Application Type	Efficacy Supplement - BLA
STN	125683/265
CBER Received Date	September 18, 2023
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Division / Office	DCEGM /OCE
Priority Review	No
Reviewers Names Clinical Clinical Pharmacology	Shelby Elenburg, MD (Reviewer/Team Lead, GMB1) Yang Chang, Ph.D., Pharm.D. (Reviewer, GMB1)
Review Completion Date / Stamped Date	July 18, 2024
Supervisory Concurrence Branch Chief, GMB1 OCE Director, Acting DCEGM Director	 Elizabeth Hart, MD Lola Fashoyin-Aje, MD, MPH
Applicant	Grifols Therapeutics LLC
Established Name	Immune Globulin Subcutaneous, Human-klhw, 20% (IGSC 20%)
Trade Name	XEMBIFY
Pharmacologic Class	Biologic
Formulation(s), including Adjuvants	Immune Globulin Subcutaneous (human) 20%
Dosage Form(s) and Route(s) of Administration	Sterile Solution, Subcutaneous
Dosing Regimen	Previously Approved: • Initial weekly SC dose in grams = current IGIV dose x 1.37/Number of weeks between IGIV dose • For IGSC, use same weekly IGSC dose • For alternate dosing, divide weekly dose by number of times administered per week New Additional Dosing Proposed by Applicant in Efficacy Supplement: • Multiply weekly dose x 2 for alternate biweekly (every 2 weeks) dosing • For treatment-naïve patients: loading dose of 150mg/kg/day for 5 consecutive days followed by maintenance 150mg/kg/dose administered weekly • Maximum rate of infusion 35 mL/hour/site
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

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
AMS	aseptic meningitis syndrome
AR	adverse reaction
AUC	area under the concentration versus time curve
$AUC_{0\text{-}7\ days}$	area under the concentration-time curve from 0 to 7 days
$AUC_{0\text{-}14\ days}$	area under the concentration-time curve from 0 to 14 days
$AUC_{0\text{-}\tau}$	AUC over a regular dosing interval at an approximate steady-state condition
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyneuropathy
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
C_{min}	minimum concentration
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
C_{trough}	trough concentration
CV	coefficient of variation
DAF	dose adjustment factor
DCEGM	Division of Clinical Evaluation General Medicine (CBER)
DPM	Division of Pharmacometrics (CDER)
eCTD	electronic Common Technical Document
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
G	gram
GLSM	geometric least squares mean
GMB1	General Medicine Branch 1 (CBER)
HSCT	hematopoietic stem cell transplant
IG	immune globulin/ immunoglobulin
IgA	immune globulin/ immunoglobulin A
IgG	immune globulin/ immunoglobulin G
IgG_{ENDO}	endogenous levels of IgG
IGIV	immune globulin intravenous (generic terminology)
IGIV-C 10%	Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified
IGSC	immune globulin subcutaneous (generic terminology)
IGSC 20%	Immune Globulin Subcutaneous (Human), 20% Caprylate/ Chromatography Purified
IND	investigational new drug
iPSP	initial Pediatric Study Plan
ISR	infusion site reaction
ITP	idiopathic thrombocytopenic purpura

IV	intravenous
L	liter
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MM	multiple myeloma
OCE	Office of Clinical Evaluation (CBER)
OCP	Office of Clinical Pharmacology (CDER)
OTS	Office of Translational Sciences (CDER)
PD	pharmacodynamics
PI	primary humoral immunodeficiency
PID	primary immunodeficiency
PK	pharmacokinetics
PPK	population pharmacokinetics
PV	pharmacovigilance
PMR	post marketing requirement
PREA	Pediatric Research Equity Act
RMP	risk management plan
SAE	serious adverse event
SBI	serious bacterial infection
sBLA	supplemental biologics license application
SC	subcutaneous
T_{max}	time to reach C_{max}
TRALI	transfusion-related acute lung injury
US	United States
USPI	United States Package Insert

1. EXECUTIVE SUMMARY

On September 18, 2023, Grifols Therapeutics submitted an efficacy supplement for Xembify[1], a 20% immune globulin (IG) subcutaneous (IGSC 20%) indicated for replacement therapy for primary humoral immunodeficiency (PI) in patients 2 years and older. The efficacy supplement proposes three changes to product dosing as follows:

- an increase in maximum infusion rate per site, to 35 mL/hour/site;
- a biweekly dosing regimen for treatment-experienced patients switching from another IG product, and,
- a loading and maintenance dosing regimen (150 mg/kg/day for 5 days followed by maintenance 150 mg/kg/week) for treatment-naïve patients who have not previously received IG replacement therapy.

The Applicant submitted data from two clinical studies and one population pharmacokinetics (PPK) modeling and simulation study to support the proposed changes to the infusion rate and the inclusion of the proposed dosing regimens. Data from Study GTI1503 were provided as evidence to support the safety and tolerability of the proposed increase to the infusion rate, the effectiveness of the product already having been established with the approval of the original BLA. Data from Study GC1906 provide the basis for the Applicant's request to approval of the proposed biweekly dosing regimen. Finally, Study GC1906 also provided the evidence to support the proposed loading and maintenance dosing regimen. Analyses from the PPK modeling and simulation study GI003 support the biweekly dosing regimen and the loading and maintenance dosing regimen.

Increased Infusion Rate

At the time of initial approval, Xembify was approved for subcutaneous (SC) infusion at a maximum rate per infusion site of 25 mL/hour/site. The Applicant provided data from Study GTI1503, the EU registrational study, to support the current request to increase the maximum infusion rate to 35 mL/hour/site. Study GTI1503 was a prospective, multi-center, open-label, single-arm Phase 3 study to evaluate efficacy, pharmacokinetics (PK), safety and tolerability of Xembify administered weekly for 52 weeks in patients with PI conducted in the EU and Australia. The study permitted an increase in infusion rate after a patient demonstrated initial tolerability of infusions administered at 25 mL/hour/site, with maximum rates determined by individual tolerability. Study GTI1503 enrolled a total of 61 patients; seven patients achieved rates of ≥35 mL/hour/site sustained over at least 3 consecutive infusions. Of the seven patients, four were children 10 to 15 years of age.

The main outcome supporting the Applicant's request for approval was tolerability of infusions administered at higher infusion rates per site. Of the seven patients who achieved sustained infusion rates of at least 35 mL/hour/site, five (71%) completed the 52-week study receiving Xembify infusions at rates ≥35 mL/hour/site with no rate de-escalation to <35 mL/hour/site due to infusion site reactions (ISRs), treatment- emergent adverse events (TEAEs), or other adverse events (AEs). All ISRs that began following infusions received at higher infusion rates were mild. One patient discontinued the study early (after infusion 40) due to an infusion site subcutaneous fibroma (mild) that was considered related to study treatment. One patient required a rate de-escalation from a

[1] For readability, Xembify is generally referred to without the ® registered trademark symbol throughout this memo.

maximum sustained infusion rate of 38 mL/hour/site to 25 mL/hour/site due to a treatment-related event of infusion site necrosis (mild). The AEs that led to study discontinuation in one patient and rate de-escalation in another were mild ISRs that are risks already characterized for IGSC products, regardless of rate of administration.

Study GTI1503 demonstrated tolerability of infusions received at rates ≥35 mL/hour/site that was similar to tolerability of the currently approved maximum of 25 mL/hour/site. This data is sufficient to support increasing the maximum infusion rates to ≥35 mL/hour/site in patients who are at least 10 years of age. There is no data in younger children, and these children may not tolerate higher infusion rates due to smaller body size and smaller subcutaneous space to accommodate the higher rate. Children 2 to <10 years of age should continue to receive the currently approved maximum rate of 25 mL/hour/site. Additional studies to evaluate an increased infusion rate in children 2 to less than 10 years of age are not necessary, as this would not provide a meaningful clinical benefit based on the smaller volume doses indicated for these younger children.

Biweekly Dosing

To demonstrate the safety and effectiveness of Xembify administered biweekly (every 2 weeks) for treatment- experienced patients with PI and using a loading and maintenance dosing regimen in patients with PI who are treatment-naïve, the Applicant submitted the results of Study GC1906. Study GC1906 was a Phase 4, multi-center, open-label, single-sequence study conducted over a period of 33 weeks. The study assessed longitudinal PK parameters and safety. Patients in the treatment-experienced cohort received weekly Xembify dosing initially and transitioned to biweekly dosing (at double their weekly dose) at Week 16. Serial PK assessments were performed during weekly (Period 1) and biweekly (Period 2) dosing comparing IgG exposure for the two dosing frequencies. The primary PK objective of the study was to determine whether biweekly administration of Xembify produced a steady-state area under the curve (AUC) of total IgG that was non-inferior to that produced by weekly administration of Xembify in treatment-experienced patients with PI.

The treatment-experienced cohort enrolled 27 adult patients, including 23 patients who were evaluable for the PK analyses with serial PK assessments in both the weekly and biweekly dosing periods of the study. For the PK analysis of non-inferiority of biweekly dosing, the $AUC_{(0\text{-}7\ days)}$ for the biweekly dosing period was calculated by dividing the $AUC_{(0\text{-}14\ days)}$ by 2 for comparison with $AUC_{(0\text{-}7\ days)}$ for the weekly dosing. The geometric least-squares mean (GLSM) ratio of the $AUC_{(0\text{-}7\ days)}$ for Xembify administration biweekly compared to weekly is 104% (90% CI: 100%-107%), indicating that biweekly Period 2 was non-inferior to weekly Period 1.

Results of the analysis of the primary PK endpoint indicate that biweekly administration of Xembify produced steady-state AUCs of total IgG that is non-inferior to weekly administration in treatment-experienced patients with PI. Mean total IgG concentrations were stable over time during both the weekly and biweekly dosing periods. Weekly and biweekly dosing regimens of Xembify appear to provide similar IgG exposure. There were no new or concerning safety findings in the patients treated with biweekly IGSC.

In addition to clinical data submitted to support the proposed dosing regimen changes, the Applicant also re-submitted data and analyses from a population pharmacokinetic

(PPK) study conducted at the time of the original BLA. For biweekly dosing, the PPK modeling is consistent with the PK observed for adults in study GC1906. Modeling suggests similar responses between pediatric and adult patients with PI, and differences in PK assessments are not expected to be impacted by patient age. Thus, there is adequate data to support biweekly dosing in children 2 years of age and older.

Loading and Maintenance Dosing for Treatment-Naïve Patients

An additional cohort in Study GC1906 evaluated the pharmacokinetics of a loading and maintenance dosing regimen of Xembify administered to immunoglobulin replacement therapy- naïve patients. The objective of this cohort was to assess whether a loading dose of Xembify 150mg/kg/day administered for five consecutive days, followed by a maintenance dose of 150mg/kg infused weekly, achieved and maintained total IgG trough levels of >500 mg/dL through Week 32 (End of Treatment). Dose adjustments were permitted to maintain IgG trough levels.

A total of six adult patients were evaluated in this cohort. Five of the six patients achieved IgG trough levels > 700 mg/dL at Week 1 (Day 8); the exception was one patient who had an IgG level <40 mg/dL at baseline and whose Week 1 IgG trough level was 672 mg/dL. All six patients achieved IgG trough levels >700 mg/dL by Week 8 and maintained trough levels through the end of study; three of the six patients required dose adjustments. The loading and maintenance dose regimen appears sufficient to rapidly raise and sustain IgG to protective levels in treatment-naïve patients. There were no new or concerning safety findings in the treatment-naïve patients treated with this dosing regimen.

PPK modeling provides additional PK data to support the dosing regimen for treatment-naïve patients. Simulated PPK analysis (including data from previously treated pediatric and adult patients with PI) showed similar IgG exposure to treatment- naïve patients following a loading dose and maintenance dose regimen of Xembify. The IgG exposure following a loading dose plus maintenance dose regimen is expected to be similar between treatment-naïve pediatric and adult patients. Thus, there is adequate data to support the proposed new dosing regimen for treatment-naïve patients with PI who are at least 2 years of age.

Conclusions

The evidence of Xembify's effectiveness was demonstrated in Study GTI1502 that was the primary basis for approval of the original BLA. This sBLA contains clinical data to support tolerability of the increased maximum infusion rate per site and PK data for the biweekly and loading dose regimens that supports extrapolation of efficacy from the approved dosing regimens. The data provided in the sBLA did not identify any new safety signals. Based on the review of the clinical and PK modeling data submitted, the review team recommends approval of the sBLA. Accordingly, the US Prescribing Information (USPI) was revised with the following three changes to dosing for patients with PI:

1. Increase the maximum rate of infusion per site to 35 mL/hour/site for patients 10 year and older (and maintain the currently approved rate of 25 mL/hour/site for patients 2 to <10 years);

2. Include biweekly dosing as an option, with dose calculated by doubling the weekly SC dose;
3. Add a loading dose regimen of 150 mg/kg/day for 5 consecutive days followed by a weekly maintenance dose of 150 mg/kg for treatment-naïve patients with PI.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

To support the proposed changes in dosing regimens in this efficacy supplement, the Applicant submitted clinical and pharmacokinetic (PK) data from two clinical studies, GTI1503 and GC1906, discussed in Section 6.1 and Section 6.2, respectively.

Demographic information for the safety populations in Studies GTI1503 and GC1906 are detailed in Table 1.

Table 1: Patient Demographics for Studies GTI1503 and GC1906

Characteristic	**Statistic**	**GTI1503 (N=61)**	**GC1906 (N=33)**
Age (years)	Median (Min, Max)	17 (2, 69)	54 (22,73)
Age Category (years)	--	--	--
≤16	n (%)	29 (48)	0
≥2 - ≤5	n (%)	5 (8)	0
>5 - ≤12	n (%)	14 (23)	0
>12 - ≤16	n (%)	10 (16)	0
>16	n (%)	32 (53)	33 (100)[a]
>16 - <65	n (%)	29 (48)	30 (91)[a]
≥65	n (%)	3 (5)	3 (9)
Sex	--	--	--
Male	n (%)	42 (69)	13 (39)
Female	n (%)	19 (31)	20 (61)
Ethnicity	--	--	--
Hispanic or Latino	n (%)	10 (16)	0
Not Hispanic or Latino	n (%)	49 (80)	33 (100)
Unknown	n (%)	2 (3)	0
Race	--	--	--
White	n (%)	57 (93)	33 (100)
Black or African American	n (%)	0	0
Asian	n (%)	0	0
Native American or Alaska Native	n (%)	2 (3)	0
Unknown	n (%)	2 (3)	0

[a] All patients in Study GC1906 were >18 years of age, no patients were between 16 and 18 years of age
Source: Adapted from Table 1-9 and Table 1-10 in sBLA 125683/265 Module 2.7.4 Summary of Clinical Safety

Interim pediatric safety and efficacy data from Study GTI1503 (non-IND, international Phase 3) contributed to the initial approval of Xembify, with relevant demographic details described in the Clinical Review Memo, dated July 3, 2019. To support the increased maximum infusion rate in this efficacy supplement, the Applicant conducted analyses of tolerability comparing infusion rates for all Study GTI1503 participants, but independent reviewer analysis was performed only for a sub-population of 7 patients from Study GTI1503 who received Xembify at sustained infusion rates of ≥35 mL/hour/site. Relevant

demographic details for the sub-population who received Xembify at higher infusion rates are detailed in the GTI1503 study section (6.1.10).

Pharmacokinetic data from Study GC1906 contributed to the review for the requested changes to dosing regimens within this supplement, including the addition of biweekly dosing and the loading and maintenance dose regimens for treatment initiation in treatment-naïve patients with PI. Details regarding patient demographics separated by study cohort are detailed in the GC1906 study section (6.2.10).

> ***Clinical Reviewer Comment:*** *It is difficult to make inferences based on subgroups defined by age, race and ethnicity due to limited sample size in the respective studies, particularly in the small subset of patients that contributed data for the increased infusion rate in Study GTI1503 and the small post-marketing pharmacokinetic study GC1906. The majority of study participants across studies were non-Hispanic white patients with PI. While the study populations do not adequately represent the diversity of patients with PI in the U.S., this reviewer believes that the results are interpretable and can be extrapolated to the entire U.S. population with PI as racial and ethnic differences are not expected to influence PK or side effect profiles for immunoglobulin replacement products.*

In addition to new data submitted to support the proposed dosing regimen changes, the Applicant also re-submitted data and analyses from a population pharmacokinetic (PPK) study conducted at the time of the original BLA that supported the proposed biweekly dosing regimen and the loading dose regimen to allow initiation of immunoglobulin therapy with Xembify in treatment-naïve patients with PI. Additional modeling was performed by the Applicant from the PPK data during the course of the review of this efficacy supplement to support extrapolation of results of adult clinical data to the pediatric PI population. Demographic data for the PPK modeling study are detailed in Table 2. Ethnicity was not reported amongst demographics for the PPK study populations, and age categories were only separated by children and adults rather than broken down by individual pediatric subgroups.

Table 2: Demographic Data for the Population PK Analysis Population

Characteristic	**Statistic**	**Study 060001 (N=32)**	**Study T5004-441 (N=11)**	**Study GTI1502 (N=52)**	**Study GI003 – Total (N=95)**
Age Category (years)	--	--	--	--	--
2-17	n (%)	3 (9)	11 (100)	15 (29)	29 (31)
≥18	n (%)	29 (91)	0	37 (71)	66 (70)
Weight (kg)	Median (Min, Max)	74 (51, 153)	32 (19, 101)	66 (17, 124)	66 (17, 153)
Sex	--	--	--	--	--
Male	n (%)	7 (22)	7 (64)	26 (50)	40 (42)

Female	n (%)	25 (78)	4 (36)	26 (50)	55 (58)
Race	--	--	--	--	--
White	n (%)	31 (97)	11 (100)	48 (92)	90 (94)
Black or African American	n (%)	1 (3)	0	1 (2)	2 (2)
Native American or Alaska Native	n (%)	0	0	3 (6)	3 (3)

Source: Adapted from Table 5 in sBLA 125683/265 Module 5.3.3.5 Pharmacokinetic Study Analysis Report

1.2 Patient Experience Data

Published systematic reviews describe the burden of disease on patients with PI, including the impact on activities of daily life from infections,[2] as well as the treatment burden related to route of administration and site of care.[3] A recently published study on patient preferences for immunoglobulin replacement in patients with PI[4] identified number of needle sticks and frequency of treatment infusions as additional aspects of therapy that are meaningful to patients. The Applicant submitted data on patient-reported outcomes including data related to infections and quality of life. The Applicant also submitted data on clinician- reported outcomes related to infections and adverse events, including those related to product tolerability. Outcomes related to infection are primarily described in the Clinical Review Memo for the original Xembify approval dated July 3, 2019, and thus are not a major focus in this efficacy supplement.

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	--
☐	Observer-reported outcome	--
☒	Clinician-reported outcome	--
☐	Performance outcome	--
☐	Patient-focused drug development meeting summary	--
☐	FDA Patient Listening Session	--
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	--
☐	Observational survey studies	--

[2] Song J, Zhang L, Li Y, Quan S, Liang Y, Zeng L, Liu Y. 20% subcutaneous immunoglobulin for patients with primary immunodeficiency diseases: A systematic review. *Int Immunopharmacol*. 2015 Apr;25(2):457-64.
[3] Jones GL, Vogt KS, Chambers D, Clowes M, Shrimpton A. What is the Burden of Immunoglobulin Replacement Therapy in Adult Patients With Primary Immunodeficiencies? A Systematic Review. *Front Immunol* (2018) 9:1308. doi: 10.3389/fimmu.2018.01308.
[4] Gonzalez JM, Ballow M, Fairchild A, Runken MC. Primary Immune Deficiency: Patients' Preferences for Replacement Immunoglobulin Therapy. *Front Immunol*. 2022 Feb 4;13:827305. doi: 10.3389/fimmu.2022.827305. PMID: 35185918; PMCID: PMC8854788.

☐	Natural history studies	--
☐	Patient preference studies	--
☐	Other: (please specify)	--
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	--
☐	Patient-focused drug development meeting summary report	--
☐	FDA Patient Listening Session	--
☐	Other stakeholder meeting summary report	--
☐	Observational survey studies	--
☒	Other: (please specify)	Literature as described in this section

Clinical Reviewer Comment: *Increased flexibility in dosing schedules (to include the possibility of less frequent biweekly dosing) provides a meaningful benefit to patients as frequency of infusions is a source of treatment burden for some patients and is one of several identified factors that influence patient choices in immunoglobulin products. Increased infusion rates that allow for faster completion of infusions would be meaningful to patients. Additionally, while many patients initiate first immunoglobulin replacement therapy after diagnosis with intravenous (IV) formulations, the ability to initiate therapy with a subcutaneous (SC) formulation that may be able to be self-administered in the home is likely to be meaningful to some select patients with PI. In particular, ability to initiate immunoglobulin replacement therapy with an SC product is likely desirable for select patients at higher risk of systemic side effects with IV formulations, for patients with poor venous access, for patients who do not have easy access to hospitals or infusion centers, and for patients who desire flexibility in timing of administration that is convenient and does not require time away from work or school for infusion-related clinical visits.*

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Primary immunodeficiencies (PIDs) are a large heterogenous group of disorders resulting from inborn errors of immunity. They are characterized by absent or poor function in one or more components of the immune system. Consequently, affected patients are unable to mount an immune response to microorganisms and may experience recurrent protozoal, bacterial, fungal and viral infections. The estimated overall prevalence of PIDs in the United States is approximately 1 in 1200 live births, with the exception of immunoglobulin A (IgA) deficiency, which occurs in approximately 1 in 200 to 1 in 500 persons.

PIDs are broadly classified based on the component of the immune system that is primarily disrupted. Disorders of the adaptive immune system include B-cell (humoral) immune deficiencies (also referred to as antibody deficiencies), T-cell (cellular) immune deficiencies, and combined (B-cell and T-cell) immunodeficiencies. Primary humoral immunodeficiency (PI) is a form of PID that is characterized by impaired B-cell immunity, and thus, impaired ability to produce specific antibodies in response to pathogenic microorganisms. PI diseases include, but are not limited to, X-linked agammaglobulinemia, Common Variable Immunodeficiency, Wiskott-Aldrich Syndrome, Severe Combined Immunodeficiency, and congenital agammaglobulinemia. Patients with PI present with recurrent, often severe bacterial and viral infections affecting the respiratory tract, gastrointestinal system, skin, as well as other organs.

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

Replacement therapy, comprised of polyclonal human normal immune globulin (IG) infusions, is standard treatment for PI. IG is manufactured through fractionation of plasma pooled from many plasmapheresis donors and contains immune antibodies. IG restores serum IgG to protective levels and provides the patients with specific antibodies to prevent or minimize the frequency or severity of severe bacterial and viral infections. For many patients, therapy is expected to be lifelong and increases life expectancy. Additional infection prevention includes infection avoidance measures, vaccination, and prophylactic antibiotics. Treatment of infections often requires broad antimicrobial coverage and prolonged treatment courses. Bone marrow transplantation is a treatment option for some forms of PI (such as Severe Combined Immunodeficiency) but is limited by availability of appropriate donors and is associated with multiple risks including graft versus host disease, rejection of the graft, complications of conditioning agents, and death.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are numerous marketed immune globulin (IG) products, which can be administered intravenously or subcutaneously, with similar efficacy but different safety profiles between the two routes of administration. There are currently eight licensed Immune Globulin Subcutaneous (Human) (IGSC) products approved for adults and children 2 years of age and older with PI in the U.S.: Cuvitru® (Baxalta US, Inc.), Hizentra® (CSL Behring), Xembify® (Grifols Therapeutics), Cutaquig® (Octapharma), Gammagard Liquid® (Baxter Healthcare Corporation), Gamunex-C®, (Grifols Therapeutics), Gammaked® (Kedrion Biopharma), and Hyqvia® (Baxter Healthcare Corporation, Baxter Bioscience).

Hyqvia® contains a hyaluronidase component that allows for dosing at 3–4-week intervals similar to IV formulations, and for faster infusion rates. Hyqvia® is therefore excluded from the discussion comparing dosing regimens for IGSC products in the remainder of this section due to a dissimilar dosing regimen relative to other IGSC products.

IGSC products utilize weekly administration as the standard dosing frequency (with the exception of Hyqvia®). IGSC formulations with higher concentrations of IG (16.5% and 20%) are approved at alternative dosing frequencies as often as daily and with as much as two weeks between infusions.

Typical infusion rates for IGSC products (excluding the dissimilar product Hyqvia®) are noted to be between 10-35 mL/hour/site by infusion pump for volumes between 10-40 mL/site.[5] Approved maximum infusion rates per sites vary from 10-60 mL/hour/site based on product. Maximum approved infusion rates per site for individual products may differ based on body size or age. Maximum infusion rate is typically determined based on demonstrating sustained tolerability in an adequate number of patients. See Table 3 for details of infusion parameters for approved IGSCs excluding Xembify® and the dissimilar product Hyqvia®.

[5] Perez E E., et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Aller Clin Immunol*. 2017;139:S1-S46.

Table 3: Dosing Characteristics for Other Immune Globulin Products Marketed for Subcutaneous Administration* in the U.S.

Product	Dosage Formulation	New Start [a]	Dosing Frequency Options	Maximum Infusion Rate Per Site (in mL/hour/ site),[b] Adults [c]	Maximum Infusion Rate Per Site (in mL/hour/ site), [b] Pediatrics[c]
Cuvitru®	20% Liquid	No	Daily to every 2 weeks	60	60
Hizentra®	20% Liquid	No	Daily to every 2 weeks	25	25
Cutaquig®	16.5% Liquid	No	Daily to every 2 weeks	52 (for age ≥17 years)	25 (for age 2-16 years)
Gammagard Liquid® [d]	10% Liquid	No [d]	Weekly [d]	30 (for ≥40kg body weight) [d]	20 (for <40kg body weight) [d]
Gamunex-C® / Gammaked® [d,e]	10% Liquid	No [d]	Weekly [d]	20 (for adults and children ≥25kg body weight) [d]	10 (for children <25kg body weight) [d]

*Excluding Hyqvia® due to dissimilar dosing regimen to other SC products due to hyaluronidase component. Hyqvia® is approved for dosing every 3-4 weeks and is approved for new start.
[a]New Start= Approved for initiation of immunoglobulin replacement with subcutaneous formulation in treatment-naïve patients with primary immunodeficiency
[b] Maximum approved infusion rate per infusion site when at maintenance infusion rates; some products have lower rates for the first one or two infusions with the product
[c] Based on age or weight where specified
[d] Gammagard Liquid®, Gamunex-C®, and Gammaked® are approved for both intravenous (IV) and subcutaneous (SC) administration, the information presented is for SC administration only; all three IV formulations are approved for new therapy initiation in treatment-naïve patients.
[e] Gamunex-C® and Gammaked® are the same product, marketed by Grifols Therapeutics and Kedrion Biopharma, respectively.
Source: Clinical reviewer's review of product USPI for each product

Clinical Reviewer Comment: *While there are approved IGSC products that allow for every other week dosing, this dosing regimen could provide more convenient dosing to patients receiving Xembify who do not want to (or are unable to) switch products.*

Within this efficacy supplement, the Applicant has presented clinical data to support Xembify initiation in treatment-naïve patients. This would be the first IGSC product (excluding the dissimilar product Hyqvia®) approved for initial therapy in treatment-naïve patients with PI, which could provide a meaningful benefit for select patients with PI, particularly those with risk factors for systemic reactions to IGIV or those with a preference for home-based care for quality of life reasons.

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, dose, route of administration, and maximum infusion rate. As shown in Table 3, maximum infusion rates vary significantly amongst the IGSC products, with

some allowing for much higher rates than others. Tolerability of faster infusion rates is likely influenced by multiple factors, including individual patient characteristics (e.g., age/body weight and amount of subcutaneous space), body site of product administration, number of infusion sites, product formulation (e.g., 20% solutions versus 10% solutions) and other product characteristics (e.g., osmolality, pH, sodium, and glucose content). In general, common ARs for immune globulins (including those administered subcutaneously) include local Infusion Site Reactions (ISRs) (e.g., swelling, redness, heat, discomfort at the injection site), headache, fatigue, nausea, diarrhea, vomiting, and/or pyrexia. Most patients experience ISRs with IGSC infusions, but few are severe and often ISRs decrease in frequency and severity over time with repeated infusions of the IGSC product.[4] Systemic ARs are more likely with IGIV products but can occur with IGSC products. IGIV products carry an obligate boxed warning for thrombosis, renal dysfunction, and acute renal failure. IGSC products carry an obligate boxed warning for thrombosis. Warnings and Precautions for this class of products include hypersensitivity/ anaphylaxis, aseptic meningitis, hemolysis, transfusion-related acute lung injury (TRALI) and transmission of infectious agents.

> ***Clinical Reviewer Comment:*** *This reviewer believes that maximum tolerable infusion rates need to be individualized to the product as well as to the patient. Within this efficacy supplement, the Applicant has provided clinical data on tolerability of increased rates of infusion to support increasing the maximum infusion rate of Xembify to 35 mL/hour/site. The increased rate would place Xembify somewhere in the middle of maximum infusion rates for similar marketed products for adults but potentially provide a faster infusion rate option for children compared to most other similar products. Regardless, the increased rate would allow for faster infusions specifically of Xembify which could be meaningful to patients who are already receiving it.*

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

IGSC 20% (Xembify) was approved as replacement therapy for patients 2 years and older with PI in the United States on July 3, 2019. It was approved by Health Canada in December 2019, and Marketing Authorization was granted in the EU in September 2021.

In the EU, Xembify is approved at maximum infusion rates of 35 mL/hour/site based on data unavailable at the time of initial U.S. licensure but included in this efficacy supplement.

Xembify is currently registered in 12 countries for PI and in some countries for hypogammaglobulinemia secondary to chronic lymphocytic leukemia (CLL), multiple myeloma (MM), hematopoietic stem cell transplantation (HSCT) or other underlying diseases or treatments.

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

Xembify was approved as replacement therapy for patients 2 years and older with PI in the United States on July 3, 2019. No meetings were held regarding the submission of an efficacy supplement between the original approval and submission of the efficacy supplement on September 18, 2023.

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. Submission modules were in the common technical document structure.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The Applicant affirms that the studies were conducted in compliance with Good Clinical Practices and conforms with appropriate local laws and regulations and the Declaration of Helsinki.

3.3 Financial Disclosures

> ***Clinical Reviewer Comment****: No financial conflicts of interest were identified and this reviewer has no concerns.*

Covered clinical study (name and/or number): GTI1503
Was a list of clinical investigators provided: Yes
Total number of investigators identified: 25
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): 0
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/a

Significant payments of other sorts: n/a

Proprietary interest in the product tested held by investigator: n/a

Significant equity interest held by investigator in sponsor of covered study: n/a

Is an attachment provided with details of the disclosable financial interests/arrangements: No, n/a

Is a description of the steps taken to minimize potential bias provided: No, n/a

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0

Covered clinical study (name and/or number): GC1906
Was a list of clinical investigators provided: Yes
Total number of investigators identified: 15
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): 0
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/a

Significant payments of other sorts: n/a

Proprietary interest in the product tested held by investigator: n/a

Significant equity interest held by investigator in sponsor of covered study: n/a

Is an attachment provided with details of the disclosable financial interests/arrangements: No, n/a

Is a description of the steps taken to minimize potential bias provided: No, n/a

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0

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

4.1 Chemistry, Manufacturing, and Controls

Xembify is a currently marketed product. No new chemistry, manufacturing, and controls information was provided in this supplement.

4.2 Assay Validation

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

No new nonclinical information was provided in this supplement.

4.4 Clinical Pharmacology

The clinical pharmacology evaluation of this efficacy supplement was mainly based on the clinical study GC1906 and population PK (PPK) study GRI003, discussed in Section 6.2 and Section 6.3, respectively. Study GC1906 evaluated PK exposure for varied dosing regimens for treatment-experienced and treatment-naïve adult patients with PI. The PPK study GRI003 simulated the steady state PK parameters of adult and pediatric treatment-experienced and treatment-naïve patients at different dosing regimens. This PPK study supported the original BLA approval and details regarding the study are included in the Clinical Review Memo for Xembify dated July 3, 2019, including details regarding the modeling to support biweekly dosing, as well as loading and maintenance dose regimens in treatment-naïve patients with PI. Additional modeling was performed

by the Applicant during the course of the supplement review to support extrapolation of adult clinical PK data (from Study GC1906) for the new dosing regimens to pediatric patients with PI.

4.4.1 Mechanism of Action

Xembify contains a broad spectrum of IgG antibodies, some of which are directed toward infectious agents. Xembify is intended to restore serum IgG to protective levels and provide patients with specific antibodies to prevent or minimize the occurrence or severity of severe bacterial and viral infections.

4.4.2 Human Pharmacodynamics (PD)

Xembify's distribution of IgG subclasses is proportional to that of human plasma in a healthy population. Administration of the product increases IgG levels in a dose-dependent fashion. Adequate doses of Xembify may restore abnormally low IgG levels to the normal range.

4.4.3 Human Pharmacokinetics (PK)

Biweekly Dosing Regimen

In Study GC1906, PK parameters between weekly and biweekly (every 2 weeks) dosing regimens for treatment-experienced adults with PI included 23 patients evaluable for serial PK assessments for both the weekly and biweekly dosing periods, and 2 additional patients evaluable only for the weekly period. The geometric least-squares means (GLSM) ratio of the $AUC_{(0\text{-}7\ days)}$ for Xembify administration biweekly compared to weekly is 104% (90% CI: 100%-107%). Results from the statistical analysis of the primary PK endpoints indicate biweekly administration of Xembify produced a steady-state AUC of total IgG that was non-inferior to that produced by weekly administration of Xembify in treatment-experienced patients with PI. See Section 6.2 for additional details.

Loading and Maintenance Dosing for Treatment-Naïve Patients

Study GC1906 also evaluated IgG levels following a loading and maintenance dose regimen in treatment-naïve patients with PI. Following successful completion of 5 consecutive days of loading doses, 5 out of 6 treatment-naïve patients attained an IgG trough level >700 mg/dL at Week 1 (Day 8). All 6 patients attained IgG trough levels >700 mg/dL by Week 8 and were maintained through the end of the study at Week 32. See Section 6.2 for additional details.

Population PK Support for Extrapolation to Pediatric Patients with PI

Population PK (PPK) study GRI003 demonstrates simulated steady state C_{max}, C_{min}, and $AUC_{0\text{-}T}$ values of pediatric patients are within the 5th to 95th percentile of adult values in both weekly and biweekly dosing regimens. Simulated population PK analysis (including data from previously treated pediatric and adult patients with PI) showed similar IgG exposure to treatment-naïve patients following a loading dose and maintenance dose regimen of Xembify. The IgG exposure following a loading dose plus maintenance dose regimen is expected to be similar between treatment-naïve pediatric and adult patients. See Section 6.3 for additional details.

4.5 Statistical

No statistical concerns were identified and the statistical reviewer confirmed analyses performed to support labeling changes. Please refer to the Biostatistics review memo for additional details.

4.6 Pharmacovigilance

The Division of Pharmacovigilance recommended routine pharmacovigilance per the Applicant's Risk Management Plan (RMP) version 3.0-USA-3, dated January 11, 2024.

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

5.1 Review Strategy

This memo documents the joint review of Clinical and Clinical Pharmacology. The Clinical Pharmacology reviewer was responsible for synthesis and documentation of Section 4.4 Clinical Pharmacology, and discussions of PK analyses in Studies GC1906 (Section 6.2) and GI003 (Section 6.3) as well as contributing to the conclusions related to PK and PPK analyses. The Clinical reviewer was responsible for all other aspects of the memo and also reviewed the PK and PPK analyses. The overall conclusions for the application were primarily the responsibility of the Clinical reviewer.

Certain sub-sections of the review memo were not relevant to this efficacy supplement and were thus removed. The Table of Contents reflects that sections/sub-sections were not renumbered for the omitted sub-sections.

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

Documents within STN 125683/265 (including original amendment and additional submissions during interactive review) that served as the basis for the Clinical and Clinical Pharmacology review are within the following eCTD modules and locations:

- Module 1
  - 1.1 Forms
  - 1.2 Cover Letters
  - 1.3 Administrative Information
  - 1.12 Other Correspondence
  - 1.14 Labeling
  - 1.16 Risk Management Plan
- Module 2
  - 2.2 Introduction
  - 2.5 Clinical Overview
  - 2.7 Clinical Summary
- Module 5
  - 5.2 Tabular Listing of all Clinical Studies
  - 5.3 Clinical Study Reports
  - 5.4 Literature References

5.3 Table of Studies/Clinical Trials

The studies that support the dosing changes requested in this sBLA are described in Table 4.

Table 4: Clinical and Pharmacokinetic Modeling Studies of Xembify

Study ID	Phase	Study Design	Dose Adjustment Factor (DAF)	Study Treatments, Dose	Study Objectives	Primary Endpoint	Number of Patients	Role in Efficacy Supplement
GTI1503	3	Multi-center, open-label, single arm (EU and Australia)	Previous IG regimens: IGSC 20% 1:1	IGSC 20%, minimum dose: 100 mg/kg/week; a total of 52 weekly SC infusions	Efficacy, PK, and safety of IGSC 20%	Weekly administered IGSC 20% over a 1-year period achieved less than 1 SBI per patient per year	61 in SC phase	Clinical data to support increased rate of infusion per site
GC1906	4	Multi-center, open-label, single sequence (U.S.)	SC infusion of IGSC 20% Treatment-experienced patients: 1:1.37 entering on IGIV; if entering on SC commercial immune globulin 1:1 Treatment-naïve patients: entered at 150 mg/kg/day loading dose	Treatment-experienced: 16 weekly IGSC 20% followed by 9 biweekly IGSC 20% doses Treatment-naïve: loading dose of 5 consecutive daily doses of IGSC 20% followed by weekly infusions through Week 32	Efficacy, PK, and safety of IGSC 20% administered at different dosing regimens	Treatment-experienced patients: Steady-state AUC of total IgG of a weekly dose of IGSC 20% vs a biweekly dose of IGSC 20% Treatment-naïve patients: IgG levels following loading dose and during weekly maintenance	33: 27 treatment-experienced, 6 treatment-naive	Clinical data to support biweekly and loading/ maintenance new start dosing regimens

Study ID	Phase	Study Design	Dose Adjustment Factor (DAF)	Study Treatments, Dose	Study Objectives	Primary Endpoint	Number of Patients	Role in Efficacy Supplement
GRI003	N/A	Population PK modeling and simulation from 3 clinical studies (060001, T5004-401, GTI1502) [a]	IV infusion of IGIV-C 10%: SC infusion of IGSC 20% 1:1.37	IV dosing IGIV-10% every 3-4 weeks (060001) SC dosing with IGIV-C 10% weekly (T5004-401) SC dosing with IGSC 20% weekly (GTI1502)	Predictive PPK model for IGSC 20% to guide dosage regimens	N/A: 2-compartment PPK model (IGIV + IGSC) for IgG PK characterization, dosing regimen simulation, and patient-specific covariates assessment	95 from 3 clinical studies	PPK modeling [b] to support biweekly and loading/ maintenance new start dosing regimens

AUC = area under the concentration versus time curve, IgG = immunoglobulin G, IGIV = intravenous immunoglobulin; IV = intravenous, N/A = not applicable; PK = pharmacokinetics, PPK = population pharmacokinetics, SB I= serious bacterial infection, SC = subcutaneous,

[a] Studies 06001 and T5004-401 evaluated PK, safety, and tolerability of crossover from IV to SC infusions of Gamunex-C® to support additional route of SC administration of Gamunex-C®; Study T5004-401 was conducted specifically in a pediatric PI population. Study GTI1502 evaluated PK, safety, and tolerability of IGSC 20% and was the registrational trial for Xembify in the U.S.

[b] PK data from clinical studies 060001, T5004-401, and GTI1502 were pooled and analyzed in the Applicant's population PK (PPK) modeling and simulation study GRI003 that supported initial approval of Xembify and was submitted in the efficacy supplement to support new dosing regimens.

Source: Adapted from Table 1-1 sBLA 125683/265, Module 2.5 Clinical Overview and sBLA 125683/265, Module 5.2 Tabular Listing of All Clinical Studies

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee Meeting was held.

5.4.2 External Consults/Collaborations

The Division consulted Division of Pharmacometrics (DPM) within the Center for Drug Evaluation and Research (CDER)/Office of Translational Sciences (OTS)/Office of Clinical Pharmacology (OCP) to assist with the evaluation of the Applicant's population PK (PPK) analysis. Aspects of the consult are incorporated into the discussion of PK analyses to support the proposed labeling changes where relevant elsewhere in this memo.

5.5 Literature Reviewed

Literature reviewed relevant to patient preferences is discussed in Section 1.2 Patient Experience Data, and relevant to pharmacologically related products in Section 2.3 Safety and Efficacy of Pharmacologically Related Products.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study #1 – Study GTI1503

Study Title: "A Multi-Center, Open-Label, Single-Arm Trial to Evaluate Efficacy, Pharmacokinetics, and Safety and Tolerability of IGSC 20% in Subjects with Primary Immunodeficiency"

> ***Clinical Reviewer Comment:*** *This study was performed outside the U.S. to support international registration. For the purposes of this efficacy supplement, data from a subset of patients who received IGSC 20% (Xembify) at infusion rates >25 mL/hour/site were reviewed to support the proposed increase in maximum infusion rate in the label, and the review within this section is primarily focused on that population. However, because interim results from this study supported the initial approval in children 2 years and older in the U.S., brief commentary is included in this section regarding safety and efficacy findings for the entire study population primarily to confirm findings from the interim study results that supported initial approval. Because safety and efficacy of Xembify were already reviewed in the context of the registrational study GTI1502 for the original BLA submission and discussed in the Clinical Review Memo for Xembify dated July 3, 2019, a comprehensive independent review of safety and efficacy in this study was not conducted by the FDA clinical reviewer as part of this efficacy supplement. The clinical reviewer focused on adjudication and independent review of the safety and tolerability for increased rates of infusion for the sub-population of patients who received Xembify at infusion rates above those currently approved.*

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective of this Phase 3 study was to evaluate whether Xembify administered over a one-year period achieved less than 1 serious bacterial infection (SBI) per patient per year in patients with primary humoral immunodeficiency (PI).

Key secondary objectives evaluated IgG trough levels and other infection-related outcomes. The primary safety objective was to assess the safety and tolerability of Xembify as IG replacement therapy in patients with PI.

6.1.2 Design Overview

The study was a prospective, multi-center international, open-label, single-arm Phase 3 study evaluating the efficacy, PK, safety and tolerability of IGSC 20% (Xembify) in patients with PI. The study consisted of three study stages: Screening/Previous Regimen Phase, IGSC 20% Treatment Stage 1 (13 weekly doses of IGSC 20%), and IGSC 20% Treatment Stage 2 (39 weekly doses of IGSC 20%). The study was not conducted under IND and was performed at multiple centers in the EU and Australia.

6.1.3 Population

The study enrolled pediatric and adult patients (aged 2 to 75 years) with PI who had been on a previous IG replacement therapy regimen (either IGIV or IGSC) with a stable dose for at least 3 consecutive months prior to Screening. Patients who had never received IGIV or IGSC were not eligible for study participation. Patients must not have had an SBI within the 3 months prior to screening and must have had documentation of IgG trough levels ≥500 mg/dL on current IG replacement therapy regimen.

6.1.4 Study Treatments or Agents Mandated by the Protocol

In the Previous Regimen Phase, patients were to have study visits for infusions with their pre-study IGIV or IGSC regimen to obtain two trough IgG levels prior to the infusion to establish IgG troughs with the previous regimen. For patients entering the study on IGSC, the second trough was allowed to be obtained at Baseline immediately prior to the first infusion with Xembify. For patients entering the study on IGIV, patients entered Treatment Stage 1 one week after the completing the last IgG trough sample.

Following the Previous Regimen Phase, patients transitioned to weekly treatments with Xembify for 52 weeks (13 weekly doses in Treatment Stage 1 and 39 weekly doses in Treatment Stage 2). Dose adjustments (in mg/kg) for IgG trough levels or clinical response were allowed during Treatment Stage 1, but no dose adjustment was permitted in Treatment Stage 2 unless absolutely medically necessary as discussed with the Grifols Medical Monitor.

6.1.5 Directions for Use

Directions for use did not differ from approved directions aside from changes to the dosing regimen to allow higher rates of product infusion. If the Xembify infusion was well tolerated during 2 infusions with an initial target rate of ≤25 mL/hour/site, the infusion rate could be increased in a stepwise manner at the investigator’s discretion up to a maximum of 60 mL/hour/site. If the higher rate was well tolerated, subsequent infusions could begin at that rate; the investigator could also decrease the infusion rate at any time based on the patient’s tolerability.

6.1.6 Sites and Centers

The study was conducted at 22 sites in the EU and Australia.

6.1.7 Surveillance/Monitoring

Study monitoring as detailed in the protocol schedule included assessment of vital signs, physical examination findings, and laboratory parameters (hematology, chemistry, haptoglobin, urinalysis, and direct antiglobin) at study visits, as well as assessments for adverse events and concomitant therapies.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint defined for the study was number and rate (per patient year) of SBIs. Secondary endpoints assessed other infection-related endpoints and IgG trough concentrations.

For the purposes of this efficacy supplement, criteria for success on tolerability of increased infusion rates was not pre-defined in the protocol.

> ***Clinical Reviewer Comment:*** *The study design and pre-defined endpoints are appropriate for a pivotal study supporting efficacy of the product in PI in adults and children greater than 2 years of age.*
>
> *Although tolerability of increased infusion rates was not pre-defined, the conduct of the study as a registrational study allowed for detailed data collection regarding dosage parameters (including infusion rate) for each infusion, adverse events including ISRs with each infusion, and reasons for decreases in rate or study discontinuation. This detailed data for each patient who received* Xembify *at increased infusion rates is sufficient for review and a determination about tolerability, particularly in light of a well-established safety profile from the initial Xembify approval in the U.S. that includes ISRs as a common AR similar to other IGSC products.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

Most variables were analyzed with descriptive statistics or estimation of rates of events or days per person-year and associated 95% confidence interval (CI) using the generalized linear model procedure for Poisson regression.

For the purposes of the assessment of tolerability of increased infusion rates, analyses were primarily descriptive.

> ***Clinical Reviewer Comment:*** *As tolerability as an endpoint to support comparison of different infusion rates was not pre-specified or pre-defined, the analyses to support the proposed increase in maximum infusion rate were not agreed upon prior to submission of this efficacy supplement. Descriptive post-hoc analyses may or may not be informative depending on the definition of tolerability and criteria for success, but the small sample size of patients who achieved higher rates of infusion allows for post-hoc patient-level analysis of individual patient tolerability.*

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The Safety Population consisted of all 61 patients enrolled in the study who received at least one Xembify infusion.

The population who received Xembify at infusion rates >25ml/hour/site, the currently approved maximum infusion rate, constituted the increased rate cohort, which was the primary analysis population to support the rate change within the efficacy supplement. Table 5 details the breakdown of all study participants by per-patient maximum infusion rates of Xembify per site. Fourteen patients received at least one Xembify infusion at a rate greater than the approved rate of 25 mL/hour/site. Although 9 patients received Xembify at a maximum infusion rate of >35 mL/hour/site, only 7 received sustained (at least 3 infusions) rates of at least 35 mL/hour/site of Xembify.

Table 5: Per-Patient Maximum Infusion Rate Per Site in Study GTI1503

Rate (mL/hour/site)	Statistic	Stage 1 (N=61)	Stage 2 (N=60)	Overall (N=61)
≤25	n (%)	60 (98)	46 (77)	47 (77)
>25 - ≤35	n (%)	0	5 (8)	5 (8)
>35 - ≤45	n (%)	1 (2)	3 (5)	3 (5)
>45 - ≤55	n (%)	0	4 (7)	4 (7)
>55	n (%)	0	2 (3)	2 (3)

Source: Adapted from Table 1-5 in sBLA 125683/265 Module 2.7.4 Summary of Clinical Safety

6.1.10.1.1 Demographics

Demographics for the entire Safety Population are detailed in Table 1. Of the seven patients who were administered Xembify at sustained rates of at least 35 mL/hour/site to support the increased rate in this efficacy supplement, six (86%) were male and four (57%) were children aged 10-15 years, while the remaining three were adults.

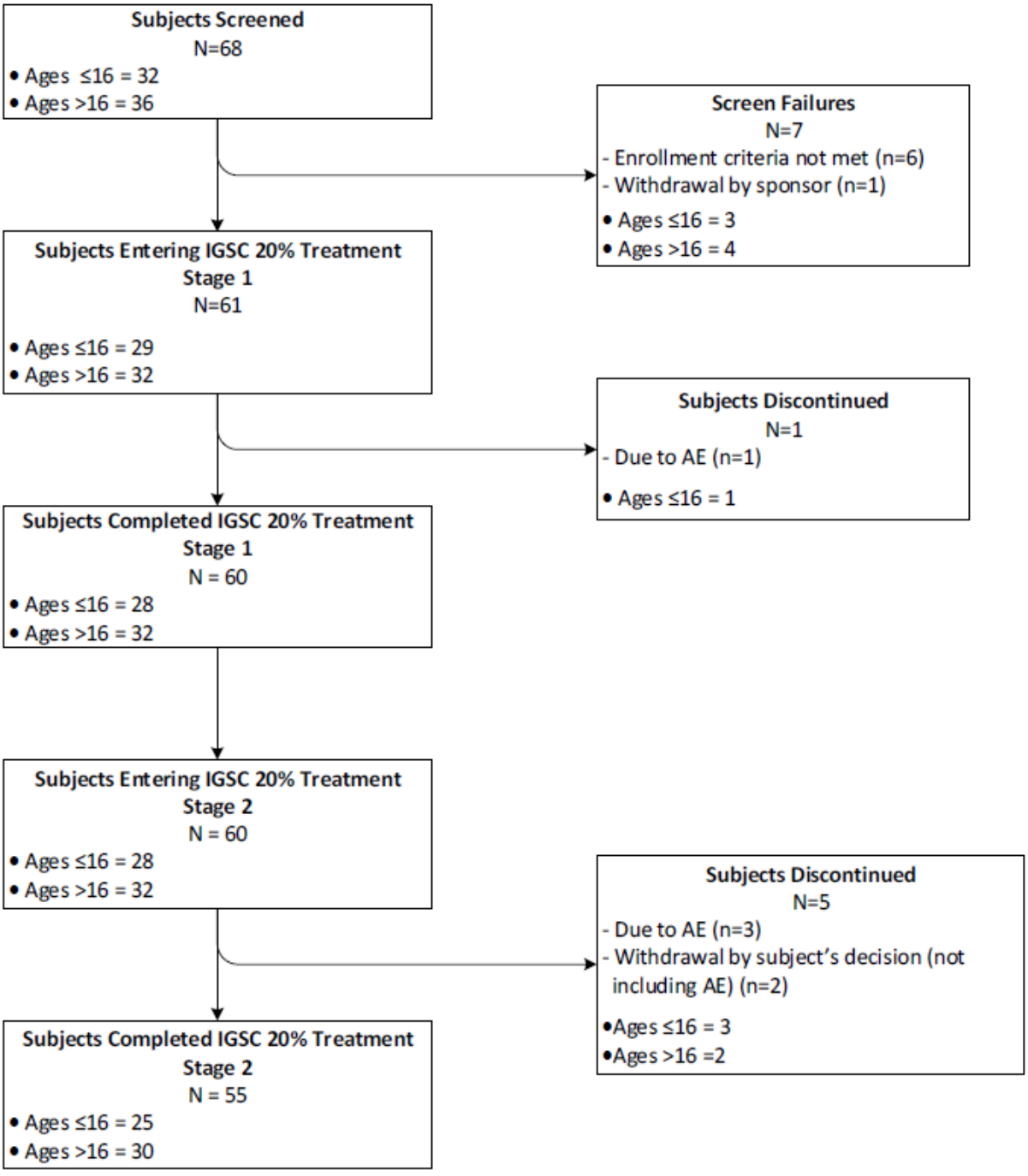
6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

There were no patient-level medical or behavioral characteristics that were considered relevant to the interpretation of study results for the purposes of this efficacy supplement.

6.1.10.1.3 Patient Disposition

For the entire study population, patient disposition is shown in Figure 1.

Figure 1: Patient Disposition in Study GTI1503



AE= adverse event
Source: Figure 1-2 in sBLA 125683/265 Module 2.7.4 Summary of Clinical Safety

6.1.11 Efficacy Analyses

At the time of Xembify approval on July 3, 2019, interim study data in pediatric patients contributed to the totality of data to support approval in the pediatric population. Because efficacy of Xembify, including SBI rate and secondary infectious outcomes, was already

reviewed with the original approval (please see Clinical Review Memo for Xembify dated July 3, 2019), the efficacy discussion for this study will focus on a brief update on SBIs from the completed study and tolerability of increased infusion rates.

6.1.11.1 Analyses of Primary Endpoint(s)

The Applicant reports that there was one SBI in a 10-year-old patient for an annualized SBI rate of 0.017 events per patient-year (upper 99% confidence limit: 0.036) during Xembify treatment.

> ***Clinical Reviewer Comment:*** *Although the single SBI was in a pediatric patient, the final clinical study data including the SBI rate continues to support similar efficacy for pediatric and adult patients with PI receiving Xembify, with a similar SBI rate to that of Study GTI1502 that supported the initial approval of Xembify in patients 2 years and older with PI. Since the interim study data from Study GTI1503 was used to support approval in pediatric patients with PI, this reviewer recommends updating the USPI with this new SBI information now that the study has been completed. Additional infectious data is not informative and this clinical reviewer does not recommend updating the USPI with secondary endpoint data from this study.*

6.1.11.2 Analyses of Secondary Endpoints

Secondary endpoints evaluated in the study to support international licensure were not reviewed as part of this efficacy supplement, as these outcomes were already assessed in Study GTI1502 to support U.S. licensure.

6.1.11.3 Sub-population Analyses

Aside from the evaluation of the sub-population that received Xembify at increased infusion rates, no sub-populations were analyzed to support this efficacy supplement.

6.1.11.4 Dropouts and/or Discontinuations

Among the population that received increased infusion rates, one patient discontinued Xembify early due to a related infusion site fibroma that resolved.

> ***Clinical Reviewer Comment:*** *The AE of infusion site fibroma is discussed separately in Section 6.1.11.5. Despite the fibroma, the patient achieved sustained infusions rates >35 mL/hour/site and completed most study follow-up prior to discontinuation, so it is not felt this early study discontinuation significantly impacted the assessment of tolerability of the increased infusion rate.*

6.1.11.5 Exploratory and Post Hoc Analyses- Tolerability of Increased Infusion Rates

The Applicant performed a post-hoc analysis comparing rates of infusion site reactions (ISRs) and adverse events (AEs), including treatment- emergent AEs (TEAEs) between patients who received Xembify at rates of up to 25 mL/hour/site and those who received infusions at rates in excess of 25 mL/hour/site as an evaluation of tolerability. This analysis forms the basis of the request for an increased maximum infusion rate per site in this efficacy supplement.

<u>Applicant's Analysis: Population and Infusion Characteristics</u>

A total of 14 patients were administered a total of 261 Xembify infusions at rates >25 mL/hour/site. The mean and median values for the infusion rates per site were 39.4 mL/hour/site and 37.5 mL/hour/site, respectively. The Applicant reports that the faster infusion rates led to mean total infusion times of 0.76 hours in the subset of patients who received Xembify at rates >25 mL/hour/site as compared to 1.2 hours in the subset of patients who received Xembify at infusion rates ≤25 mL/hour/site.

Applicant's Analysis of Tolerability

The Applicant's post hoc analysis showed that the rate of ISRs per infusion did not vary substantially by the infusion rate per site. The majority (74-80%) of infusions were not associated with ISRs regardless of rate of infusion, as shown in Table 6. All ISRs were recorded in the case report form (CRF) in the study, even if not characterized and recorded as an AE (see further discussion in Section 6.1.12.1. Table 6 includes rates per infusion of non-AE ISRs and ISRs recorded as AEs for each infusion rate category. Only 2% of infusions were associated with ISRs recorded as AEs in both infusions administered up to the currently approved rate (25 mL/hour/site) and infusions administered at >35 mL/hour/site. Non-AE ISRs were reported with 18-25% of infusions, regardless of rate of infusion. All ISRs that began at higher infusion rates were considered mild in severity and were consistent with ISRs reported at lower infusion rates. One patient who received infusions at rates >35 mL/hour/site had ISRs of mild or moderate severity while still receiving infusions at a rate of 25 mL/hour/site that worsened to or remained moderate in severity at rates >35 mL/hour/site.

Table 6: Rate of Infusion Site Reactions (ISRs) per Infusion by Rate of Infusion per Site

ISR with Infusion	Statistic	≤25 mL/hr/site (N=2783)[a]	>25 - ≤35 mL/hr/site (N=95)[a]	≤35 mL/hr/site (N=2878)[a]	>35 mL/hr/site (N=166)[a]	Any (N=3044)[a]
No ISR	n (%)	2048 (74)	76 (80)	2124 (74)	132 (80)	2256 (74)
Non-AE ISR[b]	n (%)	689 (25)	19 (20)	708 (25)	30 (18)	738 (24)
AE-ISR[c]	n (%)	46 (2)	0	46 (2)	4 (2)	50 (2)

AE= adverse event; CRF= case report form; ISR= infusion site reaction; SC=subcutaneous
Note: Infusion Rate per Site (mL/hr/site) = Total Infusion Rate (mL/hr) / Total Number of Infusion Sites
Tolerability categories increase in severity from top to bottom. If a patient experienced more than 1 ISR during one infusion period, only the most severe ISR is included in the table.
[a] N= total number of infusions
[b] ISR that did not meet the criteria of an AE and that was associated with the infusion as recorded in the CRF
[c] ISR that met the criteria of an AE and that occurred during or within 72 hours of the infusion
Source: Table 6.2-1 sBLA 125683/265 Module 1.12.11 Basis for Submission Statement

Clinical Reviewer Comment: *The Applicant used the mean and median infusion rates per site in the subset of patients who achieved rates >25 mL/hour/site to justify the increase in maximum rate to 35 mL/hour/site. However, 6 of the 14 patients only achieved maximum sustained rates of 30-33 mL/hour/site, and thus do not have tolerability data to support the proposed maximum of 35 mL/hour/site. Additionally, given Xembify is a chronic therapy administered at regular intervals, tolerance of a single infusion at an increased infusion rate is not meaningful for the assessment of patient tolerability of that rate. One patient*

received a single infusion at a rate >35 mL/hour/site for the last infusion of the study (and otherwise had a maximum sustained rate of 25 mL/hour/site), and one of the patients who achieved a maximum sustained rate of 30 mL/hour/site received a single infusion at a rate >35 mL/hour/site. This clinical reviewer noted that 7 (50%) of the patients received Xembify at sustained (at least 3 consecutive) infusions at rates ≥35 mL/hour/site. The clinical reviewer focused her analysis on assessing maximum infusion rate tolerability in these 7 patients rather than the 14 patients initially identified by the Applicant. Because ISRs are common with IGSC therapy and often are not bothersome enough to patients to warrant changes in the dosing regimen, evaluation of ISRs or common AEs was felt unlikely to be informative to tolerability of the increased rate. Rates of ISRs as analyzed by the Applicant and as shown in Table 6 were therefore not independently confirmed by the reviewer. This clinical reviewer defined tolerability as ability to maintain sustained infusion rates ≥35 mL/hour/site without early study discontinuation or rate de-escalation to <35 mL/hour/site due to AEs.

Reviewer's Analysis: Population and Infusion Characteristics

Seven patients received at least 3 consecutive infusions of Xembify at rates of ≥35 mL/hour/site, including 4 children aged 10-15 years and 3 adults. Maximum infusion rates within this subgroup ranged from 38 to 80 mL/hour/site, with maximum *sustained* infusion rates of 38 to 65 mL/hour/site.

Reviewer's Analysis of Tolerability

As the sponsor did not define tolerability, the clinical reviewer defined tolerability as ability to maintain sustained infusion rates ≥35 mL/hour/site without early study discontinuation or rate de-escalation to <35 mL/hour/site due to AEs. Of the seven patients, two experienced adverse reactions (ARs) that resulted in study discontinuation or a decreased infusion rate to <35 mL/hour/site as follows:

- One adult patient discontinued from the study early (after infusion 40) while at a sustained infusion rate of 50 mL/hour/site due to an AR of subcutaneous fibroma (mild) that was initially reported while the patient was receiving Xembify at a rate of 15 mL/hour/site.
- One adolescent patient 15 years of age received Xembify at a sustained maximum infusion rate 38 mL/hour/site but experienced an AR of infusion site necrosis (mild) that resulted in a decrease in Xembify infusion rate to 25 mL/hour/site for the remainder of the study.

Increases and decreases in rate based on individual patient tolerability were allowed in the protocol. Other patients in this high-rate subgroup had fluctuations in dose that included decreases in rate, but no other patients had their infusion rates decreased below 35 mL/hour/site once these rates had been achieved for at least 3 infusions. Also, no other patient in this cohort had a decrease in rate that was documented as related to AEs or ISRs.

It was not possible to compare rate de-escalation in the high-rate subgroup to rate de-escalation in study participants who received infusions at rates up to the currently approved 25 mL/hour/site in a meaningful way due to variability in infusion rates over time for individual patients and missing data regarding reasons for rate changes. Despite these limitations in comparing rate de-escalation, one patient who received infusions at

rates <25 mL/hour/site required rate de-escalation due to events of infusion site induration. The same patient discontinued early from the study due to withdrawal of consent, which occurred one week after a decrease in rate and change in body site for infusion, so although an AE is not documented as the reason for withdrawal, it can not be ruled out. Three patients who received infusions at rates ≤25 mL/hour/site discontinued from the study early due to adverse events that were considered unrelated to treatment (nephrotic syndrome, anxiety, worsening of aortic valve insufficiency). One additional patient who received infusions at rates ≤25 mL/hour/site discontinued from the study early due to voluntary withdrawal received high dose IGIV for 24 hours due to an SAE of thrombocytopenia and then never received another SC infusion on study prior to study withdrawal. Although the SAE was deemed not related to study drug and an AE is not documented as the reason for withdrawal, early discontinuation due to an AE can not be ruled out.

> ***Clinical Reviewer Comment:*** *This reviewer does not believe that these ARs in the high-rate subgroup that led to study discontinuation or decrease in rate were clearly due to the increased rate of Xembify the patients were receiving.*
>
> *The patient who had a subcutaneous fibroma initially developed this while receiving Xembify at a rate of 15 mL/hour/site, and then tolerated a higher sustained infusion rate for most of the remainder of the study prior to the patient's early discontinuation. Although the early discontinuation was related to the fibroma, it is not clear why the patient remained in the study so long before discontinuing, as the fibroma was reported early in the study. Although worsening of the fibroma was not reported, there is some uncertainty whether the increased infusion rate could have deleteriously impacted the fibroma (i.e., undocumented worsening or persistence). However, this reviewer believes that it is unlikely the increased rate contributed to the patient's early discontinuation from the study, based on when the fibroma initially appeared and that there were no attempts to decrease the infusion rate prior to study discontinuation.*
>
> *It is not clear if the higher rate of product administration was a contributing factor in the AR of infusion site necrosis, as the patient received weekly infusions at 38 mL/hour/site for more than 2 months before the necrosis was reported, but the investigator chose to decrease the rate of administration as a result, so relatedness to increased rate can not be excluded.*

Reviewer's Additional Post Hoc Analyses to Support Tolerability

The Clinical reviewer assessed AEs for each patient in the high-rate subgroup to evaluate if there were any new safety signals, increased severity of reported ARs, or apparent increased frequency of a particular AR that might be attributable to the increased infusion rate. There were no obvious differences in non-ISR AEs or ARs related to rate of infusion and no new non-ISR safety signals identified.

Frequency

The Clinical reviewer noted reporting of common ISRs amongst the high-rate subgroup that are expected with IGSC (and previously characterized for Xembify with the initial approval) regardless of rate of infusion, including infusion site erythema, pain, pruritus, warmth, induration, swelling, and bleeding. These ISRs were common across study

participants regardless of rate of infusion with no apparent differences in frequency noted.

Severity

One patient of the 7 (14%) who received infusions at rates >35 mL/hour/site had ISRs of mild or moderate severity while still receiving infusions at a rate of 25 mL/hour/site that worsened to or remained moderate in severity at rates >35 mL/hour/site. All other ISRs reported in the high-rate subgroup were mild in severity regardless of rate at time of onset. Of the patients who received infusions at rates ≤25 mL/hour/site, 14 of 47 (30%) had ISRs (either AE or non-AE ISRs) that were moderate to severe in severity. There was no apparent increase in severity of ISRs with infusions administered at higher rates.

Infusion Site Extravasation

Five ISRs of "infusion site extravasation" were reported amongst 2 recipients of higher rate (≥35 mL/hour/site) infusions, and extravasation was not an AE characterized with the original Xembify approval, so this was examined further. There was one event recorded as an AE for one patient, and 4 events recorded as non-AE ISRs for the second patient. Review of patient-level safety, efficacy, and PK data in the time periods before and after the reported extravasation events in the high-rate subgroup indicated there was no apparent effect of product extravasation on reported infections, and IgG trough levels remained stable.

When evaluating extravasation events in patients who received infusions at rates up to the currently approved maximum of 25 mL/hour/site, extravasation was recorded as an AE in one patient and noted incidentally as a reason for infusion interruption in the eDiary information for another patient (for whom it was not recorded as an AE or an ISR). It is not clear if risk of extravasation is impacted by infusion rate, and the potential for increased risk of product extravasation with increased rates of infusion can not be ruled out.

> ***Clinical Reviewer Comment:*** *ISRs are common ARs in patients receiving IGSC therapy, including with Xembify, and this can occur irrespective of rate of administration. The overall rate and severity of ISRs was not especially high for the patients who received infusions at rates ≥35ml/hour/site.*
>
> *Extravasation at infusion sites is likely a common AR with SCIG administration, though inconsistency in reporting within this study (i.e., whether an event was characterized as an AE or an ISR and the finding of an incidental event in eDiary documentation) leads to uncertainty about how accurate reporting within the study reflects actual extravasation events that occurred. If extravasation is common and expected at times with SC administration of products, it is possible that other events occurred but were not considered by the investigator to be an AE or ISR and thus were not reported. An increased risk of extravasation related to higher rates of infusion in the study could not be ruled out. Extravasation, particularly with higher rates of infusion, has the potential to lead to a greater amount of product not ultimately being administered to the patient and impacting efficacy. The patients in the high-rate subgroup who experienced extravasation at infusion sites had no SBI or notable changes in infectious outcomes and their IgG trough levels were maintained. Therefore, this reviewer is not concerned that*

extravasations events at infusion rates ≥35mL/hour/site will negatively impact efficacy.

Reviewer's Conclusions Regarding Tolerability

Although success related to tolerability was not pre-specified, this reviewer's assessment of tolerability is based on:

- The number of patients in the study who received infusions at rates ≥35 mL/hour/site and were able to maintain higher rates for multiple consecutive infusions (at least 3). Nine patients received at least one infusion at a rate of ≥35 mL/hour/site, and of those, seven (78%) were able to maintain these rates for at least 3 consecutive infusions. This reviewer interprets this to mean that the majority of patients who attempted higher infusion rates were able to maintain them.
- Five (71%) of the seven patients who received Xembify at sustained rates ≥35 mL/hour/site were able to maintain rates without AEs that led to study discontinuation or decrease of infusion rate to <35 mL/hour/site. This reviewer interprets this to mean that the majority of patients who achieved sustained higher infusion rates were able to maintain higher infusion rates without ISRs or AEs that were bothersome enough to the patient to consider decreasing the infusion rate.
- The lack of new safety signals or increased severity or frequency of ISRs and ARs in the sub-population of patients who received higher rates of infusion as compared to those who received lower rates.
- Although an increased risk of infusion site extravasation related to increased infusion rates could not be ruled out based on the data provided within the submission, extravasation events in the high-rate subgroup did not appear to negatively impact product efficacy.

Considering that tolerability is individual to the patient and the proposed change to the infusion rate is to the maximum rate and not a target or set infusion rate, the clinical data suggests tolerability of infusion rates of 35 mL/hour/site is similar to tolerability of the currently approved rate (25 mL/hour/site, as defined in the original Xembify approval) in patients 10 years of age and older. Because the youngest child who achieved higher sustained infusion rates was 10 years old and because of the expectation that younger children will have lower body weight and smaller subcutaneous space that may not accommodate faster rates, it is unclear if children younger than 10 years of age would tolerate the increased rates of infusion.

Assessments are limited by small sample size in the subgroup who received Xembify at sustained rates of at least 35 mL/hour/site, but similar tolerability profile across rates as reported by the Applicant supports the increase of maximum rate. Additionally, this study was the registrational study for Xembify approval in the EU, where it was approved for administration at maximum rates of 35 mL/hour/site, suggesting the EMA review came to similar conclusions.

This reviewer supports increasing the maximum rate to 35 mL/hour/site for patients 10 years and older with PI, and maintaining the currently approved maximum rate of 25 mL/hour/site for children 2 to <10 years of age with PI.

6.1.12 Safety Analyses

6.1.12.1 Methods

Treatment-emergent adverse events (TEAEs) in the SC phase were summarized by MedDRA Preferred Term, drug causal relationship, and temporal relationship with infusions. In the study, all local ISRs were recorded in the CRF, but were only considered TEAEs if they met the following criteria per the protocol:

1) signs/symptoms led to infusion interruption or discontinuation,
2) required concomitant medication, or
3) had an impact on the general condition of the patient.

For the purposes of comparing ISRs for varied rates of product administration, a detailed analysis of all ISRs (even those not recorded as AEs) was evaluated.

Because the safety of Xembify was previously evaluated in Study GTI1502 for the purposes of the original approval (please see Clinical Review Memo for Xembify dated July 3, 2019), additional safety analyses for the entire Safety Population in this study were not necessary, and the review focused on the safety specifically evaluating ISRs, TEAEs, and AEs that led to study discontinuation or infusion rate decreases within the study sub-population that received Xembify at rates ≥35 mL/hour/site.

6.1.12.2 Overview of Adverse Events

Adverse events observed in the Safety Population were similar to those observed in Study GTI1502 and as reported in the USPI for Xembify. Rates of adverse events could not be directly compared due to differences in study design and were not additive to the overall safety of Xembify, and thus were reviewed only where relevant to this efficacy supplement as documented in the remainder of this section. There were no safety concerns identified by the Applicant that were different between pediatric or adolescent patients as compared to adult patients with PI in the study. There were no safety concerns identified related to the increased rate of infusion per infusion site.

6.1.12.3 Deaths

There were no deaths reported in the study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 7 treatment-emergent serious adverse events (SAEs) in 7 patients (12%) were reported by the Applicant in the Safety Population: urinary tract infection, nephrotic syndrome, medical device site joint pain, joint dislocation, aortic valve incompetence, pneumonia, and thrombocytopenia. All but one SAE (nephrotic syndrome) resolved and none of the SAEs were assessed as related to the study drug.

> ***Clinical Reviewer Comment:*** *SAEs reported in the Safety Population were not relevant to the assessment of tolerability related to increased infusion rates in support of this efficacy supplement and need not be addressed in the USPI. SAEs were reported by the Applicant but were not independently confirmed.*

6.1.12.5 Adverse Events of Special Interest (AESI)

AESIs were not identified or reported by the Applicant for this study.

6.1.12.6 Clinical Test Results

There were 9 laboratory abnormalities reported as TEAEs in 6 patients in the Safety Population. All were mild or moderate in severity and resolved or were resolving except for an AE of blood IgG decreased which had an unknown outcome.

> ***Clinical Reviewer Comment****: Clinical test results within this section are as reported by the Applicant in clinical summaries but these were not independently confirmed as they are not additive to the safety of Xembify already established with the initial approval.*

6.1.13 Study Summary and Conclusions

Study GTI1503 was ongoing at the time of original BLA approval, but interim safety and efficacy data from pediatric patients supported the approval of Xembify in pediatric patients (refer to Clinical memo for original BLA). Final clinical data supports similar efficacy in pediatric and adult patients with PI as demonstrated in the registrational trial Study GTI1502 that was the primary basis for approval, and provides additional supportive evidence of efficacy (based on SBI rate) in the pediatric population.

Regarding the increased rate of product administration, the data supports an increased maximum infusion rate of 35 mL/hour/site for patients 10 years and older with PI. Tolerability of sustained rates ≥35 mL/hour/site in 7 patients as assessed by infusion site reactions and discontinuation or decreasing of rate due to AEs was similar to tolerability of rates <35 mL/hour/site. Due to lack of data in children less than 10 years of age, it is unclear if higher infusion rates would be tolerated. Therefore, maintaining the currently approved rate of 25 mL/hour/site for children less than 10 years of age is appropriate.

Additionally, as dosing is weight-based and younger children are expected to receive smaller total volumes than adults, it was not felt that infusion rates ≥35 mL/hour/site would be of meaningful benefit due to minor impact on total infusion time. Therefore, the review team did not feel it was necessary to pursue a post-marketing requirement assessing the tolerability of increased rates of infusion in children less than 10 years of age.

6.2 Study #2 – Study GC1906

Study Title: “A Multi-center, Single-Sequence, Open-label Study to Evaluate IGSC 20% Biweekly Dosing in Treatment-Experienced Subjects and Loading/Maintenance Dosing in Treatment-Naïve Subjects with Primary Immunodeficiency”

6.2.1 Objectives (Primary, Secondary, etc.)

The primary pharmacokinetic (PK) objective of this Phase 4 study was to determine whether biweekly (every 2 weeks) administration of Xembify produced a steady-state area under the curve (AUC) of total immune globulin G (IgG) that was non-inferior to that produced by weekly administration of Xembify in treatment-experienced patients with primary humoral immunodeficiency (PI).

Secondary Objectives:

- To determine if Xembify replacement therapy maintained steady-state mean trough total IgG levels when administered biweekly (every 2 weeks) that were comparable to steady-state mean trough total IgG levels obtained when Xembify was administered weekly in treatment-experienced patients with PI.
- To evaluate maximum concentration (C_{max}) and time to reach C_{max} (T_{max}) of total IgG at steady state in Xembify given weekly and biweekly (every 2 weeks) in treatment-experienced patients.
- To evaluate if a loading dose of Xembify consisting of 5 consecutive daily doses of 150 mg/kg/day (Week 0, Days 1 to 5) followed by weekly infusions of Xembify 150 mg/kg starting Week 1 (Day 8) through Week 32 achieved and maintained total IgG trough >500 mg/dL in treatment-naïve patients with PI.
- To evaluate the rate of serious bacterial infections (SBIs) in all patients.
- To evaluate all infections of any kind as determined by the investigator in all patients.
- To evaluate validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (e.g., rapid streptococcal antigen detection test) in all patients.
- To evaluate the number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic) in all patients.
- To evaluate the number of hospitalizations due to infection in all patients.

Safety objectives included safety and tolerability of:

- biweekly and weekly dosing regimens of Xembify as an IgG replacement therapy in treatment-experienced patients with PI.
- the loading/ maintenance dosing regimen of Xembify in treatment-naïve patients with PI.

Exploratory objectives included quality of life assessments.

6.2.2 Design Overview

Study GC1906 was a Phase 4, multi-center, open-label, single-sequence study over 33 weeks of Xembify treatment consisting of two cohorts: a treatment-experienced cohort and a treatment-naïve cohort.

> ***Clinical Reviewer Comment:*** *Given the study outcomes were primarily pharmacokinetic in nature, a 33-week study appears appropriate for the outcomes of interest. SBI rates to provide evidence of efficacy were already established in the registrational study (GTI1502) for the original approval, and thus did not need to be specifically assessed by a 12-month study. The open-label study design is appropriate*.

6.2.3 Population

Treatment-Experienced Cohort:
The treatment-experienced cohort enrolled adult patients 18-75 years of age with PI who were already maintained on IG replacement therapy for a minimum of 3 months. Patients were not to have had an SBI in the prior 3 months and were to have baseline IgG trough levels ≥500 mg/dL.

Treatment-Naïve Cohort:
The treatment-naïve cohort enrolled patients 6-75 years of age with PI with features of hypogammaglobulinemia requiring IG replacement therapy but who had never received IG replacement therapy. Patients were not to have SBI nor required hospitalization for infection during screening or at baseline and were to have baseline IgG trough levels ≤400 mg/dL.

> ***Clinical Reviewer Comment:*** *It is not clear why the treatment-experienced cohort intended to enroll only adult patients while the treatment-naïve cohort could enroll pediatric patients. It is expected that patients with PI of all ages would benefit from the dosing regimen changes. However, it is also understood that the PPK modeling performed to support the premise of the dosing regimens evaluated in this study incorporated data from both pediatric and adult patients with PI. Although inclusion of children in the study would be preferred, results of PK assessments in adults likely can be extrapolated to pediatric patients with PI based on the PPK modeling and the simulation approach.*

6.2.4 Study Treatments or Agents Mandated by the Protocol

Treatment-Experienced Cohort:

In Treatment Period 1, treatment-experienced patients received 16 weekly Xembify infusions (Week 0 to Week 15).

- Patients entering the study on intravenous formulations (IGIV) were administered Xembify using a dose adjustment of 1.37 times the equivalent weekly dose.
- Patients entering the study on subcutaneous formulations (IGSC) received the same mg/kg equivalent weekly dose as given prior to study entry without a dose adjustment factor (DAF).

In Treatment Period 2, patients received 9 biweekly (every two weeks) Xembify infusions at equivalent doses (i.e., two times the weekly dose) between Weeks 16 and 32.

Treatment-Naïve Cohort:

Treatment-naïve patients received a loading dose consisting of 5 consecutive daily doses of Xembify at a dose of 150 mg/kg/day, followed by weekly infusions of 150 mg/kg starting Week 1 (Day 8) through Week 32 (end of treatment phase). During the treatment phase, individual doses were adjusted to maintain a target IgG trough ≥ 700 mg/dL. The final follow-up visit was conducted at Week 33.

6.2.5 Directions for Use

Directions for use did not differ from approved directions aside from changes to the dosing regimen as described. In this study, Xembify was administered using a subcutaneous infusion pump.

6.2.6 Sites and Centers

The study was conducted at 14 centers in the United States.

6.2.7 Surveillance/Monitoring

Study monitoring as detailed in the protocol schedule included assessment of vital signs, physical examination findings, and laboratory parameters at study visits, as well as assessments for adverse events and concomitant therapies.

6.2.8 Endpoints and Criteria for Study Success

Success was defined by pharmacokinetic (PK) assessments in this study.

Pharmacokinetics:

Primary PK Endpoint in Treatment-Experienced Cohort:

- AUC of Xembify administered weekly: Steady-state AUC of total IgG over a regular dosing interval (τ), every week (i.e., $AUC_{0-\tau}$, weekly or $AUC_{0-7\ days}$), compared to
- AUC of Xembify administered biweekly: Steady-state AUC of total IgG over a biweekly dosing interval (τ) (i.e., $AUC_{0-\tau}$, biweekly or $AUC_{0-14\ days}$).

Secondary PK Endpoints

- Treatment-experienced cohort: Steady-state mean trough (pre-dose) concentration of total IgG following SC administration of Xembify given weekly and biweekly (every 2 weeks).
- Treatment-experienced cohort: C_{max} and T_{max} of total IgG at steady state of Xembify given weekly and biweekly.
- Treatment-naïve cohort: ability of a loading dose of Xembify 150 mg/kg/day and maintenance infusion of Xembify 150 mg/kg/week to achieve and maintain total IgG trough >500 mg/dL through Week 32 (End of Treatment).

Secondary efficacy endpoints included infection-related endpoints in all treated patients.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Descriptive statistics included number of non-missing observations, mean, standard deviation, median, minimum and maximum values for continuous/quantitative data or absolute and relative frequency and percentages for categorical/qualitative data. Data were generally analyzed separately for the treatment-experienced and treatment-naïve cohorts. Treatment-experienced patient data, when applicable, was analyzed separately for the two dosing frequencies (weekly and biweekly) of Xembify. Data in the treatment-naïve cohort was analyzed separately, when applicable, for the loading and maintenance phases of Xembify dosing.

The hypothesis testing for the primary PK analysis of AUC non-inferiority were tested at 1-sided with α=0.05. When applicable, formal statistical comparisons of other PK parameters were tested at 2-sided with α=0.10. All other statistical tests were 2-sided at a significance level of 0.05.

Please refer to the Biostatistics review memo for additional details.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The Safety Population consists of all 33 treated patients, regardless of cohort. Outcomes were otherwise analyzed separately for the Treatment-Experienced cohort (N=27) and the Treatment-Naïve cohort (N=6).

> ***Clinical Reviewer Comment:*** *This study was intended primarily as a PK study to support biweekly dosing and a loading and maintenance dose regimen for patients with PI who are naïve to IG replacement therapy. The sample size is small and it is not generalizable to the PI population in the U.S. (particularly given the demographics, discussed in the next section). However, PK modeling and experience with larger clinical trials of similar products increase confidence that results could be extrapolated to the greater population of PI patients in the U.S.*

The PK Population consists of the treatment-experienced population who were evaluable for serial PK assessments. Of the 27 patients enrolled in the Treatment-Experienced cohort, 25 patients comprised the PK Population: 23 patients were evaluable for both the weekly and biweekly study periods, and 2 additional patients were evaluable for the weekly period only.

6.2.10.1.1 Demographics

Thirty-three patients enrolled in the study, including 27 treatment-experienced patients and 6 treatment-naïve patients. Twenty (61%) of the patients were female, and all were White and non-Hispanic. All patients were adults, with a mean age of 54 years. No pediatric or adolescent patients enrolled in the study. Demographics are provided in more detail in Table 7.

Table 7: Patient Demographics for Study GC1906

Characteristic	Statistic	Treatment-Experienced (N=27)	Treatment-Naïve (N=6)	All Patients (N=33)
Age (years)	Median (Min, Max)	54 (22, 73)	57.5 (46, 65)	54 (22,73)
Age Category (years)	--	--		--
<18	n (%)	0	0	0
≥18 - ≤ 65	n (%)	24 (89)	6 (100)	30 (91)
>65	n (%)	3 (11)	0	3 (9)
Sex	--	--	--	--
Male	n (%)	11 (41)	2 (33)	13 (39)
Female	n (%)	16 (59)	4 (67)	20 (61)
Ethnicity: Not Hispanic or Latino	n (%)	27 (100)	6 (100)	33 (100)
Race: White	n (%)	27 (100)	6 (100)	33 (100)

Source: Adapted from Table 1-10 in sBLA 125683/265 Module 2.7.4 Summary of Clinical Safety

> ***Clinical Reviewer Comment:*** *Enrolled patients were all White, non-Hispanic or Latino adults with PI, and the sample size was small. Although the enrolled population is not generalizable to the PI population in the U.S., race, ethnicity,*

and age are not likely to be contributing factors to differences in PK assessments related to the new dosing regimens proposed in this efficacy supplement. Additionally, PK modeling helps increase confidence in generalizability of results.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

There were no patient-level medical or behavioral characteristics that were considered relevant to the interpretation of study results for the purposes of this efficacy supplement.

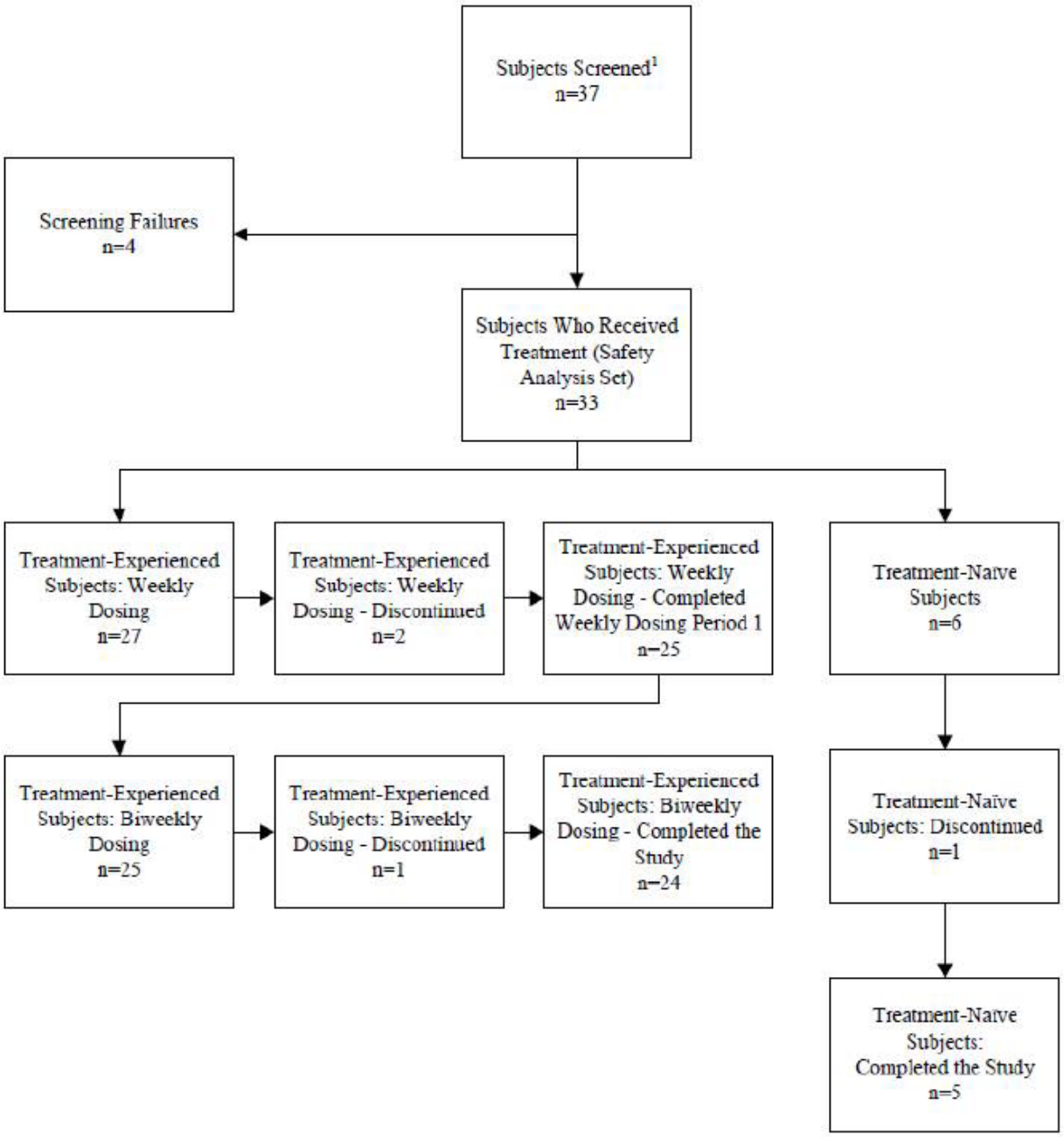
6.2.10.1.3 Patient Disposition

Within the treatment-experienced cohort, 29 patients were screened and 27 patients enrolled and were evaluable for safety and efficacy. For the PK analysis, 23 patients were evaluable with serial PK assessments in both the weekly and biweekly dosing periods of the study. Two additional patients were evaluable for PK in the weekly dosing period only. Of the 27 patients enrolled, 24 (96%) completed the study and 3 prematurely discontinued, 2 for AEs and 1 for withdrawal by patient for reason other than AE.

Within the treatment-naïve cohort, 8 patients were screened and 6 patients enrolled and were evaluable for safety, efficacy, and PK parameters. Five (83%) patients completed the study and 1 prematurely discontinued due to withdrawal by the patient for reason other than AE.

Patient disposition for the study is shown in Figure 2.

Figure 2: Patient Disposition in Study GC1906



[1] Two patients were initially screen failures and were subsequently re-screened and treated. These patients are counted only once as screened patients.
Source: Figure 1-3 in sBLA 125683/265 Module 2.7.4 Summary of Clinical Safety

6.2.11 Efficacy Analyses

Although infection data was collected in this study, SBI rate and efficacy of the product were already evaluated based on data from Study GTI1502 for the purposes of the original approval. No SBIs were reported in the study, however this is not additive to the already-defined SBI rate for the product and infection data was not considered for the purposes of the review, which focused on PK analyses to define success related to the new dosing regimens. The PK analyses for this study are detailed below and summarized in Section 4.4.3 Human Pharmacokinetics (PK).

6.2.11.1 Analyses of Primary Endpoint(s)

The primary PK objective of this Phase 4 study was to determine whether biweekly (every 2 weeks) administration of Xembify produces a steady-state $AUC_{(0\text{-}\tau)}$ [$AUC_{(0\text{-}7\ days)}$ for weekly and $AUC_{(0\text{-}14\ days)}$ for biweekly] of total IgG that is noninferior to that produced by weekly administration of Xembify in treatment-experienced patients with PI. As the dosing intervals are different between the weekly and biweekly dosing frequencies, the $AUC_{(0\text{-}14\ days)}$ for the biweekly dosing was divided by 2 for comparison with $AUC_{(0\text{-}7\ days)}$ for the weekly dosing. The GLSM ratio of the $AUC_{(0\text{-}7\ days)}$ for Xembify administration biweekly compared to weekly is 104% (90% CI: 100%-107%), indicating that biweekly Period 2 (n=23) was non-inferior to weekly Period 1 (n=23).

6.2.11.2 Analyses of Secondary Endpoints

Treatment-Experienced Cohort: Mean Total IgG Trough Levels at Steady State Following Weekly and Biweekly Xembify

The mean total IgG trough levels were calculated as the average pre-infusion concentrations at Weeks 12, 14, and 16 for the weekly dosing period and Weeks 28, 30, and 32 for the biweekly dosing period. Similar mean serum IgG concentrations at Weeks 12, 14, and 16 indicate that steady state was achieved following weekly Xembify infusion dosing prior to the serial PK sampling at Week 14. As with weekly dosing, similar mean serum IgG concentrations at Weeks 28, 30, and 32 indicate that steady state was maintained following biweekly Xembify infusion dosing prior to the serial PK sampling at Week 30. Furthermore, mean trough concentrations were similar between Periods 1 (weekly) and 2 (biweekly), such that the ratio of mean trough concentrations following biweekly dosing (Period 2) compared to mean trough concentrations following weekly dosing (Period 1) was 0.971 (see Table 8). For all treatment-experienced patients, weekly (Period 1) and biweekly (Period 2) infusions of IGSC 20% achieved and maintained steady-state total IgG trough concentrations >500 mg/dL through Week 15 (End of Treatment Period 1) and Week 32 (End of Treatment Period 2), respectively. In summary, the trough levels of total IgG concentrations were stable over time following weekly or biweekly Xembify administration and similar between Periods 1 and 2.

Table 8: Steady-State Mean Trough Concentrations of Total IgG Following Weekly (Period 1) or Biweekly (Period 2) Xembify Administration in Treatment-Experienced Patients

Statistic	C_{trough} Period 1 Week 12 (mg/dL)	C_{trough} Period 1 Week 14 (mg/dL)	C_{trough} Period 1 (Week 16 (mg/dL)	Mean C_{trough} Period 1 (mg/dL)	C_{trough} Period 2 Week 28 (mg/dL)	C_{trough} Period 2 Week 30 (mg/dL)	C_{trough} Period 2 Week 32 (mg/dL)	Mean C_{trough} Period 2 (mg/dL)	Mean C_{trough} Ratio, Period 2/ Period 1
n	24	24	25	23	23	24	24	22	20
Mean (SD)	1030 (206)	953 (189)	1018 (184)	994 (191)	1002 (221)	953 (202)	984 (191)	979 (198)	0.971 (0.0678)
%CV	20.0	19.9	18.1	19.2	22.0	21.2	19.4	20.2	7.0
Min, Max	748, 1696	733, 1405	749, 1463	744, 1521	631, 1552	668, 1505	678, 1505	659, 1521	0.85, 1.17

C_{trough} = trough concentration of IgG; CV =coefficient of variation; n = number of patients evaluable; SD = standard deviation
Source: Adapted from Table 11-1, sBLA 125683/265 Module 5.3.5.1, Study SC1906 Clinical Study Report

Treatment-Experienced Cohort: Pharmacokinetic Parameters of Total IgG at Steady State of Weekly and Biweekly Xembify

Patients in the PK Population receiving weekly Xembify administration (n=25) achieved peak total IgG concentrations (C_{max}) of 1076 mg/dL and the mean T_{max} was 79 hours. The arithmetic mean $AUC_{(0\text{-}7\ days)}$ value for total IgG after weekly dosing was 170386 h*mg/dL. Similarly, patients in the PK Population receiving biweekly Xembify administration (n=23) achieved a total IgG C_{max} of 1151 mg/dL with mean T_{max} as 103 hours. The mean $AUC_{(0\text{-}7\ days)}$[6] value for total IgG after biweekly dosing was 174561 h*mg/dL (see Table 9).

Table 9: Steady State PK Parameters for Xembify Weekly and Biweekly Dosing in Adult PK Population

Period	Statistic	$AUC_{(0\text{-}7\ days)}$ (h*mg/dL)*	C_{max} (mg/dL)	T_{max} (hour)
Weekly	n	23	25	25
--	Mean±SD	170386 ± 35949	1076 ± 228	79 ± 40
Biweekly	n	23	23	23
--	Mean±SD	174561 ± 36974	1151 ± 243	103 ± 44

*: arithmetic mean
$AUC_{(0\text{-}7\ days)}$ =area under the curve for weekly administration ; C_{max} = maximum concentration of IgG; n = number of patients evaluable; SD = standard deviation; T_{max} = time to maximum concentration of IgG
Source: Adapted from Table 11-2, sBLA 125683/265 Module 5.3.5.1, Study SC1906 Clinical Study Report

Treatment-Naïve Cohort: Ability of a Loading and Maintenance Dose Regimen of Xembify to Achieve and Maintain Target IgG Trough Levels

A cohort of treatment-naïve adults with PI (n=6) were evaluated for the trough IgG levels following initiation of a Xembify loading dose regimen (150 mg/kg/day for 5 consecutive days) and after weekly maintenance Xembify dosing regimen (150 mg/kg/week through

[6] As the dosing intervals are different between the weekly and biweekly dosing frequencies, the $AUC_{(0\text{-}14\ days)}$ for the biweekly dosing was divided by 2 for comparison with $AUC_{(0\text{-}7\ days)}$ for the weekly dosing.

32 weeks). Following the initial loading dose and prior to initiating maintenance dosing, five (83%) patients attained an IgG trough level >700 mg/dL at Week 1 (Day 8). The single patient who did not achieve an IgG trough level >700 mg/dL at Week 1 (672 mg/dL) had a baseline IgG level (<40 mg/dL) substantially lower than the baseline levels used in the PK modeling (see Section 6.3.11.3) to support the loading dose regimen. Three (50%) patients required dose adjustments. All 6 patients attained IgG trough levels >700 mg/dL by Week 8 and were maintained through the end of the study at Week 32 with Xembify doses between 150-180 mg/kg/week.

> ***Clinical Reviewer Comment:*** *The one patient who did not achieve IgG levels >700 mg/dL by Week 1 had very low baseline IgG levels, and thus it is not necessarily unexpected that the loading dose regimen was insufficient to achieve target IgG levels as rapidly. Regardless, the patient was able to achieve protective levels by Week 8 with dose adjustments, and dose adjustments are expected for any dosing regimen with any IG product as the dose needs to be individualized to the clinical status of the patient.*

6.2.11.3 Sub-Population Analyses

Results were analyzed separately for the Treatment- Experienced and Treatment-Naïve cohorts. No additional sub-population analyses were conducted for this study.

6.2.11.4 Dropouts and/or Discontinuations

A total of four (12%) patients prematurely discontinued from the study. Two patients (1 treatment-experienced patient receiving weekly dosing and 1 treatment-experienced patient receiving biweekly dosing) discontinued due to TEAEs:

1) The treatment-experienced patient receiving weekly dosing experienced dyspnea with headache that was mild in severity and considered possibly related to study treatments.
2) The treatment-experienced patient receiving biweekly dosing had infusion site pain that was moderate in severity. The event was assessed as unrelated to treatment.

One patient each from the treatment-experienced cohort and the treatment-naïve cohort withdrew consent for reasons other than AEs.

> ***Clinical Reviewer Comment:*** *Although the infusion site pain was assessed as unrelated to treatment, it is felt by this reviewer that infusion site pain is likely attributable to the infusion, even if not directly attributable to the study drug. Regardless, the discontinuation of the two treatment-experienced patients did not significantly impact the PK analyses that serve as the basis of approval of the biweekly dosing regimen, and the two TEAEs do not appear to indicate a different safety profile in weekly versus biweekly product administration, nor a safety profile that is different from that defined for Xembify in the initial approval or from similar products within the class.*

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety analyses were conducted by listing and tabulating adverse events (AEs) including suspected adverse reactions (ARs), vital signs, physical exam findings and results of laboratory tests. Data were summarized with descriptive statistics and compared between study groups, where relevant. Safety data were analyzed separately for the treatment-experienced and the treatment-naïve patients.

6.2.12.2 Overview of Adverse Events

The safety of Xembify was already established with the original approval. Adverse events observed in the study were similar to those observed in the registrational Study GTI1502 and as reported in the USPI for Xembify. Rates of adverse events between studies could not be directly compared due to differences in study design and were not additive to the overall safety of Xembify, and thus were reviewed only where relevant as documented in the remainder of this section.

Within the treatment-experienced cohort, safety of weekly and biweekly dosing of Xembify generally appeared similar and ARs were similar to those reported in the registrational Study GTI1502.

Among the treatment-naïve cohort, ARs occurring in more than one patient included infusion site swelling in 2 (33%) patients during or after 13 infusions and infusion site bruising in 2 (33%) patients during or after 2 infusions.

> ***Clinical Reviewer Comment:*** *ARs observed in the treatment-naïve cohort are commonly described ARs with SCIG and are not unique to the treatment-naïve cohort, nor do they appear to be occurring at particularly high rates in the treatment-naïve population.*

6.2.12.3 Deaths

There were no deaths reported in the study.

6.2.12.4 Nonfatal Serious Adverse Events

The Applicant reported a total of 4 (12%) of study patients experienced treatment-emergent SAEs including the following:

Treatment-Experienced Patients:

- One patient had two SAEs that required hospitalization for three infections, one during the weekly period (viral pneumonia) and one during the biweekly period (*Clostridium dificile* and cellulitis). The investigator attributed the *Clostridium dificile* and cellulitis as possibly related to treatment.
- Additional SAEs in treatment-experienced patients assessed as unrelated to treatment included dehydration, acute pancreatitis, and worsening of Barrett's esophagus.

Treatment-Naïve Patients:

- One patient experienced compression fracture with back pain that was considered unrelated to treatment.

No patients discontinued as a result of the SAEs and all SAEs resolved.

> ***Clinical Reviewer Comment:*** *SAEs were not independently reviewed and adjudicated, as safety of Xembify was established with the initial approval and no new safety signals attributable to treatment and the new dosing regimens were reported. This reviewer agrees that with the well-established safety profile of IG products, the non-infectious SAEs appear unrelated to study treatments. The SAEs of infections requiring hospitalization may be related to underlying disease or study treatments. None of these infections qualify as SBIs, but even if conservative adjudication led to considering the pneumonia a potential bacterial pneumonia, this still would be well within the accepted rate of SBIs per patient-year for the determination of efficacy of IG products. Additionally, it is somewhat encouraging that the pneumonia occurred during the weekly period of Xembify administration – if anything, biweekly administration would be more likely to contribute to inconsistent IgG troughs and potential "wearing off" effect between doses as compared to weekly dosing. Therefore, it would be more concerning if the pneumonia occurred during biweekly dosing. It is expected that antigen-specific antibodies in IgG pools from typical healthy donors would be more likely to contain specific IgG to respiratory bacterial and viral pathogens than to Clostridium dificile and cellulitis, and therefore it may have been unlikely that the Xembify would have been able to prevent the infections and hospitalizations in the biweekly period. With hospitalizations for infections for the same patient in both the weekly and biweekly periods, this still is consistent with similar efficacy of the weekly and biweekly dosing regimens for that patient.*

6.2.12.5 Adverse Events of Special Interest (AESI)

AESIs were not identified or reported by the Applicant for this study.

6.2.12.6 Clinical Test Results

Mean values for vital signs, hematology, chemistry, and urinalysis results remained within normal limits with no remarkable changes from baseline values. All patients were negative for direct antiglobulin. One treatment-naïve patient had a haptoglobin level below the lower limit of normal at baseline, Week 8, and Week 32.

No clinically significant vital sign or laboratory abnormalities were reported in the study. One patient had events of mild hypertension that were ongoing, and moderate hypotension that resolved. Fluctuations in laboratory parameters that were recorded as AEs during the study included, in one patient each:

- mild free hemoglobin and moderate hematocrit increase which resolved,
- moderate hypokalemia which resolved, and
- moderate hypoglycemia which resolved.

> ***Clinical Reviewer Comment****: Clinical test results within this section are as reported by the Applicant in clinical summaries but these were not independently confirmed as they are not additive to the safety of Xembify already established with the initial approval.*

6.2.12.7 Dropouts and/or Discontinuations

Dropouts/discontinuations are addressed in Section 6.2.11.4 .

> ***Clinical Reviewer Comment:*** *The discontinuations due to AEs did not substantially impact the evaluation of safety because both occurred in the treatment-experienced group, safety of weekly Xembify administration was already demonstrated to support the original approval, and the AE that occurred in the patient receiving the new dosing regimen of biweekly Xembify was mild and an anticipated risk regardless of dosing schedule.*

6.2.13 Study Summary and Conclusions

Administration of weekly and biweekly Xembify in treatment-experienced patients and of the loading dose regimen followed by weekly maintenance administration of Xembify in treatment-naïve patients was safe and well-tolerated with a safety profile similar to that already demonstrated for the initial approval of Xembify.

Results of the analysis of the primary PK endpoint indicate that biweekly administration of Xembify produced steady-state AUCs of total IgG that were similar to those from weekly administration in treatment-experienced patients with PI. Additionally, for treatment-experienced patients, mean total IgG concentrations were stable over time during both the weekly and biweekly dosing periods. Weekly and biweekly dosing regimens of Xembify appear to provide similar IgG exposure.

In the treatment-naïve cohort, all 6 patients achieved IgG trough levels > 700 mg/dL at Week 1 (Day 8) following the loading dose regimen of 150 mg/kg/day for 5 days except for 1 patient who had a very low IgG level at baseline. Following dose adjustments in 3 (50%) of patients, all 6 patients achieved and sustained IgG trough levels >700 mg/dL by Week 8 and maintained trough levels through the end of study. The loading dose regimen appears sufficient to rapidly raise IgG to protective levels in treatment-naïve patients.

Results of PK analyses in this study are consistent with those predicted by the PPK modeling (see Section 6.3 Study #3 – Study GI003), and the totality of the data supports approval of the biweekly dosing regimen for treatment-experienced patients and the loading dose/maintenance dose regimen for treatment-naïve patients. Although the study only enrolled adults, PPK modeling allows for extrapolation of these new dosing regimens to pediatric patients. Modeling suggests similar responses between pediatric and adult patients with PI, and differences in PK assessments are not expected to be impacted by patient age for these dosing regimens.

6.3 Study #3 – Study GI003

Study Title: “Pharmacokinetic Modeling and Simulation of Subcutaneous and Intravenous IgG Dosing in Primary Immunodeficiency Patients”

6.3.1 Objectives (Primary, Secondary, etc.)

The objective of Study GI003 was to develop a predictive population pharmacokinetics (PPK) model for characterization of PK after single and repeated dosing by IGIV and IGSC to inform clinical decision-making regarding dosage regimens of IGSC 20%

(Xembify). Two of the key objectives of the study for the purposes of this efficacy supplement were to simulate IgG kinetics following different dosing regimens for IGSC and evaluate the effect of loading doses of IGSC regimens for treatment-naïve patients.

6.3.2 Design Overview

Clinical study data from all patients treated with both IGIV (Gamunex-C® 10%) and IGSC (Gamunex-C® 10% or IGSC 20%- Xembify®) were included in a population PK analysis which included data from 3 clinical studies performed in the U.S. and Canada:

1. Study 060001 (U.S.): Open-label, single-sequence, crossover study from Gamunex-C® administered IV to SC to evaluate the PK, safety, and tolerability of SC administration of Gamunex-C® in patients with PI.
2. Study T5004-401 (U.S. and Canada): Open-label, single-sequence, crossover study from Gamunex-C® administered IV to SC to evaluate the PK, safety, and tolerability of SC administration of Gamunex-C® in pediatric patients with PI.
3. Study GTI1502 (U.S. registrational study for Xembify®): Open-label, multi-center, single-sequence study to evaluate PK, safety, and tolerability of IGSC 20% (Xembify®) administered for 6 months in patients with PI.

This population PK (PPK) study supported the original BLA approval and details regarding the study are included in the Clinical Review Memo for Xembify dated July 3, 2019, including details regarding the modeling to support biweekly dosing, as well as loading and maintenance dose regimens in treatment-naïve patients with PI. The Applicant conducted additional analyses during the course of the efficacy supplement review to demonstrate ability to extrapolate clinical PK data in adults to pediatric patients with PI for the new dosing regimens. Relevant aspects of PPK modeling are highlighted in Section 4.4.3 Human Pharmacokinetics (PK) and discussed in the context of the analysis of data to support the new dosing regimens in Section 6.2 Study #2 – Study GC1906.

6.3.3 Population

The study performed modeling and simulation for PK parameters in pediatric and adult patients with PI. Demographics for Study GI003 are detailed in Table 2.

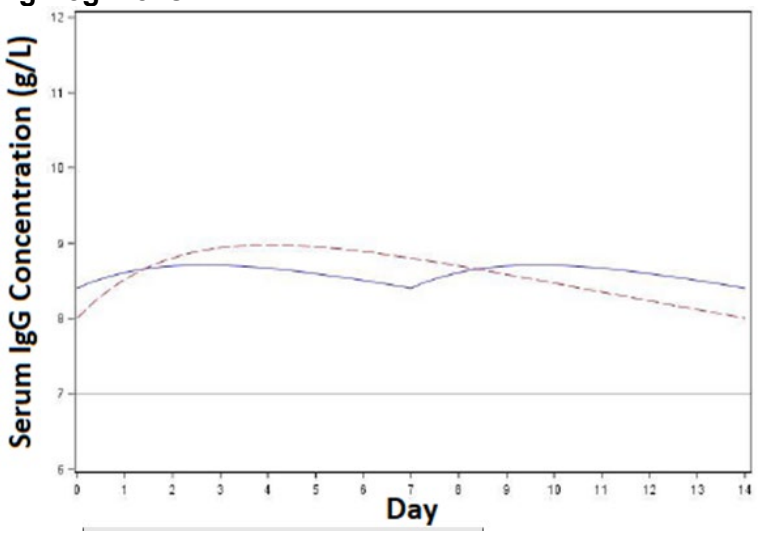
6.3.11 Population Pharmacokinetics Simulation Analyses

6.3.11.1 Evaluation of Different Frequency SC Dosing Regimens

Modeling and simulation indicated that the administration of a single biweekly SC dose, which is equivalent to double the weekly SC dose, resulted in comparable median IgG serum concentrations over the serum concentration-time profile compared to weekly SC dosing regimen (Figure 3). The serum IgG exposure over a 14-day steady-state period in PI patients was equivalent between both dosing regimens, with similar predicted median $AUC_{0\text{-}T}$[7], C_{max}, and C_{trough} values and the exposure ratios between biweekly and weekly SC dosing regimens were around 1.0 (Table 10).

[7] As the dosing intervals are different between the weekly and biweekly dosing frequencies, the $AUC_{(0\text{-}7\ days)}$ for the weekly dosing was multiplied by 2 for comparison with $AUC_{(0\text{-}14\ days)}$ for the biweekly dosing.

Figure 3: Simulated Median Steady-State Serum IgG PK Profiles of SC Weekly and Biweekly Dosing Regimens



IGSC Doses: 100mg/kg (7g) weekly and 200 mg/kg (14 g) biweekly
Blue line: weekly IGSC regimen
Red dashed line: biweekly IGSC regimen
Source: Figure 17, sBLA 125683/265, Module 5.3.3.5. PPK Report

Table 10: Comparison Between Steady-State IgG Exposures After Weekly and Biweekly SC Dosing Regimens

Parameter	Statistic	Weekly IGSC Dosing[a]	Biweekly IGSC Dosing[a]	Ratio (Biweekly/Weekly)
$AUC_{(0\text{-}14\ days)}$, (g·day/L)	Median (5^{th}-95^{th} percentiles)	121.0[b] (114.1-128.5)	120.2 (114.6-129.9)	0.98 (0.91-1.07)
C_{max}, (g/L)	Median (5^{th}-95^{th} percentiles)	8.8 (8.3-9.4)	9.1 (8.6-9.7)	1.02 (0.95-1.11)
C_{trough}, (g/L)	Median (5^{th}-95^{th} percentiles)	8.4 (7.9-9.0)	8.1 (7.5-8.6)	0.94 (0.87-1.03)

AUC = area under the concentration versus time curve, C_{max} = maximum concentration of IgG, C_{trough} = trough concentration of IgG; IgG = immunoglobulin G; IGSC = immune globulin subcutaneous
[a] IGSC weekly dose: 100 mg/kg (7g); IGSC biweekly dose: 200 mg/kg (14g)
[b] $AUC_{(0\text{-}7\ days)}$ x 2 to adjust for weekly instead of biweekly dosing
Source: Adapted from Table 14, sBLA 125683/265, Module 5.3.3.5. PPK Report

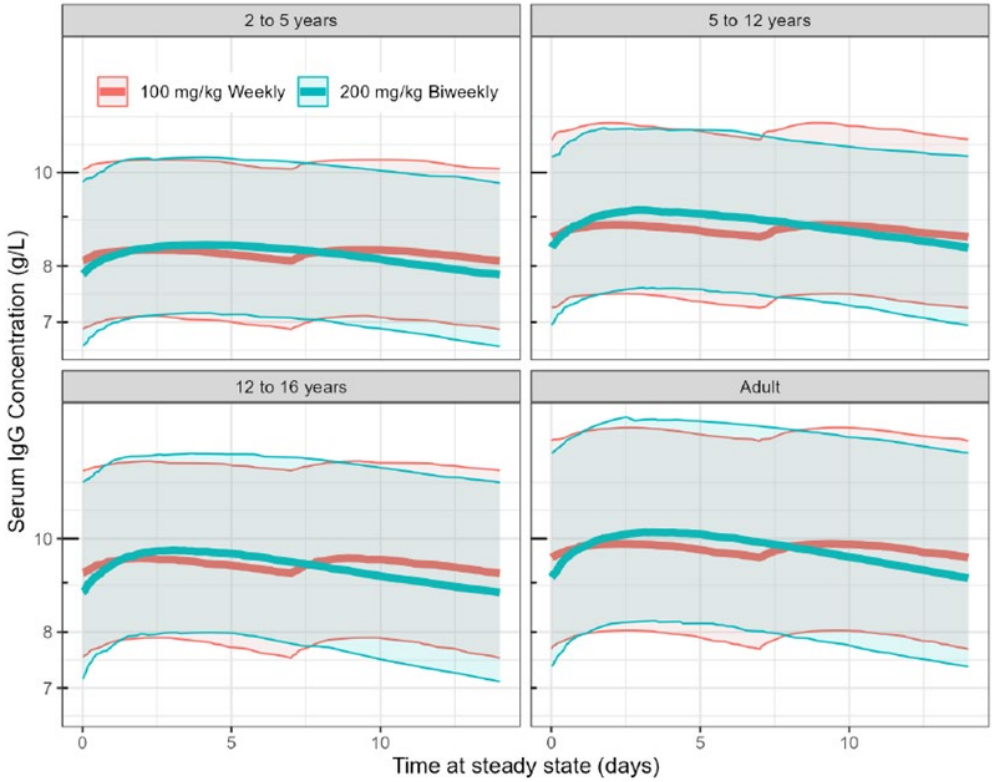
6.3.11.2 Evaluation of the Age Effect on PK of IgG

Although not performed with the original study, during the course of the review of the efficacy supplement, the Applicant conducted additional modeling and simulation of weekly and biweekly dosing regimens by age group to support extrapolation of clinical results in adult patients in Study GC1906 to pediatric patients with PI.

The simulation results of the IgG SC exposure comparison between 100 mg/kg weekly and 200 mg/kg biweekly in different age groups indicated that the PK of IgG was not influenced by age (pediatric versus adult). The concentration- time profiles of serum IgG at steady state (Figure 4) by age group showed considerable overlap between weekly and biweekly dosing for all age groups. When 100 mg/kg weekly and 200 mg/kg biweekly are compared based on age group (Figure 5) overlapping concentration- time profiles and similar range of exposures at steady-state were observed based on tested PK parameters (C_{max}, C_{min} and $AUC_{(0\text{-}7\ days)}$) in the pediatric age groups of 2 to 5 years,

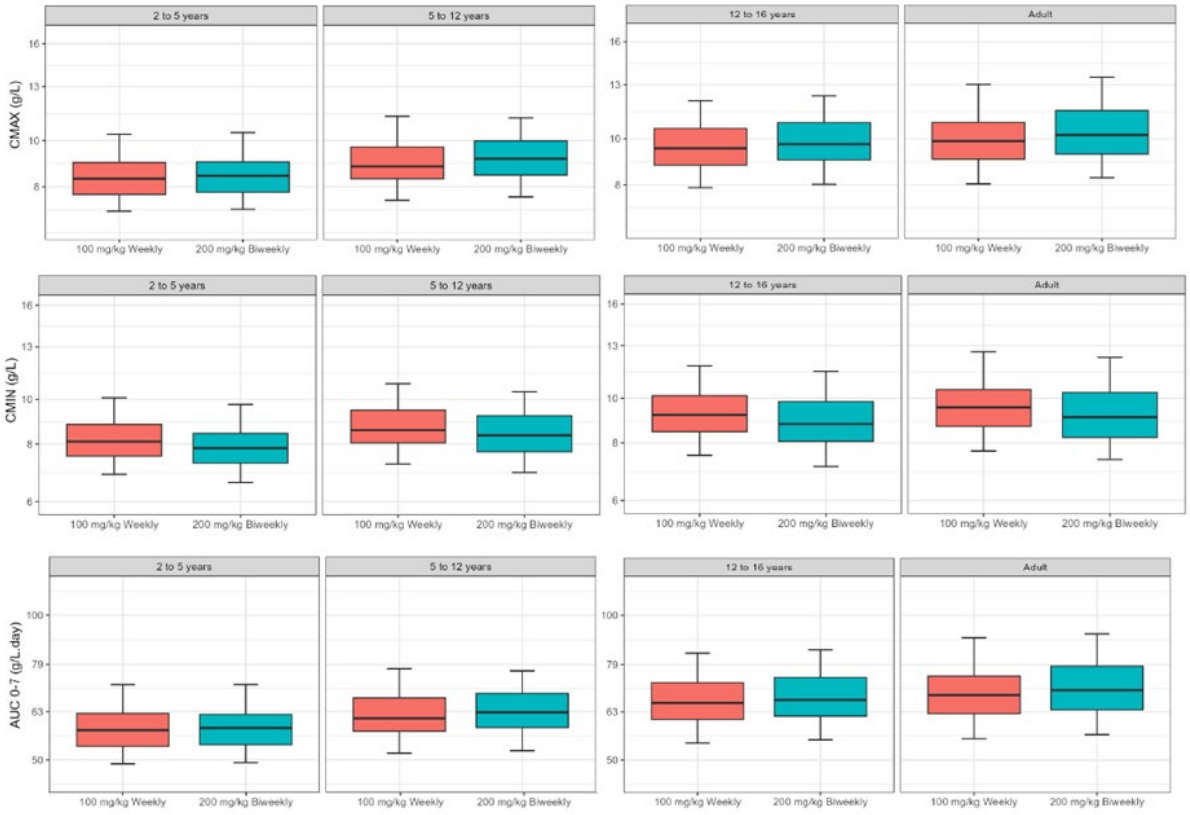
>5 to 12 years, >12 to 16 years, and adults. As observed in Figure 6, the majority of simulated steady state values for pediatric patients are within the 5th and 95th percentiles of the adult values.

Figure 4: Median Serum IgG Concentration- Time Profile at Steady State Simulation Grouped by Age



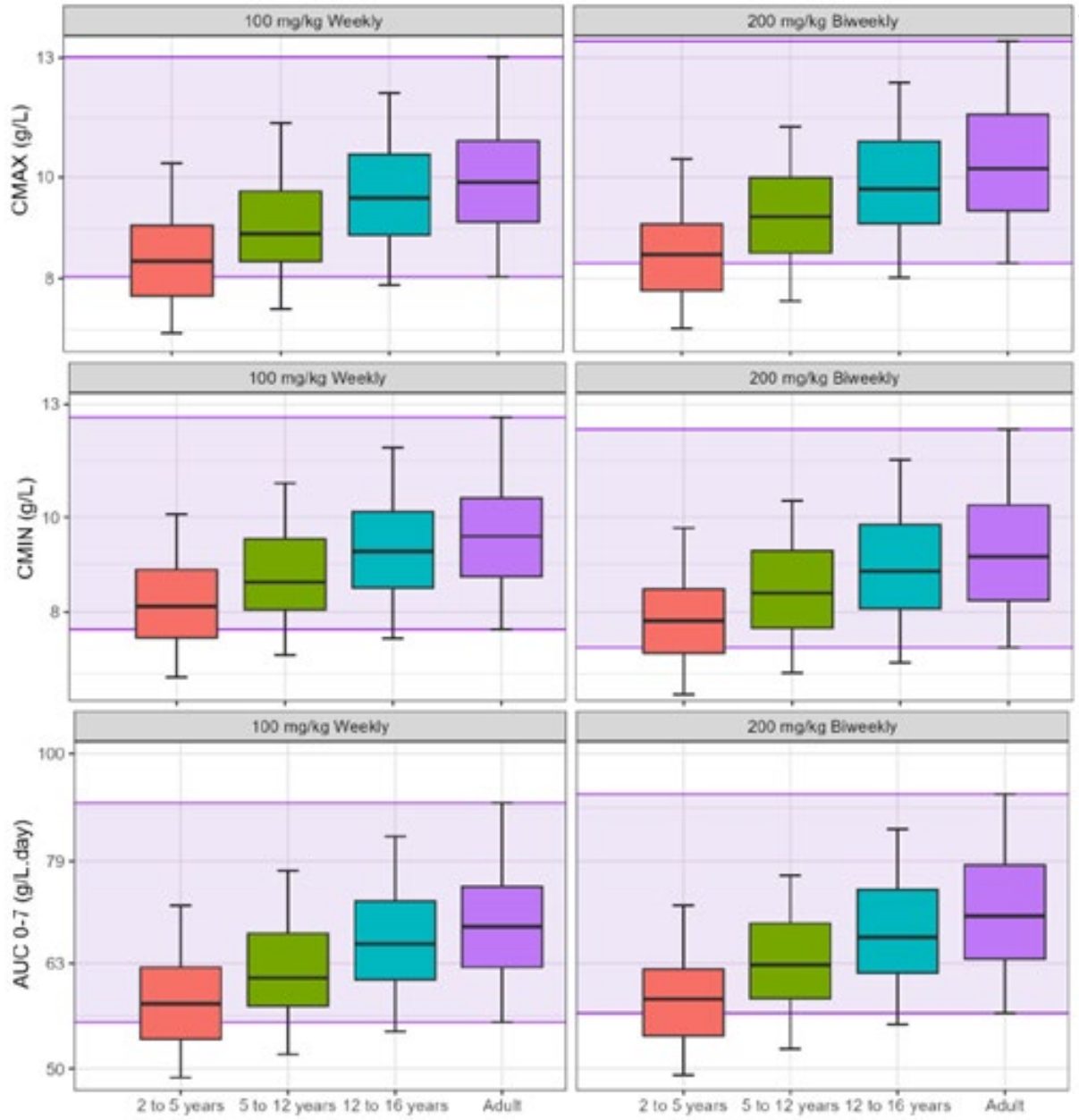
Note: Each bold curve represents the median serum IgG concentration time profile with the 95th CI upper and lower limits marked with fine line curves.
Source: Figure 1 of Applicant's Response to Clin-Pharm Information Request Submitted on 30 May 2024.

Figure 5: Boxplot Summary of C_{max}, C_{min} and $AUC_{(0\text{-}7\ days)}$ Grouped by Dose



Note: The line splitting the box in two represents the median value. The bottom edge of the box represents the lower quartile; the top edge of the box shows the upper quartile. The values at which the horizontal lines stop are the values of the 5th and 95th percentiles of the data. Outliers were excluded from this plot. The blue box plot represents 200 mg/kg biweekly and the orange box plot represents 100 mg/kg weekly administration. As the dosing intervals are different between the weekly and biweekly dosing frequencies, the $AUC_{(0\text{-}14\ days)}$ for the biweekly dosing was divided by 2 for comparison with $AUC_{(0\text{-}7\ days)}$ for the weekly dosing.
Source**:** Figure 2 of Applicant's Response to Clin-Pharm Information Request Submitted on 30 May 2024.

Figure 6: Boxplot Summary of C_{max}, C_{min} and $AUC_{(0\text{-}7\ days)}$ Grouped by Age



Note: The line splitting the box in two represents the median value. The bottom edge of the box represents the lower quartile; the top edge of the box shows the upper quartile. The values at which the horizontal lines stop are the values of the 5th and 95th percentiles of the data. Outliers were excluded from this plot. The shaded region represents the 5th to 95th percentile of adult exposure range. As the dosing intervals are different between the weekly and biweekly dosing frequencies, the $AUC_{(0\text{-}14\ days)}$ for the biweekly dosing was divided by 2 for comparison with $AUC_{(0\text{-}7\ days)}$ for the weekly dosing.
Source: Figure 3 of Applicant's Response to Clin-Pharm Information Request Submitted on 30 May 2024.

6.3.11.3 Evaluation of Loading Dose Regimens in Treatment-Naïve Patients with PI

The starting IG replacement therapy doses currently tend to be 400-600mg/kg/dose administered every 3-4 weeks for IGIV, and divided for weekly SC administration, this amounts to 100-150 mg/kg per week for SCIG. The currently recommended average

minimum serum total IgG level to remain free from infection is 7 g/L. Therefore, the study simulated results of multiple loading dose regimens taking into consideration these standard initial doses to determine which regimens might achieve target serum IgG target levels as quickly as possible. The endogenous levels of IgG (IgG_{ENDO}) of 1.5 and 4 g/L, starting doses of 100-150 mg/kg per week for SCIG, and average lower IgG level to remain free from infection of 7 g/L were taken into consideration for the simulation of loading dose regimens in treatment-naïve PI patients. All simulations performed are summarized in Table 11.

Table 11: Loading Dose Regimen Simulations Performed in the PPK Study

Loading Dose Regimen	IgG_{ENDO} (g/L)	Timing of Loading Dose Administration	Loading Dose (mg/kg)
IGSC – 2 times/week (days 1-2)	1.5 and 4	Weeks 1 and 2	100 and 150
IGSC – 3 times/week (days 1-3)	1.5 and 4	Weeks 1 and 2	100
IGSC – 5 times/week (days 1-5)	1.5 and 4	Weeks 1 and 2	100
--	1.5 and 4	Week 1	150
IGIV (day 1) then weekly IGSC (100 mg/kg, days 2 and 7)	1.5 and 4	Day 1 (IGIV) Days 2 and 7 (IGSC)	400 (IGIV) 100 (IGSC)
IGIV (day 1) then weekly IGSC (150 mg/kg, days 2 and 7)	1.5	Day 1 (IGIV) Days 2 and 7 (IGSC)	400 (IGIV) 150 (IGSC)

IgG = immunoglobulin G; IgG_{ENDO} = endogenous IgG level; IGIV = immune globulin intravenous; IGSC = immune globulin subcutaneous
Source: Adapted from Table 5.2, sBLA 125683/265, Module 5.3.3.5. PPK Report [Appendix 5]

Simulations of the median PK profiles considering different loading dose schemes for weekly 100 mg/kg and 150 mg/kg SC dosing regimens are shown in Figure 7 and Figure 8, respectively.

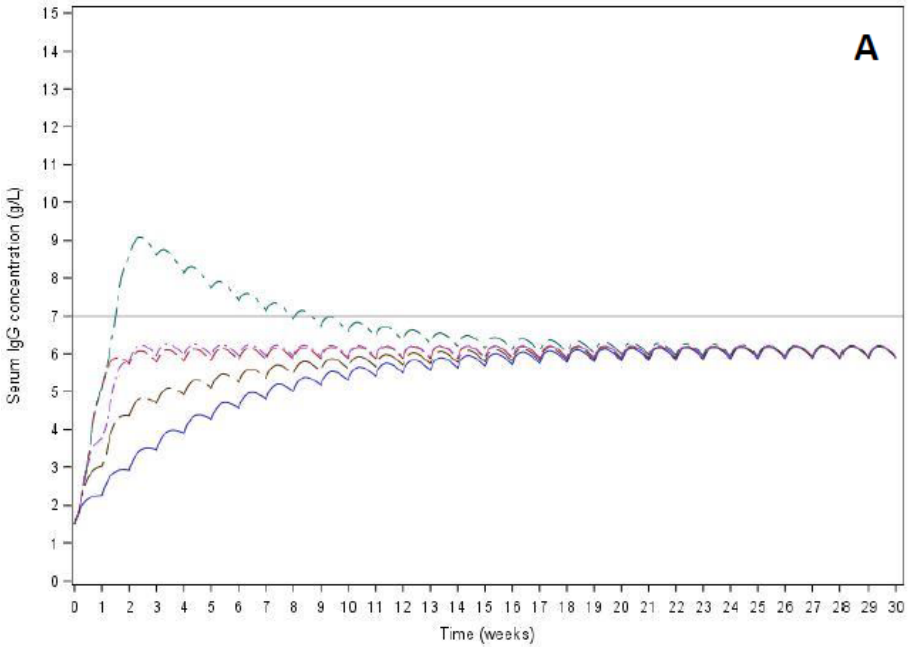
With an IGSC dosing regimen of 100 mg/kg/dose and IgG_{ENDO} level of 1.5 g/L (Figure 7, Panel A), the target IgG level of 7 g/L was only reached for the regimen including a loading dose of IGSC 100 mg/kg 5 times/week for two weeks, but IgG levels decreased below target levels on week 8 when switching to the maintenance SC dosing of 100 mg/kg weekly. When a basal level of 4g/L was considered (Figure 7, Panel B), the predicted time to achieve the target IgG level was 5.1 weeks without a loading dose regimen. Following a loading schedule of 5 times/week for 1 or 2 weeks, target IgG levels were rapidly obtained on the first week of administration, but a decrease was observed when switching to the maintenance dosing (100 mg/kg weekly). Trough IgG levels higher than 8 g/L were observed for all regimens during the weekly maintenance SC dosing period from week 8 onward.

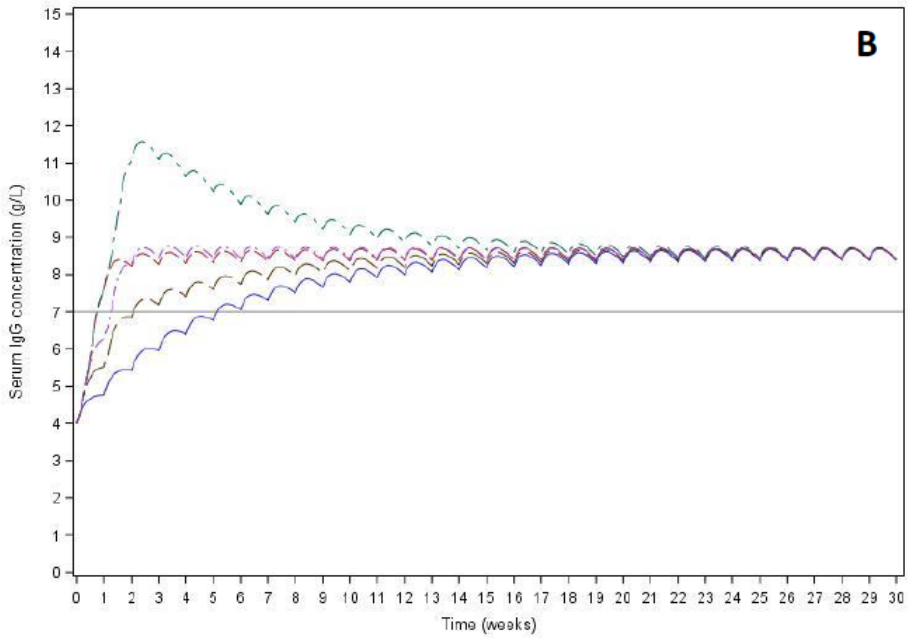
When IGSC therapy was initiated at 150 mg/kg/week for an IgG_{ENDO} of 1.5 g/L (Figure 8, Panel A), the predicted time to reach IgG levels of 7 g/L without a loading dose was 7.5

weeks and with a loading dose of 150mg/kg/dose twice a week was approximately 4 weeks. Intensive loading doses of 150mg/kg/day for 5 days provided appropriate levels above 7 g/L rapidly (within approximately one week), with IgG levels maintained with a weekly IGSC maintenance dosing of 150 mg/kg. When IgG_{ENDO} levels of 4 g/L are considered (Figure 8, Panel B), target IgG levels were also achieved in approximately 1 week with the intensive 5-day loading dose regimen.

As age has no appreciable effect on the IgG PK (see Section 6.3.11.2), the IgG exposure following a loading dose plus maintenance dose regimen is expected to be similar between treatment-naïve pediatric and adult patients.

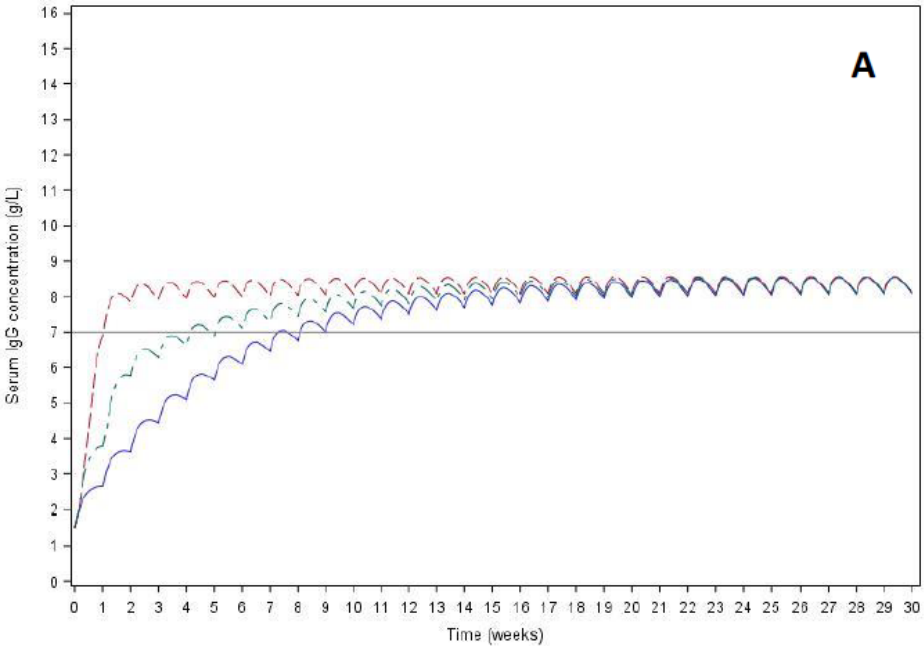
Figure 7: Simulated Median IgG Concentration–Time Profiles for Different SC Loading Dose Regimens (2-, 3-, and 5- Times/Week) of a 100mg/kg Dose, Assuming an IgG_{ENDO} of (A) 1.5 g/L and (B) 4 g/L

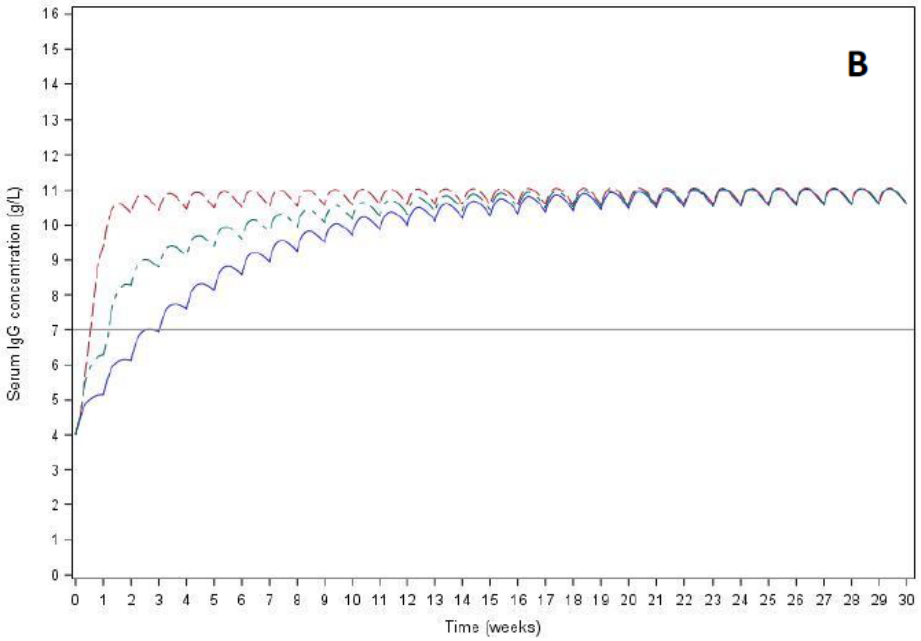




Median serum IgG concentrations
Blue line: Without loading dose
Red dashed line: Loading dose of 5 times/week (on week 1)
Green dotted line: Loading dose of 5 times/week (on week 1 and 2)
Black dashed line: Loading dose of 2 times/week (on week 1 and 2)
Purple dotted line: Loading dose of 3 times/week (on week1 and 2)
Source: Adapted from Figure 21, sBLA 125683/265 Module 5.3.3.5. PPK Report

Figure 8: Simulated Median IgG Concentration–Time Profiles for Different SC Loading Regimens (2- and 5-Times/Week) of a 150 mg/kg Dose, Assuming an IgG_{ENDO} of (A) 1.5 g/L and (B) 4 g/L





Median serum IgG concentrations
Blue line: Without loading dose
Red dashed line: Loading dose of 5 times/week (on week 1)
Green dotted line: Loading dose of 2 times/week (on week 1 and 2)
Adapted from Figure 22, sBLA 125683/265, Module 5.3.3.5. PPK Report

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Primary humoral immunodeficiency

An integrated assessment of efficacy was not performed as the data submitted to support the requested efficacy claims came from individual trials.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The safety of Xembify is detailed in the Clinical Review Memo for Xembify dated July 3, 2019. Additional safety data submitted with this supplement relevant to the proposed labeling changes is discussed separately for each study in the respective study sections (6.1.12 and 6.2.12 Studies GT1503 and GC1906, respectively). The Applicant requested to update the post-marketing experience section of the USPI to include aseptic meningitis, which is discussed in Section 8.4.8.

8.4 Safety Results

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 in the clinical studies in this efficacy supplement. However, aseptic meningitis was reported in the post-marketing setting, and the Applicant submitted labeling changes to include aseptic meningitis in the post-marketing experience of the USPI. Upon further review of post-marketing reports by the Pharmacovigilance review team, the USPI was updated to include AEs specific to Xembify reported in the post-marketing setting versus post-marketing reports for IGSC products in general. As a result, hypersensitivity reactions and anaphylaxis were also included in the USPI as adverse events in post-marketing reports following Xembify administration.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

No new data for dose dependency for adverse events was submitted in this efficacy supplement.

8.5.2 Time Dependency for Adverse Events

No new time dependency for adverse events was described or identified in this efficacy supplement.

8.5.3 Product-Demographic Interactions

No product-demographic interactions were identified.

8.5.4 Product-Disease Interactions

No new data for product-disease interactions was submitted in this efficacy supplement.

8.5.5 Product-Product Interactions

No new data for product-product interactions was submitted in this efficacy supplement.

8.5.6 Human Carcinogenicity

No new human carcinogenicity data was submitted in this efficacy supplement.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This product does not have drug abuse potential.

8.5.8 Immunogenicity (Safety)

No new immunogenicity data was submitted in this efficacy supplement.

8.5.9 Person-to-Person Transmission, Shedding

No new data regarding person-to-person transmission or shedding was submitted in this efficacy supplement.

8.6 Safety Conclusions

The safety profile of Xembify, including at the newly proposed dosing regimens, is similar to other class members, and is unchanged from the safety conclusions in the original Xembify approval.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No new human reproduction or pregnancy data was submitted in this efficacy supplement.

9.1.2 Use During Lactation

No new human lactation data was submitted in this efficacy supplement.

9.1.3 Pediatric Use and PREA Considerations

As part of the original BLA, safety and effectiveness of Xembify were evaluated in 14 pediatric patients (2-16 years of age) with PI in Study GTI1502 (U.S. registrational study, not discussed in this sBLA) and in 29 pediatric patients in Study GTI1503 (EU registrational study). The safety and efficacy profiles were similar between pediatric and adult patients with PI and PREA requirements were fulfilled per the agreed iPSP with the original Xembify approval in 2019.

An agreed iPSP was not submitted for the studies conducted to support the dosing regimen changes within this efficacy supplement. As the Sponsor did not have any meetings prior to submitting the request for the dosing changes, there was no Agency communication in advance of the sBLA to discuss PREA requirements for the proposed changes. Following additional clarification and interactive sBLA review, the Applicant submitted (and FDA agreed to) a partial waiver for:

1. All dosing changes for pediatric patients <2 years of age with PI because studies are impossible or highly impracticable;
2. Children ages 2 years to <10 years of age for the increased infusion rate as this would not provide a meaningful advantage. The proposed change (increase) in maximum infusion rate per site would not substantially change the infusion time due to smaller volume infusions in these patients. This would not be a meaningful advantage from a clinical perspective for ages 2 to <10 years of age.

PI is rarely diagnosed prior to 2 years of age, and when it is, availability of approved products and early definitive treatment makes enrollment of children <2 years in immune globulin clinical trials highly impractical. A waiver for patients with PI <2 years of age for all dosing changes is acceptable.

Data to support the proposed change in rate came from Study GTI1503, the registrational study to support international licensure. The clinical data supports an increased rate in children ≥ 10 years of age. As noted in the waiver request, based on the smaller volumes that younger children receive (as doses are weight based) this change would not substantially change the time of infusion and therefore does not provide a meaningful advantage for this age group. A waiver for patients with PI between 2 and <10 years of age for the increased infusion rate of 35 mL/hour/site is acceptable.

The study conducted to evaluate the biweekly dosing regimen and naïve/new start regimen allowed for enrollment of children, but ultimately only enrolled adults. Results of

the PPK modeling allowed for extrapolation of these dosing regimen changes to the pediatric population 2 years of age and older with PI.

No additional studies of the new dosing regimens in this efficacy supplement are required in pediatric patients, and therefore no PREA PMR is indicated.

9.1.4 Immunocompromised Patients

Xembify is indicated for primary immunodeficiency.

9.1.5 Geriatric Use

The small number of geriatric patients in each study preclude the assessment of safety specifically in the geriatric population. No new data regarding specific safety concerns in the geriatric population were submitted in this efficacy supplement.

10. CONCLUSIONS

Based on the submitted data, new dosing regimens of Xembify appear equally safe and effective when compared to the currently approved dosing regimens. The data supports the following dosing regimen changes:

- increase in maximum rate of infusion for patients 10 years and older to 35 mL/hour/site (with the currently approved maximum rate of 25 mL/hour/site to remain for patients less than 10 years of age).
- Addition of biweekly dosing option to allow for dosing frequency ranging between daily to every two weeks.
- Addition of a loading dose regimen and maintenance dose regimen to initiate immunoglobulin replacement therapy with Xembify in treatment-naïve patients with PI.

Additional requested changes to the USPI related to adverse events in the post-marketing setting are reasonable. The safety profile of Xembify as established in the original approval has not changed, and post-marketing safety reports are consistent with known class risks already described in Warnings & Precautions in the USPI.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

The risk-benefit assessment is detailed in Table 12.

Table 12: Risk-Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Primary humoral immunodeficiency (PI) is a form of PID that is characterized by impaired B-cell immunity, and thus, impaired ability to produce specific antibodies in response to pathogenic microorganisms. PI diseases include, but are not limited to, X-linked agammaglobulinemia, Common Variable Immunodeficiency, Wiskott-Aldrich Syndrome, Severe Combined Immunodeficiency, and congenital agammaglobulinemia. • Patients with PI present with recurrent, often severe bacterial and viral infections affecting the respiratory tract, gastrointestinal system, skin, as well as other organs.	• PI and associated antibody deficiencies are serious, chronic conditions associated with considerable morbidity and mortality. • Immunoglobulin replacement therapy administered via IV or SC route has been shown to reduce the incidence of serious infections through provisions of passive immunity.
Unmet Medical Need	• There are numerous approved immune globulin replacement products, and therefore there is not an unmet medical need for additional products except during periods of product shortages. • Systematic reviews indicate there are treatment burdens related to the various immunoglobulin replacement products, including frequency of infusions and time away from school or work for treatment.	• There is not currently unmet medical need, per se, due to similar products on the market, but even with available products there remain treatment burdens that impact quality of life for patients.
Clinical Benefit	• The bioequivalence of the product to an approved IGIV product and ability to prevent SBIs in adults and children 2 years and older with PI has already been demonstrated for the original Xembify approval. • PK assessments support the ability of a loading dose of Xembify to achieve protective IgG levels quickly after therapy initiation in treatment-naïve patients with PI. • PK analyses support similar IgG exposure between weekly and biweekly dosing of Xembify. • Tolerability data supports an increased maximum infusion rate per site in patients 10 years of age and older with PI.	• The ability to begin initial IgG replacement therapy with a SC product able to be self-administered in the home provides a benefit over the majority of products intended for treatment-naïve patients which are primarily IV infusions that require administration by a health professional at a site outside the home. • Some treatment burdens may be alleviated in select patients with PI who desire less burdensome dosing regimens and increased flexibility for IGSC infusions.
Risk	• The risks associated with Xembify administration are similar to other IGSC products as already demonstrated in the original BLA approval, with infusion site reactions being most common. Risks in the clinical studies in this efficacy supplement appear similar to those already established for Xembify. • Serious adverse events reported in clinical studies were generally not attributable to Xembify. • There were no deaths reported in the clinical studies.	• Safety in the clinical studies submitted in the efficacy supplement appears similar to that already demonstrated in the original approval, with no new safety signals or apparent increase in risks associated with the new dosing regimens.
Risk Management	• Subcutaneous immune globulin products carry an obligate boxed warning for thrombosis. • Other serious risks of immune globulin products include hypersensitivity and anaphylaxis, decline in renal function, hemolysis, TRALI, aseptic meningitis, and transmission of infectious agents. • No new serious risks were identified related to the new dosing regimens in this efficacy supplement.	• The package insert and the current pharmacovigilance plan are adequate to manage the risks. Routine post-marketing surveillance is recommended.

11.2 Risk-Benefit Summary and Assessment

The safety and efficacy of Xembify in patients 2 years and older with PI has already been established. Data submitted to the BLA efficacy supplement is sufficient to establish: similar IgG exposure between weekly and biweekly doses of Xembify, the ability to achieve and maintain target IgG troughs with Xembify loading and maintenance doses in a treatment-naïve PI population, and tolerability of an increased maximum infusion rate of 35 mL/hour/site in patients 10 years and older with PI. The new dosing regimens provide increased flexibility to patients with PI that are likely to provide a meaningful benefit to patients with no evidence of any increase in risk over the already established dosing regimens. The benefit-risk profile of the new dosing regimens is favorable.

11.3 Discussion of Regulatory Options

The regulatory options for this BLA efficacy supplement are approval or complete response.

When considering approval, additional options include modification of the indication (e.g., to only approve the new dosing regimens for adults) or the dosing regimens (e.g., to modify the maximum infusion rate) with considerations for post-marketing requirements if the new dosing regimens are not approved in pediatric PI populations.

11.4 Recommendations on Regulatory Actions

Based on a favorable benefit-risk assessment for the proposed dosing regimen changes, the Clinical and Clinical Pharmacology reviewers recommend approval of the efficacy supplement for the following dosing regimen changes:

- Addition of a biweekly dosing of IGSC 20% (Xembify) option for treatment-experienced patients 2 years of age and older with PI;
- Addition of a loading dose regimen of 150 mg/kg/day for 5 consecutive days followed by a maintenance dosing regimen of 150 mg/kg/week for treatment-naïve patients 2 years of age and older with PI;
- An increase in the maximum infusion rate to 35 mL/hour/site for patients 10 years and older with PI, and maintaining the currently approved maximum rate of 25 mL/hour/site for patients 2 to <10 years of age with PI.

11.5 Labeling Review and Recommendations

At the time of this review, labeling negotiations concluded.

The primary Clinical and Clinical Pharmacology issues requiring revision were as follows:

- Inclusion of PK assessments to support biweekly dosing and the loading and maintenance dose regimens in treatment-naïve patients
- Inclusion of a discussion on tolerability of increased infusion rates per site
- Specification of maximum rates of infusion per site based on age (10 years and older versus <10 years of age)
- Removing superfluous safety and efficacy information from the two new clinical studies that is not additive to the information already provided in the USPI from the original Xembify approval

- Modifications to post-marketing safety reports section to adequately represent reports submitted for Xembify versus other IGSC products
- Modification to Warnings and Precautions section to adequately address safety signals observed with Xembify, including reordering of subsections to reflect those most relevant to Xembify as the first ones listed

11.6 Recommendations on Postmarketing Actions

No post-marketing actions are being recommended for this efficacy supplement. Routine post-marketing surveillance remains appropriate.