

BLA Clinical Review Memorandum

Application Type	BLA
STN	125683/0
CBER Received Date	July 9, 2018
PDUFA Goal Date	June 5, 2019
Division / Office	CBER/OTAT/GEN MED1
Priority Review (Yes/No)	No
Reviewer Name(s)	Deborah S. Belsky, MD MPH FAAFP
Review Completion Date / Stamped Date	
Supervisory Concurrence	Elizabeth Hart, MD Acting Team Leader, GMB1
	Rachel Witten, MD, Acting Branch Chief, GMB1
Applicant	Grifols Therapeutics LLC
Established Name	Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%)
(Proposed) Trade Name	XEMBIFY
Pharmacologic Class	Biologic
Formulation(s), including Adjuvants, etc.	Immune Globulin Subcutaneous (human), 20%
Dosage Form(s) and Route(s) of Administration	Sterile Solution, Subcutaneous
Dosing Regimen	Weekly SC Dosing Initial weekly SC dose in grams = current IGIV dose (0.3-0.8g/kg) x 1.37/Number of weeks between IGIV dose For IGSC, use same weekly IGSC dose

	Dose should be adjusted based on patient's serum IgG trough and clinical condition ○
Indication(s) and Intended Population(s)	Replacement therapy for Primary Humoral Immunodeficiency (PI) in adults and children ages 2 years and older.
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY 1

1. EXECUTIVE SUMMARY 1

 1.1 Demographic Information: Subgroup Demographics and Analysis Summary..... 4

 1.2 Patient Experience Data 4

2. CLINICAL AND REGULATORY BACKGROUND..... 5

 2.1 Disease or Health-Related Condition(s) Studied 5

 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)..... 6

 2.3 Safety and Efficacy of Pharmacologically Related Products 6

 2.4 Previous Human Experience with the Product (Including Foreign Experience) 7

 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 7

 2.6 Other Relevant Background Information..... 8

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES..... 8

 3.1 Submission Quality and Completeness 8

 3.2 Compliance With Good Clinical Practices And Submission Integrity 8

 3.3 Financial Disclosures 8

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES..... 9

 4.1 Chemistry, Manufacturing, and Controls 9

 4.2 Assay Validation..... 9

 4.3 Nonclinical Pharmacology/Toxicology 9

 4.4 Clinical Pharmacology..... 9

 4.4.1 Mechanism of Action 10

 4.4.2 Human Pharmacodynamics (PD)..... 10

 4.4.3 Human Pharmacokinetics (PK) 10

Clinical Review
BLA 1256830, XEMBIFY

4.5 Statistical.....	10
4.6 Pharmacovigilance.....	10
5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW	10
5.1 Review Strategy.....	10
5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review.....	11
5.3 Table of Studies/Clinical Trials.....	11
5.4 Consultations	12
5.4.1 Advisory Committee Meeting (if applicable).....	12
5.4.2 External Consults/Collaborations	12
5.5 Literature Reviewed (if applicable).....	13
6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS	13
6.1 Trial #1 (GT11502).....	13
6.1.1 Objectives (Primary, Secondary, etc.).....	13
6.1.2 Design Overview	14
6.1.3 Population.....	16
6.1.5 Directions for Use.....	17
6.1.6 Sites and Centers.....	18
6.1.7 Surveillance/Monitoring	18
6.1.8 Endpoints and Criteria for Study Success.....	19
6.1.9 Statistical Considerations & Statistical Analysis Plan	20
6.1.10 Study Population and Disposition.....	21
6.1.11 Efficacy Analyses	25
6.1.12 Safety Analyses.....	33
6.1.13 Study Summary and Conclusions	41
7. INTEGRATED OVERVIEW OF EFFICACY	46
7.1 Indication #1 Primary Immunodeficiency	46
8. INTEGRATED OVERVIEW OF SAFETY	46
8.1 Safety Assessment Methods	46
8.2 Safety Database.....	46
8.2.1 Studies/Clinical Trials Used to Evaluate Safety	46
8.2.2 Overall Exposure, Demographics of Pooled Safety Populations	Error! Bookmark not defined.
8.2.3 Categorization of Adverse Events.....	Error! Bookmark not defined.
8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials.....	Error! Bookmark not defined.
8.4 Safety Results	Error! Bookmark not defined.
8.4.1 Deaths	47
8.4.2 Nonfatal Serious Adverse Events.....	47
8.4.3 Study Dropouts/Discontinuations	48
8.4.4 Common Adverse Events.....	48
8.4.5 Clinical Test Results	48
8.4.6 Systemic Adverse Events.....	48
8.4.7 Local Reactogenicity	48
8.4.8 Adverse Events of Special Interest	48
8.5 Additional Safety Evaluations	48
8.5.1 Dose Dependency for Adverse Events	48
8.5.2 Time Dependency for Adverse Events	48
8.5.3 Product-Demographic Interactions.....	48
8.5.4 Product-Disease Interactions	48
8.5.5 Product-Product Interactions	48
8.5.6 Human Carcinogenicity	48

Clinical Review
BLA 1256830, XEMBIFY

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound	48
8.5.8 Immunogenicity (Safety).....	48
8.6 Safety Conclusions	49
<u>9. ADDITIONAL CLINICAL ISSUES</u>	<u>49</u>
9.1 Special Populations.....	49
9.1.1 Human Reproduction and Pregnancy Data.....	49
9.1.2 Use During Lactation	49
9.1.3 Pediatric Use and PREA Considerations	49
9.1.5 Geriatric Use.....	50
9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered	50
<u>10. CONCLUSIONS</u>	<u>50</u>
<u>11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS.....</u>	<u>50</u>
11.1 Risk-Benefit Considerations.....	50
11.2 Risk-Benefit Summary and Assessment.....	53
11.3 Discussion of Regulatory Options	53
11.4 Recommendations on Regulatory Actions.....	53
11.5 Labeling Review and Recommendations	53
11.6 Recommendations on Postmarketing Actions	53
Appendix 1: GT11503	54

GLOSSARY

AE	adverse event
AR	adverse reaction
AUC	Area under the curve
BLA	biologics license application
CI	confidence interval
CMC	Chemistry manufacturing and controls
CMV	cytomegalovirus
CSR	clinical study report
CVID	common variable immunodeficiency
DAF	Dose Adjustment Factor
DCF	dosing conversion factor
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
FSR	Final Study Report
GLSM	geometric least square means
IGIV	Immune Globulin Intravenous (Human)
IGIV-C	Gammunex-C
IGIV-C 10%	Gammunex-C 10%
IGSC	Immune Globulin Subcutaneous (Human)
IP	Investigational Product
IPSP	Initial Pediatric Study Plan
IV	Intravenous
PI	primary (humoral) immunodeficiency
PID	primary (humoral) immunodeficiency
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PopPK	predictive population pharmacokinetic
PP	per protocol
PREA	Pediatric Research Equity Act
PT	preferred term (MedDRA)
QoL	quality of life
SAE	serious adverse event
SAR	serious adverse reaction
SBI	serious bacterial infection
SC	subcutaneous
SOC	system organ class (MedDRA)
SS	safety analysis set
TEAE	treatment emergent adverse event
TEE	thromboembolic event
XLA	X-linked agammaglobulinemia

1. EXECUTIVE SUMMARY

Grifols submitted an original biologics license application (BLA) for their product, Immune Globulin Subcutaneous (Human) (IGSC), 20% Caprylate/Chromatography Purified, with the proposed proprietary name of XEMBIFY, intended as a replacement therapy for the treatment of primary humoral immunodeficiency (PI). In the U.S., there

are currently six licensed immunoglobulin products for SC administration for treatment of PI.

The primary evidence of safety and effectiveness in the BLA comes from study GTI1502, which was a multi-center, prospective, open label, single-arm, single-sequence study conducted in the U.S. and Canada. The primary objective was to assess bioequivalence of XEMBIFY to IGIV Gamunex-C 10% (IGIV-C 10%) and safety of XEMBIFY. The study also provided sufficient data on the annualized rate of serious bacterial infections (SBI) to assess efficacy. SBI were pre-specified to include bacteremia/sepsis, bacterial meningitis, bacterial pneumonia, osteomyelitis/septic arthritis, and visceral abscess.

Study GTI1502 consisted of a run-in phase, an IV phase and a SC phase. Prior to beginning the SC phase, all subjects had achieved steady-state on IGIV-C 10%. For the SC phase, all subjects were switched to XEMBIFY using an IV to SC dose adjustment factor (DAF) of 1.37 and were treated weekly with XEMBIFY for 24 weeks. No dose adjustments were made in this study after determination of the initial SC dose.

A total of 53 subjects were enrolled in the study; 49 subjects participated in the SC phase of the study, and 41 subjects had evaluable PK data. Of the 49 subjects who received XEMBIFY, seven subjects discontinued the SC phase; four subjects withdrew due to adverse events; one subject refused blood samples and was withdrawn; and two subjects withdrew by own request. One additional subject participated in the study but did not have evaluable PK data. Therefore, only 41 subjects in the SC phase had adequate PK data and were considered valid for PK analysis. The PK population consisted of all subjects who received study drugs and had sufficient and valid total IgG concentration vs. time data for either the IV or SC Phase. The age distribution of the 41 subjects on XEMBIFY who contributed data for the PK analysis was as follows: 1 (age 2-5 years), 5 (ages >5-12 years), 5 (>12-16 years), 30 (>16 years). The geometric LSM ratio of the $AUC_{(0-7)}$ for XEMBIFY versus IGIV-C 10% was 104%, demonstrating bioequivalence.

The subject enrollment period for this study was January 2016 through December 2017, with nearly equal numbers of infusions across seasons for the run-in, IV and SC phases of the study, thereby, bridging the concern for seasonality as described in the FDA guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. In the SC phase, one subject suffered a SBI, cellulitis and sepsis following a cat-bite. The annualized SBI rate for XEMBIFY per subject year was 0.05 (upper bound of one-sided 99% confidence limit: 0.11); therefore, these data met the standard for IG licensure by ruling out an incidence of 1.0 SBI per subject-year.

Due to the limited PK and clinical data on children 2-5 years from study GTI1502, supportive data from pediatric subjects ages 2-5 years come from an ongoing study, GTI1503 (non-IND). GTI1503 is a prospective, multi-center, open-label, single-arm, efficacy, pharmacokinetic, safety and tolerability study of IGSC 20% in subjects with PI being conducted in Europe and Australia. The primary endpoint assesses the rate of SBI per patient-year after 52 weeks of IGSC 20%. Data from this study were submitted in a 120-day update to the BLA. The DAF from IGIV 10% to XEMBIFY was 1:1, rather than the 1.37 DAF used in GTI1502. Preliminary mean steady state trough concentration in four pediatric subjects ages >2-<5 years exceeded >500 mg/dL, and

Clinical Review
BLA 1256830, XEMBIFY

their mean trough ratio SC/pre-regimen fell within the range 0.88 to 1.34 (minimum and maximum, respectively), with a geometric mean of 1.034, (with 1:1 conversion factor) demonstrated bioequivalence. There were no SBIs in this age group.

The safety population included 49 subjects who received 1053 infusions in study GTI 1502, including 14 subjects between 2 to 16 years of age. The most common adverse events in subjects receiving XEMBIFY were infusion site reactions (ISR), including infusion site erythema, pain, swelling, bruising, nodule, pruritis, induration, scab and edema. Cough and diarrhea also occurred in >5% subjects during infusions of XEMBIFY. During study GTI1502, four subjects discontinued XEMBIFY due to adverse events: infusion site nodule, infusion site discomfort, arthralgia/myalgia, and skin papule/plaque. There were no deaths during either study GTI1502 or GTI1503. There were no reports of thromboembolic events, hypersensitivity or anaphylaxis reactions, aseptic meningitis, renal failure, hemolysis, transfusion-related acute lung injury, or Creutzfeldt-Jakob disease, which are reported and potential adverse reactions among this class of products.

This clinical reviewer recommends approving XEMBIFY for the treatment of children aged two years and older and adults with PI based on the applicant's demonstration of bioequivalence with a licensed IGIV product, Gamunex-C 10%, and the annualized SBI rate for XEMBIFY per subject year being 0.05 (upper bound of one-sided 99% confidence limit: 0.11), ruling out an incidence of 1.0 SBI per patient-year. This reviewer believes that the safety of this product is comparable to other IGSC products, and that XEMBIFY has a favorable benefit/risk profile.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1 summarizes demographic characteristics for the GTI1502 study population. The study enrolled a total of 53 subjects, 38 adults and 15 pediatric subjects. The study population had a mean age of 37 (\pm 21) years, with an age range of 2 to 72 years. Subjects ranged in weight at baseline from 16.7kg to 123.8 kg. The population was primarily Caucasian with an equal distribution of males and females.

Table 1. Demographic and Baseline Characteristics – Study GTI1502

	GTI1502 Enrollment Population (n=53)	GTI1502 PK Population (n=41)	GTI1502 SC Completers (n=42)
Age (Years)			
2-4	2	1	1
>5-12	7	5	6
>12 -16	6	5	5
>16	38	30	30
Sex			
Male	27	20	21
Female	26	21	21
Ethnicity			
Hispanic or Latino	5	4	5
Not Hispanic or Latino	48	37	37
Race			
White	48	37	38
Black/African American	2	1	1
American Indian/ Alaskan Native	3	3	3
Country			
USA	46	38	39
Canada	7	3	3

Source: Reviewer’s Table based on applicant’s ADSL dataset

Clinical Reviewer Comments: It is difficult to make inferences based on subgroups defined by age, race and ethnicity due to limited sample size.

1.2 Patient Experience Data

The applicant did not submit data from stakeholders including patient preference data. During study GTI1502, the applicant collected from subjects, data on number of days of school/work/daily activities missed due to infections. The literature describes interference with daily life as meaningful for patients.

Table 2. Patient Experience Data Relevant to this Application

<input checked="" type="checkbox"/>	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
<input checked="" type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
<input checked="" type="checkbox"/>	Patient reported outcome (PRO)	See section 6.1
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Primary Immunodeficiency Disease (PI) denotes disorders resulting from defects of the immune system that are inherited or acquired and may represent isolated defects or combined disorders of humoral or cellular immune functions. There are more than 300 distinct disorders identified affecting approximately 1 in 2000 live births. The major antibody deficiency syndromes of clinical significance include X-linked agammaglobulinemia (XLA), Common Variable Immunodeficiency (CVID), Wiskott-Aldrich Syndrome, Hyper IgM Syndrome, Severe Combined Immunodeficiency (SCID), Chronic Granulomatous Disease (CGD), and IgG subclass deficiency. These disorders are marked by hypogammaglobulinemia, which increases susceptibility to infections. Patients with PI are at increased risk for recurrent, severe respiratory tract and other infections (both viral and encapsulated bacterial in origin). At present, most primary immunodeficiencies are not curable. Hematopoietic cell transplantation may be curative

for some patients with PI. Replacement therapy with immunoglobulins provides antibodies to help prevent viral and bacterial diseases, and is the mainstay of treatment.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The general management of PI involves preventing and treating infections. Prevention of infections consists of avoidance measures, vaccination (excluding live viral or antibacterial vaccines), prophylactic antibiotics, and immune globulin therapy. Treatment of infections often involves broad spectrum antimicrobials and prolonged treatment courses. Following specific infectious exposures, specialized immune globulins that contain high titers of antibodies directed against particular infectious organisms may be pooled to prepare “hyperimmune globulins.” For instance, Palivizumab, a humanized monoclonal anti-Respiratory Syncytial Virus (RSV) antibody may be used for patients with PI to prevent RSV infection.

2.3 Safety and Efficacy of Pharmacologically Related Products

The FDA Guidance for Industry: “Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency” (hereinafter referred to as the FDA Guidance for IGIV products) states that a statistical demonstration of a serious infection rate per person-year of less than 1.0 is adequate to provide substantial evidence of effectiveness to support licensure.¹ Numerous marketed immune globulin products (both intravenously and subcutaneously administered) have demonstrated serious bacterial infection (SBI) rates of less than 1.0 per person-year. There are currently four licensed and marketed Immune Globulin Subcutaneous (Human) (IGSC) products in the U.S.: Cuvitru® (Baxalta US, Inc.), Hizentra® (CSL Behring), Hyqvia® (Baxter Healthcare Corporation, Baxter BioScience), and Cutaquig® (Octapharma Pharmazeutika Produktionsges.m.b.H). All are indicated for replacement therapy in patients with PI. Vivaglobin (CSL Behring) is also approved for this indication, but is no longer marketed in the U.S. Additionally, Gamunex-C brand IGIV 10% is approved for subcutaneous administration for PI. The safety profile for immune globulins as a class is well-established. The incidence of adverse reactions (AR) reported in clinical studies supporting licensure varies according to the product, route of administration, and maximum infusion rate. In general, common ARs for immune globulins typically include local reactions (i.e. swelling, redness, heat, discomfort at the injection site), headache, fatigue, nausea, diarrhea, vomiting, and/or pyrexia. Immune Globulin Intravenous (Human) as a drug class carries an obligate boxed warning for thrombosis, renal dysfunction, and acute renal failure. Immune Globulin Subcutaneous (Human) products carry an obligate boxed warning for thrombosis.

¹ Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. U.S. Department of Health and Human Services, Food and Drug Administration, CBER, June 2008.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

There is no previous human experience with XEMBIFY. Study GTI1502, submitted with this BLA, is the only human experience in North America. There is an ongoing 12-month clinical study, GTI1503, in Europe and Australia.

The manufacturing of XEMBIFY is based on the applicant's currently licensed IG products Gamunex-C 10% for IV and SC administration with the addition of a nanofiltration step (b) (4) to further concentrate the IgG to 20%. Gamunex-C (IV/SC) is approved for the treatment of PI.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Pre-Submission:

No Pre-BLA meeting was held for this submission.

Initial Pediatric Study Plan (IPSP)

Grifols requested a waiver for neonates aged less than 1 month, and infants/toddlers from 1 month to less than 2 years due to the rarity of the condition in this age range and the impracticality of conducting these studies.

Data from children 2-18 years of age were from study GTI1502 and a non-IND study, GTI1503. GTI1503 is a Phase 3 Efficacy, PK and Safety Study in children 2 to less than 18 years to evaluate weekly administration of ISGC 20% over one-year.

Post Submission FDA Request for information:

- Email Correspondence 22 August 2018 requesting study status and enrollment information for non-IND Study GTI1503. The requested information was submitted on 23 August 2018.
- Email Correspondence dated 31 August 2018 requesting information related to non-IND study GTI1503 for IGSC 20% Phase 3 Study in Europe and Australia:
 - All available interim safety data as a 120-day safety update to include Study GTI1503, but not limited to data from this study.
 - Submit any key revisions to the original protocol and their dates of implementation for non-IND Study GTI1503
 - Submit case reports for any serious adverse events (SAEs) that may have occurred within GTI1503 and your assessment as to whether any SAEs are related to the administration of IGSC 20%.
 - 120-Day safety update for the ongoing, non-IND study GTI1503 for IGSC 20% Phase 3 Study in Europe and Australia.

The requested information was submitted to FDA on 7 November 2018.

- Email Correspondence 26 April 2019 related to Labeling and Adverse Events reporting.
A partial response to FDA was received on 13 May 2019 with regard to local infusion site reactions. The remainder of the response was received on 22 May 2019.

- Email Correspondence 1 June 2019 (IR #31) regarding labeling and local infusion site reactions. Response to IR # 31 was received on 5 June 2019.

2.6 Other Relevant Background Information

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. It was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to the FDA Guidance for Electronic Submissions. The submission contained the five modules in the common technical document structure.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The applicant affirms that the study was conducted in compliance with Good Clinical Practices and conforms with appropriate local laws and regulations and the Declaration of Helsinki.

3.3 Financial Disclosures

Financial disclosures are summarized in table 3.

Table 3. Financial Disclosures

Covered clinical study (name and/or number): GTI1502: An open-label, multi-center study to evaluate the safety and pharmacokinetics of IGSC20% administered for 6 months in subjects with Primary Immunodeficiency.		
Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 21		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N		
Significant payments of other sorts: Y		
Proprietary interest in the product tested held by investigator: N		

Significant equity interest held by investigator in sponsor of covered study: N		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 25		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

A single investigator is noted to have received a grant exceeding (b) (4), (b) (6) that is unrelated to the study protocol.

Clinical Reviewer Comment: This reviewer does not believe that the (b) (4), (b) (6) grant resulted in a conflict of interest. Since the Investigator only enrolled a single subject, this reviewer does not believe that the overall study results were impacted by the Investigator.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please refer to CMC reviewer's memo for details.

XEMBIFY is a solution manufactured from human plasma. It is manufactured using a (b) (4) cold ethanol fractionation, precipitation and filtration with sodium caprylate, (b) (4) chromatography (b) (4) anion exchange (b) (4), followed by several (b) (4) steps to the final formulation. The (b) (4) is formulated to contain 18-22% protein, 10-40 micrograms per milliliter of Polysorbate 80, 0.16 to 0.26M of glycine content with a pH of 4.1 to 4.8 (pH 4.1 to 4.8 at shelf life). The product is manufactured by Grifols Therapeutics Inc. and it is (b) (4) process as for IGIV-C 10% with the addition of a (b) (4) step (b) (4) to further concentrate the IgG to 20%. Ingredients within the IGSC 20% that are not in IGIV-C 10% include (b) (4) caprylate, and Polysorbate 80. No CMC issues were identified that impacted the safety or efficacy of the product.

4.2 Assay Validation

Please refer to the CMC reviewer's memo for details.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical pharmacology/toxicology reviewer's memo for details. No nonclinical pharmacology/toxicology review issues were identified that impacted the safety or efficacy of the product.

4.4 Clinical Pharmacology

Please refer to the clinical pharmacology reviewer's memo for detail.

In study GTI1502, a primary objective was to determine a dose of weekly-administered IGSC 20% that produced a steady-state area under the curve (AUC) for total IgG that was bioequivalent to that observed at baseline steady-state for the licensed IV form of the product (IGIV-C 10%) in PI subjects. A dose adjustment factor of 1.37 was used. Among the 41 subjects who had evaluable PK data for both the IV and SC phases, the steady state SC/IV AUC ratio using geometric least square means (GLSM) analysis was 1.04, with a confidence interval of (1.01, 1.08). Thus, the primary PK endpoint for this study was met, with the upper and lower bounds of the confidence intervals for the SC/IV AUC ratio being within the FDA's established range (0.80, 1.25) for bioequivalence. The study supported bioequivalence of XEMBIFY to IGIV-C.

4.4.1 Mechanism of Action

XEMBIFY contains a broad spectrum of IgG antibodies, some of which are directed towards infectious agents. XEMBIFY's distribution of IgG subclasses is proportional to that of human plasma. Isoagglutinins toward antigens on erythrocytes as well as IgA (b) (4) antibodies are present but at low levels.

4.4.2 Human Pharmacodynamics (PD)

XEMBIFY contains primarily IgG antibodies, with an IgG subclass distribution that is similar to human plasma. Administration of the product increases IgG levels in a dose-dependent fashion.

4.4.3 Human Pharmacokinetics (PK)

Please refer to the clinical pharmacology reviewer's memo for details. The primary PK endpoint was met, in that the ratio of the AUC_(0-T) at steady-state on weekly XEMBIFY to the steady state AUC_(0-T) from the prior IGIV-C 10% administration demonstrated bioequivalence at the 90% confidence interval.

4.5 Statistical

Please refer to the statistical reviewer's memo for details. The statistical reviewer confirmed the applicant's primary efficacy analysis and supportive analyses that are being included in labeling.

4.6 Pharmacovigilance

Please refer to the pharmacovigilance reviewer's memo for details. The pharmacovigilance reviewer did not identify safety issues that would necessitate additional risk management measures beyond standard pharmacovigilance.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The applicant included data from one study in the original BLA application: IND Study GTI1502. During the time of the BLA review, GTI1503, a clinical study of the product in Europe and Australia was ongoing. An interim 120-day safety report was requested and submitted by the applicant that included data from GTI1503, a Phase 3 multi-center, open-label, single arm trial to evaluate efficacy, pharmacokinetics, and safety and tolerability of IGSC 20% in subjects with PI.

The review strategy also included this reviewer familiarizing herself with an overview of PI and its clinical management and treatment options from published literature reviews. This reviewer referenced the FDA Guideline for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency (<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm078526.pdf>). This reviewer also studied the labels and clinical review memos from commercially available subcutaneous immunoglobulin products.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Within the original BLA submission, the following sections were reviewed in detail: Section 5. Clinical Study Reports to include all sections within 5.3.3.2 and all the subsections to also include the PopPK modeling study. It also included Section 5.3.5 Reports of Efficacy and Safety Studies and that included section 5.3.5.4 regarding GTI1503 and the interim 120 day safety data report for this study. Other sections reviewed included all cover letters noted under Section 1.2, Section 1.3 Administrative Information to include Section 1.3.3 Debarment Certification and Section 1.3.4 Financial Certification and Disclosure. Section 1.9 Pediatric Administrative Information, Section 1.12 Other Correspondence and the correspondence relevant to the clinical review, Section 1.14 Labeling, Section 1.16 Risk Management Plan, Section 1.18 Proprietary names, Section 2 Common Technical Document Summaries

5.3 Table of Studies/Clinical Trials

Within the BLA, the applicant submitted data from one completed clinical study, GTI1502, a PK modeling and simulation study, and interim safety, pharmacologic and SBI data from study GTI1503. See Table 4 for a summary of clinical studies included in this application.

Table 4. Summary of Clinical Studies Included in this Application

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK and Safety	GTI1502	5.3.3.2	PK, Safety and Tolerability	Open-label, single-arm, multi-center	IV Phase is with IGIV-C 10% (every 3-4 weeks) SC dosing with IGSC 20% (weekly)	53	PI	Run-In phase is 3-4 months IV phase is 4-5 weeks SC phase is 24 weeks	Complete; Full Clinical Study Report
PK, Efficacy & Safety	GTI1503 (non-IND)	5.3.5.4	Efficacy (SBI rate <1/subject/year), Safety, PK (comparable mean trough levels between IGSC 20% and prior immunoglobulin therapy regimen)	Open-label, single-arm, multi-center	IGSC 20% weekly	61	PI	52 weeks	In Progress; 120-day Safety Update
PK modeling and simulation	Not Applicable	5.3.3.2	Develop a predictive population PK model for the administration of IGSC 20% in patients with PI to better guide clinical decisions on dosage regimens	Computer generated modeling & simulation of dosing regimens based on data from clinical studies GTI1502 & 060001 (BLA 125046); T5004-401 (BLA 125046)	Modeled dose regimens: IV dosing with IGIV-C 10% (every 3-4 weeks) SC dosing with IGIV-C 10% (weekly) SC dosing with IGSC 20% (weekly)	95 (from 3 studies)	PI	No treatment received	Complete; Study Report

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee meeting was not needed for the review, as the Review Team did not identify any scientific issues or new safety concerns that needed advisory committee input.

5.4.2 External Consults/Collaborations

No external consultations were needed or obtained for the review of this BLA.

5.5 Literature Reviewed (if applicable)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 (GTI1502)

Study GTI1502 was an open label, single-arm, single-sequence, multi-center study to evaluate the safety and pharmacokinetics of IGSC 20% in subjects with primary immunodeficiency.

6.1.1 Objectives (Primary, Secondary, etc.)

The safety objective:

- To assess the safety and tolerability of IGSC 20% as an IgG replacement therapy in subjects with PI.

The primary pharmacokinetics objective:

- To determine a dose of weekly subcutaneously administered IGSC 20% that produced a steady state AUC of total IgG that was non-inferior to regularly administered IV dose of IGIV-C 10% in PI subjects.

The secondary pharmacokinetics objective:

- To determine if IGSC 20% replacement therapy maintained mean steady-state trough total IgG levels comparable to the mean trough total IgG levels with the IGIV-C 10% replacement therapy in PI subjects.

The exploratory objectives included evaluation of the following:

- Maximum concentration (C_{max}) and time to reach maximum concentration (t_{max}) in PI subjects at steady state
- Trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Antibody levels for *Streptococcus pneumoniae* (*S. pneumoniae*), *Hemophilus influenzae* (*H. influenzae*), and *Clostridium tetani* (*C. tetani* [tetanus])
- The rate of SBIs
- All infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the investigator
- Validated infections documented by positive radiograph, fever ($>38^{\circ}\text{C}$ oral or $>39^{\circ}\text{C}$ rectal), culture, or diagnostic testing for microorganisms, e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test)
- Number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic, and therapeutic). Use of prophylactic antibiotics was distinguished from antibiotics used for treatment of acute infection.
- Number of hospitalizations due to infection
- Number of days of work/school/daily activities missed due to infections and their treatment

- Trough measles antibody titers (functional assay) for informational purposes

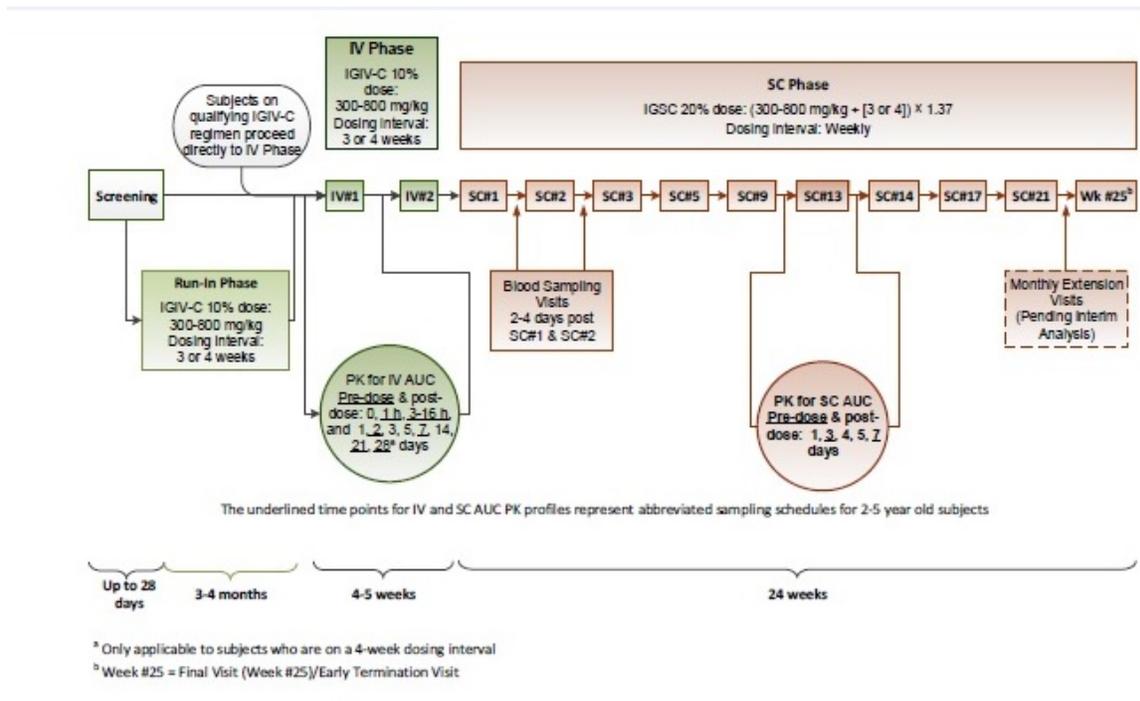
Reviewer comment: Since the annualized rate of SBI was a prospectively defined and adjudicated endpoint, the review team considered the assessment to be sufficiently rigorous and robust to allow for a conclusion of efficacy based on the rate of SBI.

6.1.2 Design Overview

The clinical study was a prospective, multi-center, open-label, single-sequence, six-month, PK, safety, and tolerability study of IGSC 20% in subjects with PI to be carried out in approximately 30 study centers. Planned enrollment included approximately 50 subjects to include 30 adults and 12-18 pediatric subjects ages 2 to 16 years stratified by age category with a target of four to six children ages 2-5 years, >5 to 12 years, and >12 to 16 years of age completing treatment with subcutaneously administered IGSC 20%.

The study consisted of a screening phase, a run-in phase, and IV Phase (IV administration of IGIV-C 10% treatment), a SC Phase (SC administration of IGSC 20% treatment), and an end of Study/Early Termination (EOS/ET) visit. See Figure 1 for details.

Figure 1. GTI1502 Clinical Study Plan



Source: Replicated from Applicant's submission, section 2.7.2.

During the screening phase, subjects who were on IVIG other than IV IGIV-C 10% entered a three-month run-in phase with IGIV-C 10% (Group2). Subjects on SCIG therapy or on limited IVIG therapy entered a Run-In Phase of four months with IGIV-C 10% (Group3). The run-in phase dose of IGIV-C 10% was between 300 and 800 mg/kg per infusion every three to four weeks for at least three consecutive months. Both of

these groups would then enter a four to five-week IV phase (five weeks if received IGIV every three weeks) of IGIV-C 10% followed by a PK assessment after the second IV dose. Subjects on qualifying IVIGIV-C 10% at screening (Group 1) entered directly into the four to five-week IV Phase with IGIV-C 10%. After the second dose of IGIV-C 10% in the IV Phase, subjects entered the 24-week SC phase with IGSC 20% seven days after the second IGIV-C 10% dose. Subjects then received 24 weekly SC doses with an initial adjustment factor ratio of 1:1.37 (IGIV-C 10%; IGSC 20%).

Subjects in the IV phase received two IV infusions of IGIV-C 10%. Subjects who entered directly into the IV Phase at screening (Group 1), received a dose of IGIV-C 10% equivalent to their current IgG dose. For Groups 2 and 3, subjects received the same dose of IGIV-C 10% as last dose administered in the run-in period. PK profiling began before the first IGIV-C 10% infusion and continued throughout the subject's dosing period of three or four weeks. Prior to initiating the SC phase, a second dose of IGIV-C 10% was administered to ensure adequate total IgG levels.

The IV to SC dose adjustment factor of (DAF) of 1.37 times was used to determine the initial SC dose. PK profiles began after 12 weeks of weekly SC therapy for total IgG just prior to the 13th SC infusion and the last sample collected immediately prior to the 14th SC infusion.

The IV and SC PK profiles were compared in the first six adult/adolescent subjects ages ≥ 12 to 75 years as an interim PK analysis. If the DAF was deemed acceptable such that the SC dose of IGSC 20% was non-inferior to the subject's IV dose, all subjects were to continue and complete treatment and assessments through Week 25. If not, a revised DAF would be employed for all subjects and an additional 24 weeks of IGSC 20% treatment at the new dose. Subjects ages 2-5 years were assessed using an abbreviated sampling schedule for PK profiles.

Interim PK analysis

The ratio of the geometric least squares mean (LSM) for area under the concentration-time curve from 0 to 7 days following SC infusion ($AUC_{0-7, SC}$) versus adjusted area under the concentration-time curve from 0 to 7 days following IV infusion ($AUC_{0-7, IV}$) was required to be above 90% of the desired 1.0 (≥ 0.9) for the DAF to be acceptable. The mean trough concentrations for the SC administration of IGSC 20% could not fall below 500mg/dL in more than three of six adult/adolescent subjects or a DAF increase would be required to reach an optimal IGSC 20% to ensure effectiveness against bacterial infections.

Eight subjects (aged 27 to 72 years) were included in the interim analysis and were found to have a ratio of 0.95 for the LSM $AUC_{0-7 \text{ days}, SC}$ versus adjusted $AUC_{0-7 \text{ days}, IV}$. Mean trough levels for individual subjects were all ≥ 757 mg/dL and across all eight subjects the mean trough IgG level was 1169 mg/dL.

Clinical Reviewer's Comment: The findings of the interim analysis confirmed that the dose adjustment factor of 1.37 for the study was adequate for meeting the intended PK objective.

Subjects enrolled early in the trial continued beyond the 24 weeks until the interim PK study results were validated. They continued to return to the study center every four weeks and had the same study procedures performed to include laboratory assessments, IgG subclass levels, and specific antibody titers for *S. pneumoniae*, *H.*

influenzae, and *C. tetani* every 9 weeks. When the adequacy of dosing based on a DAF of 1.37 was confirmed, these subjects then returned to the clinic for end of study procedures.

6.1.3 Population

This study included male or female subjects ages 2 to 75 years of age and had a diagnosis of PI requiring IgG replacement treatment. In addition to this criteria, the following inclusion criteria applied.

Inclusion Criteria

- No SBI within the last three months prior to or during screening
- IgG replacement therapy (IV or SC infusion) for \geq three months
- Screening trough levels of \geq 500 mg/dL. (Subjects not meeting this criteria, could be rescreened after stable dose adjustment for three months prior to rescreening.)
- Access to medical records to document diagnosis, previous infections, and treatment.
- Signed an Informed Consent Form (patient or caregiver / guardian).

Exclusion Criteria

- Significant acute or chronic disease that may interfere with completion of the trial or place the subject at undue medical risk
- Known serious adverse reaction immunoglobulin or any severe anaphylactic reaction to blood or any blood-derived product.
- History of blistering skin disease, clinically significant thrombocytopenia, bleeding disorder, diffuse rash, recurrent skin infections or other disorder where SC therapy would be contraindicated during the study
- Isolated IgG subclass deficiency, isolates specific antibody deficiency disorder, or transient hypogammaglobulinemia of infancy
- Known selective immunoglobulin A (IgA) deficiency (with or without antibodies to IgA)
- Pregnant or nursing women
- Significant proteinuria
- Elevated liver function tests
- Hemoglobin $<$ 9
- Deep venous thrombosis (DVT) or thromboembolism (myocardial infarction, cerebrovascular accident or transient ischemic attack)
- Anti-coagulation therapy
- Hyperviscosity syndrome
- Secondary immune deficiency such as a leukemia or other medical condition
- Hepatitis B or C infection
- Uncontrolled hypertension
- Receiving Immunosuppressants including chemotherapeutic agents, immunomodulators, long-term corticosteroids
- Substance use disorder
- Involved in other clinical study (non-observational) 30 days prior to screening
- Unwilling or able to comply with protocol
- Mentally challenged and unable to provide independent consent

Clinical Reviewer's Comment: The enrollment criteria are typical for this type of study. It

is possible that the study population may have less frequent serious infections since subjects with a SBI in the past 3 months were excluded.

6.1.4 Study Treatments or Agents Mandated by the Protocol

All subjects in the PK study had to be on IGIV-C 10% prior to moving into the IGSC-20% in order to compare the trough PK level between IGIV-C and IGSC 20%. The SC dose was calculated as follows:

$$\text{Initial weekly dose (g)} = \frac{\text{previous IGIV dose (g)}}{\text{number of weeks between IGIV doses}} \times 1.37$$

The same dose calculation was used for all subjects.

6.1.5 Directions for Use

Subjects received IGIV-C 10% in the clinic. Subjects entering the SC phase received a pump specifically designed for SC infusions and were trained on its use. The first three SC infusions were supervised in clinic before self-administration at home. All subjects were counselled as to the importance of the specific dosing regimen and not to round-up or under dose to ensure accurate PK analysis during the study period. The first SC administration occurred seven days after the second IGIV-C 10% dose and then weekly +/- one day for 24 weeks.

The number of injection sites, infusion rate and specific times of the day for the SC infusion were allowed to be individualized by subject and investigator. Up to 8 infusion sites per infusion were permitted. The same or rotated anatomical sites for infusion were allowed throughout the study. The minimum distance between infusion sites were no less than two inches and the target infusion rate was no greater than 25mL/hour/site as tolerated by the subject and the investigator's discretion. Target infusion rates, once achieved, were not changed unless not tolerated by the subject, or conversely, if well tolerated during two infusions, the rate and volume of infusion per site could increase by 20% at the discretion of the Investigator.

The volume, number of infusion sites, infusion start date/time, infusion end date/time, locations and initial and final rate of infusion for each infusion site and any other information such as concomitant medications, missed days of work/school/daily activities due to infections and related treatment, as well as to include local infusion site reactions (ISR) were recorded in the subject's diary.

Premedication with oral ibuprofen, acetaminophen and antihistamines were not allowed for SC infusions. Topical medications such as steroids and antihistamines were also not allowed prior to infusions. These medications were allowed during the study for general use (and to treat an AE).

Clinical Reviewer's Comment: Eight infusion sites were allowed in the study; however, six infusion sites were the maximum number of sites used by subjects during the clinical trial.

6.1.6 Sites and Centers

Twenty one sites enrolled subjects and reported data. Only sites in which investigational product was shipped are included.

Site/Study Unit	Investigator
Site 101 (FL, U.S.):	Mark Ballow
Site 102 (FL, U.S.):	Mark Stein
Site 103 (MI, U.S.):	Pavadee Poowuttikul
Site 105 (NC, U.S.):	John Sleasman
Site 106 (GA, U.S.):	Lisa Kobrynski
Site 108 (CA, U.S.):	Raffi Tachdjian
Site 109 (CA, U.S.):	Maria Ines Garcia-Lloret
Site 109 (CA, U.S.):	Robert Roberts
Site 113 (VA, U.S.):	Santhosh Kumar Bangalore Vasantha Kumar
Site 114 (OK, U.S.):	Amy Liebl Darter
Site 115 (TX, U.S.):	William R. Lumry
Site 116 (MO, U.S.):	H. James Wedner
Site 117 (MN, U.S.):	Ralph Shapiro
Site 118 (IL, U.S.):	James Moy
Site 119 (IN, U.S.):	James, Hariss III
Site 120 (CO, U.S.):	Erwin Gelfand
Site 121 (OK, U.S.):	Iftekar Hussain
Site 123 (TX, U.S.):	Lisa Forbes
Site 202 (Ontario, Canada.):	Chaim Roifman
Site 207 (Quebec, Canada):	Elie Haddad
Site 208 (Ontario, Canada):	Donald Cameron

6.1.7 Surveillance/Monitoring

Safety assessments included vital signs, laboratory parameters (i.e. hematology, clinical chemistry, hemolysis markers, and viral markers), and adverse event (AE) monitoring. The following assessments were performed at study site visits as outlined in the protocol schedule of assessments: a full physical exam at screening and final visit/early termination (excluding breast and genitourinary exams), chest x-ray as appropriate at screening visit, and subsequent visits: vital signs, body weight, height, laboratory parameters (i.e. hematology, clinical chemistry, urinalysis, (pre-IV#2 measles titer), pre-subcutaneous dose retained viral markers (tested only if clinical signs/symptoms consistent with Hepatitis A, B, C, HIV or parvovirus B19), abbreviated physical exams and specific signs/symptoms check during subcutaneous administrations, including special tests (DAT, serum free hemoglobin, haptoglobin -drawn two to four days post SC#1), pregnancy test, pre SC dose Wells Score and D-Dimer testing if indicated. Prior and concomitant medications, and adverse events including SBIs, recorded days lost from work/school/daily activities due to infections and treatment. An electronic Case Report Form (eCRF) was used during the study.

A stopping rule for the study included if five subjects on IGSC 20% had an unanticipated clustering of serious adverse events, the sponsor would constitute a Safety Review Committee (SRC) made of impartial members from Grifols, independent of the clinical trial team, to determine plausibility and whether the SAE were definitely, probably or

possibly related to the IP. A consideration for discontinuing the study would be determined by the SRC.

A subject SC infusion diary (non-electronic) was provided to each subject to document the following information: ISRs, concomitant medications (including antibiotics, prophylactic and therapeutic), details of study drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume of each SC dose, duration and rates of infusion), days of missed work/school/daily activities due to infections and related treatment.

Reviewer's Comment:

Subjects were discontinued from the study if they experienced an SBI during the run-in or IV phases. See section 6.1.11 for further details regarding the SBIs.

Auditing of Study Data

Grifols auditors conducted two site audits in this study (sites 105, 121). Laboratory validations for quantitative determination of IgG in serum samples, validation of 24 month frozen stability for Hemophilus influenzae b Antibody, IgG, and 24 month frozen stability for Tetanus Antibody, IgG method validations were conducted by (b) (4) [REDACTED]. Total serum IgG trough levels, PK measurements for total serum IgG; IgG subclasses; antigen-specific antibodies against Streptococcus pneumoniae (S. pneumoniae), Hemophilus influenzae (H. influenzae), and Clostridium tetani (C. Tetani or tetanus), were assessed. According to the sponsor, monitoring and audit procedures were followed with GCP guidelines. Each center was visited at regular intervals by a monitor to ensure compliance with the study protocol and protocol amendments, GCP and legal aspects to include on-site checking of the CRFs for completeness and clarity, cross-checking source documents and clarifying administrative matters.

6.1.8 Endpoints and Criteria for Study Success

Pharmacokinetic

Primary Endpoint: Steady-state area under the curve (AUC) of total IgG over a regular dosing interval defined as follows:

- $AUC_{0-T, SC}$, the AUC over a weekly dosing interval (τ) at an approximate steady-state condition following weekly SC infusion, i.e., $AUC_{0-7 \text{ days}, SC}$.
- $AUC_{0-T, IV}$, the AUC over a regular dosing interval (τ) at an approximate steady-state condition following the regular IV infusion, either every 3 weeks or every 4 weeks, i.e., $AUC_{0-21 \text{ days}, IV}$ or $AUC_{0-28 \text{ days}, IV}$, respectively.

Secondary Endpoints:

- Mean steady-state trough (pre-dose) concentration of total IgG following IV administration of IGIV-C 10% or SC administration of IGSC 20%.

Exploratory Variables:

- t_{max} and C_{max} in PI subjects at steady state
- Trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)

Clinical Review
BLA 1256830, XEMBIFY

- Antibody levels for *S. pneumoniae*, *H. influenzae*, and *C. tetani* (tetanus)
- Rate of SBIs
- All infections of any kind (serious/nonserious) as determined by the Investigator
- Validated infections
- Number of days on antibiotics
- Number of hospitalizations due to infection
- Number of days of work/school/daily activities missed due to infections and their treatment
- Trough measles antibody titers (functional assay) for informational purposes

Safety

- Adverse events (AEs), suspected adverse drug reactions (suspected ADRs), adverse reactions (ARs), serious AEs (SAEs), and discontinuations due to AEs and SAEs
Note: All ISRs were recorded in the eCRF. For local ISRs where the symptoms/signs led to infusion interruption or discontinuation, required concomitant medication, or had an impact on the general condition of the subject as judged by the Investigator, they were considered as AEs.
- Vital signs during clinic visits (SBP and DBP, heart rate [HR], temperature [T], respiratory rate [RR])
- Physical Assessments: physical exams were recorded as normal or abnormal, according to the physician's judgment criteria, and findings were recorded.
- Laboratory assessments including chemistry, hematology, and urinalysis.
- Total number of non-serious infections and proportion of subjects who experienced non-serious infections of any kind (including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the investigator

Efficacy

This study was designed to assess bioequivalence by comparing the AUC of IGSC-20% to the AUC of IGIV-C 10%. The applicant assessed IgG subclasses, titers for *S. pneumoniae*, *H. influenzae*, and *C. tetani* and measles in the product to determine whether the different manufacturing process for the IGSC affected key components of the product. The rate of SBIs per subject year on IGSC-20% was assessed; however, formal statistical analyses of efficacy based on SBI rate were not pre-specified.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Descriptive statistics, unless otherwise specified, included the number of non-missing observations, mean, standard deviation, median, minimum, and maximum values for continuous/quantitative data or absolute and relative frequency counts and percentages for categorical/qualitative data. The applicant used SAS version 9.5 or higher for any statistical analyses and data presentations.

Hypothesis testing for the primary PK analysis of bioequivalence is tested at one-sided with $\alpha = 0.05$. All other statistical inferences were tested at two-sided $\alpha=0.05$, as applicable.

Missing Data

Unless noted otherwise, missing observations were not imputed.

Samples with concentrations below the limit of quantification (BLQ) were treated as missing.

IgG Concentration Missing Values

Any invalid IgG concentration values were treated as missing (e.g., hemolyzed sample, trough drawn post-infusion). As necessary and indicated, any extrapolated or interpolated values using PK principles were documented in the clinical study report (CSR).

Sample Size Determination

The planned enrollment of 50 subjects (30 adults, 12-18 pediatric) was based on safety assessment considerations. It was calculated that a sample size of 42-48 with at least 24 administrations of IGSC 20% would provide the clinical experience data on a total of more than 1008- 1152 IGSC 20% dosing administrations for the safety assessment. The planned minimum enrollment of 42 completing subjects was considered adequate to establish that the AUC for total IgG for IGSC 20% is bioequivalent to that achieved by IGIV- 10%.

Clinical Reviewer's Comment: The applicant used the term non-inferior throughout the BLA. However, the correct terminology is bioequivalence and is therefore used in all sections of this review.

PK Data Handling

Specified times for serial PK blood sample draws are specified in the protocol. Samples drawn outside the protocol are included in the PK analysis if the actual sample collection data and clock time for each sample is recorded and actual elapsed time from the start of infusion can be calculated.

Due to variable infusion duration for individual subjects, the nominal time (hours) may be adjusted by using the average infusion duration among all subjects in the PK population when plotting mean or median concentration vs. time curve.

All time calculations are based on actual time elapsed and not scheduled time or nominal time.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Safety Population

All subjects who received any amount of study drug(s) are included in the safety analysis (IGIV-C 10% and / or IGSC 20%).

IgG Population

All subjects who receive study drug (s) and have any total IgG concentration data. The summary total IgG concentration data was based on the IgG population.

PK Population

Includes all subjects who receive study drugs and have sufficient and valid total IgG concentration vs. time data for either the IV or SC Phase to allow calculation of AUC_{0-T,SC} or AUC_{0-T,IV} (the primary PK endpoint). Valid analyses for PK parameters (AUC values) will only occur for PK profiles with at least 3 quantifiable samples following data imputations.

6.1.10.1.1 Demographics

Demographic characteristics for the GTI1502 study population are summarized in Section 1.1, Table 1. The demographic and baseline characteristics are summarized for the Safety population.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects screened had PI with an average time since diagnosis of 10.33 years. Upon study entry, 41/53 subjects were diagnosed with common variable immunodeficiency (CVID) and 5/53 were diagnosed with X-linked agammaglobulinemia. In the 12 months prior to study entry, 35/53 subjects received IGIV treatment and 25 were receiving IGSC treatment. The type of PI and IgG treatment history is summarized in Table 5.

Table 5. Summary of Primary Immunodeficiency and IgG Treatment History (Safety Population)

Total (N=53)		
Time Since Primary Immunodeficiency Diagnosis (years)		
	Mean±SD	10.33±10.655
	Median	6.67
	Min, Max	0.3, 41.1
Type of Primary Immunodeficiency n (%)		
	Common Variable Immunodeficiency (CVID)	41 (77.4)
	X-Linked Agammaglobulinemia	5 (9.4)
	Hyper IgM Immunodeficiency Syndrome	2 (3.8)
	Primary Hypogammaglobulinemia	2 (3.8)
	Severe Combined Immunodeficiency (Post Transplantation)	2 (3.8)
	Autosomal Recessive Agammaglobulinemia	1 (1.9)
Brand of IgG Treatment for Past 12 Months^a n (%)		
	Gamunex-C 10%	16 (30.2)
	Hizentra	10 (18.9)
	Hyqvia	8 (15.1)
	Gammagard	7 (13.2)
	Privigen	6 (11.3)
	Octagam	4 (7.5)
	Subgam Vf	3 (5.7)
	Gammagard Liquid 10%	3 (5.7)
	Gammaked 10%	3 (5.7)
	Bivigam	2 (3.8)
	Gammaplex	2 (3.8)
	IgG Carimmune	1 (1.9)

Clinical Review
BLA 1256830, XEMBIFY

	Immune Globulin (20%) Solution "nos"	1 (1.9)
	Subgam 16% Trial	1 (1.9)
Route of IgG Treatment for Past 12 Months^a n (%)		
	IV	35 (66.0)
	SC	25 (47.2)
Frequency of IgG Treatment for Past 12 Months^a n (%)		
	Every Week	15 (28.3)
	Every 2 Weeks	5 (9.4)
	Every 3 Weeks	6 (11.3)
	Every 4 Weeks	33 (62.3)

^a IgG treatments are not mutually exclusive.

Source: Replicated from applicant's table 8-7.

The medical history findings were diverse with 47/53 subjects presenting with immune system disorder (excluding PI), metabolism and nutrition disorders 21/53, musculoskeletal and connective tissue disorders 20/53, nervous system disorders (25/53) and psychiatric disorders (23/53). The most frequent findings were asthma (20/53 subjects, 37.7%), and allergic rhinitis (19/53, 35.8%).

Medical history that possibly overlapped with PI included sinusitis (12 subjects), chronic sinusitis (11 subjects), pneumonia (11 subjects), rhinitis (10 subjects) and ear infection (seven subjects), and cough (six subjects).

Medical history findings that may have overlapped with adverse reactions documented in the setting of immune globulin use include drug hypersensitivity (eight subjects, 15.1%), headache (12 subjects, 22.6%), migraine (six subjects, 11/3%), and fatigue (six subjects, 11.3%).

Concomitant medications are summarized in Table 6.

Table 6. Most Frequent Concomitant Medications (≥20% of Subjects in Any One Phase) During The Study (Safety Population)

ATC Level 4	Study Phase			
	Run-In (N=44) n (%)	IV (N=52) n (%)	Run-in+IV (N=53) n (%)	SC (N=49) n (%)
Any Medication Class	41 (93.2)	49 (94.2)	49 (92.5)	47 (95.9)
Corticosteroids	16 (36.4)	21 (40.4)	22 (41.5)	22 (44.9)
Selective beta-2-adrenoreceptor agonists	15 (34.1)	18 (34.6)	19 (35.8)	20 (40.8)
Propionic acid derivatives	10 (22.7)	11 (21.2)	11 (20.8)	17 (34.7)
Piperazine derivatives	10 (22.7)	14 (26.9)	14 (26.4)	14 (28.6)
Glucocorticoids	9 (20.5)	10 (19.2)	15 (28.3)	13 (26.5)
Vitamin D and analogues	7 (15.9)	12 (23.1)	12 (22.6)	12 (24.5)
Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics	7 (15.9)	10 (19.2)	11 (20.8)	11 (22.4)
Anilides	12 (27.3)	13 (25.0)	15 (28.3)	11 (22.4)
Other antidepressants	5 (11.4)	11 (21.2)	11 (20.8)	10 (20.4)
Proton pump inhibitors	8 (18.2)	11 (21.2)	11 (20.8)	10 (20.4)

Source: Applicant's table 8-9.

6.1.10.1.3 Subject Disposition

A total of 61 subjects were screened for participation, of which eight were screen failures. Subjects were enrolled from 4 Jan 2016 through the last study visit of 14 December 2017. Fifty-three subjects entered the study. Nine entered directly into the IV phase without run-in. Forty-four subjects entered the run-in phase, but one subject discontinued due to loss to follow-up. Therefore, 52 subjects entered the IV phase, 49 subjects then entered the SC phase. Fifty subjects from the IV phase had PK data valid for the PK analysis. Three subjects did not complete the IV phase: one due to AE of bacterial pneumonia, sepsis, and two subjects who withdrew by their own request. Seven subjects of 49 discontinued the SC phase: four subjects had AEs (infusion site nodule; infusion site discomfort and intentional medical device removal; arthralgia, myalgia; papule, skin plaque); two withdrew by own request; and one subject refused blood samples, for a final total of 41/49 subjects in the SC phase had adequate PK data and were valid for PK analysis.

Subject disposition according to age group is shown in Table 7.

Table 7. Subject Disposition (All Enrolled Subjects)

Phase	Subject Status	Age Group				Total n (%)
		2-5 n (%)	>5-12 n (%)	>12-16 n (%)	>16 n (%)	
Run-in	Entered and valid for safety analysis	2	7	6	29	44
	Valid for IgG concentration analysis	2 (100.0)	7 (100.0)	6 (100.0)	29 (100.0)	44 (100.0)
	Completed	2 (100.0)	7 (100.0)	6 (100.0)	28 (96.6)	43 (97.7)
	Subjects who prematurely discontinued	0	0	0	1 (3.4)	1 (2.3)
	Lost to follow-up	0	0	0	1 (3.4)	1 (2.3)
IV	Entered and valid for safety analysis	2	7	6	37	52
	Subjects valid for IgG concentration analysis	2 (100.0)	7 (100.0)	6 (100.0)	37 (100.0)	52 (100.0)
	Subjects valid for PK analysis	2 (100.0)	7 (100.0)	6 (100.0)	35 (94.6)	50 (96.2)
	Completed	2 (100.0)	7 (100.0)	5 (83.3)	35 (94.6)	49 (94.2)
	Subjects who prematurely discontinued	0	0	1 (16.7)	2 (5.4)	3 (5.8)
	AE (Subject (b) (6) : bacterial pneumonia, sepsis) Withdrawal by subject	0	0	0	1 (2.7)	1 (1.9)
SC	Entered and valid for safety analysis	2	7	5	35	49
	Subjects valid for IgG concentration analysis	2 (100.0)	7 (100.0)	5 (100.0)	35 (100.0)	49 (100.0)
	Subjects valid for PK analysis	1 (50.0)	5 (71.4)	5 (100.0)	30 (85.7)	41 (83.7)
	Completed	1 (50.0)	6 (85.7)	5 (100.0)	30 (85.7)	42 (85.7)
	Subjects who prematurely discontinued	1 (50.0)	1 (14.3)	0	5 (14.3)	7 (14.3)

Clinical Review
BLA 1256830, XEMBIFY

AE (Subject (b) (6) : infusion site nodule; Subject (b) (6) : infusion site discomfort, intentional medical device removal by patient; Subject (b) (6) : arthralgia, myalgia; Subject (b) (6) : papule, skin plaque)	1 (50.0)	0	0	3 (8.6)	4 (8.2)
Withdrawal by subject	0	0	0	2 (5.7)	2 (4.1)
Other (refused blood samples)	0	1 (14.3)	0	0	1 (2.0)

Note: Percentages are based on the number of subjects entered and treated with study drug (Safety Population) within each phase.

Source: The table is replicated from the applicant's table 8-1.

The number of subjects valid for each population is summarized from the applicant's Table 8.

Table 8. Subject Disposition for Analysis

Characteristic	Total n (%)
Subjects valid for safety analysis	53
Subjects valid for IgG concentration analysis	53 (100)
Subjects valid for pharmacokinetic analysis (PK)	50 (94.3)

Note: Percentages are based on the number of subjects valid for safety analysis (Safety Population).

Source: This is replicated from the applicant's table 8-1.

Subject Disposition for PK Analysis is summarized in the Table 9.

Table 9. Subject Disposition for PK Analysis (PK Population)

Characteristic	Total n (%)
Subjects valid for pharmacokinetic analysis (PK)	50
Subjects with sufficient and valid IV serial PK profile for AUC calculation	49 (98)
Subjects with sufficient and valid SC serial PK profile for AUC calculation	39 (78)
Subjects with sufficient and valid IV and SC serial PK profiles for calculating ratio of AUC_{SC}/AUC_{IV}	38 (76)
Subjects with IV serial PK profile for calculating C_{max} and T_{max}	49 (98)
Subjects with SC serial PK profile for calculating C_{max} and T_{max}	41 (82)

Note: Percentages are based on the number of subjects valid for PK analysis (PK Population).

Source: This is replicated from the applicant's table 8-5.

6.1.11 Efficacy Analyses

Serious Bacterial Infections (SBIs)

SBIs were assessed as an additional endpoint in this study. No SBIs were reported during the run-in phase. SBI in the Safety Population included one subject in the IV phase (who completed the four-month run-in period) who had bacterial pneumonia four days after starting the IV phase and subsequently had sepsis four days later. The individual subject who had a pneumonia and sepsis, counted as two SBIs. In the SC

phase, one subject suffered a cat bite and developed sepsis on Day 140 of the SC phase. In both instances the SBIs were treated and resolved.

Since the SC phase was only 6 months in duration, there is the potential for seasonality of infections to bias the results. However, the study enrollment period was longer than an entire year, from 4 January 2016 through 14 December 2017, spanning all seasons. The applicant submitted information related to the summary of infusions by season in Table 10. The table demonstrates a relatively equal number of infusions during the spring and summer as during the fall and winter.

Table 10. Summary of Infusions by Season in Safety Population

Season	Statistic	Study Phase		
		Run-In (N=44)	IV (N=52)	SC (N=49)
Total Number of Infusions	n	158	103	1053
Spring-Summer	n (%)	80 (50.6)	57 (55.3)	526 (50.0)
Fall-Winter	n (%)	78 (49.4)	46 (44.7)	527 (50.0)

Source: Replication of applicant's table 14.1.5/5

The applicant calculated the SBI rate for each phase of the study based on the subject-years for each phase of the study: 11.85 subject-years for the run-in phase, 4.88 subject-years in IV phase, 16.73 subject-years in the combined run-in +IV phases, and 20.28 subject-years in the SC phase. The applicant calculated the mean annualized SBI rate as 0 in the run-in phase, 0.5 in the IV phase, 0.1 in the combined run-in +IV phases, and 0.04 in the SC phase. The FDA statistical reviewers calculated the annualized SBI rate for IGSC-20% per subject-year to be 0.05 (upper bound of one-sided 99% confidence limit: 0.11).

Table 11. Serious Bacterial Infections in similarly licensed IGSC products

Endpoint	XEMBIFY (IGIV 20%)- Investigational Product	Hizentra	Cuvitru	Cutaquig
SBI Rate per subject year	.05	0	0.01	0

Source: Reviewer's Table.

Clinical Reviewer Comment: Although the applicant observed subjects for only 24 weeks on XEMBIFY, this reviewer believes that an accurate annualized SBI rate can be calculated since the length of the enrollment period and the seasonal coverage of infusions bridges the concern for seasonality as referenced in the FDA Guidance. The applicant demonstrated efficacy based on the SBI rate and ruling out an incidence of 1 SBI per subject-year. However, the study design and data are too limited to support a conclusion of superiority regarding relative reduction in SBI rate on IGIV 20% compared to IGIV-C.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary PK endpoint of steady state AUC values was calculated from 49 subjects from the IV phase and 39 subjects from the SC phase. Three versions of the population were calculated: the full PK population (49 subjects in IV phase, 39 subjects in SC phase); the PK population with the original 8 subjects used in the interim analysis excluded (41 subjects in IV phase, 31 subjects in SC phase); and only subjects in the PK population with sufficient and valid serial PK profiles allowing calculation of the AUC parameter in both the IV and SC phases (38 subjects in IV phase, 38 subjects in SC phase).

Table 11 summarizes the primary PK endpoint steady state AUC.

Table 11. Statistical Analysis of Primary PK Endpoint of Steady State AUC_{0-7days} (h*mg/dL) of Total IgG

	Mean±SD	Geometric Mean	Geometric LSM	GLSM Ratio, SC/IV	90% CI, GLSM Ratio, SC/IV
PK Population					
IV Phase ^a (n=49)	212150.5±41832.11	207921.5	207822.8		
SC Phase (n=39)	218315.6±48121.25	213141.4	215829.3	1.04	(1.00, 1.07)
PK Population: Interim 8 Subjects Excluded					
IV Phase ^a (n=41)	212190.7±43625.64	207554.5	207326.8		
SC Phase (n=31)	221905.1±47538.66	216935.3	220783.6	1.06	(1.03, 1.10)
PK Population: Only Subjects with Sufficient and Valid Serial PK Profile in both IV and SC Phases					
IV Phase ^a (n=38)	209425.9±43940.16	204762.0	204762.0		
SC Phase (n=38)	218537.6±48746.97	213227.8	213227.8	1.04	(1.01, 1.08)

Geometric least-squares means (GLSMs), GLSM ratio, and 90% CI of GLSM ratio are determined from a mixed-effect model for the log-transformed parameter value with study phase as a fixed effect and subject as a random effect.

Note: IV Phase is the reference phase. SC Phase is the test phase being compared to the reference.

^aAUC_{0-7 days} in the IV Phase is calculated as AUC_{0-21 days/3} for subjects on an every-3-week IV dosing schedule and as AUC_{0-28 days/4} for subjects on an every-4-week IV dosing schedule.

Source: This is reproduced from the applicant's table 9-5.

The analysis demonstrates consistency across the three populations. The applicant subscribes that the PK endpoint of steady state AUC steady state AUC_{0-7 days} for the PK population is above 0.80, demonstrating non-inferiority of SC to IV administration. In addition, the overall 90% CI falls within the range of 0.80 to 1.25, an accepted criterion for concluding "bioequivalence" between the two treatments based on guidelines in FDA IVIG guidance. Further, the data confirm that the dose adjustment factor that was used in the study (1.37 times the IV dose) was adequate, since it produced a SC steady-state AUC for total IgG that was bioequivalent to that of IGIV-C 10%.

The study averaged the three- and four-week dosing regimens to produce the AUC under the IV phase. There were a total of 6 subjects in the IV phase who received every three-week dosing, four subjects who converted from every three-week dosing to the SC administration in the age >16 years, two subjects ages >12 -<16 years, and none in the younger age groups.

Clinical Reviewer's Comment: This reviewer does not believe that bioequivalence was impacted by the averaging of the every 3 and every 4-week dosing to calculate the AUC, but it is worth noting that a separate PK study to evaluate every three-week dosing and conversion to SC dosing was not performed.

In Vivo Characterization of the Product:

Additional evidence of similarity of the in vivo PK profiles for the IGSC product compared to the reference IGIV product are provided by the following data regarding IG Trough levels.

The applicant performed sub-analyses of trough levels comparing the IGIV to the IGSC phases across IgG subclasses, *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Clostridium tetani* (referred to as bacterial antibodies), and measles antibody titers. For IgG subclass analyses, trough concentrations of IgG subclasses during the IV and SC phases were compared demonstrating increased percentages across all IgG subclasses in the SC Phase (IgG1 32.4%, IgG2 34.7%, IgG3 21.2%, IgG4 40.9%). See table 12 for details.

Table 12. Trough Concentrations of IgG Subclasses During the IV and SC Phases for the IgG Population

IgG Subclasses	Statistics	IV#1 (N = 50)	IV#2 (N = 51)	SC Week 9 (N = 44)	SC Week 17 (N = 41)	Final/Early Termination Visit (N = 50)	Change from IV to SC ^a
IgG1	Mean (mg/dL) [Range]	601.4 [246, 1160]	608.2 [278, 1270]	805.4 [348, 1420]	794.2 [501, 1420]	828.6 [365, 1620]	32.4%
IgG2	Mean (mg/dL) [Range]	270.87 [73.3, 477.0]	271.31 [84.9, 420.0]	365.57 [120.0, 652.0]	360.98 [169.0, 621.0]	366.94 [132.0, 550.0]	34.7%
IgG3	Mean (mg/dL) [Range]	22.770 [3.34, 78.10]	23.484 [3.43, 81.40]	28.456 [8.54, 149.00]	25.357 [7.08, 61.30]	27.588 [4.90, 133.00]	21.2%
IgG4	Mean (mg/dL) [Range]	27.401 [2.44, 98.80]	27.701 [8.26, 86.20]	39.025 [17.60, 96.30]	38.124 [19.40, 82.80]	38.068 [13.00, 93.70]	40.9%

^a Change from IV to SC (%) = (mean trough concentration in SC Week 9 - mean trough concentration in IV#2) ÷ mean trough concentration in IV#2 × 100.

Source: Reproduced from applicant's table 9-7.

The average trough levels of bacterial antibodies generally increased at SC Week 9 with a larger increase observed at SC Week 17. These increases were maintained throughout the SC phase at the Final Study Visit. The trough levels of bacterial antibodies were consistent across the different age groups after subjects switched from the IV to SC administration.

Trough levels of measles antibodies were measured at IV Study Visit #2 and the SC Final Visit/Early Termination Visit phases. The trough levels were comparable between IV and SC phases and across individual age groups except for the ≥2 to ≤5 where there was an increase in mean measles antibody titers from the IV phase (0.475 IU/mL) to the SC phase (1.120 IU/mL), although there were only 2 subjects in this group.

6.1.11.2 Analyses of Exploratory Endpoints

Infections of Any Kind

Total infections included 29 infections in the run-in phase, 17 in the IV phase, 48 in the SC phase. The rate of events per person per year was comparable between phases. Run-in (2.447; 95% CI [1.608-3.537], IV phase (3.486; 95% CI [2.133-5.318]), combined

run-in+IV phases (2.750; 95% CI [1.937-3.764]), and SC phase (2.367; 95% CI [1.601-3.345]). The most frequent events were sinusitis (7/53, 13.2% in the combined Run-in + IV phases), and sinusitis and respiratory tract infection in the SC phase (9/49, 18.4% and 5/49, 10.2%, respectively). The incidence of all infections were comparable between the SC phase and combined Run-in +IV phases. The percentage and number of subjects who had at least one infection for each study phase is as follows: Run-in phase, 45.5% (20/44 subjects) , IV phase, 26.9% (14/52 subjects), run-in+IV phases 50.9% (27/53 subjects) SC phase, 53.1% (26/49 subjects). The Infections are summarized in table 12.

Table 12. Infections of Any Kind Occurring in ≥2 Subjects in the Combined Run-in+IV Phases or SC Phase (Safety Population)

System Organ Class Preferred Term	Study Phase			
	Run-In (N=44) n (%)	IV (N=52) n (%)	Run-in+IV (N=53) n (%)	SC (N=49) n (%)
No. of infections	29	17	46	48
Subjects with at least 1 infection	20 (45.5)	14 (26.9)	27 (50.9)	26 (53.1)
Infections and infestations	20 (45.5)	14 (26.9)	27 (50.9)	26 (53.1)
Sinusitis	5 (11.4)	3 (5.8)	7 (13.2)	9 (18.4)
Upper respiratory tract infection	3 (6.8)	0	3 (5.7)	5 (10.2)
Bronchitis	2 (4.5)	2 (3.8)	3 (5.7)	3 (6.1)
Pharyngitis streptococcal	1 (2.3)	0	1 (1.9)	3 (6.1)
Acute sinusitis	2 (4.5)	1 (1.9)	3 (5.7)	2 (4.1)
Gastroenteritis viral	1 (2.3)	0	1 (1.9)	2 (4.1)
Influenza	1 (2.3)	0	1 (1.9)	2 (4.1)
Otitis media	1 (2.3)	1 (1.9)	2 (3.8)	2 (4.1)
Cellulitis	0	0	0	2 (4.1)
Skin infection	0	1 (1.9)	1 (1.9)	2 (4.1)
Urinary tract infection	4 (9.1)	0	4 (7.5)	2 (4.1)
Vulvovaginal mycotic infection	0	0	0	2 (4.1)
Ear infection	1 (2.3)	1 (1.9)	2 (3.8)	1 (2.0)
Gastroenteritis	0	2 (3.8)	2 (3.8)	0
Summary				
Annualized rate of events ^a (mean±SD)	2.292±3.220	3.518±6.437	2.753±3.573	2.571±3.928
Total Duration of Exposure (years)	11.85	4.88	16.73	20.28
Rate of events per person per year ^b	2.447	3.486	2.750	2.367
System Organ Class Preferred Term	Study Phase			
	Run-In (N=44) n (%)	IV (N=52) n (%)	Run-in+IV (N=53) n (%)	SC (N=49) n (%)
95% CI ^c	1.608-3.537	2.133-5.318	1.937-3.764	1.601-3.345

Note: For incidence, at each level of summation (system organ class and preferred term), subjects are counted only once per study phase.

^a Annualized rate of events is calculated for each individual subject as the number of events divided by the duration of exposure in years for the subject.

^b Rate of events per person per year is calculated as the total number of events divided by the total duration of exposure in years across all subjects.

^c 95% CI is determined from a generalized linear model for Poisson regression for the log-transformed number of events with log-transformed duration of exposure in years as an offset variable.

Source: This table is reproduced from the applicant's table 10-23.

Validated Infections

Infections were validated if documented by positive radiograph, fever ($>38^{\circ}\text{C}$ oral or $>39^{\circ}\text{C}$ rectal), culture, diagnostic testing for microorganisms, e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test) or other evaluation (e.g., nasal smear, physical examination, strep test).

There were seven validated infections in the run-in phase, four in the IV phase, eleven in the combined run-in+IV phases, and ten in the SC phase. The rate of events per person per year was comparable between the IV phases and SC phase: run-in (0.591, 95% CI [0.307-1.012]), IV phase (0.820, 95% CI [0.367-1.548]), combined run-in+IV phases (0.658, 95% CI [0.378-1.051]), and SC phase (0.493, 95% CI [0.273-0.809]). Across age groups, the annualized rate of events was comparable between the SC phase and the combined run-in +IV phases with the exception of the >12 to ≤ 16 -year-old age group in which the combined run-in+IV phases had higher rates of events per person (0.917, 95% CI [0.175-2.676]) and mean annualized rate of events (0.927 [1.450]) than the SC phase (0.00 for both parameters).

Days on Antibiotics:

The rate of therapeutic antibiotic treatment was higher in the SC phase and IV phase than the run-phase and combined run-in + IV phases. This was consistent across age categories. Subjects might be receiving both prophylactic and therapeutic antibiotics. The applicant's table summarizes these findings for the Safety Population.

Table 13. Days on Antibiotics (Safety Population)

Antibiotic Type	Characteristic	Study Phase			
		Run-in (N=44)	IV (N=52)	Run-in+IV (N=53)	SC (N=49)
Prophylactic	Total number of days on antibiotics	383	187	570	561
	Annualized rate of days ^a (mean±SD)	35.286±107.0776	40.438±128.1305	37.450±113.7847	31.081±102.8023
	Min, Max	0.00, 369.60	0.00, 594.84	0.00, 435.84	0.00, 386.12
	Total duration of exposure (years)	11.85	4.88	16.73	20.28
	Rate of days per person per year ^b 95% CI ^c	32.322 (15.837 - 57.533)	38.350 (19.588 - 66.411)	34.080 (17.842 - 58.045)	27.660 (13.647 - 49.011)
Therapeutic	Total number of days on antibiotics	173	137	310	586
	Annualized rate of days ^a (mean±SD)	13.388±28.5034	28.183±52.5590	16.183±28.7717	27.074±63.0440
	Min, Max	0.00, 159.80	0.00, 161.14	0.00, 160.11	0.00, 367.41
	Total duration of exposure (years)	11.85	4.88	16.73	20.28
	Rate of days per person per year ^b (95% CI) ^c	14.600 (8.508 - 23.075)	28.096 (17.011 -43.188)	18.535 (12.102 - 26.922)	28.893 (17.291 - 44.792)

^a Annualized rate of days is calculated for each individual subject as the number of days divided by the duration of exposure in years for the subject.

^b Rate of days per person per year is calculated as the total number of days divided by the total duration of exposure in years across all subjects.

^c 95% CI is determined from a generalized linear model for Poisson regression for the log-transformed number of days with log-transformed duration of exposure in years as an offset variable.

Source: Reproduced applicant's table 10-26.

Clinical Reviewer's Comment: No significant inference can be made related to IGSC 20% versus IGIV-C 10% from these data. It appears that days on therapeutic antibiotics is comparable for the SC and IV phases; however, the confidence interval is wide which reduces the ability to ascertain a true difference in the rate of antibiotic use in different phases of the study. The antibiotic use during the SC phase of the study is similar to that of other SCIG products.

Hospitalizations due to Infections:

The rates of hospitalizations due to infections across all age categories and all phases of the study were similar. There were no hospitalizations in the run-in phase, 1 in the IV phase as previously mentioned (pneumonia followed by sepsis) and in the SC phase, 1 hospitalization due to cat bite cellulitis leading to sepsis.

Absences from Work or School Due to Infection:

Absences from work, school and daily activities due to infections and related treatment were relatively equivalent across the study phases as seen in table 14.

Table 14. Rate of Days of Work, School, and Daily Activities Missed Due to Infections and Related Treatment (Safety Population)

	Run-In (N=44)	IV (N=52)	Run-In +IV (N=53)	SC (N=49)
Rate of Days per Person per Year ^a	3.207	2.666	3.049	2.268
(95% CI) ^b	(1.494 - 5.898)	(1.180 - 5.063)	(1.584 - 5.221)	(1.055 - 4.174)

^a Rate of days per person per year is calculated as the total number of days divided by the total duration of exposure in years across all subjects.

^b 95% CI is determined from a generalized linear model for Poisson regression for the log-transformed number of days with log-transformed duration of exposure in years as an offset variable.

Source: Adapted from applicant's table 10-28 from CSR.

6.1.11.3 Subpopulation Analyses

This was a homogeneous study population and due to the small number of subjects, subpopulation analyses were not possible. This study is not designed to be able to detect differences in clinical outcomes among sub-populations.

6.1.11.4 Dropouts and/or Discontinuations

A total of six subjects did not meet screening criteria, two additional subjects voluntarily withdrew during screening. During the run-in phase, one subject was lost to follow-up. During the IV phase, two subjects withdrew from the study and one subject had the adverse event of pneumonia and sepsis. In the SC phase, two subjects withdrew from the study, and five subjects had AEs (nodules at the SC infusion sites; unable to tolerate needles; refusal of blood draw; arthralgia and muscle pain in shoulder, back and calves; erythematous papules and plaques).

6.1.11.5 Exploratory and Post Hoc Analyses

The relevant pre-specified exploratory analyses that contributed to clinical demonstration of effectiveness are presented above. No post hoc analyses were done.

6.1.12 Safety Analyses

6.1.12.1 Methods

Adverse events were assessed and classified by the Investigators. If the causality was "definite," "probable," "possible," or "doubtful/unlikely," the event was defined as a suspected adverse drug reaction (ADR). A suspected ADR with a causal relationship of "definite" was defined as an adverse reaction (AR); thus, ARs were a subset of suspected ADRs. If the causal relationship was labeled as "unrelated," then it was considered that the AE was not imputable to the study treatment and it was not a suspected ADR. AEs were classified as treatment-emergent AEs (TEAEs) or non-treatment emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start of study treatment (i.e., start of the infusion at Run-In Visit 1 for

subjects who were enrolled into the Run-In Phase, or at IV#1 for subjects who were enrolled directly into the IV Phase). A TEAE was defined as an AE which occurred on or after the start of study treatment. The incidence of AEs, suspected ADRs, ARs, non-serious AEs, SAEs, and AEs by severity and causal-relationship to the investigational product was summarized by study phase using descriptive statistics. At each level of summation, a subject was only counted once per system organ class or preferred term using the most severe or highest causal relationship AE. All infections and local ISRs that met the definition of an AE were summarized with other AEs.

Exposure to IP:

The mean volume infused per site per infusion was 20.6mL/site (SD: 11.51mL/site). The volume of infusion was influenced by age as the dosing is specified in mg/kg dose of IGSC 20%. The mean volume in subjects (≥ 2 and ≤ 5 years) was 9.7 mL/site (SD: 3.29 mL/site). The mean volume in the adult subjects (>16 years) was 21.7 mL/site (SD: 12.77 mL/site). The abdomen and thigh were most common sites for infusion. Subjects used four, followed by two infusion sites per infusion, 56.2% and 30.5% respectively. Table 15 summarizes SC infusions in the safety population.

Table 15. Summary of SC infusions (Safety Population)

SC Infusions	Study Phase SC (N = 49)
Total number of SC infusions	1053
Number of infusion sites used per infusion (mean±SD)	3.3±1.06
No. of infusion sites used per infusion ^a	No. of infusions (% of infusions)
1	30 (2.8)
2	321 (30.5)
3	86 (8.2)
4	592 (56.2)
6	24 (2.3)
Distribution of SC infusion sites	
Total number of subjects infused ^b	49
Abdomen, n (%)	46 (93.9)
Thigh, n (%)	19 (38.8)
Buttocks, n (%)	3 (6.1)
Side(s), n (%)	3 (6.1)
Arm, n (%)	1 (2.0)
Back, n (%)	1 (2.0)
Hip, n (%)	1 (2.0)
Total number of SC infusion sites used ^c	3442
Abdomen, n (%)	2513 (73.0)
Thigh, n (%)	746 (21.7)
Buttocks, n (%)	83 (2.4)
Arm, n (%)	46 (1.3)
Side(s), n (%)	32 (0.9)
Back, n (%)	18 (0.5)
Hip, n (%)	4 (0.1)
Volume infused per site per infusion (mL/site) ^d (mean±SD)	20.6±11.51
Infusion rate per site per infusion (mL/hour/site) ^e (mean±SD)	16.0±6.90
By-subject maximum volume infused per site per infusion (mL/site) (mean±SD)	23.5±20.29
By-subject maximum infusion rate per site per infusion (mL/hour/site) (mean±SD)	17.5±8.09

^aThe denominator for the percentages is the total number of SC infusions

^bSC infusion sites are not mutually exclusive. The denominator for the percentages is the total number of subjects infused.

^cThe denominator for the percentages is the total number of SC infusion sites used.

^dVolume infused per site (mL/site) = total volume infused (mL) / total number of infusion sites.

^eInfusion rate per site (mL/hour/site) = total infusion rate (mL/hour) / total number of infusion sites.
Source: Reproduced from applicant's submission, table 10-2.

Clinical Reviewer's Comment: The safety population included all subjects who received any amount of study drugs (IGIV-C 10% and/or IGSC 20%). From the total safety population, 11 subjects were excluded from the safety analysis. Three subjects had insufficient IgG concentration data to allow calculation of the AUC parameter in either

the IV or SC phase for the PK analysis. Eight subjects were not dosed and therefore were excluded from the Safety, IgG and PK analyses.

Protocol Deviations by Subject (Safety Population)

There were 41/53 subjects with at least 1 major protocol deviation (77.4% of the safety population). Only three subjects were without any protocol deviation and 50 (94.3%) had at least one protocol deviation. The most common major protocol deviation involved the consent process (31 subjects or 51.6%), followed by the IP not handled/stored appropriately (11 subjects or 17.7%) and IP not dosed correctly (6 subjects or 9.7%). Table 16 summarizes protocol deviations.

Table 16. Summary of Protocol Deviations by Subject (Safety Population)

Characteristic	Total N=53 n (%)
Subjects without any protocol deviation	3 (5.7)
Subjects with at least one protocol deviation ^a	50 (94.3)
Subjects with at least one major protocol deviation ^a	41 (77.4)
Number of major protocol deviations	62 (100.0)
Type of major protocol deviation^b	
Consenting process incomplete or not done properly	32 (51.6)
IP was not handled/stored appropriately	11 (17.7)
IP was not dosed correctly	6 (9.7)
Exclusion criteria met	4 (6.5)
Unauthorized staff performed assessment	4 (6.5)
Procedure/assessment or visit not performed (missing)	2 (3.2)
Procedure/assessment not performed in order per protocol	1 (1.6)
SAE reporting not within required timeframe	1 (1.6)
Subject did not enroll in correct treatment phase	1 (1.6)

^a The denominator is the number of subjects in the Safety Population

^b Protocol deviations are not mutually exclusive. The denominator is the number of major protocol deviations.

Source: This table is reproduced from the applicant's table 8-2.

The high number of major deviations in the consenting category were mainly due to lack of proper execution of the Health Insurance Portability and Accountability Act of 1996 (HIPPA) form at multiple study centers for multiple subjects at the time of subject consent. The HIPPA form for these subjects was signed at a later study visit.

Clinical Reviewer Comments: Although there was a high number of protocol deviations, these do not appear to have affected interpretability and generalizability of the data.

6.1.12.2 Overview of Adverse Events

In study GTI1502, there were no deaths. There were no SAE that were related to the study product according to the Investigator, applicant and FDA clinical reviewer. Four subjects withdrew from the SC phase of the study due to adverse reactions which were infusion site nodules, infusion site discomfort, skin papules/plaques, and arthralgia/myalgia.

There were 236 AEs in the safety population, of which 220 were considered TEAEs, occurring after a dose of either IGSC 20% or IGIV-C. Most (141, 64%) TEAEs occurred during the SC phase of the study; there were only 52 (24%) during the run-in phase and 27 (12%) during the IV phase. 84% (41/49) subjects had a TEAE during the SC phase of the study, including 79% (11/14) of the children enrolled in the study. The TEAEs were generally similar between children and adults. Table 17 shows the most common TEAEs by SOC and PT during the SC phase of the study. Most AEs were mild or moderate in severity.

Table 17. Adverse Reactions besides infections in > 5% Safety Population during SC Phase of GTI1502

Adverse Reaction*	By Subject n (%)[†] (N=49 subjects)	By Infusion n (rate)[‡] (N=1053 infusions)
Infusion site erythema	19 (39%)	123 (0.117)
Infusion site pain	9 (18%)	32 (0.030)
Infusion site swelling	8 (16%)	124 (0.118)
Infusion site bruising	8 (16%)	26 (0.025)
Infusion site nodule	8 (16%)	13 (0.012)
Infusion site pruritus	5 (10%)	28 (0.027)
Infusion site induration	4 (8%)	6 (0.006)
Infusion site scab	3 (6%)	6 (0.006)
Infusion site edema	3 (6%)	5 (0.005)
Cough	3 (6%)	4 (0.004)
Diarrhea	3 (6%)	3 (0.003)

* Including all adverse reactions that occurred after the first dose of XEMBIFY regardless of causality, excluding infections.

[†] Number and percentage of subjects with the adverse reaction.

[‡] Rate per infusion is calculated as the total number of adverse reactions divided by the total number of infusions.

Source: Applicant's table in response to labeling discussions.

There were 61 ADRs, 0.06 per infusion during the SC phase of the study. Most were local ISR. The incidence of TEAEs within 72 hours of infusion is of interest due to the temporal relationship with the infusion. Table 18 summarizes these results.

Table 18. Incidence of TEAEs Commencing During or Within 72 hours of an Infusion by Study Phase (≥5% of Subjects) Safety Population

Preferred Term	Study Phase			
	Run-in (N = 44) n (%)	IV (N = 52) n (%)	Run-in+IV (N = 53) n (%)	SC (N = 49) n (%)
Number of subjects with at least 1 TEAE during or within 72 hours of an infusion	7 (15.9)	4 (7.7)	10 (18.9)	35 (71.4)
Infusion site nodule	0	0	0	5 (10.2)
Infusion site bruising	0	0	0	3 (6.1)
Infusion site pain	0	0	0	3 (6.1)
Sinusitis	1 (2.3)	1 (1.9)	2 (3.8)	3 (6.1)
Upper respiratory tract infection	0	0	0	3 (6.1)

Note: At each level of summation (preferred term), subjects are counted only once per study phase.

Source: This is replicated from applicant's table 10-10.

Reviewer's Comment:

While ISRs were considered by the applicant to be TEAEs only if the signs/symptoms led to infusion interruption or discontinuation, required concomitant medication, or had a general impact on the subject's general condition as per the Investigator. This reviewer considers all ISRs to be AEs.

To further evaluate ISRs, the total number of local ISRs reported were 390, of which 41 were considered to be AEs by the applicant. 349 were not considered to be AEs. The rate of local ISRs per infusion was 0.370 or 37% (390 events/1053 infusions). The rate of local ISRs in recently approved CUTAQUIG Immune Globulin Subcutaneous (Human), 16.5% Liquid was twenty-three percent (814 local ISRs/3497 infusions). With XEMBIFY, the highest rate of local infusion site reaction (ISRs) occurred when infused in the thigh 73.5% (205 ISR/279 infusions); followed by the abdomen 18.4% (142 ISR/773 infusions). Of the most commonly used sites, abdomen, followed by thigh, then arm (23 infusions), back (5 infusions), buttocks (26 infusions), and side (15 infusion and one ISR), it is logical that the most common infusion sites would have more reactions. However, clearly there is a higher number of ISRs when using the thigh versus the abdomen as an infusion site. In the abdomen, the most common local ISR was infusion site erythema (39) followed by infusion site bruising (17). In the thigh, infusion site swelling (94) followed by infusion site erythema (83). See table 19 for more details.

Table 19. Rates of Local Infusion Site Reactions Per Infusion During the SC Phase (≥ 0.02 , non-TEAEs) (Safety Population)

Preferred Term	Infusion Site							Total n (rate)
	Abdomen n (rate)	Thigh n (rate)	Arm n (rate)	Hip n (rate)	Back n (rate)	Buttocks n (rate)	Side(s) n (rate)	
Number of infusions	773	279	23	1	5	26	15	1053
Number of infusion site reactions	142 (0.184)	205 (0.735)	1 (0.043)	0	0	0	1 (0.067)	349 (0.331)
Infusion site erythema	39 (0.050)	83 (0.297)	0	0	0	0	0	122 (0.116)
Infusion site swelling	28 (0.036)	94 (0.337)	0	0	0	0	0	122 (0.116)
Infusion site pain	29 (0.038)	0	0	0	0	0	0	29 (0.028)
Infusion site pruritus	14 (0.018)	13 (0.047)	0	0	0	0	0	27 (0.026)
Infusion site bruising	17 (0.022)	6 (0.022)	0	0	0	0	0	23 (0.022)
Infusion site induration	4 (0.005)	0	1 (0.043)	0	0	0	0	5 (0.005)
Infusion site nodule	0	3 (0.011)	0	0	0	0	1 (0.067)	4 (0.004)

Note: Rate is calculated as the number of local infusion site reactions (events) divided by the number of infusions.

At each level of summation (preferred term), infusion site reactions (events) are counted only once if they occurred at the same infusion site and visit in the same subject.

Source: This table is replicated from applicant's table 10-18.

On 26 April 2019, a revised table was requested to identify infusion site reactions that occurred in $\geq 5\%$ of subjects to better ascertain the most commonly seen reactions. This information is presented in Table 20.

Table 20. Infusion Site Reactions in > 5% of Subjects Associated with Infusions of XEMBIFY

Infusion Site Reaction*	By Subject n (%)[†] (N=49 subjects)	By Infusion n (rate)[‡] (N=1053 infusions)
Infusion site erythema	19 (38.8%)	123 (0.117)
Infusion site pain	9 (18.4%)	32 (0.030)
Infusion site swelling	8 (16.3%)	124 (0.118)
Infusion site bruising	8 (16.3%)	26 (0.025)
Infusion site nodule	8 (16.3%)	13 (0.012)
Infusion site pruritus	5 (10.2%)	28 (0.027)
Infusion site induration	4 (8.2%)	6 (0.006)
Infusion site scab	3 (6.1%)	6 (0.006)
Infusion site edema	3 (6.1%)	5 (0.005)

* Including all infusion site reactions regardless of whether they met the criteria of adverse events specified in the study protocol.

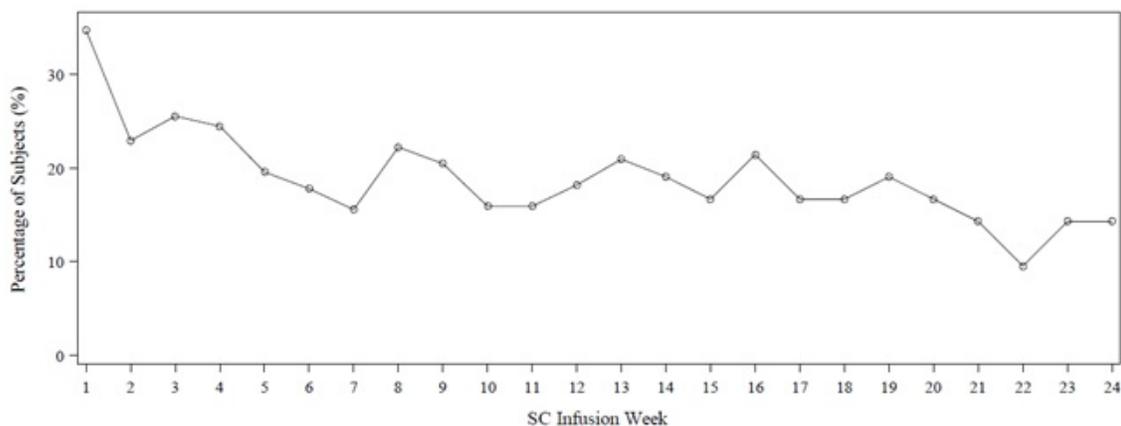
† Number and percentage of subjects with the infusion site reaction.

‡ Rate per infusion is calculated as the total number of infusion site reactions divided by the total number of infusions.

Source: Applicant's table in response to IR from 26 April 2019.

Infusion site reactions declined over-time, as depicted in Figure 2.

Figure 2. Percentage of Subjects with ISRs by SC Infusion Week in Safety Population



Source: Replicated from Applicant's Figure 14.3.1/1.

Clinical Reviewer's Comment: This reviewer believes that the decline in ISRs is not related to subject drop-out, but due to a decline in the number of actual ISRs. This is consistent with the human experience for other products in the class.

6.1.12.3 Deaths

There were no deaths reported during this study.

6.1.12.4 Nonfatal Serious Adverse Events

There were 6 SAE occurring in 3 subjects in the safety population of GTI1502. One adult subject while receiving IGIV-10% had pneumonia and sepsis. One adult subject while receiving IGSC-20% had cellulitis and sepsis following a cat bite. One adult subject had worsened neck pain due to degenerative disc disease that required hospitalization. The Investigator considered this SAE to be unrelated to the investigational product.

Clinical Reviewer Comments: This reviewer agrees with the Investigators adjudication of the degenerative disc disease being unrelated to the study product. The SBI that occurred prior to the subject receiving IGSC-20% was not informative, and the SBI that occurred on IGSC-20% was discussed in the efficacy section.

6.1.12.5 Adverse Events of Special Interest (AESI)

There were no thromboembolic events, renal insufficiency, cases of anaphylaxis/hypersensitivity or aseptic meningitis reported.

6.1.12.6 Clinical Test Results

Two subjects had Coombs tests that were positive in the run-in phase with one possibly related to the study of mild severity that did not resolve. The other subject had elevated Coombs direct test positive categorized as mild, doubtful or unlikely to be related to the study and this resolved. In the SC phase one subject had a moderately elevated blood glucose, neutrophil count and increase in white blood cells that were unrelated and occurred on day 58 of the study. All of these abnormalities resolved. Another subject in the SC phase had moderately elevated alanine aminotransferase and aspartate aminotransferase and mildly elevated blood bilirubin level on day 170 that were considered doubtful or unlikely to be related to the study. These findings had not resolved.

Clinical Reviewer Comment: No clinical diagnosis of hemolysis were reported in the study. Most IGIV-associated hemolysis is thought to be extravascular hemolysis with nadir hemoglobin achieved approximately 7 to 10 days following administration.

6.1.12.7 Dropouts and/or Discontinuations

See section 6.1.11.4 of the review for additional details.

6.1.13 Study Summary and Conclusions

The results of study GTI1502 combined with interim pediatric data from the GTI1503 study provide substantial evidence of effectiveness and safety and thereby support the licensure of this product for treatment of PI in adults and children two years of age and older.

6.2 Trial #2

Pharmacokinetic Modeling and Simulation of Subcutaneous and Intravenous IgG Dosing in Primary Immunodeficiency Patients

6.2.1 Objectives (Primary, Secondary, etc.)

The aim of the study was to develop predictive population pharmacokinetic (PopPK) model for the administration of IGSC 20% in patients with PI to better inform clinical decisions on dosage regimens.

Objectives:

- Develop a PopPK model for characterization of PKs of IgG after single and repeated dosing by IGIV and IGSC route of administration in PI patients.
- Assess effects of patient-specific covariates on IgG concentrations
- Estimate relative bioavailability of IGSC administration and determine appropriate dose adjustment factor (DAF) that would result in comparable IgG exposure (i.e., AUC) when switching from IGIV to IGSC administration
- Simulate the IgG kinetics following different dosing regimens by subcutaneous (SC) route.
- Evaluate the impact of skipped doses with and without dose replacement following different IGSC dosing regimens.
- Evaluate the effect of loading doses on SC regimens for treatment-naïve patients.

6.2.2 Design Overview

Clinical study data from all PID patients who received both IGIV (Gamunex-C® 10%) and IGSC (Gamunex-C® 10% or IGSC20%) formulations were included in a population PK analysis. The data used were from three studies performed in the U.S. and Canada.

1. Study Number 060001. An open-label, single-sequence, crossover trial to evaluate the pharmacokinetics, safety, and tolerability of subcutaneous Gamunex-C® 10% in subjects with PID.
2. Study Number T5004-401. An open-label, single-sequence, crossover study to evaluate the pharmacokinetics, safety and tolerability of subcutaneous Gamunex-C® in pediatric subjects with PID.
3. Study Number GTI1502. An open-label, multi-center study to evaluate the safety and pharmacokinetics of IGSC 20% administered for 6 months in subjects with PID.

PopPK Methodology

The applicant started with simple PK models with first order elimination. *Administration of IGIV was modeled as an infusion directly into the central compartment.* According to the applicant, SC infusions were modeled as an exogenous IgG from the depot site into the central compartment as a first-order process with an absorption rate constant (K_A). The bioavailability (FSC) of IGSC was estimated. The assumption on endogenous plasma IgG (IgGENDO) concentrations was required as IgGENDO was not identifiable by the model. The IgGENDO assumption was made based on literature reports in patients with PID.

Individual subject, dose and infusion duration were included in the model. Various residual error models were also assessed.

PopPK modeling included the structural base model development, covariate analysis and model validations. The final PopPK model was used in simulation to predict serum PK profiles of IgG in various sub-populations identified to influence the PK of IgG after SC administration.

6.2.3 Population

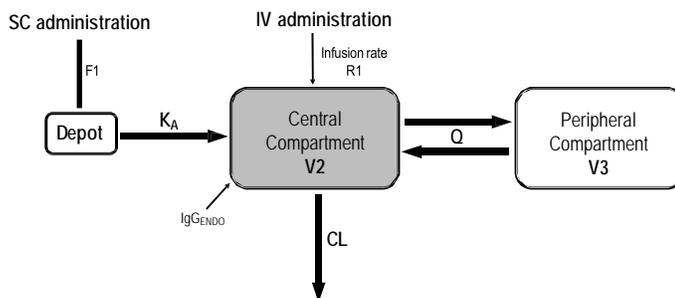
A total of 95 PID subjects from three studies were included in the PopPK analysis and 1594 serum IgG concentrations were included in the final PK dataset. Of the 95 subjects, 55 subjects were female (57.9%), 90 subjects (94.7%) were white and 5 subjects (5.3%) were classified as other (African American, American Indian and Alaska native). The number of adult subjects (aged ≥ 18 years) and pediatric subjects (aged 2-18 years) was 66 (69.5%) and 29 (30.5%), respectively. The median (range) of body weight from all subjects was 65.7 kg (16.7-153.0).

6.2.13 Study Summary and Conclusions

According to the applicant, serum IgG concentrations included trough concentrations and PK profiles from subjects after IGIV (95 subjects, 981 samples) and IGSC (85 subjects, 613 samples) administration. Each subject contributed with a median (range) of 11 (5-13) samples after IGIV treatment and of 6 (1-17) after IGSC treatment, which were collected up to 313 days of both administration routes. All subjects had previously been treated with stable doses of IGIV (Gamunex-C® 10%) at a dose interval of 3 or 4 weeks for at least 3 months and trough total serum IgG concentration levels (trough) were determined in all subjects prior to initiating study treatment regimen.

A two-compartment model with first-order elimination from the central compartment demonstrated good model stability and predictability for determining the PK of IgG following IV and SC administration. The PopPK model was externally validated against published IgG concentration data from different studies conducted following SC administration and described in the literature. See Figure 3 for a diagram of the applicant's schematic.

Figure 3. Diagram of Applicant's 2-compartment population PK model (IGIV+IGSC)



CL: clearance (L/day)
F1(F_{SC}): bioavailability of IGSC
R1: rate of intravenous infusion (g/day)
IgG_{ENDO}: endogenous serum IgG level (g/L)
K_A: first-order absorption constant of IGSC dose (day⁻¹)
Q: intercompartmental clearance (L/day)
V2: volume of distribution of central compartment (L)
V3: volume of distribution of peripheral compartment (L)
Bioavailability of IGIV was assumed as 1.0

Source: This Figure is reproduced from the applicant's submission.

The final model showed that IgG PK was not influenced by (a) the IGSC formulation used in the different studies (10% vs. 20%), (b) gender, and (c) age (pediatric vs. adult). Body weight was identified as a significant covariate having an effect on clearance.

The model was used to simulate trials conducted to test the equivalence of systemic IgG exposure following a switch from every-4-weeks IGIV dosing to biweekly IGSC, using either 1.0 or 1.37 based on current European and US labels, respectively. Using the 1.37 dose adjustment factor, steady-state biweekly IGSC was found to be similar that that of a single IGIV dose every 4 weeks, although with a lower peak and higher trough IgG concentration. This model predicts that biweekly IGSC 20% dosing may be a viable alternative to weekly SC therapy to allow more flexible and optimized dosage regimens for PI patients. Table 21 demonstrates the predicted change according the Applicant's model.

Table 21. Predicted median ratios (5th-95th percentiles) of AUC, C_{max} and C_{trough} and IgG trough concentrations after switching between IgG dosing regimens. Dose adjustment factor of 1.37.

IgG dosing regimen switch		PK parameter			Predicted change in C _{trough} (%)
From:	To:	AUC	C _{max}	C _{trough}	
IGIV 10% (every 4 weeks)	IGSC 20% (weekly) ^a	0.973 (0.944-1.004)	0.612 (0.483-0.751)	1.218 (1.057-1.418)	22% increase
	IGSC 20% (biweekly) ^{a,b}	0.974 (0.948-0.998)	0.640 (0.513-0.779)	1.144 (0.999-1.321)	14% increase
Weekly IGSC 20%	IGSC 20% (biweekly) ^b	1.030 (0.884-1.133)	1.040 (0.890-1.153)	0.907 (0.817-1.044)	9% decrease
	IGSC 20% (2 times/week)	1.008 (0.851-1.132)	0.999 (0.836-1.124)	1.039 (0.879-1.156)	4% increase
	IGSC 20% (3 times/week)	0.981 (0.860-1.100)	0.969 (0.851-1.090)	1.024 (0.883-1.143)	2% increase
	IGSC 20% (5 times/week)	1.016 (0.911-1.182)	0.991 (0.901-1.168)	1.043 (0.939-1.217)	4% increase
	IGSC 20% (daily)	1.009 (0.896-1.067)	0.981 (0.883-1.050)	1.053 (0.922-1.117)	5% increase

Ratios based on comparison of second regimen vs. first regimen

^a Weekly dose assuming a dose adjustment factor of 1.37 when switching from IGIV dosing regimen

^b Biweekly dose = 2 x weekly dose

C_{max}: maximum IgG concentration

C_{trough}: minimum IgG concentration during a 28-day period (for the IGIV to IGSC 20% switches), a 14-day period (for the weekly to biweekly IGSC 20% switch), or a 7-day period (for the weekly to more frequent IGSC 20% switches).

AUC (area under the curve) calculated as

follows: AUC_{0-28days} for the IGIV to IGSC 20% switches

AUC_{0-14days} for the weekly to biweekly IGSC 20% switch

AUC_{0-7days} for weekly to more frequent IGSC 20% switches

Source: Replicated from the applicant's submission.

Modeling also evaluated skipped doses and recovery compensation in various dosing regimens and days skipped. The applicant also modeled the impact of a loading dose regimen and subsequent dosing to reach a maintenance level.

The applicant concluded that based on the PopPK model developed:

- The PK of IgG following IV and SC administration was adequately described by a two-compartment model with first-order elimination from the central compartment. Administration of IGIV was modeled as an infusion directly into the central compartment. Absorption of exogenous IgG from the depot site of SC infusions into the central compartment was modeled as a first-order process with an absorption rate constant (KA).
- Serum clearance (CL) of IgG, volume of distribution of the central and peripheral compartments, inter-compartmental clearance (Q), absorption constant from the depot (KA), and the absolute bioavailability of IgG after SC administration obtained from the modelling are consistent and comparable with previously reported values.
- PK of IgG was not influenced by the IgG formulation used in the different studies (10% vs. 20%), sex, and age (pediatric vs. adult). Body weight was

identified as the only covariate with a significant influence on the PopPK model.

- IgG exposure following a switch from every-4-weeks IGIV dosing to biweekly IGSC, using either 1.0 or 1.37 correction factors would be comparable and sufficient to provide clinically effective trough IgG concentrations.
- The same total weekly IGSC dose can be administered at different intervals (from daily to biweekly), with minimal impact on serum IgG concentrations.
- The simulation of IgG concentrations following IGSC treatment in PID patients which are treatment naïve showed that target IgG trough levels (7 g/L) may be reached within one week using a loading dose regimen of 5 times the weekly maintenance dose within the first week.
- All IGSC dosing regimens evaluated in this study provide viable alternative administration options to maintain adequate immunoprotection in PID patients, which increase the clinician benefit of dosing flexibility provided by a range of administration routes, dosages, and treatment regimens.

Clinical Reviewer's Comment: This reviewer found the modeling approach to be reasonable, but does not believe that these data can inform dosing since there are no available clinical safety data for dosing regimens beside weekly. This reviewer is particularly concerned about the safety ramifications for dosing every 2-weeks compared to weekly. Until there are clinical data, this reviewer does not support labeling the product for every 2-week dosing based solely on this modeling study.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1 Primary Immunodeficiency

Clinical Efficacy is based on study GTI1502. See section 6.1 for discussion of efficacy from this study to support licensure. Section 7 is not applicable to this application.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

No integrated summary of safety was included in the submission. The application initially only contained clinical data from the Phase 3 study, GTI1502. However, during the clinical review, a 120-day safety update with interim safety data from study GTI1503 was requested and provided by the applicant. GTI1503 is a non-IND, multi-center, open-label, single-arm trial to evaluate the efficacy, pharmacokinetics and safety of IGSC 20% in subjects who are at least 2 years of age with PI in Europe and Australia. (See Appendix 1 and 2 for additional information).

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Study GTI1502 was an open-label, uncontrolled, single arm, multi-center Phase 3 study. Subjects with PI from ages 2 and up were enrolled who had been receiving IGIV

treatments. Subjects were either entered into a Run-in phase with IGIV-C 10% if not previously on this product or entered directly into an IV phase for 2 doses with IGIV-C 10%. Subsequently all subjects were entered into the SC phase in which the IP IGSC 20% (XEMBIFY) was administered 7 days following IV#2 with IGIV-C 10% and administered weekly doses for 24 weeks using a calculated correction factor of 1.37 times the IGIV-C 10% dose divided by the weekly interval of IV dosing. The study duration was 6 months and primarily focused on dose and PK as well as safety.

There were no deaths. There were no cases of thromboembolic events, hypersensitivity reactions/anaphylaxis, aseptic meningitis, renal insufficiency, clinical hemolysis or suspected viral transmissions.

One subject during the IV phase had a SBI of pneumonia and sepsis, and 1 subject during the SC phase had a cat bite cellulitis resulting in sepsis. There were 5 withdrawals in the SC phase, 2 related to ISRs, 1 due to intolerability of the needle, 1 due to refusal for blood draws and 1 subject due to arthralgias. Other common AEs were related to infections, ISRs, cough and diarrhea. There were no significant hematologic laboratory changes across age group or phases of study from initiation of the study through completion.

Laboratory abnormalities that were considered possibly related to IGIV 20% included one subject who had moderate elevation of ALT and AST and mild elevation of BUN on day 170 in the SC phase. This did not resolve, but was considered doubtful/unlikely to be related to the study product.

Additional supportive safety data is from Study GTI1503. GTI1503 is an on-going non-IND, multi-center, open-label, single-arm trial to evaluate the efficacy, pharmacokinetics and safety of IGSC 20% in subjects who are at least 2 years of age with PI in Europe and Australia.

There have been no deaths. There have been no cases of thromboembolic events, hypersensitivity reactions/anaphylaxis, aseptic meningitis, renal insufficiency, clinical hemolysis or suspected viral transmissions. There were 9 SAEs; 3 occurred pre-treatment and 3 were unrelated due to hospitalizations for underlying conditions; 1 was a urinary tract infection (UTI), 1 was thrombocytopenia, 1 was nephrotic syndrome. All SAEs were considered unrelated. The subject who experienced the SAE of thrombocytopenia dropped-out of the study. There were no reports of study discontinuation due to an AEs. No common AEs were reported.

As study GTI1503 is still ongoing, datasets were not provided. Therefore, no pooled safety data were reviewed. Most sub-sections of section 8 are not applicable to this BLA. (Refer to Section 6.1 for data on study GTI1502 and Appendix 1 and 2 for additional data on study GTI1503).

8.4.1 Deaths

There were no deaths.

8.4.2 Nonfatal Serious Adverse Events

There were no investigational product-related SAEs.

8.4.3 Study Dropouts/Discontinuations

8.4.4 Common Adverse Events

8.4.5 Clinical Test Results

8.4.6 Systemic Adverse Events

8.4.7 Local Reactogenicity

8.4.8 Adverse Events of Special Interest

There were no cases of thromboembolic events, hypersensitivity reactions/anaphylaxis, aseptic meningitis, renal insufficiency, clinical hemolysis, or suspected viral transmissions reported.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

8.5.2 Time Dependency for Adverse Events

8.5.3 Product-Demographic Interactions

8.5.4 Product-Disease Interactions

8.5.5 Product-Product Interactions

8.5.6 Human Carcinogenicity

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This product does not have drug abuse potential.

8.5.8 Immunogenicity (Safety)

Immunogenicity is not routinely assessed in IGIV studies and was not assessed in the IP.

8.5.9 Person-to-Person Transmission, Shedding

Immune globulin products may have the potential for transmissible infectious diseases, but CMC and current state of science minimize the chance of the product containing infectious agents that would transmit to the subject. Therefore, it is unlikely that an infectious agent will be further transmitted from the recipient of this product to then support person-to-person transmission. No transmission was reported.

8.6 Safety Conclusions

XEMBIFY demonstrated a similar safety profile as other class members.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

GTI1502 did not enroll a sufficient number of children under 5 years of age to assess PK, efficacy and safety in this population. This study is insufficient as the sole source of efficacy and safety data for children aged 2-<5 years to support licensure of the IP.

Supportive data from pediatric subjects ages 2-5 years come from an ongoing study, GTI1503 (non-IND). GTI1503 is a prospective, multi-center, open-label, single-arm, efficacy, pharmacokinetic, safety and tolerability study of IGSC 20% in subjects with PI being conducted in Europe and Australia. The primary endpoint assesses the rate of SBI per subject-year after 52 weeks of IGSC 20%. Data from this study were submitted in a 120-day update to the BLA. The DAF from IGIV 10% to XEMBIFY was 1:1, rather than the 1.37 DAF used in GTI1502. Preliminary mean steady state trough concentration in four pediatric subjects ages >2-<5 years exceeded >500 mg/dL, and their mean trough ratio SC/pre-regimen fell within the range 0.88 to 1.34 (minimum and maximum, respectively), with a geometric mean of 1.034, (with 1:1 conversion factor) demonstrated bioequivalence. There were no SBIs in this age group.

Clinical Reviewer Comments: The totality of the safety and effectiveness data from GTI1502 with supportive data from GTI1503 support licensure of the product in children ages 2 and older.

9.1.1 Human Reproduction and Pregnancy Data

No clinical studies were conducted in pregnant subjects. Hence, no human data are available to indicate the presence or absence of drug-associated risk.

9.1.2 Use During Lactation

No clinical studies were conducted in lactating subjects. Hence, no human data are available to assess the presence or absence of XEMBIFY in human milk, the effects of XEMBIFY on the breastfed child, and the effects of XEMBIFY on milk production/excretion. Immunoglobulins, in particular IgA and IgM, are excreted into the milk³.

9.1.3 Pediatric Use and PREA Considerations

The original BLA application triggers PREA, as new immunoglobulin products are considered to contain new active ingredients.

On 2 March 2016, Grifols submitted an initial Pediatric Study Plan (PSP) for IGSC 20% requesting a partial waiver for the pediatric population 0 to less than 2 years of age and submission of a pediatric assessment for the population aged 2 to less than 17 years. FDA agreed to the PSP.

The combined pediatric safety, efficacy, and PK data from GTI1502 and GTI1503 fulfill the requirement as agreed in the PSP and provide data in the pediatric population ages > 2 years.

9.1.4 Immunocompromised Patients

XEMBIFY is indicated for primary immunodeficiency.

9.1.5 Geriatric Use

The small number of geriatric subjects (i.e., 4 adult subjects were aged >65 years) precluded assessment of efficacy and safety in the geriatric population.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

10. CONCLUSIONS

Based on the submitted data, XEMBIFY appears to be safe and effective for replacement therapy in primary humoral immune deficiency.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See table below.

³Hurley WL and Theil PK. Perspectives on Immunoglobulins in Colostrum and Milk. *Nutrients* 2011; 3:442-474.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Primary Immunodeficiency (PI) represents a heterogenous group of disorders resulting from inherited defects of the immune system. The major antibody deficiency syndromes of clinical significance include X-linked agammaglobulinemia (XLA), Common Variable Immunodeficiency (CVID), Wiskott-Aldrich Syndrome, Hyper IgM Syndrome, Severe Combined Immunodeficiency (SCID), Chronic Granulomatous Disease (CGD), and IgG subclass deficiency. Patients with PI are at increased risk for recurrent, severe respiratory tract infections (both viral and encapsulated bacterial in origin, particularly infections due to Pneumococcus and Hemophilus Influenza) as well as other infections. 	<ul style="list-style-type: none"> PI and its antibody deficiency syndromes are serious, chronic conditions associated with considerable morbidity and mortality. Immunoglobulin replacement therapy (administered by the intravenous or subcutaneous routes) has been shown to reduce the incidence of serious infections through provision of passive immunity.
Unmet Medical Need	<ul style="list-style-type: none"> There are multiple immunoglobulin products (both intravenous and subcutaneous) approved for PI, including four subcutaneous immunoglobulin products: Hyqvia®, Hizentra®, Cuvitru®, and Cutaquig®. Gamunex-C, an IGIV, is also indicated for subcutaneous administration in PI. 	<ul style="list-style-type: none"> There is no unmet medical need. Additional products may benefit patients in the event of a shortage.
Clinical Benefit	<ul style="list-style-type: none"> GTI1502: One six-month, open label, single-arm, non-controlled study of safety and pharmacokinetics was conducted at 21 sites in the U.S. and Canada that included a total of 53 subjects, including 16 pediatric subjects aged ≥2 to <16 years. PK, safety and efficacy data were submitted for 42 subjects who completed the study (30 adults and 12 pediatric subjects). Serious bacterial infections (SBIs) rate of 0.049 in the SC phase of the study supports efficacy of XEMBIFY GTI1503: Data submitted from the non-US study in Europe and Australia to evaluate XEMBIFY in a 1:1 dose adjustment factor provides supportive safety and effectiveness data based on trough levels in children ages 2 through 4 years of age 	<ul style="list-style-type: none"> PK data demonstrate that the product is bioequivalent to an approved IVIG product. The product is effective in preventing SBIs in adults and children ages 2 -16.
Risk	<ul style="list-style-type: none"> The most common risks of XEMBIFY administration identified in the clinical studies are local infusion site reactions to include nodule, bruising, pain and erythema. The majority of infusion site reactions were mild and did not require suspending infusions and resolved without sequelae. The most frequent systemic adverse reactions (suspected adverse reactions plus adverse reactions) occurring in the setting of XEMBIFY administration excluding infections were arthralgia and myalgia. There were no deaths, thrombotic events, clinical hemolysis events, anaphylaxis, or aseptic meningitis events reported. Two SAEs occurred but were not related to SC administration of XEMBIFY. It cannot presently be excluded that any or all risks of IGSC listed in WARNINGS AND PRECAUTIONS for IGSC product, such as thrombosis or hemolysis, may also occur following XEMBIFY® administration; however, based on their lack of observation of confirmed cases in study GTI1502, the maximum incidence of any of the listed reactions in adults is expected to be less than 10%. 	<ul style="list-style-type: none"> The frequency (i.e. percent of subjects) with local infusion site reactions observed with XEMBIFY is slightly higher than that observed with other approved SCIG products (i.e., Cutaquig®, Hyqvia®, Hizentra®, and Cuvitru®) It may be that the higher the concentration of SC product, the more local ISRs are to be expected. However, the number of infusions that required intervention or cessation was small. The rate of infections, both serious and non-serious combined was similar to the rates reported during clinical trials of U.S-licensed IGSC products.

Clinical Review

BLA 1256830, XEMBIFY

Risk Management	<ul style="list-style-type: none">• Subcutaneous immune globulin products carry an obligate boxed warning for thrombosis.• Other serious risks of immune globulin products include hypersensitivity and anaphylaxis, especially in IgA deficient patients with antibodies to IgA, decline in renal function, hemolysis, TRALI, aseptic meningitis, and transmission of infectious agents.	<ul style="list-style-type: none">• Patients should be monitored for signs and symptoms of hypersensitivity, aseptic meningitis syndrome, hemolysis, and TRALI.• Patients should be informed that XEMBIFY™ is manufactured from human plasma and hence, may contain transmissible infectious agents.• Routine post marketing surveillance is recommended.
------------------------	--	---

Table 22. Risk-Benefit Framework

11.2 Risk-Benefit Summary and Assessment

Given the substantial morbidity and mortality risk from serious bacterial infections inherent in PI and the generally favorable safety profile observed in the IND Phase 3 trial, this reviewer considers the benefit-risk profile of the product as a treatment for PI favorable.

11.3 Discussion of Regulatory Options

The regulatory options for this BLA submission are approval or a complete response(CR).

11.4 Recommendations on Regulatory Actions

The Clinical Reviewer recommends approval for the BLA, since the clinical benefits of XEMBIFY outweigh its risks, given the favorable safety profile and demonstrable efficacy in preventing SBIs among study subjects with PI.

11.5 Labeling Review and Recommendations

At the time of this review, labeling negotiations concluded.

The primary clinical issues requiring revision were as follows:

- Dosing to exclude every two-week dosing since the PopPK study is not sufficient without safety data
- Dosing and Administration section for clarity and to be consistent with GTI1502 trial experience
- Warning and Precautions section to be consistent with class labeling
- Safety section to provide information that will be informative to patients and prescribers and accurately reflects the GTI1502 clinical trial experience.
- Revise the clinical trial experience to more accurately describe the clinical trial and to provide more information about clinical efficacy
- Include appropriate laboratory monitoring tests under the hemolysis section

For more details, including information on name and formatting of the label, please refer to the labeling review memo.

11.6 Recommendations on Postmarketing Actions

Routine post-marketing surveillance is appropriate for the product. Since the data in the BLA combined with 120-day update data regarding SBIs and IgG trough data from the ongoing GTI1503 study provide sufficient safety, PK, and efficacy information to support licensure of the product to treat PI in children ages 2 and older, the applicant will not need to conduct post-marketing studies in children.

Appendix 1: GT11503

GT11503 is a non-IND multi-center, open-label, single-arm trial to evaluate the efficacy, pharmacokinetics and safety of IGSC 20% in patient with PI in Europe and Australia that is ongoing with data lock anticipated for July 2019. Approximately 60 subjects will be enrolled in order to have approximately 20 adult and 20 pediatric subjects treated with IGSC 20% who complete the entire study. The study includes a Screening/Previous Regimen Phase, IGSC 20% Treatment Stage 1 (13 IGSC 20% weekly doses), and IGSC 20% Treatment Stage 2 (39 IGSC 20% weekly doses).

In the previous regimen phase, whether IGIV or IGSC, subjects undergo two infusions in the clinic to obtain 2 trough IgG levels. Subjects entering on SCIG will obtain the second trough level and immediately have an initial infusion of IGSC 20%.

Treatment Stage 1 begins with the first dose of the IP, IGSC 20%. It is infused as a 1:1 dose-equivalent regimen. All subjects receive 13 IGSC 20% infusions at weekly intervals. Dosing occurs at the clinical site for SC#1,3,5,9,13. All other dosing may be accomplished at home.

If trough level is below 500mg/dL, a dose adjustment will be made at clinic visits.

Subjects enter Treatment Stage 2 after the 13th dose and there are no dose adjustment permitted in this phase unless medically necessary. PK sampling is performed in a subset of adult subjects to serve as a PK subset at SC#17. A total of 52 doses of IGSC 20% will be administered (13 +39 weekly doses combining stage 1 and 2) with a follow up visit at week 53.

The primary objective of the Phase 3 study is to evaluate whether weekly administered IGSC 20% over a one year period will achieve less than 1 SBI per subject per year in PI subjects.

Secondary objectives:

To determine if IGSC 20% replacement therapy maintains mean trough IgG levels that are comparable to the mean trough blood levels with the previous IgG replacement regimen.

Safety objectives:

To assess the safety and tolerability of IGSSC 20% as an IgG replacement therapy in subjects with PI.

Endpoints:

The primary efficacy variable is the number of SBIs.

Secondary endpoint is trough concentrations of total IgG of previous regimen as compared to IGSC 20% replacement therapy to maintain mean trough IgG levels that are comparable.

The first subject enrolled on 29 June 2016 and the first dose of IGSC 20% was administered 3 August 2016. The study is still in the clinical phase. See table 23 for demographic data.

Table 23 GTI1503 Demographic Characteristics

Demographic variables		Total (N=61) n (%)
Age Category (years)	<18	31 (50.8)
	18-64	27 (44.3)
	≥65	3 (4.9)
Sex	Male	42 (68.9)
	Female	19 (31.1)
Race	White	57 (93.4)
	Black or African	0
	Asian	0
	American Indian or Alaska Native	2 (3.3)
	Unknown	2 (3.3)

Source:

On 22 August 2018 FDA requested a status on the non-IND study GI1503 referenced in the Pediatric Study plan section of the BLA. A request for the number of subjects enrolled and whether the study is ongoing or complete. The applicant responded on 23 August 2018 indicating that the study was ongoing and estimated completion date May 2019 and 61 subjects enrolled.

On 31 August 2018, FDA requested all available interim safety data as a 120-day safety update to include GTI1503, but not limited to data from this study protocol. The applicant responded that IND 016528 included safety data information for both GTI1502 and GTI1503 from 1 June 2017 through 31 May 2018. The applicant stated that 120 safety update would not be available until November 2018 for which Grifols committed to submit. FDA also requested key revisions to the original protocol and their dates of implementation of the non-IND study GI1503.

Clinical Reviewer's Comments: These revisions were provided and reviewed. None of the revisions present any specific clinical concerns that would alter the interpretation of the data. The inclusion of all infusion site reactions improves the quality of the data. For full details see copied submission response below.

FDA also requested case reports for any serious adverse events (SAEs) that may have occurred and the assessment of whether any SAE is related to the study drug. Grifols reported 9 SAEs: 3 individuals were pre-treatment, and 6 SAEs were not related to the study product. Case reports were submitted for each individual.

On 21 December 2018, FDA requested individual subject and group mean data for the age 2-5 years pediatric subgroup for GTI1503 to include IgG trough titers, adverse events and SBIs. and the reason for any withdrawals. Also requested for the GTI1502 study was a table summarizing the category and types of infusion reactions by age group, severity and disposition by age category. On 7 January 2019, Grifols responded with information as requested. In summary, the GTI1503 IgG trough data exceeds >500mg/dL for all 4 subjects in the 2-5 years age group that completed the study. The mean trough ratio SC/Pre-Regimen for the 4 subjects fall within 0.88 to 1.34 with a geometric mean of 1.034. One subject withdrew at the SC#17 visit due to anxiety and was not included at the analysis. The IgG trough samples for SC #48 were not yet available due to a data transfer issue. There were no SBIs in this age group.

Clinical Reviewer Comments: The data from the GTI1503 study through SC# 53 (not including SC #48) all fall within the accepted therapeutic range >500mg/dL and the ratio of IP to pre-regimen geometric mean 1.034 suggest that the 1:1 conversion factor is acceptable for bio-equivalence in this study. Including the 4 subjects from the GTI1503 in addition to the 1 subject studied at the conversion factor of 1.37 from the GTI1502 study also suggests that dosing and

therapeutic outcomes for children ages 2 through 5 are substantiated in this small cohort given the lack of SBIs.

Appendix 2.

6 September 2018 Response to FDA information request of 31 August 2018:

Grifols Therapeutics LLC received an Information Request via email August 31, 2018 from Candido Alicea of CBER regarding BL125683/0 for Immune Globulin Subcutaneous (Human), 20%. A copy of the Information Request is provided in Attachment 1. FDA's requests are shown in bold font, followed by Grifols' response.

- PLEASE INCLUDE ALL AVAILABLE INTERIM SAFETY DATA AS A 120-DAY SAFETY UPDATE. THIS SHOULD INCLUDE STUDY GTI1503, BUT IS NOT LIMITED TO DATA FROM THIS STUDY PROTOCOL.**

Please refer to the DSUR that was submitted under IND 016528 sequence 0034 on July 27, 2018 that includes both IND study GTI1502 and non-IND study GTI1503 safety data information. This DSUR covers the reporting period of 1 June 2017 to 31 May 2018. The 120-day safety update will not be available until November 2018 at which time Grifols commits to submit the updated safety data for non-IND study GTI1503.

- PLEASE SUBMIT ANY KEY REVISIONS TO THE ORIGINAL PROTOCOL AND THEIR DATES OF IMPLEMENTATION FOR NON-IND STUDY GTI1503.**

Table 1: Amendments to the original Clinical Trial Protocol GTI1503, Version 1.0, 06 July 2015

Protocol Code	Protocol Version	Protocol Date	Implementation Date¹
GTI1503	Draft Version 1.1	25 November 2015	Not applicable ²
GTI1503	1.2	04 December 2015	26 February 2016 (UK)
GTI1503	2.0	22 July 2016	14 October 2016 (UK)
GTI1503	3.0	21 March 2017	18 May 2017 (Germany)

The original Clinical Trial Protocol GTI1503, Version 1.0, was dated on 06 July 2015. The original protocol Version 1.0 was amended and reissued as Amendment 1, Protocol GTI1503 Draft Version 1.1, dated on 25 November 2015. The Draft Version 1.1 of the protocol was amended and reissued as Amendment 1, Protocol GTI1503, Version 1.2, dated on 04 December 2015. The Version 1.2 of the protocol was amended and reissued as Amendment 2, Protocol GTI1503, Version 2.0, dated on 22 July 2016. The Version 2.0 of the protocol was amended and reissued as Amendment 3, Version 3.0, dated on 21 March 2017.

¹ This date corresponds to the date of the first approval of the clinical trial protocol granted by a Competent Regulatory Authority on Medicines.

² Protocol GTI1503, Draft Version 1.1., dated on 25 November 2015, was never submitted to Institutional Review Boards / Independent Ethics Committees for approval / favorable opinion and distributed to trial site for implementation.

Apart from the section “SUMMARY OF CHANGES FOR AMENDMENT” included in each version of the protocol, the main changes in each protocol version are summarized below.

Amendment 1, Protocol GTI1503, Version 1.1, dated on 25 Nov 2015, provided a number of modifications to the original Protocol GTI1503, Version 1.0, dated on 06 July 2015, as follows:

- Four Other Efficacy Variables were re-designated as Secondary Efficacy Variables

Amendment 1, Protocol GTI1503, Version 1.2, dated on 04 December 2015, provided a number of modifications to the Protocol GTI1503, Version 1.1, dated on 25 November 2015, as follows:

- Exclusion criteria proteinuria eligibility was updated to a single value rather than a range
- A new section specific on pregnancy reporting guidelines was added
- A series of updates were added to clarify that urine pregnancy tests were to be performed locally at the investigative sites

Amendment 2, Protocol GTI1503, Version 2.0, dated on 22 Jul 2016, provided a number of modifications to the protocol Version 1.2, dated on 04 December 2015, as follows:

- The primary efficacy objective to evaluate whether weekly administered SCIG 20% over a one year period would achieve not more than one serious bacterial infection (SBI) per subject per year was edited to less than 1 SBI for consistency with European Medicines Agency (EMA) guideline wording
- Increased the inclusion criterion window to allow for varying institutional standards on target population IgG through level of ≥ 500 mg/dL from within the previous 3 months to within the previous 6 months
- Wording clarifications on exclusion criteria for IgA deficiency and previous participation in studies with other investigational blood products
- Revised text for clarification on timing of withdrawal due to pregnancy
- Modifications in the Screening Visit assessments consisting in: an expanded adverse events reporting criterion to include potential systemic infusion reactions; removal of the requirement for a Screening x-ray to limit radiation exposure for pediatric subjects and to comply with local requirements for adult subjects; and removal of the requirement to repeat Screening safety labs parameters as they were not anticipated to significantly change in that timeframe for the targeted study population
- Additional updates were included to accommodate window periods to evaluate central laboratory assessments

Amendment 3, Protocol GTI1503, Version 3.0, dated on 21 Mar 2017, provided a number of modifications to the protocol Version 2.0, dated on 22 July 2016, as follows:

- Added requirement of assent in exclusion criterion 21 as both consent and assent were required for inclusion
- The restriction to local infusion site reactions in the Safety Variables section was removed to allow for the collection of all infusion site reactions

- Infusion rates were revised to reflect recent published data supporting the safety of higher infusion rates
- Added a criterion for removal of subjects who developed a SBI prior to first dose of IGSC 20%

3. PLEASE SUBMIT CASE REPORTS FOR ANY SERIOUS ADVERSE EVENTS (SAEs) THAT MAY HAVE OCCURRED WITHIN GTI1503 AND YOUR ASSESSMENT AS TO WHETHER ANY SAEs ARE RELATED TO THE ADMINISTRATION OF IGSC 20%.

To date, Grifols Pharmacovigilance received a total of 9 SAEs that have occurred within the study GTI1503 with title "A Multi-Center, Open-Label, Single-Arm Trial to Evaluate the Efficacy, Pharmacokinetics, Safety and Tolerability of 20% Immune Globulin Subcutaneous (Human) Caprylate/Chromatography Purified (IGSC) in Subjects with Primary Immunodeficiency" which is now being conducted in several countries of the European Union. Of the 9 cases, 3 individual case safety reports (ICSRs) were pre-treatment and 6 were SAEs not related to the study drug of IGSC 20%. Please see below a summary and enclosed (Attachment 2) the information in a line listing format. Please note that the study is ongoing and the data are not locked at this point. It is possible there may be changes as the data continues to be reviewed and monitored.

CASE SUMMARIES

Case (b) (6) were pretreatment and the subjects had not received the study drug when the SAEs occurred.

CASE (b) (6) :

This clinical study report was first received on 04-Jan-2017 regarding subject (b) (6), an 18-year-old White/Caucasian male subject enrolled in Germany, who presented a dislocation of an arthrodesis screw (PT: Device dislocation).

Medical history included current condition of primary immunodeficiency syndrome, hallux valgus on left foot corrected by surgery on (b) (6) and dislocated screw.

The subject started study treatment on (b) (6) with 100 mg/kg of IGSC 20% every week for primary immunodeficiency. Date of last dose of the study drug before presenting the serious adverse event was not reported.

On (b) (6) the subject was hospitalized for surgical correction due to painful arthrodesis screw left foot dislocation. The start date of the event (dislocation of an arthrodesis screw) was stated as November 2016 and stopped after surgery (b) (6). On 17-May-2017 a follow up from site was received with the inclusion of a new event term (painful state of arthrodesis screw). The patient was hospitalized on (b) (6) due to painful screw after surgery of left foot. The painful screw was removed in mask anesthesia. The outcome of the event is recovered/ resolved.

The investigator considered the event moderate in severity and not related to the study drug and related to patient's medical history. The Global Drug Safety Medical Monitor and the Clinical Assessment Monitor by the sponsor assessed the relationship as not related to the

study drug.

CASE (b) (6) :

This report was received on 26-Jun-2017 regarding a 64-year-old White male subject enrolled in United Kingdom who presented urinary tract infection.

Medical history included current condition of primary immunodeficiency syndrome, hypertension, diabetes, diverticulosis, hearing loss, depression, obesity, knee meniscus deamangement, gout, prostatism (status post transurethral resection of prostate [TURP]), peripheral neuropathy, right hemicolectomy, pernicious anaemia, colonic polyp benign and ventral hernia.

Concomitant medications included oral bendroflumethiazide for hypertension, oral Ramipril for hypertension, oral simvastatin for diabetic cholesterol, oral metformin for diabetes, oral sitagliptin for diabetes, and B12 injections for pernicious anaemia.

Subject started IGSC 20% subcutaneous administration in December 2016 (135 mg/kg/week) and received the dose for Week 28 scheduled on (b) (6) . On (b) (6) he presented to the Emergency Department with symptoms of fever, chills, and dysuria. Oral intake had been diminished during the prior 24 hours before admission. Blood tests, sputum culture, urine tests, chest-X ray done. He was admitted to hospital for suspected urinary tract infection and was treated with IV antibiotics (amoxicillin clavulanate) and IV fluids were administered.

The outcome of the event is recovering/resolving as for the information received so far. No action was taken with study treatment due to this SAE.

The investigator considered the event urinary tract infection severe in severity and not related to the study drug. The Global Drug Safety Medical Monitor and Clinical Assessment Monitor by the sponsor also assessed the relationship as not related to the study drug.

CASE (b) (6) :

This report was received on 06 Jul 2017 regarding a 10-year-old White/Caucasian male subject enrolled in Spain who underwent cardiac surgery due to aortic insufficiency. Medical history included current condition of primary immunodeficiency syndrome, current condition of cardiac failure due to congenital heart disease (he was diagnosed with aortic insufficiency in February 2009), and current condition of bronchitis.

Concomitant medications included oral captopril for aortic insufficiency and inhaled budesonide for bronchitis.

Subject started IGSC 20% subcutaneous administration in March 2017 (100 mg/kg/week) and stopped on (b) (6) . On (b) (6) the patient required prolonged hospitalization for cardiac surgery due to an aortic insufficiency caused by a congenital abnormality. The patient was treated with anticoagulant drug. The outcome of the event (cardiac surgery due to aortic insufficiency) is recovering/resolving. The study drug was interrupted and follow up information received in June 2018 included the outcome that is not recovered/not resolved, action taken with study drug that was discontinued and some other details of the event (start and stop dates). The team confirmed the end of the event with an echocardiogram on the same day.

The investigator considered the event cardiac surgery due to aortic insufficiency severe in severity and not related to the study drug. The Global Drug Safety Medical Monitor and Clinical Assessment Monitor also assessed the relationship as not related to the study drug.

CASE (b) (6) :

This report was received on 26-Oct-2017 regarding a 37-year-old White/Caucasian Female subject enrolled in Spain who presented thrombocytopenia.

Medical history included current condition of primary immunodeficiency syndrome and historical condition of folate deficiency. Concomitant medications included oral folic acid. The patient started the study treatment on (b) (6) and stopped on (b) (6). The last dose of IGSC 20% received prior the event onset was on (b) (6).

On (b) (6), the subject was admitted to hospital presenting petechia and gum bleeding. On (b) (6) her haematologist prescribed Immunoglobulin replacement therapy because he considered that the patient was not responding to initial treatment. Non-specific immunoglobulin was administered intravenously on (b) (6) and platelet recount increased, patient continues taking oral treatment until (b) (6) when patient was considered relieved from this episode by the haematologist.

The outcome of the event (thrombocytopenia) is recovered/ resolved. The patient stopped applying treatment provided by trial since (b) (6) by own decision, and communicated it to the center. Principal investigator did not make the decision to withdraw (or discontinue) the drug due to the adverse event.

The investigator considered the event thrombocytopenia moderate in severity and not related to the study drug. The Global Drug Safety Medical Monitor and Clinical Assessment Monitor by the sponsor also assessed the relationship as not related to the study drug.

CASE (b) (6) :

This report was received on 20-Mar-2018 regarding a 26-year-old White/Caucasian male subject enrolled in Germany who experienced habitual luxation of left patella.

Medical history included current condition of primary immunodeficiency syndrome and historical condition of joint dislocation.

Concomitant medications included oral ibuprofen as analgesic, oral Pantozol (pantoprazole sodium sesquihydrate) for gastric protection, oral Novalgin (caffeine, paracetamol, propyphenazone) as analgesic, and Clexane (enoxaparin sodium) heparinize.

Study treatment was started on (b) (6) and stopped on (b) (6). On (b) (6), the subject experienced habitual luxation of left patella (PT: subluxation of patella). He underwent surgical fixation of the ligamentum of the patella per reconstruction of tenders on the same day. The outcome of the event is recovered/ resolved, considered by the principal investigator on 10-Apr-2018.

The investigator considered the event habitual luxation of left patella mild in severity and not related to the study drug. The Global Drug Safety Medical Monitor and Clinical Assessment Monitor by the sponsor also assessed the relationship as not related to the study drug.

CASE (b) (6)

This report was received on 16-Aug-2018 regarding a 17-year-old White/Caucasian male subject enrolled in Hungary who experienced nephrotic syndrome.

Medical history included current condition of Common Variable Immunodeficiency since January 2012. Concomitant medications included oral Dalacin (clindamycin hydrochloride) for acute parodontitis and oral Camusc for exanthema.

Study treatment was started on (b) (6) and stopped on (b) (6). Last dose prior event was received on (b) (6).

The subject was called for a check up because of an extremely high creatinine level. Patient's weight was 4 kg higher than usual and his leg was swollen (oedema). Patient had exanthema on his body on (b) (6) and was treated with Camusc. Lab tests performed showed blood albumin (30 g/L), protein urine (extremely high), and blood creatine phosphokinase (402 u/L).

On (b) (6), he was sent to nephrologist and the diagnosis of nephrotic syndrome was confirmed on (b) (6). The patient was treated with steroids and a biopsy is planned. The outcome of the event is not recovered/not resolved. Due to the event the patient was discontinued from the study.

The investigator considered the event nephrotic syndrome moderate in severity and not related to the study drug. Study medical monitor assessed that IGSC 20% had no role in the occurrence of nephrotic syndrome in this patient rather it could be a coincident pathology in a syndrome as the CVID that is known to produce autoimmune phenomena. The Global Drug Safety Medical Monitor and Clinical Assessment Monitor by the sponsor also assessed the relationship as not related to the study drug.

MEDICAL EVALUATION AND CONCLUSION:

To date, Grifols has received 9 SAEs; 3 were pre-treatment cases and 6 SAEs were not related to the study drug (IGSC 20%).

Of the 6 SAEs, 3 SAEs were categorized as serious due to hospital admission for surgeries of their historical medical conditions such as habitual luxation of left patella, cardiac surgery due to severe aortic insufficiency and for surgical correction due to left foot dislocation.

The remaining 3 SAEs considered not related, 2 patients recovered from the events, urinary tract infection and thrombocytopenia; the other SAE involved a patient who experience nephrotic syndrome that could be a coincident issue with his underlying pathology.

Based on the available SAEs from GT11503 study, Grifols concludes that the 9 SAEs reported do not compromise the benefit-risk ratio of IGSC 20%.