

Summary Basis for Regulatory Action Template

Date: July 3, 2019

From: Jennifer Reed, Ph.D., Chair of the Review Committee

BLA/ STN#: 125683/0

Applicant Name: Grifols Therapeutics LLC

Date of Submission: July 9, 2018

Goal Date: July 9, 2019

Proprietary Name: XEMBIFY

Proper Name: Immune Globulin Subcutaneous, Human - klhw, 20%

Indication: Treatment of adult and pediatric patients 2 years of age or older with primary immunodeficiency (PI).

Recommended Action: The Review Committee recommends approval of this product.

Office of Tissue and Advanced Therapies Signatory Authority:

Wilson W. Bryan, MD, Director

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

Office of Compliance and Biologics Quality Signatory Authority:

Mary A. Malarkey, Director

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA

Document title	Reviewer name, Document date
CMC Review(s) <ul style="list-style-type: none">• CMC (product office)• Facilities review (OCBQ/DMPQ)	Jennifer Reed, PhD (OTAT/DPPT) Claire Wernly, PhD (OCBQ/DBSQC) Hsiaoling Wang, PhD (OCBQ/DBSQC) Tao Pan, PhD (OCBQ/DBSQC)

Document title	Reviewer name, Document date
<ul style="list-style-type: none"> <i>Establishment Inspection Report (OCBQ/DMPQ)</i> 	Maria Virata-Theimer, PhD (OTAT/DPPT) Pei Zhang, MD (OTAT/DPPT) Jing Lin, PhD (OCBQ/DBSQC) Bradley Dworak, PhD (OCBQ/DMPQ) Varsha Garnepudi, (OCBQ/DBSQC)
Clinical Review(s) <ul style="list-style-type: none"> <i>Clinical (product office)</i> <i>Postmarketing safety epidemiological review (OBE/DE)</i> <i>BIMO</i> 	Deborah S. Belsky, MD MPH (OTAT/DCEPT) Elizabeth Hart, MD (OTAT/DCEPT) Steve Winitzky, MD (OTAT/DCEPT) Rachel Witten, MD (OTAT/DCEPT) Faith Barash, MD, MPH (CBER/OBE) Haecin Chun, M.S. (OCBQ/BMB)
Statistical Review(s) <ul style="list-style-type: none"> <i>Clinical data</i> <i>Non-clinical data</i> 	Jiang Hu, PhD (CBER/OBE)
Pharmacology/Toxicology Review(s) <ul style="list-style-type: none"> <i>Toxicology (product office)</i> <i>Developmental toxicology (product office)</i> <i>Animal pharmacology</i> 	Evi Struble, PhD (OTAT/DPPT)
Clinical Pharmacology Review(s)	Iftekhar Mahmood, PhD (OTAT/DCEPT)
Labeling Review(s) <ul style="list-style-type: none"> <i>APLB (OCBQ/APLB)</i> 	Stephanie Donahoe (OCBQ/APLB) Alpita Popat, PharmD, MBA (OCBQ/APLB) Oluchi Elekwachi, PharmD, MPH (OCBQ/APLB)
Other Review(s) <ul style="list-style-type: none"> <i>additional reviews not captured in above categories</i> <i>consult reviews</i> 	
Advisory Committee summary	

1. Introduction

XEMBIFY is a 20% immune globulin solution for subcutaneous injection indicated for the treatment of primary humoral immunodeficiency (PI). It is manufactured by Grifols Therapeutics LLC (hereafter Grifols) at its licensed facility in (b) (4). The manufacturing process is nearly identical to that of Grifols' licensed 10% immune globulin intravenous product, GAMUNEX-C. The BLA for XEMBIFY was submitted by Grifols on July 9, 2018.

2. Background

Grifols' Immune Globulin Subcutaneous, Human-klhw 20% (IGSC 20%) product (XEMBIFY) was developed as a replacement therapy for treatment of primary

humoral immunodeficiency (PI). PI results from largely inherited, diverse defects of the immune system, and affects approximately 1-2% of the worldwide population.¹ The major antibody deficiency syndromes of clinical significance include X-linked agammaglobulinemia (XLA), Common Variable Immunodeficiency (CVID), Wiskott-Aldrich Syndrome, Hyper IgM Syndrome, Severe Combined Immunodeficiency (SCID), and IgG subclass deficiency. These disorders are marked by hypogammaglobulinemia, which increases susceptibility to infections. Patients with PI are at increased risk for recurrent severe bacterial infections (SBIs), especially respiratory tract infections. Replacement therapy with immunoglobulins provides antibodies to help prevent viral and bacterial diseases and is a mainstay of treatment. At the time of BLA submission, XEMBIFY had not been marketed in any country.

3. CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

a) Product Quality

Grifols' IGSC 20% product, with the proprietary name XEMBIFY, is intended as replacement therapy for PI in adults and pediatric patients two years of age and older. The product is presented in liquid form, in single-use glass vials with product fill sizes of 5 mL, 10 mL, 20 mL and 50 mL.

XEMBIFY is manufactured from large pools of U.S. (b) (4) Plasma (Human) (total pool volumes of (b) (4)). All manufacturing steps, including plasma pooling, fractionation and (b) (4) of the (b) (4) , aseptic filling, storage of manufacturing intermediates, analytical testing of drug substance and drug product, inspection of filled product, batch release, and stability testing, are performed at the firm's facility in (b) (4) (b) (4) . The manufacturing facility has been previously inspected and is FDA-licensed (License No (b) (4) , FEI (b) (4)). The manufacturing process for XEMBIFY is derived from the manufacturing process of the parent product, Immune Globulin Injection (Human), 10% Caprylate/ Chromatography Purified (IGIV-C), which is approved under BLA 125046 in the U.S. and is marketed as GAMUNEX-C. The IGIV-C and IGSC 20% manufacturing processes are the (b) (4) step, after which the IGSC 20% manufacturing process has an additional (b) (4) step to increase the protein concentration to 20% and the addition of polysorbate 80 (PS80) in the (b) (4) step.


Manufacture

XEMBIFY is a ready-for-use sterile, liquid preparation of (b) (4) concentrated immunoglobulin G (IgG) antibodies at 20% strength (200 mg protein/mL). The final formulation of IGSC 20% contains 18 to 22% human immune globulin, 0.16 to 0.26 M glycine, 10 to 40 µg/mL PS80 and water for injection (WFI), with a final pH of 4.1 to 4.8. PS80 was chosen as a stabilizer, while glycine was included to achieve (b) (4)

(b) (4) . An overview of the IGSC 20% manufacturing process steps is provided below.

Fractionation

(b) (4)



Final Formulation and Filling

(b) (4)

Aseptic filling into vials, application of stoppers and overseals

(b) (4) pH 4.1 to 4.8

(b) (4)

Labeling and packaging

Final product storage at 2 to 8 °C

Testing Specifications

The analytical methods and their validation and/or qualification studies for the XEMBIFY drug substance and drug product were reviewed and found adequate for their intended use.

Stability of Final Drug Product

(b) (4) Process Validation (PV) and lead commercial batches were stored at 5°C, 25°C (b) (4) ; for (b) (4) months (5°C and 25°C, PV batches), (b) (4) months (5°C, commercial batches), (b) (4) months (25°C, commercial batches), and six months (b) (4), PV and commercial batches). The stability data support the intended storage conditions of 2-8°C for up to (b) (4) months. In addition, the submitted data support storage of drug product at temperatures not more than (NMT) 25°C for up to 6 months at any time during the 24-month shelf-life, after which the product must be immediately used.

Submission of a final report for ongoing stability assessments was agreed as a post-marketing commitment.

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

Container / Closure

The drug product is filled into clear (b) (4) 5-mL and 10-mL glass vials (b) (4) and (b) (4) 20-mL (b) (4) and 50-mL vials (b) (4) with chlorobutyl gray rubber stoppers (20-mm for the 5, 10, and 20-mL vials and 32-mm for the 50-mL vials) (b) (4) lacquered aluminum seals, and plastic flip-top caps. Grifols conducted the container closure integrity testing using the (b) (4) method. All acceptance criteria were met.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of Immune Globulin Subcutaneous (Human), 20% is listed in the table below. The activities performed, and inspectional history are noted in the table.

Name/Address	FEI number	DUNS number	Inspection /	Justification/ Results
<p><i>Drug Substance and Drug Product Manufacturing and Testing including: pooling, fractionation, (b) (4) formulation, aseptic filling, labeling, testing, packaging, storage, and distribution</i></p> <p>Grifols Therapeutics LLC (b) (4)</p>	(b) (4)	(b) (4)	Waived	<p>Team Biologics (b) (4) VAI</p>

Team Biologics conducted a surveillance inspection of Grifols Therapeutics LLC in (b) (4) and an FDA Form 483 was issued. All 483 issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

d) Environmental Assessment

The BLA includes a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Product Comparability

Clinical and conformance lots of XEMBIFY were manufactured at Grifols' facility in (b) (4) , where commercial lots of XEMBIFY will be manufactured. The review committee determined that clinical and conformance lots are comparable and met the release specifications. The review committee also determined that XEMBIFY has a comparable efficacy and safety profile with other IGSC products that currently are marketed for the treatment of PI.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Single- and repeat-dose pharmacokinetic studies, and single- and repeat-dose safety and local tolerance studies were conducted in New Zealand White (NZW) rabbits with subcutaneous administration of XEMBIFY. In addition, a local tolerance study was conducted in NZW rabbits with administration of XEMBIFY via the intra-arterial, intravenous, and perivascular routes to simulate potential dosing errors. There were no unexpected systemic toxicities in these studies. Local injection site swelling occurred in animals dosed with XEMBIFY but not in animals in the GAMUNEX-C comparator groups, following single and repeat subcutaneous administration. The local injection site swelling correlated with the more severe subcutaneous and cutaneous inflammation observed in these animals, which was likely due to the higher total protein delivered in a single administration site.

The formulation of XEMBIFY does not raise toxicologic concerns.

5. CLINICAL PHARMACOLOGY

A pharmacokinetic (PK) study was conducted to evaluate the comparability of subcutaneously administered XEMBIFY (IGSC 20%) with intravenously administered comparator product (GAMUNEX-C 10%). A dose adjustment factor of 1.37 was used for SC administration. The subjects received their intravenous (IV) dose ranging from 300-800 mg/kg. Since the SC dose was weekly, the IV dose was divided either by 3 (every 3-week dosing schedule) or by 4 (every 4-week dosing schedule). XEMBIFY (test product, SC Phase) was considered non-inferior to

GAMUNEX-C 10% (reference product, IV Phase) if the lower bound of the 90% CI for the geometric least square means (LSM) ratio of area under the curve between Days 0 and 7 ($AUC_{(0-7)}$) between the Test and Reference was above 0.80 (80%).

Under steady-state conditions, the mean trough concentration following weekly SC administration of XEMBIFY was 1245 mg/dL whereas, following IV administration, the mean trough concentration was 957 mg/dL. The steady-state trough levels of XEMBIFY following SC infusions of IGSC 20% were 33% higher than those from IV infusion of IGIV-C 10%.

The $AUC_{(0-7)}$ days of XEMBIFY was comparable between IV and SC administration, but the C_{max} was about 35% lower following SC administration than IV. The 90% confidence interval indicated that the $AUC_{(0-7 \text{ days})}$ of XEMBIFY following SC administration was bioequivalent to the IgG following IV administration ($n = 38$; confidence interval range = 1.01-1.08).

Due to small sample size, the impact of age (children), sex, race, and ethnicity on the PK of XEMBIFY could not be evaluated.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The BLA was reviewed under the traditional regulatory approval pathway. The primary source of PK, effectiveness and safety information in the BLA comes from Study GTI1502. Supportive data from pediatric subjects ages 2-5 years comes from an ongoing study, GTI1503 (non-IND).

GTI1502 was an open label, multi-center, single-arm, single-sequence study to evaluate the safety and pharmacokinetics of weekly subcutaneous (SC) dosing of IGSC 20% administered for six months in subjects with PI, as compared to IV dosing with GAMUNEX-C 10% (IGIV-C 10%). The primary objective was to determine a dose of weekly XEMBIFY that produced a steady-state total IgG that was bioequivalent to that of regularly administered GAMUNEX-C 10% (IGIV-C 10%). The study also provided sufficient data on the annualized rate of SBI to assess efficacy.

A total of 53 subjects were enrolled in Study GTI1502; 49 subjects participated in the SC phase of the study, and 41 subjects had evaluable PK data. Of the 53 enrolled subjects, one subject was lost to follow-up, one developed bacterial pneumonia and sepsis and did not continue the study, and two subjects withdrew by their own request. Of the 49 subjects who received XEMBIFY, seven subjects discontinued the SC phase: four had adverse events (infusion site nodule; infusion site discomfort and intentional medical device removal; arthralgia, myalgia; papule, skin plaque); two

withdrew by own request; one subject refused blood samples, and another subject did not have adequate PK data for analysis. Therefore, only 41 subjects in the SC phase had adequate PK data and were considered valid for PK analysis. The PK population consisted of all subjects who received study drugs and had sufficient and valid total IgG concentration vs. time data for either the IV or SC Phase. The age distribution of the 41 subjects on XEMBIFY who contributed data for the PK analysis was as follows: 1 (age 2-5 years), 5 (ages >5-12 years), 5 (>12-16 years), 30 (>16 years). The weekly dose of XEMBIFY used in the study was calculated by taking the subject's IGIV dose, dividing by the number of weeks (3 or 4) of the IGIV inter-dose interval and multiplying by 1.37, the dose adjustment factor (DAF). The geometric LSM ratio of the AUC₍₀₋₇₎ for XEMBIFY versus IGIV-C 10% was 104%, demonstrating bioequivalence.

The subject enrollment period for this study was January 2016 through December 2017, with nearly equal numbers of infusions across seasons for the Run-in, IV and SC phases of the study, thereby, bridging the concern for seasonality as described in the FDA *Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*. The annualized SBI rate for IGSC-20% per subject year was 0.05 (upper bound of one-sided 99% confidence limit: 0.11); therefore, Study GTI1502 met the standard for IG licensure by ruling out an incidence of 1.0 SBI per patient-year.

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

Bioresearch Monitoring (BIMO) inspections were conducted at four clinical investigator study sites that participated in the conduct of Study GTI1502. The inspections did not reveal significant problems that impact the data submitted in support of this BLA.

b) Pediatrics

Pediatric pharmacokinetic, safety and efficacy data were available from 12 children who completed Study GTI1503, including one subject age 2-5 years,

six subjects ages >5-12 years, and five subjects ages >12-16 years. These data were supplemented with pharmacokinetic, safety and efficacy data from four children, ages >2-<5 years from the GTI1502 study.

The PK, efficacy, and safety data for pediatric subjects that are contained in the BLA, supports a treatment indication for children ages 2-16 years.

The Pediatric Review Committee (PeRC) and OTAT agreed with the applicant's plan to request a partial pediatric waiver for ages <2 years, due to impracticality of conducting clinical trials in this very young age group.

c) Other Special Populations

No human data are available to indicate the presence or absence of drug-associated risk during pregnancy or lactation. Study GTI1502 did not include a sufficient number of subjects (n = 5) ages 65 years and older to determine whether they respond differently than younger subjects.

7. SAFETY

No deaths occurred during the study. In the IV phase, there was one SBI of bacterial pneumonia and sepsis. Seven subjects discontinued XEMBIFY: four had adverse events (infusion site nodule; infusion site discomfort and intentional medical device removal; arthralgia and myalgia; papule, skin plaque); two withdrew by their own request; and one subject refused blood samples. One subject developed cellulitis and sepsis from a cat bite during the SC phase of the study.

The most common adverse reactions are shown in the table below.

Adverse Reactions in $\geq 5\%$ of Subjects During Infusions of XEMBIFY

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

Adverse Reaction*	By Subject n (%)[†] (N=49 subjects)	By Infusion n (rate)[‡] (N=1053 infusions)
Cough	3 (6%)	4 (0.004)
Diarrhea	3 (6%)	3 (0.003)

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

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

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

The rate of local infusion site reactions (ISRs) per infusion was 0.370 or 37% (390 events/1053 infusions). The highest rate of local ISR occurred when infused in the thigh 73.5% (205 ISR/279 infusions); followed by the abdomen 18.4% (142 ISR/773 infusions). Infusion site erythema was observed in 11.6 % (123/1053) of XEMBIFY infusions; however, 67.4% (83/123) of erythema reactions occurred when XEMBIFY was infused into the thigh. The duration of infusion site erythema was a median of 24.9 hours with a mean \pm standard deviation of 51 \pm 127 hours. Of the 390 ISRs, 41 (10.5%) resulted in infusion interruption or discontinuation, required concomitant medication, or had an impact on the general condition of the subject.

Local ISRs decreased over time with repeated administration. Local ISRs are comparable to other products within the class.

8. ADVISORY COMMITTEE MEETING

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

This product was not presented to the Blood Products Advisory Committee (BPAC) because it is not a novel molecular entity.

9. OTHER RELEVANT REGULATORY ISSUES

There were no other regulatory issues raised during the review of this BLA.

10. LABELING

The proposed proprietary name, XEMBIFY, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on 28 March 2019 and found to be acceptable. The proper name is XEMBIFY (immune globulin subcutaneous, human-klhw).

APLB found the package insert (PI), package, and container labels acceptable from a promotional and comprehension perspective.

Review considerations included revisions to the clinical trial experience and supporting data from GTI1503; inclusion of all adverse events occurring in $\geq 5\%$ of study subjects and revisions for clarity in the PI.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review committee recommends approval of this original BLA.

Study GTI1502 is an adequate and well-controlled study that provides evidence of effectiveness based on demonstration of bioequivalence to an approved IGIV product and an SBI rate of 0.05, (which is below the pre-specified threshold for <1.0 SBI per patient year). The submitted data satisfy the FDA's requirement for substantial evidence of effectiveness for an immunoglobulin product intended to treat PI.

b) Risk/ Benefit Assessment

The benefit/risk of XEMBIFY for treatment of PI in adults and children (2-16 years) is sufficiently favorable to support licensure. The nature and incidence of adverse events seen with XEMBIFY appeared to be typical of products in this class (IGSC).

Given the overall safety profile and absence of the occurrence of known risks for this class of products (such as thrombotic, hemolytic or other adverse events of special interest) in either the GTI1502 or safety update for GTI1503, the demonstration of bioequivalence to an approved immunoglobulin therapy for PI and documentation of a low rate of acute SBIs across seasons indicates a favorable benefit-risk profile.

c) Recommendation for Postmarketing Activities

Grifols committed to provide updated stability information at the shelf life of 24 months, including 6 months at 25°C for ^{(b) (4)} IGSC, 20% process validation batches (Study GTI_SR-000106) as a product correspondence labelled as a "Postmarketing Submission – Status Update", and a "Postmarketing Submission – Final Study Report", no later than Feb. 28, 2020.

The pharmacovigilance plan (Risk Management Plan, version 1.0, dated July 6, 2018) submitted under the original BLA 125683/0 is adequate for the postmarketing safety monitoring for XEMBIFY. The reviewed safety data do not indicate the need for a Risk Evaluation and Mitigation Strategy (REMS), a

safety post-marketing requirement (PMR) study, or a safety post-marketing commitment (PMC).

Standard pharmacovigilance is acceptable in the postmarketing period due to the lack of new safety issues compared with other products in the class.

12. References

- 1) Modell V, Quinn J, Orange J, et al. Primary immunodeficiencies worldwide: an updated overview from the Jeffrey Modell Centers Global Network. *Immunol. Res.* 2016; 64: 736-753.