Application Type	Biologics License Application – Prior Approval Efficacy Supplement
STN	BLA 125683/265
CBER Received Date	September 18, 2023
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Division / Office	DCEGM/OCE/OTP
Committee Chair	Shelby Elenburg, MD
Clinical Reviewer(s)	Shelby Elenburg, MD
Project Manager	Nancy Skeeter
Priority Review	No
Reviewer Name(s)	Yakun Wang, Ph.D., Visiting Associate, TEB2/DB/OBPV
Supervisory Concurrence	Yuqun Abigail Luo, Ph.D., Team Lead, TEB2/DB/OBPV
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Applicant	Grifols Therapeutics LLC
Established Name	Immune globulin subcutaneous, human – klhw, 20%
Trade Name	XEMBIFY
Pharmacologic Class	Immune globulin
Approved Indication	Treatment of Primary Humoral Immunodeficiency in patients 2 years of age and older
Purpose of the Supplement	To supplement the XEMBIFY license to include: • biweekly dosing for patients switching from either an intravenous immune globulin or subcutaneous immune globulin • addition of loading and maintenance dosing for treatment-naïve patients • an increase to the maximal subcutaneous infusion rate from 25 to 35 mL/hour/site • revision to the listing of post-marketing adverse reactions.

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GLOSSARY

AE	Adverse event
AR	Adverse reaction
CI	Confidence interval
eCRF	Electronic case report form
FDA	Food and Drug Administration
IgG	Immune globulin G
IGSC 20%	Immune Globulin Subcutaneous (Human), 20%
ISR	Infusion site reaction
IVIG	Intravenous immune globulin
PI	Primary immunodeficiency
PK	Pharmacokinetic
SAE	Serious adverse event
SBI	Serious bacterial infection
sBLA	Supplement Biologics License Application
SC	Subcutaneous
SCIG	Subcutaneous immune globulin
SD	Standard deviation
TEAE	Treatment-emergent adverse event

1. Executive Summary

The applicant (Grifols Therapeutics LLC) submitted an efficacy supplement biologics license application (sBLA) for XEMBIFY, Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (also referred to as IGSC 20%). The applicant proposed the labeling changes of 1) biweekly dosing for patients switching from either an intravenous immune globulin or subcutaneous immune globulin, 2) addition of loading and maintenance dosing for treatment-naïve patients, 3) an increase to the maximal subcutaneous infusion rate to 35 mL/hour/site, and 4) revision to the listing of post-marketing adverse reactions. To support the proposed labeling changes, the sponsor included the results from Study GC1906 and Study GTI1503.

Study GC1906
Study GC1906 was a Phase 4, multi-center, single-sequence, open-label study to assess the pharmacokinetics (PK), efficacy, and safety of XEMBIFY biweekly dosing in treatment-experienced patients and loading/maintenance dosing in treatment-naïve patients with primary immunodeficiency (PI).

In this study, 33 adult patients, including 27 treatment-experienced patients and 6 treatment-naïve patients, were treated. The planned in study time for each patient was 33 weeks. There were no serious bacterial infections (SBIs) reported. No deaths occurred in this study. Four (12.1%) patients reported treatment-emergent serious adverse events (SAEs). One treatment-experienced patient had two infection-related SAEs that occurred once during weekly infusions and once during biweekly infusions. No patients discontinued due to an SAE.

All the labeling changes from this study were based on PK and safety results. The efficacy endpoints were listed as secondary endpoints and were not used to support the labeling changes of this supplementary BLA submission. Please refer to clinical and clinical pharmacology's memos for more details on safety and pharmacokinetics evaluations.

Study GTI1503
Study GTI1503 was a Phase 3, multi-center, open-label, single-arm study to evaluate efficacy, pharmacokinetics, and safety and tolerability of XEMBIFY in patients with primary immunodeficiency. Sixty-one patients were treated with weekly doses of XEMBIFY with a median treatment duration of 52 weeks. There was one SBI reported in a pediatric patient, resulting in an annualized SBI rate of 0.017 with an upper limit of the one-sided 99% confidence interval (CI) of 0.036. No deaths occurred in this study. A total of 7 patients (11.5%) experienced 7 treatment-emergent SAEs overall. All treatment-emergent SAEs were deemed not related to study drug by the investigators.

To support the proposed labeling change in an increase of the maximal subcutaneous (SC) infusion rate from 25 to 35 mL/hour/site, the applicant provided a post-hoc analysis based on a subset of 14 patients (all were 10 years of age or older) who were administrated with a total of 261 infusions at a rate of 25 mL/hour/site or higher.

Infusion site reactions and treatment-emergent adverse events (TEAEs) were descriptively compared among infusions at rates ≤25 (n=2783), >25-≤35 (n=95), ≤35 (n=2878), and >35 mL/hour/site (n=166). The applicant concluded that there were no material differences or increased pattern when comparing infusions administered at rates ≤35 mL/hour/site with those >35 mL/hour/site. However, from the statistical perspective, the interpretation of this analysis is limited due to issues such as dependence in the data, small sample size, and confounding.

Please refer to clinical and clinical pharmacology reviewers' memos for more details on evaluation of data collected in the study.

Conclusion and Recommendations:

There were no major statistical issues related to the submission. My review primarily focuses on ensuring the accuracy of infection-related efficacy results. Since the primary evidence to support the proposed labeling changes in the application was from the PK and clinical perspectives, I defer to the clinical and clinical pharmacology review teams on the acceptance of the proposed labeling changes for XEMBIFY.

2. Clinical and Regulatory Background

In July 2019, the Food and Drug Administration (FDA) approved XEMBIFY, Immune Globulin Subcutaneous (Human), 20% (IGSC 20%), for the treatment of primary immunodeficiency (PI) in patients 2 years of age and older based on the review of the Biologics License Application (BLA) 125683/0. In the current BLA supplement (sBLA), the applicant proposed labeling changes of XEMBIFY for PI to include additional dosing regimens and to update the adverse events with post-marketing information.

3. Submission Quality and Good Clinical Practices

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The pharmacokinetics (PK), efficacy, and safety data supporting this sBLA came from Study GC1906 and Study GTI1503 (Table 1).

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

The basis of this statistical review includes documents in the supplemental BLA 125683/265, information requests (IRs) from the FDA, and IR responses from the applicant. Documents reviewed are listed below.

- STN 125683/265.0 Module 1.14 Labeling
- STN 125683/265.0 Module 2.5 Clinical Overview
- STN 125683/265.0 Module 2.7.3 Summary of Clinical Efficacy
- STN 125683/265.0 Module 2.7.4 Summary of Clinical Safety
- STN 125683/265.0 Module 2.7.6 Synopses of Individual Studies
- STN 125683/265.0 Module 5.2 Tabular Listing of all Clinical Studies
- STN 125683/265.0 Module 5.3.5 Reports of Efficacy and Safety Studies
- STN 125683/265.1 Module 5.3.5. the applicant submitted the missing define.xml files for Study GC1906 in response to my IR.

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the two clinical studies.

Table 1. Summary of Clinical Studies

Study Name	Study Description	Number of treated patients
GC1906	• Phase 4 • Objectives: (1) to evaluate the biweekly dosing regimen in treatment-experienced PI patients; (2) to evaluate the loading and maintenance dosing in treatment-naïve PI patients • Patients Aged from 22 to 73 years (inclusive) • 14 centers in the United States	33 adult patients: 27 treatment-experienced patients and 6 treatment-naïve patients
GTI1503	• Phase 3 • Objectives: to support marketing application of XEMBIFY for PI in European Union (EU) countries • Post-hoc objective: to evaluate an increase of the maximal subcutaneous infusion rate from 25 to 35 ml/hour/site • Patients aged from 2 to 69 years (inclusive) • 22 centers in 7 EU countries and Australia	61 patients: 29 pediatric patients aged 2 to 16 years, and 32 adult patients aged >16 years

Source: Reviewer's summary.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

In this supplement, the applicant requested the following labeling revisions:

- Add a biweekly (once every two weeks) dosing regimen of XEMBIFY for PI patients switching treatment to XEMBIFY from either an intravenous or a subcutaneous immune globulin product. The current approved XEMBIFY dosing regimens include weekly dosing and frequent dosing (2-7 times per week) for these PI patients;
- Add a specific XEMBIFY treatment regimen of loading and maintenance dosing for treatment-naïve PI patients;
- Increase the maximal subcutaneous infusion rate of XEMBIFY from 25 to 35 mL/hour/site;
- Update the adverse events information to include post-marketing experiences.

Support of this request is based on data from Study GC1906 and Study GTI1503. As FDA already considers XEMBIFY efficacious for PI in the approval of BLA 125683/0 based on another pre-marketing clinical trial, for the US the primary objectives of these two studies were to provide information for the new dosing regimens listed above and did not include efficacy assessment. The evaluation of these primary objectives is deferred to the clinical pharmacology and clinical review teams. In this memo we cover the review of infection related efficacy endpoints in the two studies.

6.1 Trial #1: Study GC1906

Study GC1906 was a Phase 4 study entitled "*A Multi-center, Single-Sequence, Open-label Study to Evaluate IGSC 20% Biweekly Dosing in Treatment-Experienced Patients and Loading/Maintenance Dosing in Treatment-Naïve Patients with Primary Immunodeficiency*."

6.1.1 Objectives

The primary objectives were to support the biweekly dosing regimen for treatment-experienced PI patients and a specific dosing regimen for treatment-naïve PI patients, via evaluation of PK parameters. Evaluation of these objectives are deferred to the clinical pharmacology and clinical reviewers.

This memo reviews infection-related efficacy objectives and endpoints.

6.1.2 Design Overview

Study GC1906 was a multi-center, single-sequence, open-label study with 2 cohorts of adult PI patients: a treatment-experienced cohort (N=27 patients) and a treatment-naïve cohort (N=6 patients).

Treatment-Experienced Cohort:

- In Treatment Period 1, patients received 16 weekly XEMBIFY doses from Week 0 to Week 15:
- In Treatment Period 2, patients received 9 biweekly XEMBIFY doses from Week 16 to Week 32. The dose in this period was calculated by multiplying the weekly dose of XEMBIFY in Treatment Period 1 by 2.

The final Follow-up Visit was conducted at Week 33.

Treatment-Naïve Cohort:
The treatment-naïve patients received a loading dose of 5 consecutive daily doses of XEMBIFY 150 mg/kg/day (Week 0, Days 1 to 5) followed by weekly infusions of 150 mg/kg starting Week 1 (Day 8) through Week 32 (end of Treatment Phase). The final Follow-up Visit was conducted at Week 33.

6.1.3 Population

Eligible participants for this study included male or female treatment-experienced patients 18 to 75 years of age (inclusive), or treatment-naïve patients 6 to 75 years of age (inclusive). Patients must have a diagnosis of PI requiring immune globulin G (IgG) replacement treatment.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Patients in the two cohorts received XEMBIFY as described in Section 6.1.2.

6.1.6 Sites and Centers
The study was conducted at 14 centers in the US.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoints were PK endpoints with PK success criteria, which are not covered in this memo. This memo will describe the following efficacy endpoints.

Secondary efficacy endpoints (related to infection)

- Total number of SBIs, proportion of patients who experienced SBIs, and rate of SBIs.
- All infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infection diarrhea, etc.) as determined by the investigator.
- 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 (for instance, rapid streptococcal antigen detection test).
- Number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic). Use of prophylactic antibiotics were distinguished from antibiotics for treatment of acute infection.
- Number of hospitalizations due to infection.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis sets

- **Safety population**: included all patients (including both treatment-experienced and treatment-naïve patients) who received any amount of XEMBIFY and will be used for safety analysis.
- **Efficacy Evaluable population**: included all subjects (including both treatment-experienced and treatment-naïve subjects) who received at least one dose of XEMBIFY. The efficacy evaluable population was the same as the safety population in this study.

Sample size estimation

The sample size was determined based on considerations related to the primary PK objectives and safety database.

Analysis plan for secondary endpoints related to infection

The Efficacy Evaluable population was to be used for the analyses of all secondary endpoints related to infection. The cohorts of treatment-experienced and treatment-naïve patients were to be analyzed separately. The endpoints were to be summarized descriptively using generalized linear models for Poisson regressions with a log link function.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Demographics of patients are summarized in Table 2. Of the total, 61% patients were females, and all patients were White and non-Hispanic. The median age was 54 years.

Table 2 Demographic Summary by Cohort

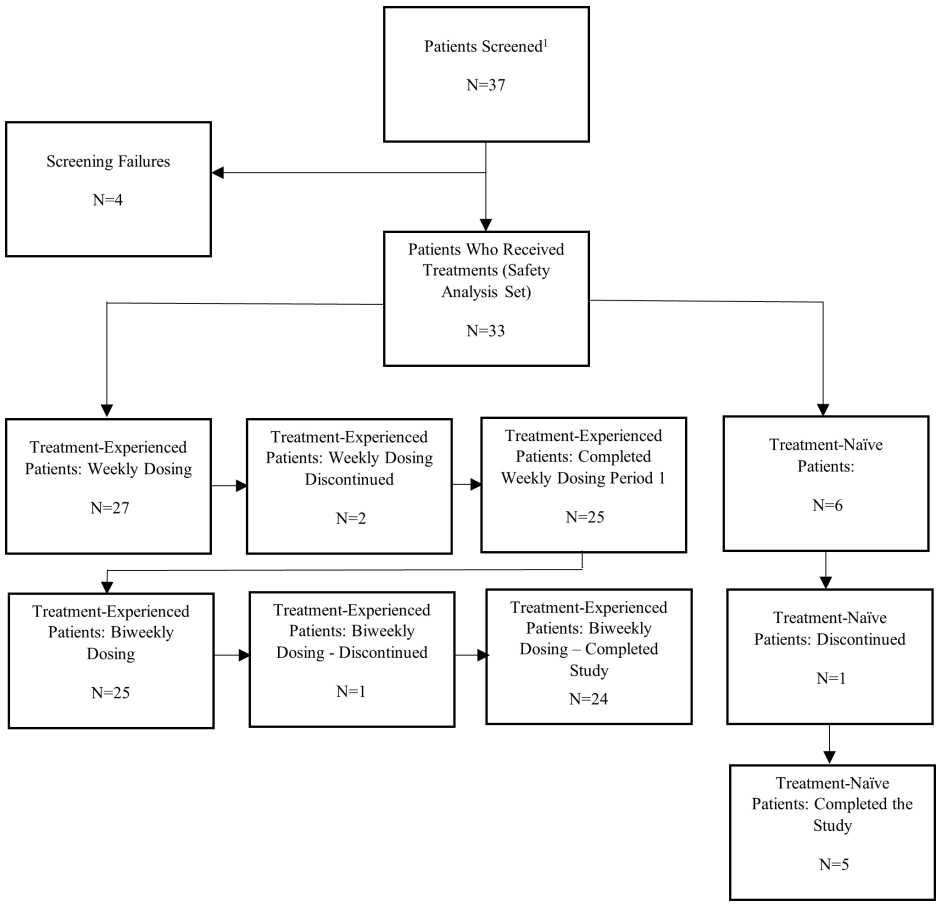
Characteristics	Treatment-Experienced (N=27)	Treatment-Naïve (N=6)
Age (Years)		
n	27	6
Median	54	58
Minimum, Maximum	22, 73	46, 65
Sex		
Male, n (%)	11 (41)	2 (33)
Female, n (%)	16 (59)	4 (67)
Race		
White, n (%)	27 (100)	6 (100)
Ethnicity		
Not Hispanic or Latino, n (%)	27 (100)	6 (100)

Source: Adapted from BLA 125683/265.0, GC1906 Clinical Study Report, Table 10-4, P65.

6.1.10.1.3 Subject Disposition

Figure 1 summarizes subject disposition. A total of 37 patients were screened (29 treatment-experienced; 8 treatment-naïve), and 33 patients (27 treatment-experienced patients; 6 treatment-naïve patients) received XEMBIFY. Of these, 29 patients completed the study. Two patients prematurely discontinued due to AEs, and the other two patients withdrew consent.

Figure 1 Subject Disposition of 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: Adapted from BLA 125683/265.0, GC1906 Clinical Study Report, Figure 10-1, P61.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Please refer to the clinical pharmacology reviewer's memo.

6.1.11.2 Analyses of Secondary Endpoints

The summary of secondary efficacy results is shown in Table 3. No SBI was observed during the study.

Table 3 Summary of Infections and Associated Events on XEMBIFY (Study GC1906)

Parameter	Treatment-Experienced: Weekly Dosing (N=27)	Treatment-Experienced: Biweekly Dosing (N=25)	Treatment-Experienced: Weekly + Biweekly Dosing (N=27)	Treatment-Naïve (N=6)
Total number of patient-years on treatment	7.8	8.5	16.3	3.6
Annual rate of SBIs* (per patient-year) (95% CI)	0	0	0	0
Annual rate of infections of any kind (per patient-year) (95% CI)	2.3 (1.2, 4.4)	2.0 (1.0, 3.9)	2.1 (1.2, 3.9)	2.5 (1.2, 5.2)
Days on antibiotics (prophylactic) (rate per patient-year) (95% CI)	15.3 (6.0, 39.3)	15.3 (6.0, 38.6)	15.3 (6.2, 37.8)	0
Days on antibiotics(therapeutic) (rate per patient-year) (95% CI)	19.8 (10.5, 37.3)	10.7 (5.2, 21.8)	15.0 (8.5, 26.5)	23.1 (8.3, 64.3)
Annual rate of hospitalizations due to infections (rate per patient-year) (95% CI)	0.1 (0.0, 0.3)	0.1 (0.0, 0.3)	0.1 (0.0, 0.3)	0
Annual rate of Validated Infections (rate per patient-year) (95% CI)	0.5 (0.2, 1.2)	0.6 (0.2, 1.6)	0.6 (0.2, 1.4)	0.3 (0.1, 1.4)

*Serious bacterial infections included bacteremia/sepsis, bacterial meningitis, bacterial pneumonia, osteomyelitis/septic arthritis, or visceral abscess.
Note: Rate per patient-year is calculated as the total number of days divided by the total duration of exposure in years across all subjects; Two-sided 95% CI is determined from a generalized linear model for Poisson regression for the log-transformed number of days with log-transformed duration of exposure in years as an offset variable.
Source: Adapted from BLA 125683/265.0, GC1906 Clinical Study Report, Tables 11-7, 11-9, and 11-10, P89, P91-92.

Reviewer Comment:
Per clinical comments, the infection-related endpoints are not informative and will not be used to support this sBLA review due to the short study duration and small cohort sizes.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths were reported in the study.

6.1.12.4 Nonfatal Serious Adverse Events

Treatment-emergent serious adverse events (SAEs) were reported in 4/33 (12.1%) patients, including dehydration, acute pancreatitis, and worsening of Barrett's esophagus respectively in three treatment-experienced patients, and a compression fracture with back pain in one treatment-naïve patient. One treatment-experienced patient had two SAEs that required hospitalizations: viral pneumonia during the weekly dosing period and *Clostridium difficile* and cellulitis during the biweekly dosing period. The applicant reported that all non-infectious SAEs were considered unrelated to XEMBIFY by the

investigator. The investigator considered the SAEs of *Clostridium difficile* and cellulitis patient possibly related to XEMBIFY. No patient discontinued as a result of an SAE.

6.2 Trial #2: Study GTI1503

Study GTI1503 was a Phase 3, prospective, multi-center, open-label, single-arm trial. The protocol of Study GTI1503 is entitled "*A Multi-Center, Open-Label, Single-Arm Trial to Evaluate Efficacy, Pharmacokinetics, and Safety and Tolerability of IGSC 20% in Patients with Primary Immunodeficiency.*" This study was intended to generate data to support marketing application to the European Union (EU). A post-hoc objective was included to investigate the effect of different infusion rates, to support the proposed labeling change in the sBLA.

6.2.1 Objectives

Primary Efficacy Objective:

- To evaluate whether weekly administered XEMBIFY over a one-year period achieved less than 1 SBI per patient per year in PI patients.

Secondary Objectives:

- To evaluate all infections of any kind (serious/non-serious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator
- To evaluate number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic, and therapeutic). Use of prophylactic antibiotics was distinguished from antibiotics for treatment of acute infection.
- To evaluate number of hospitalizations due to infection
- To evaluate number of days of work/school/daily activities missed per patient year due to infections and related treatment

6.2.2 Design Overview

In this study, there were 3 study stages: Screening/Previous Regimen Phase, XEMBIFY Treatment Stage 1 (13 XEMBIFY weekly doses), and XEMBIFY Treatment Stage 2 (39 XEMBIFY weekly doses). Sixty-one patients were enrolled with 29 pediatric patients aged 2 to ≤16 years and 32 adult patients aged >16 years.

6.2.3 Population

Eligible participants for this study included male or female patients who were 2 to 75 years (inclusive) of age and who had a diagnosis of PI requiring IgG replacement treatment. Patients were required to have not had any SBI within the last 3 months prior to screening and had no SBI up to the time of the baseline visit.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Patients received XEMBIFY as described in Section 6.2.2.

6.2.6 Sites and Centers

The study was conducted in 22 centers from 7 EU countries and Australia.

6.2.8 Endpoints and Criteria for Study Success

Only the efficacy endpoints are included in this section. Please refer to the clinical pharmacology memo for evaluation of the PK endpoints.

Primary Efficacy Endpoint

- Number of SBIs.

  Success criterion: The number of SBI <1 per person per year with one-sided test at α=0.01 level.

Secondary Efficacy Endpoints

- All infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.)
- Number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic).
- Number of hospitalizations due to infection.
- Number of days of work/school/daily activities missed per patient year due to infections and their treatment.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis sets

- **Safety population:** included all patients who received any amount of XEMBIFY and will be used for safety analysis.
- **Efficacy Evaluable population:** included all patients who received at least one dose of XEMBIFY.

Sample size estimation

Assuming that the true rate of the SBIs is 0.25 per patient per year, 40 patients treated for one year for XEMBIFY will provide at least 90% power to reject the null hypothesis of a SBI rate greater than or equal to 1.0 per person per year, using a one-sided test at the 0.01 level. In order to obtain a total of 40 patients including 20 adult and 20 pediatric evaluable patients, approximately 60 patients needed to be treated in the study to allow for a moderate to high early discontinuation rate seen in other similar studies.

Analysis plan for primary endpoint

The primary efficacy variable of SBIs was to be analyzed using the Efficacy Evaluable population. The following hypothesis testing will be performed with a one-sided test at α = 0.01 level:

H_0: $\lambda \geq 1$ SBI per person per year, versus
H_A: $\lambda < 1$ SBI per person per year,

where λ is the SBI rate during XEMBIFY treatment.

The generalized linear model procedure for Poisson regression with log link was to be used to estimate SBI rate per person per year for XEMBIFY and its one-sided 99% upper confidence bound (or equivalently, the upper bound of the two-sided 98% confidence interval). The natural log-transformed person-year was to be used in the generalized linear model as an offset variable. No covariates were to be included in the model. The estimated intercept term and the upper bound of its two-sided 98% CI were to be transformed by using the natural exponential function. If the one-sided 99% upper confidence bound was less than 1, then the null hypothesis that the SBI rate per person per year is ≥ 1 would be rejected at one-sided $\alpha = 0.01$ level.

Analysis plan for secondary and other efficacy endpoints

The analysis plan for the second efficacy endpoints were similar to the primary endpoint.

Handling of Dropouts or Missing Data

No imputation was to be performed for missing data.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

A total of 68 patients were screened, of which 7 patients were screen failures. A total of 61 patients entered Stage 1, and one patient withdrew from the study due to AE. Sixty patients completed Stage 1 and entered Stage 2 to continue the XEMBIFY treatment. Fifty-five patients completed Stage 2.

6.2.10.1.1 Demographics

Demographic and other baseline characteristics are summarized using the Efficacy Evaluable population (61 patients) in Table 4.

Overall, 69% were males, and 93% were white. The mean age was 27 years. There were about equal number of patients who were greater than 16 years of age (53%, 32/61) and patients who were ≤16 years of age (48%, 29/61).

Table 4 Demographic and Baseline Characteristics (Efficacy Evaluable Population)

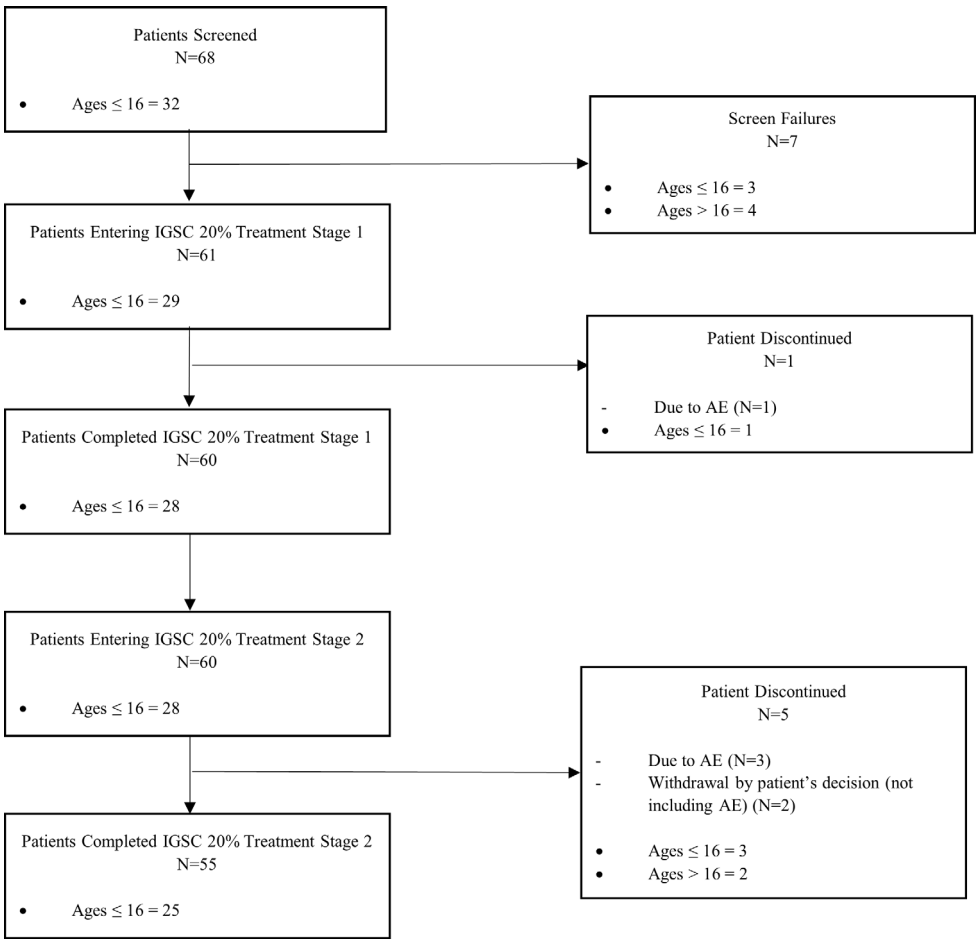
Demographic variables (N=61)	**Mean ± SD or Median [Range] or n (%)**
Age (years)	
Mean ± SD	27.3±20.0
Median [Minimum, Maximum]	17.0 [2, 69]
≤16	29 (47.5)
≥2 - ≤5	5 (8.2)
>5 - ≤12	14 (23.0)
>12 - ≤16	10 (16.4)
>16	32 (52.5)
>16 - <65	29 (47.5)
≥65	3 (4.9)
Sex	
Male	42 (68.9)
Female	19 (31.1)
Ethnicity	
Hispanic or Latino	10 (16.4)
Not Hispanic or Latino	49 (80.3)
Unknown	2 (3.3)
Race	
White	57 (93.4)
American Indian or Alaska Native	2 (3.3)
Unknown	2 (3.3)
Patient Entry Status	
Patient entered on IVIG	40 (65.6)
Patient entered on SCIG	21 (34.4)
Frequency of IgG Regimen of IVIG at Entry	
Every 3 weeks	17 (27.9)
Every 4 weeks	23 (37.7)
Frequency of IgG Regimen of SCIG at Entry	
2 Times per week	1 (1.6)
Every week	16 (26.2)
Every 2 weeks	1 (1.6)
Other	3 (4.9)

Abbreviation: IVIG= Intravenous immune globulin; SCIG= Subcutaneous immune globulin; SD= Standard deviation.
Source: Adapted from BLA 125683/265.0, GTI1503 Study Clinical Study Report, Table 10-4, P70.

6.2.10.1.3 Subject Disposition

Subject disposition is summarized in Figure 2.

Figure 2 Subject Disposition of Study GTI1503



AE = adverse event
Source: Adapted from BLA 125683/265.0, GTI1503 Study Clinical Study Report, Figure 10-1, P65.

6.2.11 Efficacy Analyses

The summary of efficacy results is shown in Table 5. For the primary endpoint of SBI rate per patient-year, there was one pediatric patient (1/61, 1.6%) had 1 event of pneumonia that was diagnosed as an SBI in Stage 2 of the study. The rate of SBI per patient-year was 0.017 (2 sided 98% CI: 0.006-0.036) overall (0 in Stage 1, 0.023 [2-sided 98% CI: 0.008-0.049] in Stage 2).

Table 5 Summary of Infections and Associated Events on XEMBIFY (Study GTI1503)

Parameter	Results (N=61)
Total number of patient-years on treatment	58.4
Annual rate of SBIs* (per patient-year)**	0.017 (98% CI: 0.006 - 0.036)
Annual rate of infections of any kind (per patient-year)**	2.4 (95% CI: 1.8 - 3.1)
Days on antibiotics (prophylactic) (rate per patient-year)**	44.4 (95% CI: 26.4 - 69.3)
Days on antibiotics (therapeutic) (rate per patient-year)**	8.9 (95% CI: 5.9 - 12.7)
Days missed work/school/unable to perform normal daily activities due to infections (rate per patient-year)**	5.0 (95% CI: 3.1 - 7.6)
Hospitalizations due to infections (rate per patient-year)**	0.017 (95% CI: 0.008 - 0.033)

*Serious bacterial infections included bacteremia/sepsis, bacterial meningitis, bacterial pneumonia, osteomyelitis/septic arthritis, or visceral abscess.
**Rate per patient-year is calculated as the total number of days divided by the total duration of exposure in years across all subjects; Two-sided 95% CI is determined from a generalized linear model for Poisson regression for the log-transformed number of days with log-transformed duration of exposure in years as an offset variable.
Source: Adapted from BLA 125683/265.0, GTI1503 Study Clinical Study Report, Tables 11-2, 11-4, 11-6, 11-7, and 11-9, on P77-78, P80-82.

Reviewer Comment:
Per clinical comments, the infection-related endpoints will not be used to support the labeling change of this sBLA.

6.2.11.3 Subpopulation Analyses

Since there was only one SBI (the primary endpoint) in the study, subgroup analysis would not provide additional meaningful information and therefore is not performed.

6.2.12 Safety Analyses

The applicant submitted this study to support the labeling change in an increase of the maximal subcutaneous (SC) infusion rate from 25 to 35 mL/hour/site (higher infusion rate). I included a summary of the post-hoc data analysis for the higher infusion rate in this section. Please refer to the clinical memo for more details of safety profile results.

A total of 14 patients in 10 years and older who were administrated with higher maximal subcutaneous infusion rate (exceeded 25 mL/hour/site) including 5 patients in 10 to ≤16 years and 9 patients in > 16 years. The maximal SC infusion rate ranged from 30 to 80 mL/hour/site, and ranges from 35 to 80 mL/hour/site for patients who achieved sustained (defined as at least 3 consecutive infusions) rates of 35mL/hour/site or greater (N=7). One patient in > 16 years old discontinued the study after Week 40 due to adverse event of infusion site subcutaneous fibroma.

The applicant conducted an analysis to examine the relationship between SC infusion rate and local tolerability with any kind of infusion site reaction (ISR) (Table 6). For infusion rates ≤ 35 mL/hour/site, 73% of infusions had no associated ISR of any kind, and 1.6% of infusions had ISRs considered by the investigator to be adverse (i.e., recorded as treatment-emergent adverse events [TEAEs]) by virtue of clinical impact or need to alter

infusion or institute treatment. For infusion rates > 35 mL/hour/site, 79.5% of infusions had no associated ISR of any kind, and 2.4% of infusions had ISRs considered by the investigator to be adverse. The applicant concluded that no material differences with the ISR of any kinds between infusion rate > 35 mL/hour/site and infusion rates ≤ 35 mL/hour/site.

Table 6 Summary of Relationship Between SC Infusion Rate and Local Tolerability in the Study GTI1503 (Safety Population)

Age Group: Overall	Without Any ISRs (n (%))	With non-AE ISRs[b] (n (%))	With AE ISRs[c] (n (%))
≤ 25 mL/hour/site (N = 2783)[a]	2048 (73.6)	689 (24.8)	46 (1.7)
>25 - ≤ 35 mL/hour/site (N = 95)[a]	76 (80.0)	19 (20.0)	0
≤ 35 mL/hour/site (N = 2878)[a]	2124 (73.8)	708 (24.6)	46 (1.6)
> 35 mL/hour/site (N = 166)[a]	132 (79.5)	30 (18.1)	4 (2.4)
Any (N = 3044)[a]	2256 (74.1)	738 (24.2)	50 (1.6)

AE = adverse event; eCRF = electronic case report form; ISR = infusion site reaction; SC = subcutaneous.
Note: Infusion Rate per Site (mL/hour/site) = Total Infusion Rate (mL/hour) / Total Number of Infusion Sites.
Local tolerability categories are presented in increasing severity from top to bottom. If a subject experiences more than 1 infusion site reaction during one infusion period, only the most severe infusion site reaction is counted in this summary table.
[a] N represents the total number of infusions
[b] ISR that did not meet the criteria of an AE and that was associated with the infusion (as recorded on the eCRF).
[c] ISR that met the criteria of an AE and that occurred during or within 72 hours of the infusion.
Source: Adapted from BLA 125683/265.0, Basis of Submission Statement, Table 6.2-1, P11.

The applicant also explored the relationship between SC infusion rate and the frequency of TEAE and concluded that there was no pattern of increased frequency of TEAEs (rates per infusion) associated with infusions at faster rate.

For children 2 to <10 years of age, the maximal subcutaneous infusion rate was still 25 ml/hour/site as the study did not include data to support a higher rate for this population. Please refer to the clinical memo for more details.

Reviewer's comment: The interpretation of the above analysis is limited due to the issues such as dependence among infusions, small/imbalanced samples, and confounding.

6.2.12.3 Deaths

No death was reported in the study.

6.1.12.4 Nonfatal Serious Adverse Events

Nonfatal Serious Adverse Events
A total of 7 patients (11.5%) experienced 7 treatment-emergent SAEs. All were deemed not related to XEMBIFY by the investigator. All but one SAEs (Patient 3503001, nephrotic syndrome) were resolved.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The applicant (Grifols Therapeutics LLC) submitted an efficacy supplement biologics license application (sBLA) for XEMBIFY, Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (also referred to as IGSC 20%). The applicant proposed the labeling changes of 1) biweekly dosing for patients switching from either an intravenous immune globulin or subcutaneous immune globulin, 2) addition of loading and maintenance dosing for treatment-naïve patients, 3) an increase to the maximal subcutaneous infusion rate to 35 mL/hour/site, and 4) revision to the listing of post-marketing adverse reactions. To support the proposed labeling changes, the sponsor included the results from Study GC1906 and Study GTI1503.

Study GC1906
Study GC1906 was a Phase 4, multi-center, single-sequence, open-label study to assess the pharmacokinetics (PK), efficacy, and safety of XEMBIFY biweekly dosing in treatment-experienced patients and loading/maintenance dosing in treatment-naïve patients with primary immunodeficiency (PI).

In this study, 33 adult patients, including 27 treatment-experienced patients and 6 treatment-naïve patients, were treated. The planned in study time for each patient was 33 weeks. There were no serious bacterial infections (SBIs) reported. No deaths occurred in this study. Four (12.1%) patients reported treatment-emergent serious adverse events (SAEs). One treatment-experienced patient had two infection-related SAEs that occurred once during weekly infusions and once during biweekly infusions. No patients discontinued due to an SAE.

All the labeling changes from this study were based on PK and safety results. The efficacy endpoints were listed as secondary endpoints and were not used to support the labeling changes of this supplementary BLA submission. Please refer to clinical and clinical pharmacology's memos for more details on safety and pharmacokinetics evaluations.

Study GTI1503
Study GTI1503 was a Phase 3, multi-center, open-label, single-arm study to evaluate efficacy, pharmacokinetics, and safety and tolerability of XEMBIFY in patients with primary immunodeficiency. Sixty-one patients were treated with weekly doses of XEMBIFY with a median treatment duration of 52 weeks. There was one SBI reported in a pediatric patient, resulting in an annualized SBI rate of 0.017 with an upper limit of the one-sided 99% confidence interval (CI) of 0.036. No deaths occurred in this study. A total of 7 patients (11.5%) experienced 7 treatment-emergent SAEs overall. All treatment-emergent SAEs were deemed not related to study drug by the investigators.

To support the proposed labeling change in an increase of the maximal subcutaneous (SC) infusion rate from 25 to 35 mL/hour/site, the applicant provided a post-hoc analysis based on a subset of 14 patients (all were 10 years of age or older) who were administrated with a total of 261 infusions at a rate of 25 mL/hour/site or higher. Infusion site reactions and treatment-emergent adverse events (TEAEs) were descriptively compared among infusions at rates ≤25 (n=2783), >25-≤35 (n=95), ≤35 (n=2878), and >35 mL/hour/site (n=166). The applicant concluded that there were no material differences or increased pattern when comparing infusions administered at rates ≤35 mL/hour/site with those >35 mL/hour/site. However, from the statistical perspective, the interpretation of this analysis is limited due to issues such as dependence in the data, small sample size, and confounding.

Please refer to clinical and clinical pharmacology reviewers' memos for more details on evaluation of data collected in the study.

10.2 Conclusions and Recommendations

There were no major statistical issues related to the submission. My review primarily focuses on ensuring the accuracy of infection-related efficacy results. Since the primary evidence to support the proposed labeling changes in the application was from the PK and clinical perspectives, I defer to the clinical and clinical pharmacology review teams on the acceptance of the proposed labeling changes for XEMBIFY.