



Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology

Pharmacovigilance Plan Review Memorandum
XEMBIFY® (125683/0)

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Subject: Pharmacovigilance Plan Review Memorandum – XEMBIFY®
Immune Globulin Subcutaneous (Human), 20%

Applicant: Grifols Therapeutics LLC

Proprietary Name: **XEMBIFY®**

Established/Proper Name: Immune Globulin Subcutaneous (Human), 20% [XEMBIFY]

BLA Submission: 125683/0

Proposed Indication: IGSC 20% is indicated for the treatment of Primary Humoral Immunodeficiency (PI) in patients 2 years of age and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich Syndrome, and severe combined immunodeficiencies.

Submission Date: July 9, 2018

Action Due Date: June 5, 2019

1. Introduction

1.1 Objectives/Scope

This memorandum is in response to a request from the Office of Tissues and Advanced Therapies (OTAT) to the Office of Biostatistics and Epidemiology (OBE) to review the Pharmacovigilance Plan submitted by Grifols Therapeutics, LLC for the original BLA 125683, Immune Globulin Subcutaneous (Human), 20% (IGSC 20%). The sponsor is seeking approval for the indication of primary humoral immunodeficiency in patients 2 years of age and older. The purpose of this review is to assess the adequacy of the submitted pharmacovigilance plan and to identify potential safety issues that may need to be addressed through post-marketing safety surveillance, post-market studies, or Risk Evaluation and Mitigation Strategy (REMS), should this product be approved.

1.2 Product Description

Immune Globulin Subcutaneous (Human), 20% (IGSC 20%) is a pooled plasma replacement therapy for patients with primary immunodeficiency diseases. IGSC 20% is a more concentrated formulation of Grifols' currently marketed immune globulin (IG) product, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified (IGIV-C 10% or Gamunex-C). Gamunex-C is currently approved for both intravenous and subcutaneous administration.¹ IGSC 20% contains a 20% solution of purified human immune globulin G (IgG), obtained using the IGIV-C 10% manufacturing process, but with a different (b) (4) step.

Immune Globulin replacement therapy has been an established treatment for Primary Immunodeficiency since 1952.² Per the sponsor, the advantage of higher concentration products (20%) is a significantly reduced infusion volume and a reduced infusion time, which could improve patient convenience and compliance.

1.3 Background

Primary Immunodeficiency (PI) diseases are a family of congenital disorders of the immune system that lead to an increase in frequency of infections, notably, but not limited to, bacterial infections of the respiratory tract.³ Results from a recent study suggest that in the United States (US) alone 1 in 2,000 children and 1 in 1,200 persons (including adults and children) are diagnosed with PI, yielding a total US PI patient population estimate of approximately 250,000 adults and children.⁴ Worldwide upper estimates suggest that six million people may be living with a PI although orders of magnitude fewer patients have been identified in registries.

Immune globulins have been used to treat a variety of conditions and has been an established treatment for Primary Immunodeficiency since 1952. Immune globulins as a class have known risks of several adverse events, including infusion site reactions, hypersensitivity, aseptic meningitis, possible transmission of infectious diseases, and risk of thrombosis and thromboembolic events.

1.4 Regulatory History

This is an original BLA for licensure of Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%), STN125683. The proposed proprietary name is "**XEMBIFY**."

XEMBIFY® Immune Globulin Subcutaneous (Human) has not been previously approved for use in any country.

¹ 2.5 Clinical Overview

² Buckley R, Schiff RI. The use of intravenous immune globulin in immunodeficiency diseases. *N Engl J Med.* 1991;11(2):110-7.

³ Reust CE. Evaluation of Primary Immunodeficiency in children. *Am Fam Physician.* 2013;187(11):773-778.

⁴ 2.5 Clinical Overview

2. Materials Reviewed

Document Reviewed	Source
1.16.1 Applicant's Risk Management Plan 2.7.4 Summary of Clinical Safety 5.2 Study Reports of Clinical Studies 2.5 Clinical Overview 1.14.1.3 Proposed Labeling and proposed Package Insert 5.3.3.2 Applicant's protocol GTI1502 5.3.3.2 Applicant's protocol GTI1503 5.3.5.4 Interim Safety Data 120-day Update GTI1503 Literature search	BLA 125683.0
Input from BLA review team	Review team discussions with CBER staff; draft clinical review memo

Pertinent published literature was also reviewed and is referenced in this memo. There are no post-licensure data for review, as this product has not been marketed in any country.

3. Clinical Studies

The clinical development program to support the safety of IGSC 20% includes data from two Phase 3 open label, multi-center studies of IGSC 20% for treatment of Primary Immunodeficiency (GTI1502 and GTI1503).

Two additional planned studies (060001 and T5004-401) will evaluate pediatric subjects concurrently with adult subjects for PK, efficacy and safety of IGSC 20% in patients with primary immunodeficiency.

3.1 Review of GTI1502: A Phase 3 open label, multi-center study to evaluate the safety and pharmacokinetics of IGSC 20% administered for 6 months in Subjects with Primary Immunodeficiency

Objective:

The stated safety objective was to “assess the safety and tolerability of IGSC 20% as an IgG replacement therapy in subjects with PI.”⁵

Study Design:

This was a prospective, multi-center, open-label, single sequence, 6-month PK, safety and tolerability study of IGSC 20% in subjects with PI to be carried out in approximately 30 study centers.

This study consisted of 2 phases, an IV phase during which subjects were treated with IGIV-C 10% followed by a SC phase in which subjects were treated with IGSC 20%. Subjects who had been receiving an IVIG other than IV IGIV-10% and subjects who had been receiving a SCIG other than study treatment drug were required to enter a Run-in phase prior to the IV phase to ensure approximately comparable steady-state conditions of serum IGIV-C 10% levels. This allowed for direct comparison of the efficacy derived from the IV administration of IGIV-C 10% and SC administration of IGSC 20%.⁶

The study was carried out in approximately 30 study centers. This clinical study included male or female subjects age 2 to 75 years of age who had PI diagnosis requiring IgG replacement. 53 subjects were enrolled in order to have approximately 30 adult subjects and 12 to 18 pediatric subjects. Pediatric enrollment was stratified by age category

⁵ GTI1502 IGSC 20%: Clinical Study Report p.1

⁶ IGSC 20%, 2.5 Clinical Overview

with a target of 4 to 6 children for each of the following age groups: 2 to 5 years, >5 to 12 years, and >12 to 16 years of age.

Results

A total of 61 subjects were screened for participation in this study. 8 subjects were screen failures and never received any study drug. The safety population included all subjects (53) who received any amount of study drugs, IGIV-C 10% and/or IGSC 20%. Pediatric subjects' age ranged from 2 to 16 years. Adult subjects age ranged from 16-75 years. 42 of the 53 (79.2%) subjects completed the study, and 11 of the 53 (20.8%) discontinued the study prematurely. Reasons for discontinuation included AEs (5 subjects), withdrawal by subject (4 subjects), lost to follow-up (1 subject), and other (1 subject refused blood samples).

Adverse events were classified as treatment emergent AEs (TEAEs) if the AE occurred on or after the start of study treatment. During the SC phase, 41/49 (83.7%) of subjects experienced a total of 141 TEAEs. Overall frequencies of subjects with any TEAE were higher in the SC phase (83.7%) as compared to the combined Run-In + IV phases (62.3%).⁷ Per the sponsor, this may have been due to a higher incidence of local injection site reactions (ISRs) reported during the SC phase. The single TEAE reported by >10% of subjects during the run-in phase was sinusitis (13.2%); TEAEs reported by >10% of subjects during the SC phase included sinusitis (18.4%), infusion site nodule (12.2%) and upper respiratory tract infection (10.2%). No thrombolytic TEAEs were reported during any study phases.

The incidences of infections were comparable between the combined Run-In + IV phases (50.9%) and the SC phase (53.1%) at the subject level. The incidence of validated infections (documented by positive radiograph, fever, culture, diagnostic testing for microorganisms or other evaluation such as nasal smear, physical examination or strep test) were comparable between the combined Run-In + IV phases (15.1%) and the SC phase (16.3%). Incidence of serious bacterial infections (SBI) was noted as a safety variable in this study. No SBI was reported during the run-in phase. During the IV phase, 2 SBIs occurred in 1 subject. During the SC phase, 1 SBI was reported in 1 subject.

Serious Adverse Events

A serious AE (SAE) was one that resulted in any of the following:

- death
- life-threatening event
- hospitalization or prolongation of existing hospitalization
- persistent or significant incapacity
- congenital anomaly or birth defect
- other important medical event which may have jeopardized the subject or required medical or surgical intervention to prevent any of the outcomes listed above

The incidence of treatment-emergent serious adverse events (SAEs) was 1 in the combined Run-In + IV phases (1.9%) and 2 in the SC phase (4.1%). A total of 6 SAEs were reported in 3 subjects, including 4 SAEs among 2 subjects during the SC phase. During the IV phase, 2 SAEs occurred in 1 subject (bacterial pneumonia and sepsis). During the SC phase, 2 subjects had a total of 4 SAEs (animal bite with cellulitis with sepsis in the first subject, and intervertebral disc degeneration in second subject). None of these SAEs are considered related to the study drug by the investigator or by this reviewer.

The rates of hospitalizations per person per year were comparable in the combined Run-In + IV phases (0.060) and in the SC phase (0.049).

There were no death reports during this study.

⁷ Table 14.3.1/2 Overall Summary of Treatment Emergent Adverse Events Population: Safety

3.2 Review of GTI1503: A Phase 3 open label, multi-center, single arm trial to evaluate efficacy, pharmacokinetics, safety and tolerability of IGSC 20% in subjects with primary immunodeficiency

This is a prospective, ongoing study conducted in Europe and Australia to evaluate the efficacy, safety and tolerability of IGSC 20 % in subjects with PI.

Study Design

The investigators planned to enroll sufficient subjects to evaluate approximately 20 adult subjects and 20 pediatric subjects who completed the study. ⁸ Subjects were required to be on a stable IgG regimen for at least 3 months prior to screening.

The study includes 3 study stages:

- Screening/Previous Regimen Phase (subjects are infused with their usual commercial regimen to obtain 2 trough IgG levels)
- IGSC 20% Treatment Stage 1 (13 weekly doses; dose may be adjusted if IgG trough is too low)
- IGSC 20% Treatment Stage 2 (39 weekly doses; no planned dose adjustments)

A final follow-up visit was scheduled 1 week after the last dose at week 53.

The safety endpoint is the number of serious bacterial infections (SBIs).

Results

61 subjects were enrolled in order to ensure at least 20 adult subjects and 20 pediatric subjects treated with IGSC 20% completed the study. However, the safety population (N=61) comprised every participant who received any dose of IGSC 20%. The first subject was enrolled in GTI1503 on 29 June 2016, and the enrollment cutoff date was 28 September 2018. Eleven of the 61 enrolled subjects remain in this ongoing study.

Subjects aged ≥ 65 years made up 4.9% of the study participants; subjects ages 18-64 years made up 44.3% of participants (n=27); and subjects <18 years of age made up 50.8% of study participants (n=31). 42 of 61 subjects (68.8%) were male and 19/61 (31.1%) were female. 93.4% of participants were Caucasian.

TEAEs experienced by study subjects are summarized in the table below.

Table 2. TEAEs experienced by study subjects

Infusion site erythema	13 (21.3)
Nasopharyngitis	13 (21.3)
Cough	9 (14.8)
Sinusitis	8 (13.1)
Upper respiratory tract infection	8 (13.1)
Bronchitis	7 (11.5)
Gastroenteritis	7 (11.5)
Infusion site pruritus	7 (11.5)
Headache	6 (9.8)
Infusion site pain	6 (9.8)
Pyrexia	6 (9.8)
Diarrhea	5 (8.2)
Lower respiratory tract infection	5 (8.2)
Viral infection	5 (8.2)
Back pain	4 (6.6)
Influenza	4 (6.6)
Infusion site swelling	4 (6.6)

⁸ 5.3.5.4 Interim Safety Data: 120-day update for GTI1503

Serious Adverse Events

Seven subjects had treatment-emergent serious adverse events, including device dislocation, urinary tract infection, thrombocytopenia, aortic valve incompetence, nephrotic syndrome, joint dislocation, and pneumonia. None of these TEAEs were considered related to IGSC 20% by the sponsor. Each of these occurred in one subject, and there was no clustering of AEs within system organ class suggestive of risk attributable to the product. Review of available case narrative information did not raise concerns of unexpected safety risks of the product.

There were no deaths reported in study GTI1503.⁹

4. Literature Review

Summaries of relevant publications and investigator conclusions are listed below:

Efficacy, safety, tolerability and pharmacokinetics of a novel human immune globulin subcutaneous, 20%: a Phase 2/3 study in Europe in patients with primary immunodeficiencies.

Borte M, Krivan G, Derfalvi B, Marodi L, Harrer T, Jolles S, Bourgeois C, Engl W, Leibl H, McCoy B, et al. Clin Exp Immunol. 2017 Jan; 187(1):146-159.

A highly concentrated (20%) immunoglobulin for subcutaneous administration was used for antibody replacement in patients with primary immunodeficiency diseases. Results demonstrated that IGSC 20% provides an effective and well tolerated therapy for patients previously on subcutaneous or intravenous treatment, without the need for dose adjustment.

Efficacy, Safety, and Pharmacokinetics of a Novel Human Immune Globulin Subcutaneous, 20% in Patients with Primary Immunodeficiency Diseases in North America.

Suez D, Stein M, Gupta S, Hussain I, Melamed I, Paris K, Darter A, Bourgeois C, Fritsch S, Leibl H, et al. J Clin Immunol. 2016 Oct;36(7):700-12.

Patients with primary immunodeficiency diseases require life-long replacement therapy. Efficacy, safety and pharmacokinetics of highly concentrated 20% Ig preparation for SC administration were evaluated in a prospective trial. The investigated IGSC treatment was shown to be effective and safe, allowing higher infusion volumes per site, resulting in fewer infusion sites and shorter infusion durations.

Shift from Intravenous or 16% subcutaneous replacement therapy to 20% subcutaneous immunoglobulin in patients with primary antibody deficiencies.

Canessa C, Iacopelli J, Pecoraro A, Spadaro G, Matucci A, Milito C, Vultaggio A, Agostini C, Cinetto F, et al. Int J Immunopathol Pharmacol. 2017 Mar;30(1):73-82.

At home administration of 20% SCIG is safe, effective and well-tolerated. Evaluation of Hizentra® safety showed no difference in side effects or adverse events reported.

Is It Safe to Switch From Intravenous Immunoglobulin to Subcutaneous Immunoglobulin in Patients With Common Variable Immunodeficiency and Autoimmune Thrombocytopenia?

Scheuerlein P, Pietsch L, Camacho-Ordonez N, Reiser V, Patel S, Burns SO, Warnatz K, Grimbache B. Front Immunol. 2018 Jul 19;9:1656.

This is a retrospective study of adult patients with CVID and at least one episode of thrombocytopenia. The study demonstrated that SCIG is at least as safe as IVIG for patients with CVID, however an IgG trough level below 7g/l is a risk factor for the development of autoimmune ITP.

Reviewer Comment: Review of relevant literature does not indicate any new safety concerns.

⁹ IGSC 20% FDA Information Request #5 GTI1503 interim safety data 120-day update

5. **Summary of Sponsor-Submitted Pharmacovigilance Plan** (Risk Management Plan, version 1.0, dated July 6 2018)

Safety concern	Proposed action
<p>Important Identified Risk: Infusion site reaction</p>	<p>Routine risk communication:</p> <ul style="list-style-type: none"> ■ <i>Package Information section 6.1 Clinical Trials Experience</i> <p>Routine pharmacovigilance</p>
<p>Important Potential Risk: Hypersensitivity reactions including anaphylactic reactions</p>	<p>Routine risk communication:</p> <ul style="list-style-type: none"> ■ <i>Package Information section 4.1 Contraindications (Hypersensitivity Reactions to Immune Globulins)</i> ■ <i>Package Information section 4.2 Contraindications (IgA Sensitive Patients with History of Hypersensitivity Reaction)</i> ■ <i>Package Information section 5.1 Warnings and Precautions (Hypersensitivity)</i> ■ <i>Package Information section 17 Patient Counselling Information</i> <p>Routine pharmacovigilance</p>
<p>Important Potential Risk: Thromboembolic events</p>	<p>Routine risk communication:</p> <ul style="list-style-type: none"> ■ <i>Package Information Boxed Warning</i> ■ <i>Package Information section 5.2 Warnings and Precautions (Thrombosis)</i> ■ <i>Package Information section 17 Patient Counselling Information</i> <p>Routine pharmacovigilance</p>
<p>Important Potential Risk: Aseptic meningitis</p>	<p>Routine risk communication:</p> <ul style="list-style-type: none"> ■ <i>Package Information section 5.3 Warnings and Precautions (Aseptic Meningitis Syndrome)</i> ■ <i>Package Information section 17 Patient Counselling Information</i> <p>Routine pharmacovigilance</p>

<p>Important Potential Risk:</p> <p>Theoretical risk of pathogen infection</p>	<p>Routine risk communication:</p> <ul style="list-style-type: none"> ■ <i>Package Information section 5.7 Warnings and Precautions (Transmission of Infectious Agents)</i> ■ <i>Package Information section 17 Patient Counselling Information</i> <p>Routine pharmacovigilance</p>
<p>Important Potential Risk:</p> <p>Interaction with live attenuated vaccines</p>	<p>Routine risk communication:</p> <ul style="list-style-type: none"> ■ <i>Package Information section 7 Drug Interactions</i> ■ <i>Package Information section 17 Patient Counselling Information</i> <p>Routine pharmacovigilance</p>
<p>Missing information: Use in women who are pregnant or lactating</p>	<p>Routine risk communication:</p> <ul style="list-style-type: none"> ■ <i>Package Information section 8.1 Use in specific populations (Pregnancy)</i> ■ <i>Package Information section 8.2 Use in specific populations (Lactation)</i> <p>Routine pharmacovigilance</p>
<p>Missing information: Use in geriatric population</p>	<p>Routine risk communication:</p> <ul style="list-style-type: none"> ■ <i>Package Information section 8.5 Use in specific populations (Geriatric use)</i> <p>Routine pharmacovigilance</p>

Routine pharmacovigilance includes adverse event reporting in accordance with 21 CFR 600.80 and quarterly periodic safety reports for 3 years (annual thereafter). Routine pharmacovigilance also includes continuous monitoring of the safety profile including signal detection, issue evaluation, updated labeling as necessary, and liaison with regulatory authorities. Routine pharmacovigilance activities are considered sufficient for post-authorization safety monitoring.

Additional safety data about the product will be provided by two future combined pediatric/adult studies (previously mentioned in Section 3), as well as from ongoing study GTI1503.¹⁰

6. Post-Marketing Data

XEMBIFY Immune Globulin Subcutaneous (Human), 20% has not been approved or marketed in any country. Therefore, there is no available post-marketing data. Because this investigational product is purified using (b) (4) manufacturing process as Gamunex-C (Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography

¹⁰ Risk Management Plan 06Jul 2018.pdf

Purified [IGIV=C 10%], a query for safety and adverse events was conducted for Gamunex-C. FAERS query performed on March 27, 2019 revealed adverse events expected with immune globulins, including injection site reactions, hypersensitivity, anaphylactic reactions, arthralgia, fatigue, headache, sinusitis, nausea, and pyrexia); no clustering of reports, or unexpected AEs was noted, and there was no new safety signal.

Empirica data mining performed on March 27, 2019 revealed EB05 > 2.0 for anaphylactic reaction, headache and aseptic meningitis. The identified AEs are among expected AEs seen with immune globulins and in the population of patients treated with these drugs. Of note, since August 2018, 3 different lots of Gamunex-C have been voluntarily withdrawn due to reports of hypersensitivity in recipients of doses from those lots.

7. Integrated Risk Assessment

Identified safety issues include:

Infusion site reaction – infusion site reactions have been reported to occur in association with IGSC 20%. Infusion site reactions are not considered to be serious. However, the frequency of such reactions warrants inclusion to the list of important identified risks

Hypersensitivity and anaphylaxis – This is considered a class effect for immune globulins. This risk occurred at a low frequency with IGSC 20%, and no events of severe hypersensitivity reactions were noted in clinical trials.

Hemolysis – This is considered a class effect for immune globulins. Immune globulin products contain blood group antibodies which may act as hemolysins and induce a positive direct antiglobulin reaction and rarely hemolysis.

Thromboembolic events – This is considered a class effect for immune globulins. There is clinical evidence of an association between immune globulin administration and thromboembolic events. No events of thromboembolic reactions were noted in clinical trials, however thromboembolic events could occur with this product. Warnings and precautions are included in the Package information and Patient information provided (see below).

Aseptic meningitis – This is considered a class effect for immune globulins. Aseptic meningitis has been reported to occur in association with immune globulin treatment. Discontinuation has resulted in remission of AMS within several days without sequelae. No events of aseptic meningitis were noted however, aseptic meningitis could occur with this product.

Theoretical risk of pathogen infection – This is considered a class effect for immune globulins. Medicinal products prepared from human plasma may carry the risk of transmission of infectious agents. Risk is mitigated by screening and selection of donors, and inclusion of effective manufacturing steps for inactivation or removal of viruses.

Interaction with live attenuated vaccines – This is considered a class effect for immune globulins. Interference with live attenuated virus vaccines is expected since it contains antibodies against a number of pathogens. Missing information includes use in women who are pregnant or lactating and use in geriatric population.

Each of these risks are addressed in the package insert:

- Thrombosis is a serious known safety issue for all immune globulin products, and as such, **XEMBIFY®** will have a boxed warning on the label, as follows:

Boxed Warning

<p style="text-align: center;">WARNING: THROMBOSIS</p> <p style="text-align: center;"><i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none">■ Thrombosis may occur with immune globulin products, including XEMBIFY. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.■ For patients at risk of thrombosis, administer XEMBIFY at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

The AE of thrombosis is labeled in section 5.2 Warnings and Precautions, in addition to the boxed warning.

- The AE of hypersensitivity including anaphylaxis is labeled in sections 4.1, 4.2 and 5.1.
- The AE of aseptic meningitis is labeled in section 5.3.
- The AE of hemolysis is labeled in section 5.5
- The AE of transmissible infectious agents is labeled in section 5.7
- The AE of interference with live attenuated virus vaccines is labeled in section 7.2

In addition to the aforementioned safety labeling, Grifols plans to further address these risks with routine pharmacovigilance. Given the known safety profile of Gamunex-C, Hizentra® 20% SQIG and the safety data submitted in clinical trials GTI1502 and GTI1503, there are no identified safety issues that are not adequately addressed by appropriate labeling and routine pharmacovigilance.

9. DE Recommendations

Should the product be approved, 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).