG Subclass 3 (Box Plots) at Steady State for BT595 and Previous Reference Immunoglobulin, Patients 6 to <76 Years of Age (N=64)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: g, grams; IgG, immunoglobulin G; L, liter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks
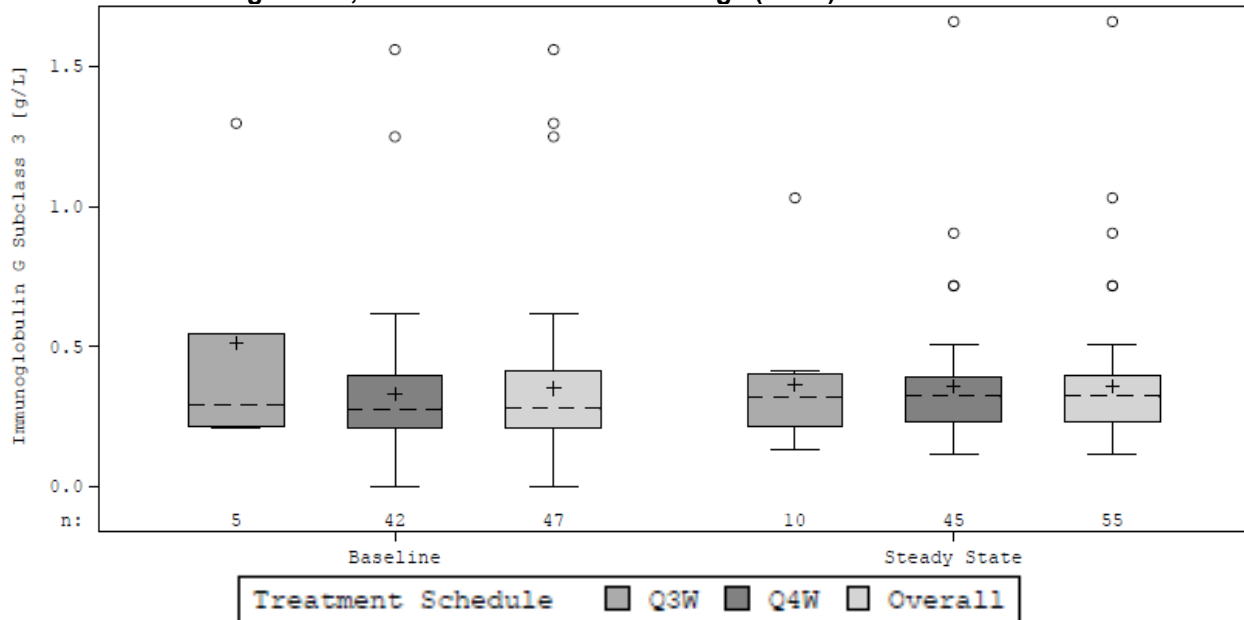
Figure 7. Trough Levels of IgG Subclass 4 (Box Plots) at Steady State for BT595 and Previous Reference Immunoglobulin, Patients 6 to <76 Years of Age (N=64)

Source: Applicant. Module 5. Study 991 Clinical Study Report.
Abbreviations: g, grams; IgG, immunoglobulin G; L, liter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks
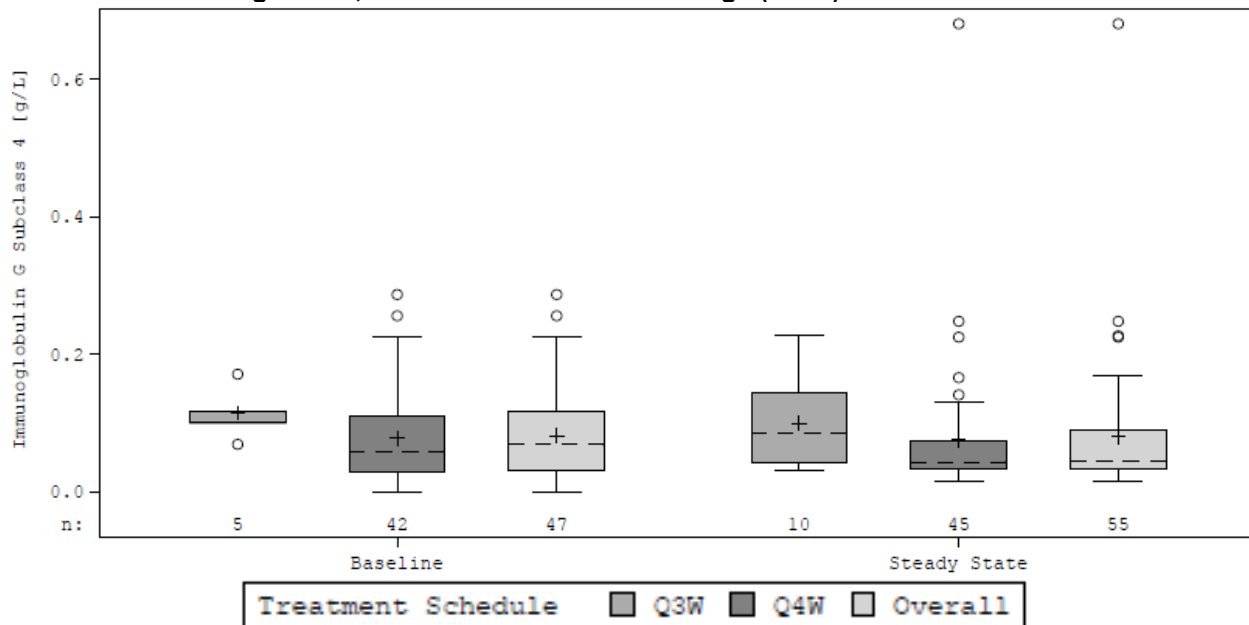
Table 3. Summary of Trough PK Concentrations for IgG Subclasses by Treatment Schedule and Age Category

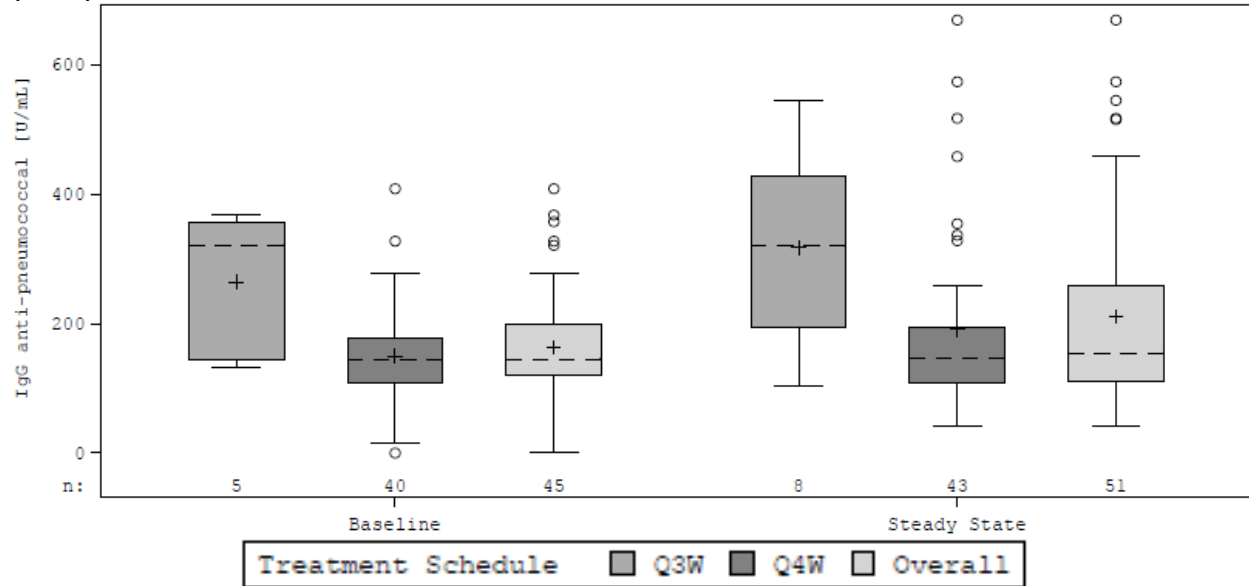| Years of Age, Dosing Schedule	n	IgG1, Mean (SD), g/L	IgG2, Mean (SD), g/L	IgG3, Mean (SD), g/L	IgG4, Mean (SD), g/L
Overall, 6 to <76	–				
Q3W, baseline	5	5.60 (1.73)	4.00 (1.14)	0.51 (0.46)	0.11 (0.04)
Q3W, infusion	10	5.41 (1.60)	3.66 (1.09)	0.36 (0.25)	0.10 (0.06)
Q4W, baseline	42	3.85 (1.38)	2.63 (0.84)	0.34 (0.28)	0.08 (0.07)
Q4W, infusion	45	4.58 (1.54)	2.66 (0.66)	0.36 (0.25)	0.08 (0.11)
6 to <12	–	–	–	–	–
Q3W, baseline	0	–	–	–	–
Q3W, infusion	2	3.78 (0.00)	2.83 (0.02)	0.14 (0.00)	0.03 (0.00)
Q4W, baseline	2	3.32 (1.14)	2.34 (0.30)	0.25 (0.16)	0.04 (0.01)
Q4W, infusion	2	4.31 (0.47)	3.15 (0.44)	0.53 (0.27)	0.03 (0.02)
12 to <17	–	–	–	–	–
Q3W, baseline	0	–	–	–	–
Q3W, infusion	1	6.44 (--)	4.37 (--)	0.41 (--)	0.11 (--)
Q4W, baseline	4	5.44 (1.69)	3.10 (0.68)	0.46 (0.09)	0.16 (0.07)
Q4W, infusion	4	4.59 (0.92)	2.69 (0.62)	0.39 (0.02)	0.12 (0.09)
Adults, 17 to <76 years	–	–	–	–	–
Q3W, baseline	5	5.60 (1.73)	4.00 (1.14)	0.51 (0.46)	0.11 (0.04)
Q3W, infusion	7	5.72 (1.62)	3.80 (1.20)	0.42 (0.27)	0.12 (0.07)
Q4W, baseline	36	3.61 (1.39)	2.53 (0.96)	0.32 (0.30)	0.07 (0.06)
Q4W, infusion	39	4.60 (1.63)	2.63 (0.68)	0.35 (0.27)	0.07 (0.11)

Source: Reviewer's analysis

Abbreviations: g, grams; IgG, immunoglobulin G; L, liter; n, number of observations contributing to statistic; PK, pharmacokinetics; Q3W, every 3 weeks; Q4W, every 4 weeks; SD, standard deviation

7.2.1.3   Antigen-Specific Immunoglobulins

The trough levels of the six analyzed antigen-specific IgGs at steady state did not differ notably between BT595 and patients' previous IVIG reference therapy, as shown by box plot presentations of the available data from patients aged ≥12 years (Figure 8, Figure 9, Figure 10, Figure 11, Figure 12, and Figure 13). No obvious differences of the steady state trough levels of the six analyzed antigen-specific IgGs between BT595 and patients' previous IVIG reference therapy were noted in the different age groups (Table 4).
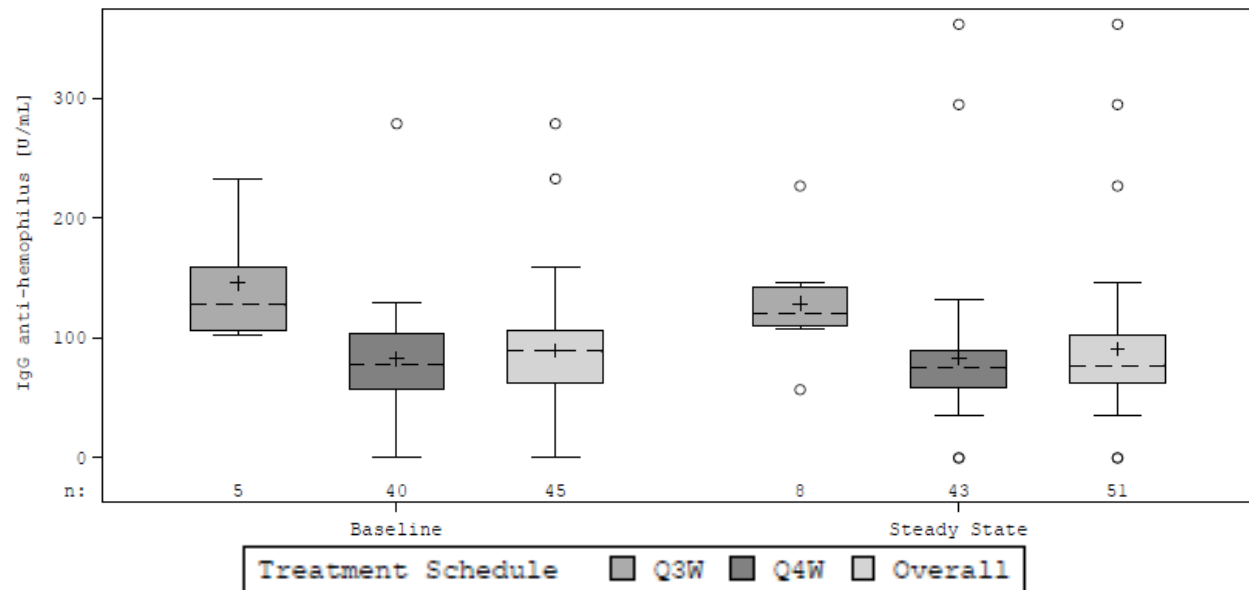
Figure 8. Trough Levels of Anti-Pneumococcal Capsular Polysaccharide IgG at Steady State (Box Plots) for BT595 and the Previous Reference Immunoglobulin, Patients 12 to <76 Years of Age (N=54)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: IgG, immunoglobulin G; mL, milliliter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks; U, units.

Figure 9. Trough Levels of the Anti-Haemophilus Influenzae Type B IgG at Steady State (Box Plots) for BT595 and Previous Reference Immunoglobulin, Patients 12 to <76 Years of Age (N=54)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: IgG, immunoglobulin G; mL, milliliter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks; U, units.

Figure 10. Trough Levels of Anti-Measles IgG at Steady State (Box Plots) for BT595 and Previous Reference Immunoglobulin, Patients 12 to <76 Years of Age (N=54)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: IgG, immunoglobulin G; mL, milliliter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks; U, units.
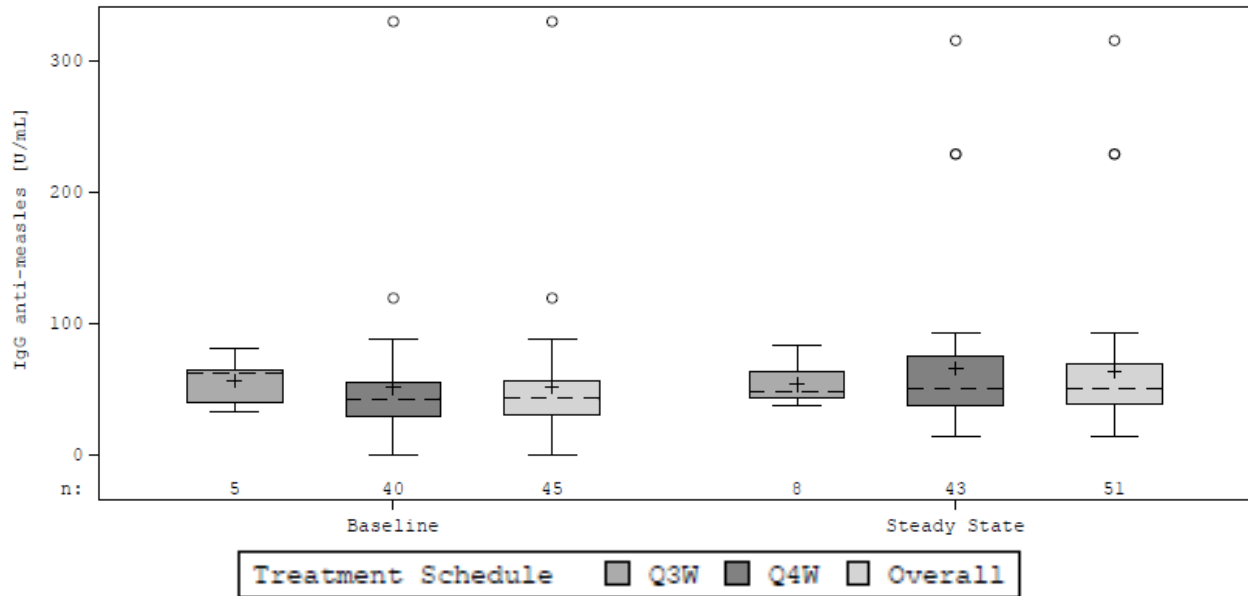
Figure 11. Trough Levels of Anti-Tetanus IgG at Steady State (Box Plots) for BT595 and Previous Reference Immunoglobulin, Patients 12 to <76 Years of Age (N=54)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: IgG, immunoglobulin G; mL, milliliter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks; U, units.

Figure 12. Trough Levels of Anti-Cytomegalovirus IgG at Steady State (Box Plots) for BT595 and Previous Reference Immunoglobulin, Patients 12 to <76 Years of Age (N=54)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: IgG, immunoglobulin G; mL, milliliter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks; U, units.
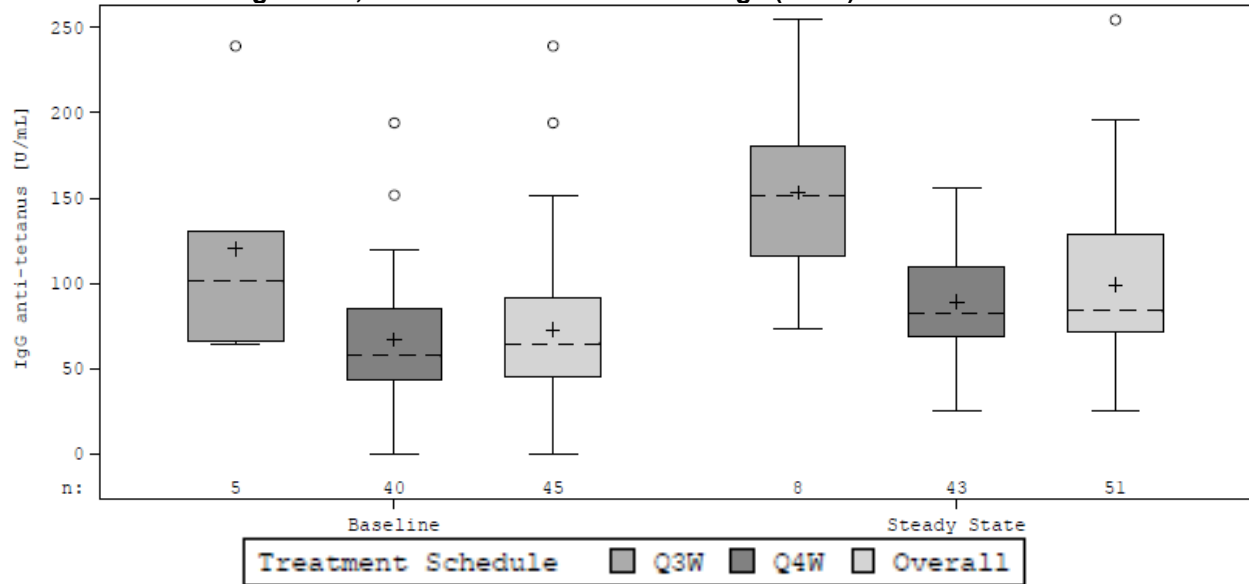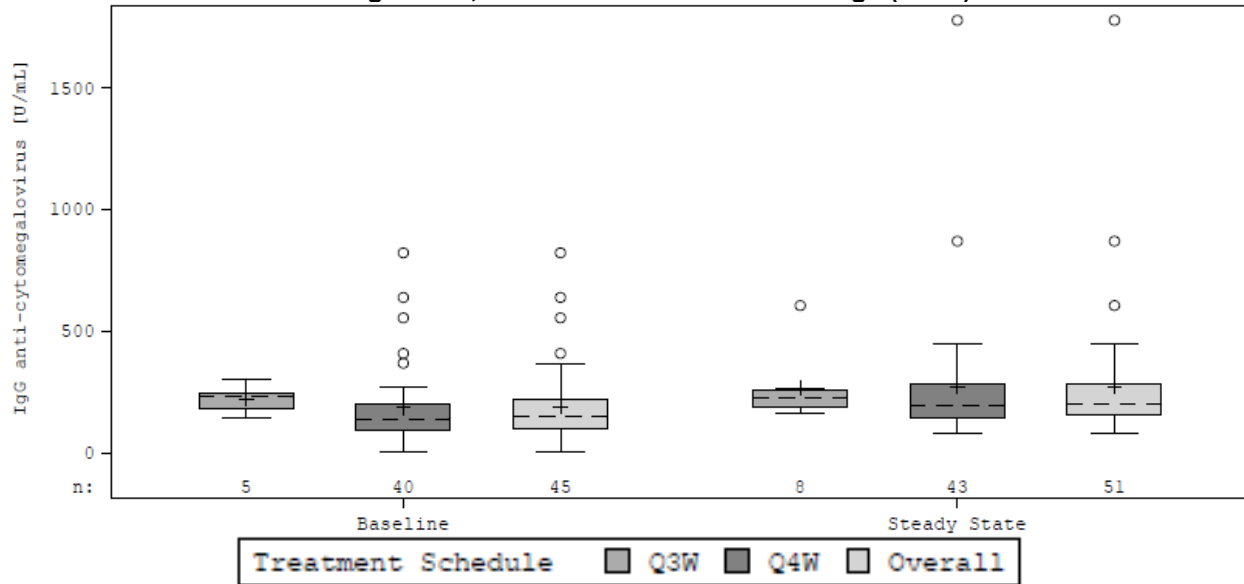
Figure 13. Trough Levels of Anti-HBs/Hepatitis B IgG at Steady State (Box Plots) for BT595 and Previous Reference Immunoglobulin, Patients 12 to <76 Years of Age (N=54)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: anti-HBs, hepatitis B antibody; IgG, immunoglobulin G; IU, international unit; L, liter; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks.
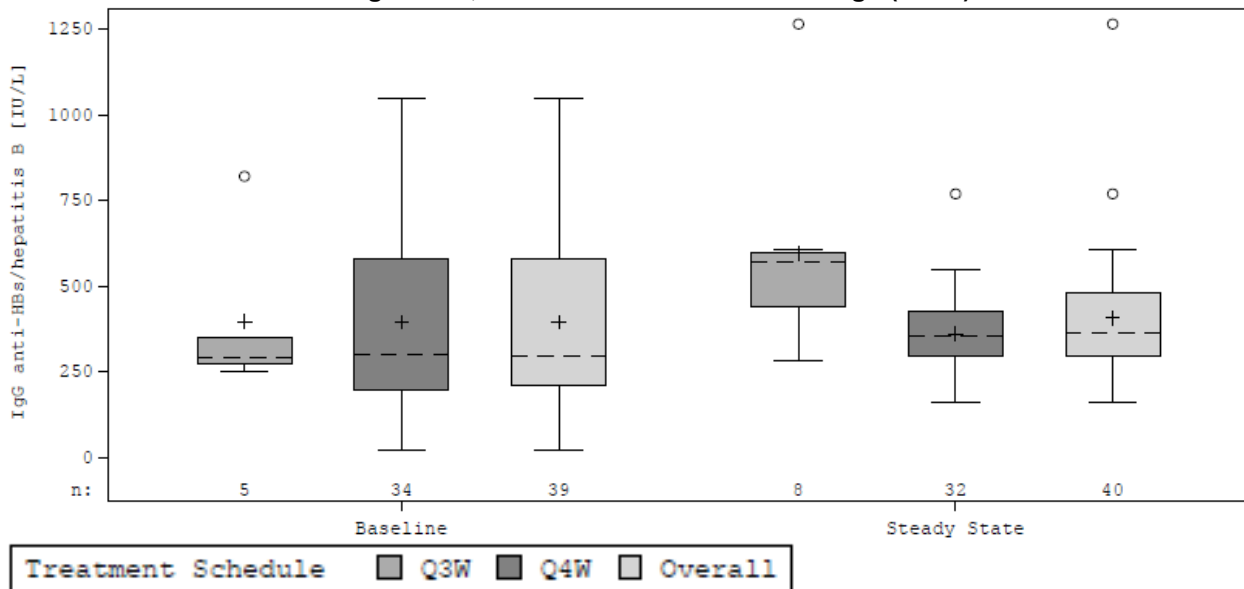
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Table 4. Summary of Trough PK Concentrations for Antigen-Specific IgG by Treatment Schedule and Age Category

Antigen-Specific IgG	Previous IVIG (Baseline), Q3W Schedule, Mean (SD), U/mL	BT595 (Steady State), Q3W Schedule, Mean (SD), U/mL	Previous IVIG (Baseline), Q4W Schedule, Mean (SD), U/mL	BT595 (Steady State), Q4W Schedule, Mean (SD), U/mL
Overall population, 12 to <76 years of age (n)	5	8	34-40	32-43
Anti-pneumococcal	264.8 (116.8)	317.7 (154.4)	150.3 (81.2)	191.0 (137.7)
Anti-HiB	145.8 (53.7)	128.9 (47.9)	82.7 (45.1)	83.7 (60.5)
Anti-measles	56.4 (19.6)	53.9 (15.5)	51.5 (50.5)	66.1 (57.9)
Anti-tetanus	120.3 (71.8)	153.2 (55.6)	67.2 (36.9)	89.2 (32.4)
Anti-CMV	222.8 (60.0)	267.5 (141.8)	186.9 (166.9)	272.8 (272.6)
Anti HBs/ Hepatitis B	395.7 (240.3)	596.0 (293.5)	395.5 (282.3)	359.7 (119.7)
Pediatric patients, 12 to <17 years of age (n)	0	1	4-5	4
Anti-pneumococcal		545.4	186.4 (58.0)	176.9 (23.1)
Anti-HiB		108.0	136.5 (95.8)	129.5 (110.53)
Anti-measles		60.4	45.1 (4.2)	46.5 (21.9)
Anti-tetanus		150.7	67.9 (29.9)	72.5 (15.0)
Anti-CMV		607.2	115.0 (54.2)	120.9 (27.0)
Anti HBs/ Hepatitis B		606.3	414.0 (270.4)	309.3 (55.7)
Adult patients, 17 to <76 years of age (n)	5	7	29-36	28-39
Anti-pneumococcal	264.8 (116.8)	285.1 (133.9)	146.3 (83.1)	192.4 (144.5)
Anti-HiB	145.8 (53.7)	131.9 (50.9)	76.7 (33.4)	79.0 (53.3)
Anti-measles	56.4 (19.6)	53.0 (16.5)	52.2 (53.2)	68.1 (60.2)
Anti-tetanus	120.3 (71.8)	153.6 (60.0)	67.1 (38.0)	91.0 (33.3)
Anti-CMV	222.8 (60.0)	219.0 (38.5)	194.8 (173.6)	288.4 (281.8)
Anti HBs/ Hepatitis B	395.7 (240.3)	594.5 (317.0)	392.3 (288.8)	366.9 (125.2)

Source: Reviewer's analysis

Abbreviations: anti-CMV, cytomegalovirus antibody; anti-HBs, hepatitis B antibody; anti-HiB, haemophilus influenzae antibody; n, number of patients in a specified category; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; mL, milliliter; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks; SD, standard deviation; U, unit.

7.2.2 Pharmacokinetic Profile and Parameters of BT595 at Steady State

7.2.2.1 Total Immunoglobulin G

The PK profile of total IgG at steady state showed that mean total IgG concentrations remained above 5 g/L at all time points assessed in both dosing schedules (Figure 14). The concentrations were lower in the Q4W schedule group compared to Q3W schedule group at all time points assessed. The mean (SD) concentrations in the Q4W schedule group (N=47) increased from 10.8 (3.96) g/L pre-dose to 24.7 (6.74) g/L at the end of

infusion and showed no additional increase 4 hours after the infusion with 24.4 (6.06) g/L. In the Q3W schedule group (N=10), mean (SD) concentrations increased from 12.6 (4.13) g/L pre-dose to 28.4 (7.37) g/L at the end of infusion and peaked 4 hours after the infusion with 29.1 (8.58) g/L.

The mean total IgG concentrations at steady state also remained above 5 g/L for each of the different age categories (6 to <12 years of age, 12 to <17 years of age, and 17 to <76 years of age) in both dosing schedule groups (Figure 15). In the Q3W schedule group, the number of patients in the pediatric subgroups (N=2) was too small for any further meaningful conclusions. In the Q4W schedule group, the concentration versus time profiles revealed no obvious differences between the subgroups of adults and adolescent patients. In both adolescent and adult subgroups, mean (SD) concentrations peaked 4 hours after the infusion.

Table 5. Summary of Trough Total IgG Concentrations Before Each Infusion

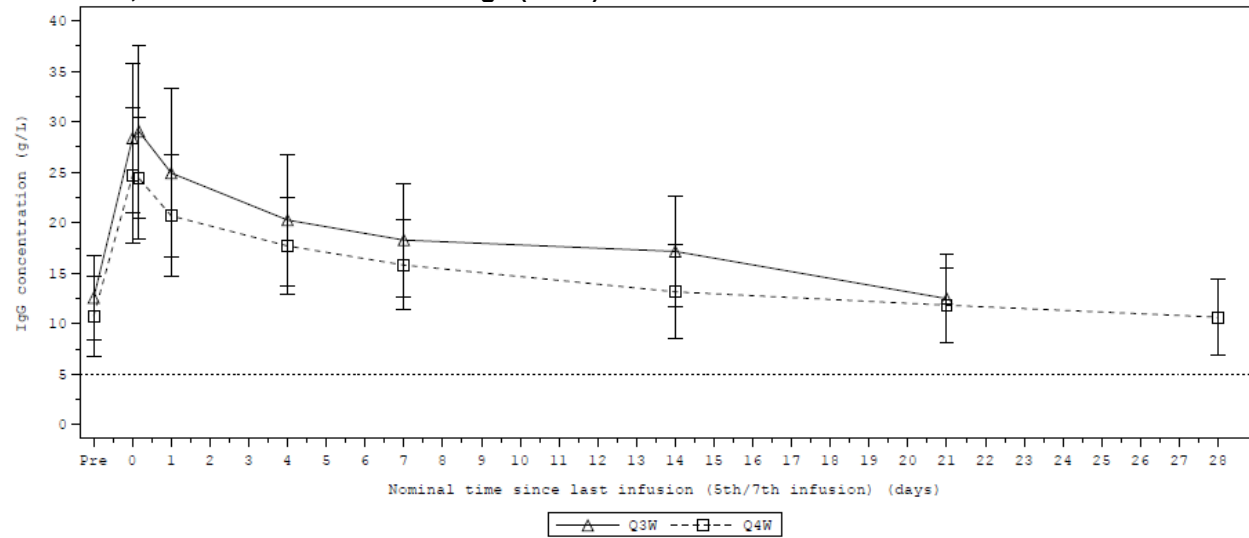| Infusion Number	Q3W, N[a]	Q3W Mean (g/L)	Q3W, SD	Q4W, N[a]	Q4W Mean (g/L)	Q4W, SD
1	11	10.26	2.72	55	7.82	2.77
2	11	10.42	2.95	50	8.28	2.59
3	11	10.51	2.99	51	8.25	2.40
4	11	10.05	3.02	51	8.41	2.30
5	11	10.27	3.24	52	8.63	3.50
6	11	10.03	3.21	51	8.20	2.29
7	9	10.03	2.28	52	8.30	2.38
8	10	10.27	2.77	50	8.31	2.11
9	10	9.89	2.18	52	8.41	2.24
10	10	10.34	2.23	52	8.26	2.30
11	10	10.19	2.70	51	8.18	2.17
12	10	10.43	2.73	52	8.34	2.09
13	9	10.09	2.63	49	8.48	2.36
14	10	10.25	2.44	48	8.44	2.17
15	10	10.54	2.25			
16	10	10.05	2.71			
17	10	9.88	2.02			
18	9	10.41	2.49			

Source: Reviewer's analysis
a. Number of patients with data available
Abbreviations: g, grams; L, liter; Q3W, every 3 weeks; Q4W, every 4 weeks; SD, standard deviation

The PK parameters of children (6 to <12 years of age) and adolescents (12 to <17 of age) are similar to those in adults (see Table 6). The Cmax was higher in the Q3W than in the Q4W schedule group while the AUC over the dosing interval (AUCtau) was lower in the Q3W schedule group due to the 7-day shorter dosing interval. Since the adult patients received slightly higher doses of BT595 than the pediatric patients, the absolute values for Cmax and AUCtau were higher in the subgroup of adults than in the pediatric subgroup, both in the Q3W schedule group and in the Q4W schedule group. The mean (SD) t1/2 was 24.2 (5.90) days in the Q3W schedule group and 31.1 (12.90) days in the Q4W schedule group. Values for individual patients varied widely and ranged from 15.5 to 29.5 days in the Q3W schedule group and from 17.8 to 70.4 days in the Q4W schedule group across all age groups.

Figure 14. Concentration Versus Time Profiles for Total IgG at Steady State by Treatment Schedule, Patients 6 to 76 Years of Age (N=57)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: IgG, immunoglobulin G; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks; Q4W, every 4 weeks.

Figure 15. Concentration Versus Time Profiles for Total IgG at Steady State by Age Group, Q3W Schedule, Patients 6 to <76 Years of Age (N=10)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: IgG, immunoglobulin G; N, number of patients in specified population; n, number of observations contributing to statistic; Q3W, every 3 weeks

Figure 16. Concentration Versus Time Profiles for Total IgG at Steady State by Age Group, Q4W Schedule, Patients 6 to <76 Years of Age (N=47)
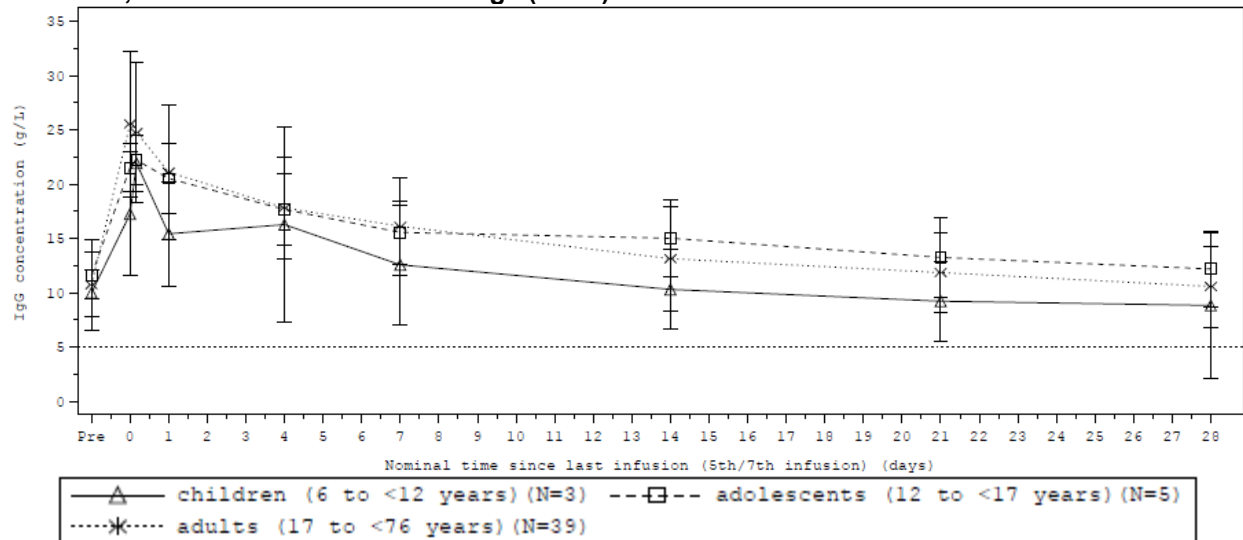

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: IgG, immunoglobulin G; N, number of patients in specified population; n, number of observations contributing to statistic; Q4W, every 4 weeks

Table 6. Key PK Parameters for Total IgG at Steady State After Infusion of BT595, Dense PK Subset, Overall and by Age Group (N=57)

Years of Age, PK Parameter	Q3W Schedule, Subset, N=10	Q3W Schedule	Q4W Schedule, Subset, N=47	Q4W Schedule,
Cmax (g/L), mean (SD)				
Overall	10	29.98 (7.65)	45	26.54 (6.08)
Adults (17 to <76)	7	32.26 (6.28)	39	27.11 (6.31)
Adolescents (12 to <17)	1	34.80	4	22.22 (2.32)
Children (6 to <12)	2	19.61 (3.87)	2	24.67 (1.23)
Tmax (day), median (range)				
Overall	10	0.22 (0.06-0.28)	45	0.20 (0.06-7.03)
Adults (17 to <76)	7	0.21 (0.06-0.27)	39	0.19 (0.06-7.03)
Adolescents (12 to <17)	1	0.28	4	0.23 (0.17-0.25)
Children (6 to <12)	2	0.19 (0.11-0.27)	2	2.24 (0.26-4.23)
AUCtau (day*g/L), mean (SD)				
Overall	10	374.33 (110.69)	42	398.51 (99.27)
Adults (17 to <76)	7	398.42 (99.04)	36	397.03 (103.56)
Adolescents (12 to <17)	1	476.98	4	415.09 (94.87)
Children (6 to <12)	2	238.71 (5.90)	2	392.11 (19.66)
CLss (mL/day/kg), mean (SD)				
Overall	10	1.49 (0.40)	42	1.22 (0.47)

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Years of Age, PK Parameter	Q3W Schedule, Subset, N=10	Q3W Schedule	Q4W Schedule, Subset, N=47	Q4W Schedule,
Adults (17 to <76)	7	1.38 (0.32)	36	1.27 (0.48)
Adolescents (12 to <17)	1	1.23	4	0.91 (0.26)
Children (6 to <12)	2	2.02 (0.32)	2	0.98 (0.14)
t1/2 (day), mean (SD)				
Overall	7	24.15 (5.90)	25	31.13 (12.90)
Adults (17 to <76)	5	24.81 (5.10)	22	29.88 (12.44)
Adolescents (12 to <17)	1	15.52	2	31.72 (2.98)
Children (6 to <12)	1	29.46	1	57.53

Source: Reviewer's analysis
Abbreviations: AUCtau, area under the curve over the dosing interval; Cmax, maximum concentration; CLss, clearance at steady state; t1/2, terminal elimination half-life; g, grams; IgG, immunoglobulin G; L, liter; N, number of patients in specified population; PK, pharmacokinetics; Q3W, every 3 weeks; Q4W, every 4 weeks; SD, standard deviation

7.2.2.2   Immunoglobulin G Subclasses 1-4

The steady state trough levels for IgG subclasses 1-4 followed the same pattern as observed for total IgG. The steady state concentration-time profiles were similar across the four subclasses and corresponded to those for total IgG. Likewise, the patterns in Cmax and AUCtau profiles were similar to that of total IgG across the four subclasses. Consistent with the total IgG data, the mean concentrations subclasses 1-4 were lower in the Q4W schedule group than in the Q3W schedule group for all four subclasses and at all time points assessed. Similar peaks as for total IgG were measured at the end of infusion and 4 hours post-infusion.

Table 7. Key PK Parameters for IgG Subclasses 1-4 at Steady State After Infusion of BT595, Dense PK Subset, Overall and by Age Group (N=57)

PK Parameter	Q3W Schedule, Subset, N=10	Q3W Schedule, Mean (SD)	Q4W Schedule, Subset, N=47	Q4W Schedule, Mean (SD)
Cmax (g/L)				
IgG1	10	12.9 (3.5)	45	10.8 (2.5)
IgG2	10	7.3 (1.78)	45	5.7 (1.3)
IgG3	10	1.1 (0.4)	45	0.9 (0.2)
IgG4	10	0.3 (0.1)	45	0.2 (0.1)
Tmax (day), median (range)				
IgG1	10	0.15 (0.08-0.27)	45	0.18 (0.05-1.11)
IgG2	10	0.25 (0.09-1.08)	45	0.11 (0.06-4.01)
IgG3	10	0.18 (0.08-1.09)	45	0.11 (0.00-21.3)
IgG4	10	0.13 (0.08-0.27)	45	0.10 (0.05-6.86)
AUCtau (day*g/L)				
IgG1	10	161.1 (43.2)	42	167.6 (39.5)
IgG2	10	103.0 (25.8)	42	100.0 (20.0)
IgG3	10	11.0 (4.4)	41	12.2 (4.1)
IgG4	10	3.0 (1.5)	41	2.6 (1.3)
t1/2 (day)				
IgG1	8	26.64 (7.29)	31	30.92 (11.48)
IgG2	8	35.28 (11.84)	36	46.84 (35.55)
IgG3	9	26.34 (13.17)	19	29.20 (11.29)

PK Parameter	Q3W Schedule, Subset, N=10	Q3W Schedule, Mean (SD)	Q4W Schedule, Subset, N=47	Q4W Schedule, Mean (SD)
IgG4	8	26.01 (15.37)	36	44.42 (71.51)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: AUCtau, area under the curve over the dosing interval; Cmax, maximum concentration; CLss, clearance at steady state; g, grams; IgG, immunoglobulin G; L, liter; N, number of patients in specified population; PK, pharmacokinetics; Q3W, every 3 weeks; Q4W, every 4 weeks; SD, standard deviation; t1/2, terminal elimination half-life, Tmax, time to peak concentration

7.2.2.3   Antigen-Specific Immunoglobulin G

The steady state trough levels of the six analyzed antigen-specific IgGs and their concentration-time profiles generally followed the same pattern as observed for total IgG and IgG subclasses 1-4. Likewise, the pattern in Cmax was similar to that of total IgG and the IgG subclasses 1-4 (except for anti-measles, where it was higher in the Q4W than in the Q3W schedule group).

Table 8. Key PK Parameters for the Six Analyzed Antigen-Specific IgGs at Steady State After Infusion of BT595, Dense PK Subset, Patients 12 to <76 Years of Age (N=52)

Parameter	Q3W Schedule, Subset, N=8	Q3W Schedule,	Q4W Schedule, Subset, N=44	Q4W Schedule,
Cmax (U/mL; IU/L for anti-HBs/ hepatitis B), Mean (SD)				
Anti-pneumococcal CPS	8	541.1 (189.7)	43	426.1 (218.3)
Anti-HiB	8	296.4 (67.7)	43	222.2 (72.1)
Anti-measles	8	140.7 (34.8)	43	184.7 (99.3)
Anti-tetanus	8	398.0 (105.6)	43	266.4 (76.0)
Anti-CMV	8	743.7 (79.0)	43	738.3 (311.7)
Anti-HBs/hepatitis B	8	1821.2 (547.2)	32	1208.5 (331.8)
Tmax (day), Median (range)				
Anti-pneumococcal CPS	8	0.21 (0.09- 1.12)	43	0.21 (0.06- 20.2)
Anti-HiB	8	0.25 (0.06- 1.12)	43	0.11 (0.06- 14.1)
Anti-measles	8	0.22 (0.08- 1.08)	43	0.20 (0.05- 3.90)
Anti-tetanus	8	0.15 (0.06- 1.10)	43	0.12 (0.05- 0.27)
Anti-CMV	8	0.17 (0.06- 1.10)	43	0.10 (0.05- 21.0)
Anti-HBs/hepatitis B	8	0.18 (0.06- 0.28)	32	0.10 (0.05- 1.11)

Parameter	Q3W Schedule, Subset, N=8	Q3W Schedule,	Q4W Schedule, Subset, N=44	Q4W Schedule,
AUCtau (day*U/mL; day*IU/L for anti-HBs/hepatitis B), Mean (SD)				
Anti-pneumococcal CPS	8	7790 (3517)	39	7464 (4858)
Anti-HiB	8	3948 (1177)	39	3304 (1690)
Anti-measles	8	1643 (407)	40	2612 (2006)
Anti-tetanus	8	4816 (1504)	40	3865 (1134)
Anti-CMV	8	8171 (1838)	40	10600 (7976)
Anti-HBs/hepatitis B	8	20000 (6362)	30	16900 (5030)
T1/2 (day), Mean (SD)				
Anti-pneumococcal CPS	1		16	30.29 (14.385)
Anti-HiB	4	32.40 (10.298)	24	28.31 (9.356)
Anti-measles	4	21.37 (5.796)	17	22.10 (5.132)
Anti-tetanus	7	22.36 (6.315)	34	29.88 (10.572)
Anti-CMV	7	24.12 (9.953)	29	24.25 (8.286)
Anti-HBs/hepatitis B	6	18.60 (6.763)	29	23.94 (6.017)

Source: Applicant. Module 5. Study 991 Clinical Study Report
Abbreviations: anti-CMV, cytomegalovirus antibody; anti-HBs, hepatitis B antibody; anti-HiB, haemophilus influenzae antibody; AUCtau, area under the curve over the dosing interval; Cmax, maximum concentration; g, grams; IgG, immunoglobulin G; IU, international unit; L, liter; mL, milliliter; N, total number of patients in specified population; PK, pharmacokinetics; Q3W, every 3 weeks; Q4W, every 4 weeks; SD, standard deviation; t1/2, terminal elimination half-life; Tmax, time to peak concentration; U, unit.

7.2.3   Population Pharmacokinetic Modeling

The Applicant used a population PK approach to characterize the pharmacokinetics of BT595 total IgG in adults and pediatric patients 2 to 76 years of age. The population PK model was used to predict the PK parameters and exposure of total IgG in adults and children on the Q3W and Q4W dosing regimens. The potential effect of the intrinsic and extrinsic factors on total IgG PK were also assessed.

According to the population PK analysis, the AUCtau and Cmax for the young child (N=1) on a Q3W regimen were 291 day*g/L and 24.1g/L, respectively. For the two young children with a Q4W regimen, their AUCtau were 366 and 460 day*g/L, with corresponding Cmax values of 20.2 and 22.7 g/L. Additionally, based on the model predictions for the typical patients, it appears that only slightly greater concentrations were achieved with the Q3W regimen compared to the Q4W regimen. No relationship between PK parameters and age and sex were identified in the covariate analysis.

Table 9. Predicted PK Parameters for Total IgG in the Young Children Age Group

Dosing Schedule	Patient	Cmax (g/L)	Tmax (day)	Ctrough (g/L)	AUCtau (day*g/L)	CLss (L/day)
Q4W	(b) (6)	20.2	0.208	8.15	366	0.0144
Q4W	(b) (6)	22.7	0.233	11.7	460	0.0217
Q3W	(b) (6)	24.1	0.104	8.04	291	0.0275

Source: Reviewer's analysis
Abbreviations: AUCtau, area under the curve over the dosing interval; CLss, clearance at steady state; Cmax, maximum concentration; Ctrough, trough concentration; g, grams; IgG, immunoglobulin G; L, liter; PK, pharmacokinetics; Q3W, every 3 weeks; Q4W, every 4 weeks.

Per the pharmacometrics reviewer, the Applicant's population PK analysis is considered acceptable for the purpose of predicting the PK and exposure parameters of total IgG in adult and pediatric patients with PI. The final population PK model is adequate to characterize the PK profile of total IgG in patients with PI receiving IV BT595 in the Q3W and Q4W dosing schedules. The Applicant's analyses were verified by the pharmacometrics reviewer, with no significant discordance identified. However, the prediction of PK parameters of total IgG in children 2 to <6 years of age may carry some uncertainty due to the small sample size in this population group.