



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Xembify

Active ingredients: Human normal
immunoglobulin

Sponsor: Grifols Australia Pty Ltd

January 2023

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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AR	Adverse reaction
ASA	Australia specific annex
AUC	Area under the concentration-time curve
AUC _{0-7days}	Area under the concentration-time curve from 0 to 7 days
C _{max}	Maximum observed concentration
CI	Confidence interval
CMI	Consumer Medicine Information
CVID	Common variable immunodeficiency
DAF	Dose adjustment factor
Fc	Fragment crystallisable region
FcRn	Neonatal Fc receptor
ISR	Injection site reaction
K _a	Absorption rate constant
LSM	Least squares mean
NBA	National Blood Authority (Australia)
PI	Product information
PID	Primary immunodeficiency disease
PK	Pharmacokinetic(s)
RMP	Risk management plan
SAE	Serious adverse event
SBI	Serious bacterial infection
SC#1	Subcutaneous Visit one
SCIg	Subcutaneous immunoglobulin
SD	Standard deviation

Abbreviation	Meaning
$T_{1/2}$	Half-life
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	Time to reach maximum observed concentration
US(A)	United States (of America)

Product submission

Submission details

<i>Type of submission:</i>	New biological entity
<i>Product name:</i>	Xembify
<i>Active ingredient:</i>	Normal immunoglobulin (Human)
<i>Decision:</i>	Approved
<i>Date of decision:</i>	8 July 2022
<i>Date of entry onto ARTG:</i>	30 June 2022
<i>ARTG numbers:</i>	355315, 380404, 380405, and 380406
<i>▼ Black Triangle Scheme:</i>	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
<i>Sponsor's name and address:</i>	Grifols Australia Pty Ltd Unit 5/80 Fairbank Rd Clayton South VIC 3169
<i>Dose form:</i>	Solution for injection
<i>Strengths:</i>	2 g/10 mL (20%) 4 g/20 mL (20%) 1 g/5 mL (20%) 10 g/50 mL (20%)
<i>Container:</i>	Vial
<i>Pack size:</i>	One vial
<i>Approved therapeutic use:</i>	<i>Indications for subcutaneous administration (SCIg)</i> <i>Xembify is indicated as replacement therapy in adult and paediatric patients for:</i> <ul style="list-style-type: none">• <i>Primary immunodeficiency diseases (PID)</i>• <i>Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.</i>
<i>Route of administration:</i>	Subcutaneous injection
<i>Dosage:</i>	Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

The dose and dose regimen are dependent on the indication.

In replacement therapy the dose may need to be individualised for each patient dependent on the pharmacokinetic and clinical response.

The dose regimen should achieve a trough level of immunoglobulin G (IgG) (measured before the next infusion) of at least 5 to 6 g/L and aim to be within the reference interval of serum IgG for age. A loading dose of at least 0.2 to 0.5 g/kg (1 to 2.5 mL/kg) body weight may be required. This may need to be divided over several days, with a maximal daily dose of 0.1 to 0.15 g/kg.

After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals (approximately once per week) to reach a cumulative monthly dose of the order of 0.4 to 0.8 g/kg. Each single dose may need to be injected at different anatomic sites.

Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dose and aim for higher trough levels.

If a dose is missed or therapy is interrupted, administration of Xembify should re-commence as soon as feasible with appropriate monitoring of IgG trough level if clinically indicated.

See Section 4.2 Dose and method of administration of the Product Information for further information including dosing for patients switching from other subcutaneous or intravenous immunoglobulin treatments.

Dose guidance

Refer to the dose adjustment table (Section 4.2 Dose and method of administration of the Product Information) for suggested dose changes (in mL) to achieve a desired IgG trough level change (increase or decrease), once Xembify treatment has been initiated.

The patient's clinical response should be the primary consideration in dose adjustment. If a patient on Xembify does not maintain an adequate clinical response or a serum IgG trough level equivalent to that of a previous treatment, adjust the dose accordingly.

See Section 4.2 Dose and method of administration of the Product Information for further information.

Paediatric population

The dosage in children and adolescents (0 to 18 years of age) is not different to that of adults as the dosage for each indication is given by body weight and adjusted to the clinical outcome in replacement therapy indications. Xembify was evaluated in 43 paediatric subjects with primary immunodeficiency disease aged 2 to 16 years

(inclusive), which included 28 subjects 12 years of age or younger. No paediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. No clinical trials have been conducted with Xembify in children aged between 0 to 2 years. However, experience with immunoglobulins suggests a safety profile similar to that for children of age 2 to 18 years and adults with Xembify is to be expected.

Method of administration

For subcutaneous use only. Subcutaneous infusion for home treatment should be initiated and monitored by a physician experienced in the guidance of patients for home treatment. Infusion pumps appropriate for subcutaneous administration of immunoglobulins can be used. The patient must be instructed in the use of an infusion pump, the infusion techniques, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions.

Xembify may be injected into sites such as abdomen, thigh, upper arm, and lateral hip. The recommended initial infusion rate depends on the individual needs of the patient and should not exceed an administration speed of 25 mL/h/site.

If well tolerated (see Section 4.4 Special warnings and precautions for use of the Product Information) for two infusions, the infusion speed can gradually be increased to 35 mL/h/site.

More than one pump can be used simultaneously. The amount of product infused into a particular site varies. In infants and children infusion sites may be changed every 5 mL to 15 mL. In adults doses over 30 mL may be divided according to patient preference. There is no limit to the number of infusion sites. Infusion sites should be at least 5 cm apart.

For further information refer to the Product Information.

Pregnancy category:

This therapeutic good is exempted from pregnancy categorisation.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Grifols Australia Pty Ltd (the sponsor) to register Xembify (normal human immunoglobulin) 2 g/10 mL (20%), 4 g/20 mL (20%), 1 g/5 mL (20%) and 10 g/50 mL (20%) solution for subcutaneous injection for the following proposed indication:

Xembify is a human immune globulin indicated for the treatment of primary immunodeficiency syndromes (PID) in adults, children and adolescents (0-18 years). This includes, but is not limited to, hypogammaglobulinaemia with chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), and patients pre- and post-allogeneic haematopoietic stem cell transplantation (HSCT).

Primary immunodeficiency disease (PID) is a broad term for diverse group of immunodeficiencies where secondary causes have been excluded. There are over 280 identified PIDs, which include a wide range of rare conditions affecting both paediatric and adult patients. Infection is the most common complication of PID and the most common reason leading to medical assessment. Primary immunodeficiency disease usually presents with signs of infection that can be repetitive, severe and difficult to treat. In addition, autoimmune disease and malignancies are complications of many PIDs.¹

In 2018 and 2019, a total of 2,292 patients in Australia accessed immunoglobulin therapy for the treatment of PID through the National Blood Authority (NBA).² Based on these data, the prevalence of PID in Australia is calculated to be approximately 9.09 per 100,000 population. However, PID patients (diagnosed or undiagnosed) who are not on immunoglobulin therapy are not included in the immunoglobulin usage data from the NBA. Consequently, the NBA data might underestimate the total population in Australia with PID who are potentially eligible for immunoglobulin therapy.

Table 1, shown below, summarises the 10 most common medication conditions for which immunoglobulin was issued in Australia for the time period of 2017 and 2018, according to NBA data.^{2,3}

¹ Duncan J, et al. Immunoglobulin (Ig) for Primary Immunodeficiency Diseases (PID). 2020. MSAC Application 1592, Assessment Report. Commonwealth of Australia, Canberra, ACT.

² Medical Services Advisory Committee (MSAC): Review of Immunoglobulin (Ig) for Primary Immunodeficiency Disease (PID) with Antibody Deficiency. MSAC CA 1592; 2020. *Medical Services Advisory Committee*. Available from [msac.gov.au](https://www.msac.gov.au).

³ National Blood Authority (NBA): 2017-18 National Report on the Issue and Use of Immunoglobulin (Ig); 2018. *National Blood Authority Australia*. Available from: [blood.gov.au](https://www.blood.gov.au).

Table 1: National Blood Authority/Medical Services Advisory Committee; Most common medical conditions in Australia for which immunoglobulin was issued (2017 to 2018)

Condition	Immunoglobulin issued (grams)	Percentage change 2016-17 to 2017-18
Acquired hypogammaglobulinaemia	1,401,789	14.1
Chronic inflammatory demyelinating polyneuropathy	1,290,612	10.2
Primary immunodeficiency diseases	725,326	3.4
Myasthenia gravis	514,017	12.6
Inflammatory myopathies	377,479	14.7
Multifocal motor neuropathy	354,434	7.0
Secondary hypogammaglobulinaemia	222,136	22.8
Immune thrombocytopenic purpura (in adults)	218,182	3.0
Kidney transplantation	126,587	2.9
Guillain-Barré syndrome	122,139	7.0

Table source: Table 7, from Medical Services Advisory Committee (MSAC): Review of Immunoglobulin (Ig) for Primary Immunodeficiency Disease (PID) with Antibody Deficiency. MSAC CA 1592; 2020. *Medical Services Advisory Committee*. Available from msac.gov.au.

Data originally published in National Blood Authority (NBA): 2017-18 National Report on the Issue and Use of Immunoglobulin (Ig); 2018. *National Blood Authority Australia*. Available from: blood.gov.au.

Therapeutic immunoglobulin is a plasma derived product manufactured to treat a range of medical conditions. In Australia, access to government funded immunoglobulin is through the national blood arrangements and is determined by the NBA's *Criteria for Clinical Use of Immunoglobulin in Australia*.⁴ Demand for immunoglobulin in Australia has increased around 11% per year since 2009 to 2010. Internationally, Australia is in the top three users of immunoglobulin, along with the United States of America (USA) and Canada. In the absence of immunoglobulin replacement therapy for PID, best supportive care is the only treatment available.

The therapeutic management of PID is via intramuscular, intravenous, and subcutaneous injections with various immunoglobulin preparations. Immunoglobulin preparations were first used in the 1950s as replacement therapy for a range of PID. Immunoglobulin was initially administered intramuscularly until the 1980s when highly purified monomeric suspensions of immunoglobulin G became available for intravenous or subcutaneous use.⁵ Immunoglobulin products are manufactured from the plasma of healthy donors. Plasma pools are derived from, on average, approximately 15,000 donors and purified via ethanol fractionation with additional steps to remove immunoglobulin aggregates.^{5, 6} The preparation is then stabilised using agents such as human albumin, glycine, polyethylene glycol or sugars (such as sucrose, maltose or glucose).⁵ The primary active ingredient of immunoglobulin preparations is immunoglobulin G. However, immunoglobulin preparations may vary in immunoglobulin G monomer, dimer, aggregate concentrations, immunoglobulin A and immunoglobulin M content, stabilisers and additives used, as well as the level of impurities present.⁶

⁴ National Blood Authority Australia, *Criteria for the clinical use of immunoglobulin in Australia*. Available from blood.gov.au.

⁵ Palabrica, F. R. R, et al. Adverse events of intravenous immunoglobulin infusions: a ten-year retrospective study, *Asia Pacific allergy*, 2013; 3: 249-256.

⁶ Ness, S. Differentiating characteristics and evaluating intravenous and subcutaneous immunoglobulin, *Am J Manag Care*, 2019; 25: S98-S104.

Immunoglobulin is primarily administered either intravenously or subcutaneously. The main difference between the two delivery methods is that intravenous administration requires venous access, can deliver larger volumes (therefore fewer doses) and is carried out by skilled healthcare professionals in a hospital setting. Subcutaneous administration, which delivers smaller volumes, may be self-administered at home following training.⁶ Intravenous administration may be associated with increased systemic adverse events, such as headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea and hypotension compared with subcutaneous administration.^{5, 6} Adverse events relating to subcutaneous administration are typically localised to the injection site.⁶ Overall, serious adverse events of immunoglobulin therapy are rare and may include hypersensitivity (for example, anaphylaxis), thromboembolism, aseptic meningitis, and renal failure (particularly with those products containing sucrose).

The sponsor stated that several subcutaneous immunoglobulin products, ranging in protein immunoglobulin G concentrations from 10% to 20%, are currently being used to treat PID most commonly by either weekly or biweekly (or more frequent) administration. The primary advantages of higher concentration subcutaneous immunoglobulin products (20%) compared with lower concentration subcutaneous immunoglobulin products (10%) are significantly reduced subcutaneous infusion volumes and shorter infusion times, thereby increasing ease of administration, improving patient convenience, and potentially increasing tolerability by reducing local infusion related reactions.

There are a number of alternative human normal immunoglobulin products available for intravenous and subcutaneous treatment of PID in Australia. Therefore, there is not an unmet clinical need for Xembify however, unforeseen supply problems (for example manufacturing issues) might reduce the availability of alternative products.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this submission, a similar submission had been approved in the United States of America (USA) on 3 July 2019 and in Canada on 10 December 2019. A similar submission was under consideration by the European Union (EU) (submitted on 30 November 2020).

Table 2, shown below, summarises these submissions and provides the indications where approved.

Table 2: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	9 July 2018	Approved on 3 July 2019	<i>Approved for the treatment of Primary Humoral Immunodeficiency 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.</i>

Region	Submission date	Status	Approved indications
Canada	25 April 2019	Approved on 10 December 2019	<i>Approved for the treatment of patients 2 years of age and older with Primary Immune Deficiency (PID) and Secondary Immune Deficiency (SID) who require immunoglobulin replacement therapy.</i>
European Union	30 November 2020	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA [PI/CMI search facility](#).

Registration timeline

The following table captures the key steps and dates for this submission.

Table 3: Timeline for submission PM-2020-06238-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	31 March 2021
First round evaluation completed	31 August 2021
Sponsor provides responses on questions raised in first round evaluation	28 October 2021
Second round evaluation completed	26 May 2022
Delegate's Overall benefit-risk assessment	15 February 2022
Registration decision (Outcome)	22 June 2022
Completion of administrative activities and registration on the ARTG	30 June 2022
Number of working days from submission dossier acceptance to registration decision*	143

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Relevant guidelines or guidance documents referred to by the Delegate are given below:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg), EMA/CHMP/BPWP/410415/2011 rev 1, 1 February 2016.⁷

Quality

The drug substance (sterile filling bulk prior to aseptic filling) is immunoglobulin (primarily immunoglobulin G) that has been purified from human plasma via a multi-step process. The drug product is formulated to contain 18 to 22% protein, 10 to 40 µg/mL of Polysorbate 80, 0.16 to 0.26 M of glycine.

The active principle, immunoglobulin G, is a glycoprotein of approximately 150 kD in molecular weight, consisting of four disulfide linked polypeptide chains: two light chains of 25 kD and two heavy chains of 55 kD. Disulfide linkage of the amino terminal portions of each pair of light and heavy chain forms an antigen binding site, resulting in two such sites per molecule. The carboxyl terminal portions of the heavy chains are likewise disulfide linked, forming the carbohydrate bearing fragment crystallisable region (Fc) portion of the molecule that can interact with complement, and for which various phagocytes and B lymphocytes bear receptors. The three resulting domains of the protein are arranged in the shape of a 'Y'. The amino terminal portions of all four chains in Immunoglobulin G contain regions with variable amino acid sequences, responsible for conferring the broad specificity of a population of antibody molecules against diverse antigens. In addition, immunoglobulin G light and heavy chains contain alternate constant regions which divide the antibody population into four distinct subclasses: immunoglobulin G1, immunoglobulin G2, immunoglobulin G3 and immunoglobulin G4.

The subcutaneous immunoglobulin 20% is supplied in glass vials and available in 5 mL, 10 mL, 20 mL and 50 mL volumes with 20 mm and 32 mm grey chlorobutyl stopper laminated with 20 mm and 32 mm lacquered aluminium overseal with plastic flip cap.

The proposed shelf life for subcutaneous immunoglobulin 20% is 36 months when stored at 2 to 8 °C. The sponsor also proposes that the product may be stored at temperatures not exceeding 25 °C for up to six months anytime during the 36 month shelf life and after that the product should be immediately used or discarded. Freezing should be avoided.

Conclusion

There are no objections on quality grounds to the registration of Xembify normal immunoglobulin (human) 20% solution for subcutaneous injection.

Nonclinical

The nonclinical dossier was satisfactory. Safety related studies were Good Laboratory Practice (GLP) compliant. While nonclinical studies with Xembify were limited, it was

⁷ European Medicines Agency (EMA): Committee for Medicinal Products for Human Use (CHMP), Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg), [EMA/CHMP/BPWP/410415/2011 rev 1](#), 1 February 2016.

justified due to the immunogenicity of human immunoglobulins administered to non-human species.

Primary pharmacology studies were conducted with the currently market authorised Gamunex (intravenous immunoglobulin 10%);⁸ containing two fold lower immunoglobulins. These provided evidence of bactericidal activity *in vitro* and *in vivo*.

Safety pharmacology studies assessed effects on the cardiovascular and respiratory systems. No remarkable adverse effects were seen on either system in rat (intravenous immunoglobulin 10%, 1000 mg/kg), rabbit (intravenous immunoglobulin 10%, 1000 mg/kg) or monkey (intravenous immunoglobulin, 2000 mg/kg) studies, which were conducted using current market authorised product (Gamunex).

The pharmacokinetic profile in rabbits, the single species used for toxicity and local tolerance testing was qualitatively similar to that of humans with long time to reach maximum concentration (T_{max}) and terminal phase half-life ($t_{1/2}$) values.

A repeat dose toxicity study and four day pharmacokinetic study (with some toxicological endpoints) was conducted in rabbits comparing intravenous immunoglobulin 10% and subcutaneous immunoglobulin 20% administered by the proposed subcutaneous route. The duration (four to five days) was limited in order to mitigate xenogenic immunity issues. No difference in toxicity profile was noted between the current market-authorized product (Gamunex) and Xembify at doses up to 1500 mg/kg/day. Toxicity findings were unremarkable and consistent with immune mediated haemolytic anaemia.

No genotoxicity, carcinogenicity or reproductive developmental toxicity studies were conducted, which is acceptable for a constituent of normal human plasma. No juvenile toxicity studies were conducted.

An increased severity of injection site changes were observed in rabbits given Xembify for five days compared with Gamunex. This is anticipated given the higher concentration and there is an increased potential for local effects in the clinical setting. Administration of Xembify was well tolerated following subcutaneous, intravenous (auricular vein), intra-arterial (auricular artery) or perivascular (between the auricular vein and artery) administration, with local tolerance broadly comparable to intravenous immunoglobulin 10%.

Conclusion

There were no nonclinical objections to registration.

Clinical

The current 2021 submission included the following clinical study reports:

- Study GTI1502, a patient pharmacokinetic and initial tolerability report of 24 weeks duration;
- Study GTI1503, an uncontrolled clinical efficacy and safety study of 52 weeks duration); and
- Study GRI003, a pharmacokinetic modelling and simulation report (population PK study report).

The additional clinical studies (Studies GTI1503, GRI003) have been submitted to address the deficiencies in the 2018 submission.

⁸ Gamunex was first registered in Australia on 5 may 2006. ARTG number: 116689.

The TGA has adopted the EMA Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg), EMA/CHMP/BPWP/410415/2011 rev 1 which applies to Xembify.⁷

Pharmacokinetics

All pharmacokinetic (PK) information relating to Xembify was derived from patients with PID. There were no PK data in healthy subjects relating to Xembify. The submitted studies providing PK information relating to Xembify in patients with PID are summarised as follows and are further discussed below:

- Study GTI1502:
 - This was the primary PK study. It was designed to evaluate the safety and PK of subcutaneous immunoglobulin 20% administered by subcutaneous infusion for up to 24 weeks in subjects with PID.
 - The primary PK objective of this study was to determine a weekly subcutaneous dose of subcutaneous immunoglobulin 20% that produced a steady state total immunoglobulin G area under concentration time curve (AUC) that was non-inferior to the regularly administered intravenous dose of intravenous immunoglobulin 10% in subjects with PID.
 - The secondary PK objective was to determine if subcutaneous immunoglobulin 20% replacement therapy could maintain mean steady state trough total immunoglobulin G levels that were comparable to those achieved with intravenous immunoglobulin 10% replacement therapy.
 - The clinical study report was dated 27 June 2018.
- Study GTI1503:
 - This single arm study was designed to evaluate the efficacy, PK, safety and tolerability of subcutaneous immunoglobulin 20% administered by subcutaneous infusion for 52 weeks in subjects with primary immunodeficiency. This study is considered to be the pivotal efficacy and safety study.
 - The PK data in this study were categorised as secondary endpoints and additional endpoints. The PK secondary endpoint were trough concentrations of total immunoglobulin G of the previous regimen during the screening/previous regimen phase and of subcutaneous immunoglobulin 20% during the subcutaneous treatment stages.
 - The additional PK endpoints were average trough concentration of immunoglobulin G subclasses and concentration of antibody levels to *Streptococcus pneumoniae* (*S. pneumoniae*), *Haemophilus influenzae* (*H. influenzae*), and *Clostridium tetani* (*C. tetani* (tetanus)).
 - The clinical study report was dated 16 December 2019.
- Pharmacokinetic Report GRI003:
 - This was a PK modelling and simulation report of subcutaneous immunoglobulin G and intravenous immunoglobulin G dosing in patients with primary immunodeficiency.
 - The aim of the study was to develop a robust and predictive population pharmacokinetic (PopPK) model for the subcutaneous administration of subcutaneous immunoglobulin 20% in patients with PID to better inform clinical decisions on dosage regimens.
 - The report was dated 4 October 2018.

Study GTI1502

This was an open label, multi-centre study to evaluate the safety and pharmacokinetics of subcutaneous immunoglobulin 20% administered for six months in subjects with primary immunodeficiency.

The study design was a prospective, multi-centre, open label, single sequence, 6-month, PK, safety, and tolerability study of subcutaneous immunoglobulin 20% in subjects with PID to be carried out in approximately 30 study centres in the USA and Canada.

Planned enrolment included 50 subjects, including approximately 30 adult subjects and 12 to 18 paediatric subjects (aged from 2 to 16 years) completing treatment with subcutaneous immunoglobulin 20%. Paediatric enrolment was stratified by age with a target of four to six children for ages 2 to 5 years, greater than 5 to 12 years, and greater than 12 to 16 years.

The primary PK objective was to determine a dose of weekly subcutaneously administered subcutaneous immunoglobulin 20% that produced a steady-state AUC of total immunoglobulin G that was non-inferior to a regularly administered intravenous dose of intravenous immunoglobulin 10% in PID subjects.

The secondary PK objective was to determine if subcutaneous immunoglobulin 20% replacement therapy could achieve comparable mean steady state trough total immunoglobulin G levels to those obtained with intravenous immunoglobulin 10% replacement therapy in PID subjects.

There were multiple exploratory objectives which included evaluation of the following:

- Maximum concentration (C_{max}) and time of maximum concentration (T_{max}) in PID subjects at steady state.
- Trough levels of immunoglobulin G subclasses (immunoglobulin G1, immunoglobulin G2, immunoglobulin G3 and immunoglobulin G4).
- Antibody levels for *S. pneumoniae*, *H. influenzae*, and (*C. tetani* (tetanus)).
- The rate of serious bacterial infections.
- The safety and tolerability of subcutaneous immunoglobulin 20% as an immunoglobulin G replacement therapy in subjects with primary immunodeficiency.

The study consisted of a screening phase, a run-in phase, an intravenous phase, a subcutaneous phase, and an end of study/early termination visit.

Subjects were treated with intravenous immunoglobulin 10% and subcutaneous immunoglobulin 20% manufactured by the sponsor. As this was an open label, single sequence study, all subjects received study drug treatment in the same order (that is intravenous immunoglobulin 10% in the intravenous phase followed by subcutaneous immunoglobulin 20% in the subcutaneous phase). An intravenous to subcutaneous dose adjustment factor of 1.37 times was used to determine the initial subcutaneous dose.

In the intravenous phase, subjects received two intravenous infusions of intravenous immunoglobulin 10%. At the first Visit (intravenous Visit 1), subjects in Group 1 who had directly entered the intravenous phase following screening received intravenous immunoglobulin 10% at a dose equivalent to their current dose while subjects in Groups 2 and 3 who had entered the run-in phase after screening received intravenous immunoglobulin 10% at the same dose as had been administered in the run-in period.

One week after the intravenous Visit 2, subjects entered the subcutaneous phase to receive weekly subcutaneous doses of subcutaneous immunoglobulin 20% for a minimum of 24 weeks (plus or minus one day). As described above, the initial subcutaneous immunoglobulin 20% dose in the subcutaneous phase was determined using an

intravenous to subcutaneous dose adjustment factor of 1.37. After 12 weeks of weekly subcutaneous therapy, determination of PK profiles for total immunoglobulin G began at the blood draw just prior to the 13th subcutaneous infusion with the last sample collected immediately prior to the 14th subcutaneous infusion (seven days total).

A total of 61 subjects were screened for participation. A total of 53 subjects entered the study. Of these 53 subjects, nine directly entered the intravenous phase without run-in and 44 entered the run-in phase. During the run-in phase, one of the 44 subjects was lost to follow up. As a result, 43 subjects completed the run-in phase and proceeded to the intravenous phase.

Overall, 52 subjects entered the intravenous phase (nine via direct entry, 43 via the run-in phase). Forty-nine completed the intravenous phase and entered the subcutaneous phase, while three discontinued the intravenous phase and did not proceed to the subcutaneous phase. Of the 49 subjects entering the subcutaneous phase, 42 completed the subcutaneous phase and seven discontinued the subcutaneous phase.

Overall, of the 53 subjects entering the study, 42 (79.2%) completed the study and 11 (20.8%) discontinued prematurely. Five subjects discontinued due to adverse events, four subjects withdrew, one subject was lost to follow up, and one subject refused blood samples.

The mean standard deviation (SD) age of the population was 36.8 (21.36) years (range: 2 to 72 years), with the majority of the population being aged greater than 16 years (38 subjects, 71.7%). There were two paediatric subjects aged greater than or equal to 2 years to less than or equal to 5 years, seven paediatric subjects aged greater than 5 years to less than or equal to 12 years, and six adolescent subjects aged greater than 12 to 16 years. The number of males and females was well balanced in the overall population (27 males, 50.9%; 26 females, 49.1%). The majority of the overall population was White (48 subjects, 90.6%).

Of the 53 enrolled subjects, 50 (94.3%) subjects had valid data for PK analysis and were included in the PK population, with AUC estimates being provided by 49 subjects in the intravenous phase and 39 subjects in the subcutaneous phase. A total of 38 subjects had sufficient and valid PK profiles in both the intravenous and subcutaneous phases allowing calculation of the AUC (subcutaneous/intravenous) ratio.

The mean (SD) time since primary immunodeficiency diagnosis was 10.33 (10.655) years (range: 0.3, 41.1 years), and the majority of subjects (n = 41, 77.4%) had common variable immunodeficiency (CVID). Of the 53 enrolled subjects, 35 (66%) had received intravenous immunoglobulin treatment in the 12 months prior to study entry and 25 (47.2%) had received subcutaneous immunoglobulin treatment, with intravenous immunoglobulin and subcutaneous immunoglobulin treatments not being mutually exclusive.

The results for the primary PK endpoint analysis of steady state area under the concentration time curve from 0 to 7 days ($AUC_{0-7\text{days}}$) for total immunoglobulin G showed that the geometric least square means (LSM) ratio (subcutaneous/intravenous) was 1.04 and the 90% confidence interval (CI) for the ratio was 1 to 1.07. The lower bound of the 90% CI of the geometric LSM ratio (subcutaneous/intravenous) was above 0.8, demonstrating non-inferiority of subcutaneous to intravenous administration. The primary PK objective of this study was achieved by demonstrating that a dose adjustment factor of 1.37 is appropriate when determining a subcutaneous dose of subcutaneous immunoglobulin 20% from an intravenous dose of intravenous immunoglobulin 10%.

Table 4: Study GTI1502 Statistical analysis of primary pharmacokinetics endpoint of steady state area under the concentration time curve from 0 to 7 days (h.mg/dL) of total immunoglobulin G and the two sensitivity analyses (pharmacokinetic population)

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

Abbreviations: GLSM = geometric least squares mean; IV = intravenous; LSM = least squares mean; PK = pharmacokinetic; SC = subcutaneous

The mean AUC_{0-7 days} ratio (subcutaneous/intravenous) was 1.05 for all subjects (n = 38), with mean values by age group ranging from 1.02 (greater than 16 years, n = 28 to 1.22, 2 to 5 years, n = 1). There were low numbers of subjects aged less than 16 years. The primary PK endpoint analysis of steady state AUC_{0-7 days} in the intravenous and subcutaneous phases was also undertaken in subgroups based on intravenous dosing frequency (every three and every four weeks), sex, race and ethnicity. In general, the AUC_{0-7 days} values in the intravenous and subcutaneous phases in these subgroups were comparable.

The secondary PK endpoint was the mean steady state trough (pre-dose) concentration of total immunoglobulin G following intravenous administration of intravenous immunoglobulin 10% or subcutaneous administration of subcutaneous immunoglobulin 20%. Mean trough concentrations were calculated using two visits during the intravenous phase (intravenous Visit 1 and intravenous Visit 2) in a total of 51 subjects and four Visits during the subcutaneous phase (subcutaneous Visit 13, subcutaneous Visit 14, subcutaneous Visit 17, and subcutaneous Visit 21) in a total of 44 subjects.

The secondary PK endpoint of steady state mean trough of total immunoglobulin G in serum following subcutaneous immunoglobulin 20% averaged 33% higher than the trough concentrations observed for the intravenous immunoglobulin 10% dose. Individual trough concentrations in the subcutaneous phase in all 44 subjects were above the 500 mg/dL therapeutic threshold, while individual trough concentrations in 50 of the 51 subjects in the intravenous phase were above the 500 mg/dL therapeutic threshold.

Table 5: Study GTI1502 Trough total immunoglobulin G concentrations (mg/dL) during the intravenous and subcutaneous phases, immunoglobulin G population

	Trough (mg/dL)								Mean Trough Ratio SC/IV
	IV Phase			SC Phase					
	IV#1	IV#2	Mean Trough ^a	SC#13	SC#14	SC#17	SC#21	Mean Trough ^b	
n	51	49	51	41	38	41	38	44	43
Mean	997.4	923.9	957.13	1247.8	1264.6	1232.0	1227.2	1244.84	1.333
CV%	37	20	25.3	23	24	23	24	21.9	15.68
Range (min, max)	335, 2740	367, 1300	351.0, 1920.0	580, 2220	588, 1930	761, 2090	601, 1950	651.5, 2047.5	0.78, 1.86

Abbreviations: CV% = coefficient of variation; IV = intravenous; max = maximum; min = minimum; n = number of subjects; PK = pharmacokinetic; SC = subcutaneous.

IV#/SC# refers to intravenous/subcutaneous visit number.

a. Mean trough in the intravenous phase is calculated as the average of the trough concentrations at intravenous Visit 1 (IV#1) and intravenous Visit 2 (IV#2).

b. Mean trough in the subcutaneous phase is calculated as the average of the trough concentrations at subcutaneous Visit 13 (SC#13), subcutaneous Visit 14 (SC#14), subcutaneous Visit 17 (SC#17) and subcutaneous Visit 21 (SC#21).

Study GT11503

Study GT11503 a multi-centre, open label, single arm trial to evaluate efficacy, pharmacokinetics and safety of subcutaneous immunoglobulin 20% in subjects with primary immunodeficiency.

The secondary objective of Study GTI1503 was to determine if subcutaneous immunoglobulin 20% replacement therapy could maintain comparable mean trough immunoglobulin G levels with those achieved with the previous immunoglobulin G replacement regimen.

Exploratory objectives included:

- evaluation of the PK profile for total immunoglobulin G ($AUC_{0-7 \text{ days}}$, C_{max} , and T_{max} in adult PID subjects at steady state (after approximately four months (16 weeks)) of weekly administration of subcutaneous immunoglobulin 20%.
- evaluation of trough levels of immunoglobulin G subclasses (immunoglobulin G1, immunoglobulin G2, immunoglobulin G3 and immunoglobulin G4).
- evaluation of antibody levels for *S. pneumonia*, *H. influenza*, and *C. tetani*.

In the screening/previous regimen phase, subjects continued to receive ongoing treatment with their previous intravenous immunoglobulin or subcutaneous immunoglobulin regimen. Two trough immunoglobulin G levels were obtained in the screening phase for prior intravenous immunoglobulin or subcutaneous immunoglobulin treatments.

In subcutaneous immunoglobulin 20% treatment Stage 1 (13 weeks), adjustment in subcutaneous immunoglobulin 20% was made at clinic visits if immunoglobulin G trough levels were less than 500 mg/dL.

The intravenous immunoglobulin regimen to subcutaneous immunoglobulin 20% dose conversion calculation formula was:

- $(\text{Greater than or equal to } 200 \text{ mg/kg (previous intravenous dose)}) / (3 \text{ or } 4 \text{ (previous intravenous dosing interval in weeks)})$

The subcutaneous immunoglobulin regimen to subcutaneous immunoglobulin 20% dose conversion calculation formula was:

- $(\text{Previous subcutaneous dose mg/kg}) / (\text{previous subcutaneous dosing interval between treatments in weeks})$

In subcutaneous immunoglobulin 20% treatment Stage 1, all subjects received 13 weekly subcutaneous immunoglobulin 20% infusions.

In subcutaneous immunoglobulin 20% treatment Stage 2, subjects received 39 weekly infusions of subcutaneous immunoglobulin 20% at the dose established in treatment Stage 1. Overall, a total of 52 doses of subcutaneous immunoglobulin 20% was planned to be administered per subject during the subcutaneous phase (13 in treatment period 1 and 39 in treatment period 2) with a final follow up visit at Week 53 (that is, one week after the last dose at Week 52).

A total of 61 subjects entered the subcutaneous phase of Study GTI1503 and were included in the efficacy evaluable population. A total of 59 (96.7%) subjects had sufficient immunoglobulin G data for trough immunoglobulin G analysis and were included in the immunoglobulin G population, and 27 adult subjects were included in the PK population.

The overall average steady state mean (SD) trough total immunoglobulin G concentration during the previous regimen phase was 891.37 (165.943) mg/dL. The average trough concentrations at previous intravenous Visit 1/previous subcutaneous Visit 1 and previous intravenous Visit 2/subcutaneous Visit 1 were mean (SD) concentrations of 875.6 (167.28) mg/dL and 906.9 (173.62) mg/dL, respectively. All individual trough concentrations were above 500 mg/dL.

The average of the mean (SD) trough immunoglobulin G concentrations for all subjects during the subcutaneous phase was 947.64 (150.262) mg/dL and was generally comparable to the average of the mean trough immunoglobulin G concentrations from the previous regimen of 891.37 (165.943) mg/dL. The average mean trough ratio (subcutaneous phase: previous regimen phase) was 1.078 (range: 0.83, 1.54). All individual trough concentrations in the subcutaneous phase were above the anticipated 500 mg/dL therapeutic threshold.

Table 6: Study GT11503 Summary of steady state trough concentrations of total immunoglobulin G during the previous regimen and subcutaneous phases, immunoglobulin G population

Statistic	Trough During Previous Regimen Phase (mg/dL)			Trough During SC Phase (mg/dL)					
	pIV#1/pSC#1*	pIV#2/SC#1	Mean Trough ^b	SC#17	SC#18	SC#20	SC#24	SC#28	SC#32
n	58	58	59	57	27	57	59	59	57
Mean±SD	875.6±167.28	906.9±173.62	891.37±165.943	958.7±161.88	1028.3±186.13	950.8±168.23	961.9±164.49	946.7±150.07	941.6±151.73
CV%	19	19	18.6	17	18	18	17	16	16
Median	859.5	907.5	874.00	942.0	1010.0	917.0	954.0	943.0	910.0
Min, Max	524, 1290	509, 1410	516.5, 1255.0	597, 1350	755, 1430	611, 1360	674, 1450	647, 1330	696, 1380
Geometric Mean	860.1	890.1	875.96	945.7	1013.0	936.7	948.7	935.2	930.4

Statistic	Trough During SC Phase (mg/dL)							Mean Trough Ratio, SC/Pre Regimen
	SC#36	SC#40	SC#44	SC#48	SC#52	SC#53	Mean Trough ^c	
n	58	56	50	56	54	50	59	59
Mean±SD	966.5±167.32	938.1±170.81	942.3±171.06	928.0±172.47	931.0±178.35	956.4±149.88	947.64±150.262	1.078±0.1425
CV%	17	18	18	19	19	16	15.9	13.22
Median	963.0	917.0	904.0	900.0	906.0	918.0	909.10	1.050
Min, Max	517, 1420	606, 1390	605, 1470	599, 1450	517, 1350	695, 1280	629.2, 1340.8	0.83, 1.54
Geometric Mean	951.9	923.3	928.1	913.2	914.5	945.2	936.48	1.069

Abbreviations: CV% = coefficient of variation; IV = intravenous; max = maximum; min = minimum; n = number of subjects; PK = pharmacokinetic; SC = subcutaneous; SD = standard deviation.

IV#/SC# refers to intravenous/subcutaneous visit number.

a. Trough concentration is taken from the previous intravenous Visit one/previous subcutaneous Visit one (pIV#1/pSC#1) Visit, or from screening Visit if a separate previous intravenous Visit two/subcutaneous Visit one (pIV#1/pSC#1) Visit was not required for the subject.

b. Mean trough in the previous regimen phase is calculated as the average of the trough concentrations at the pIV#1 and pIV#2 Visits for subjects entering study on a previous intravenous immunoglobulin regimen, or at the pSC#1 and Baseline/SC#1 Visits for subjects entering study on a previous subcutaneous regimen.

c. Mean trough in the subcutaneous phase is calculated as the average of the trough concentrations at subcutaneous Visit 17 (SC#17), subcutaneous Visit 18 (SC#18), subcutaneous Visit 20 (SC#20), subcutaneous Visit 24 (SC#24), subcutaneous Visit 28 (SC#28), subcutaneous Visit 32 (SC#32), subcutaneous Visit 36 (SC#36), subcutaneous Visit 40 (SC#40), subcutaneous Visit 44 (SC#44), subcutaneous Visit 48 (SC#48), subcutaneous Visit 52 (SC#52) and subcutaneous Visit 53 (SC#53).

The peak value at subcutaneous Visit 1 can be attributed to the one week transition between the last previous regimen intravenous immunoglobulin dose and the start of subcutaneous immunoglobulin 20% administration at Baseline/ subcutaneous Visit 1 for subjects who entered the study on intravenous immunoglobulin, given that the previous regimen of intravenous immunoglobulin dosing frequency was every three or four weeks.

When stratified by age (less than or equal to 16 years (n = 27) or greater than 16 years (n = 32)), results for immunoglobulin G trough concentrations were similar to the overall population.

Overall, the data showed that serum total immunoglobulin G trough concentrations were stable over time following subcutaneous administration of subcutaneous immunoglobulin 20% and were comparable to the mean immunoglobulin G trough concentrations obtained with the previous immunoglobulin G replacement regimen.

Conclusions on pharmacokinetics

Study GTI1502

The primary PK study was Study GTI1502. Overall, 50 subjects were included in the PK population, with 49 subjects providing AUC estimates in the intravenous phase (300 to 800 mg/kg over a three or four week dosing interval) and 39 providing AUC estimates in the subcutaneous phase.

The analysis of the primary PK endpoint of steady state AUC_{0-7} days demonstrated that a dose adjustment factor of 1.37 for the subcutaneous dose of subcutaneous immunoglobulin 20% provided comparable overall serum exposure (AUC) to total immunoglobulin G relative to the previous intravenous dose of intravenous immunoglobulin 10%. The geometric least squared mean (GLSM) ratio (subcutaneous/intravenous) for the AUC_{0-7} days for total immunoglobulin G was 1.04 (90% CI: 1 to 1.07). The lower bound 90% CI for the GLSM ratio was greater than 0.8, indicating non-inferiority of subcutaneous (subcutaneous immunoglobulin 20%) compared with intravenous (intravenous immunoglobulin 10%). The 90% CI was enclosed within the interval 0.8 to 1.25, indicating bioequivalence of subcutaneous (subcutaneous immunoglobulin 20%) and intravenous (intravenous immunoglobulin 10%).

The results for the secondary PK endpoint of mean steady state trough (pre-dose) indicated that subcutaneous immunoglobulin 20% were stable over time and were approximately 1.33-fold higher than that following intravenous immunoglobulin 10% administration.

Study GTI1503

The average of the steady state mean trough concentration of total immunoglobulin G over all subjects during the previous regimen phase was 891.37 mg/dL (coefficient of variation (CV)% = 18.6%), and the average of the mean trough immunoglobulin G concentration

over all subjects during the subcutaneous phase was 947.64 mg/dL (%CV = 14.9%). The mean trough total immunoglobulin G ratio of the subcutaneous regimen relative to the previous intravenous/subcutaneous regimen was 1.078 (range: 0.83, 1.54). All individual total immunoglobulin G trough concentrations were above the therapeutic level of 500 mg/dL.

When stratified by age (less than or equal to 16 years (n = 27) or greater than 16 years (n = 32), the results for the average of the steady state mean total immunoglobulin G trough concentration were similar to the results for the overall population.

Report GRI003 population pharmacokinetics analysis

A PK modelling and simulation study was conducted to develop a predictive PopPK model for the administration Xembify to better guide clinical decisions relating to dosage, given that not all potential dosing regimens were investigated in the clinical studies.

The PK of immunoglobulin G following intravenous and subcutaneous administration was adequately described by a two compartment model with first order elimination from the central compartment. Administration of intravenous immunoglobulin was modelled as an infusion directly into the central compartment, and absorption of exogenous immunoglobulin G from the depot site of subcutaneous infusions into the central compartment was modelled as a first-order process with an absorption rate constant (K_a).

Simulations of steady state immunoglobulin G exposures after intravenous immunoglobulin dosing followed by subcutaneous immunoglobulin dosing showed that for a dose conversion factor of 1:1.37 (intravenous immunoglobulin: subcutaneous immunoglobulin), the median AUC ratios (subcutaneous immunoglobulin/intravenous immunoglobulin) were 0.976 (fifth to ninety-fifth percentile: 0.88 to 1.09) for the subcutaneous immunoglobulin weekly regimen relative to the intravenous immunoglobulin every four weeks regimen, and 0.975 (fifth to ninety-fifth percentile: 0.88 to 1.09) for the subcutaneous immunoglobulin weekly regimen relative to the intravenous immunoglobulin every three weeks regimen. Using a dose equivalent approach, the median AUC ratios (subcutaneous immunoglobulin/intravenous immunoglobulin) were 0.806 (fifth to ninety-fifth percentile: 0.728 to 0.894) for the subcutaneous immunoglobulin weekly regimen relative to the intravenous immunoglobulin every four weeks regimen and 0.785 (fifth to ninety-fifth percentile: 0.702 to 0.887) for the subcutaneous immunoglobulin weekly regimen relative to the intravenous immunoglobulin every three weeks regimen. Simulated total immunoglobulin G exposures (AUC) demonstrated greater similarity for the subcutaneous immunoglobulin and intravenous immunoglobulin regimens using a dose conversion factor of 1:1.37 (intravenous immunoglobulin: subcutaneous immunoglobulin) than a dose equivalent factor (1:1).

Advice by pharmacometrics working group

The TGA's pharmacometrics working group considered the submission in May 2021.

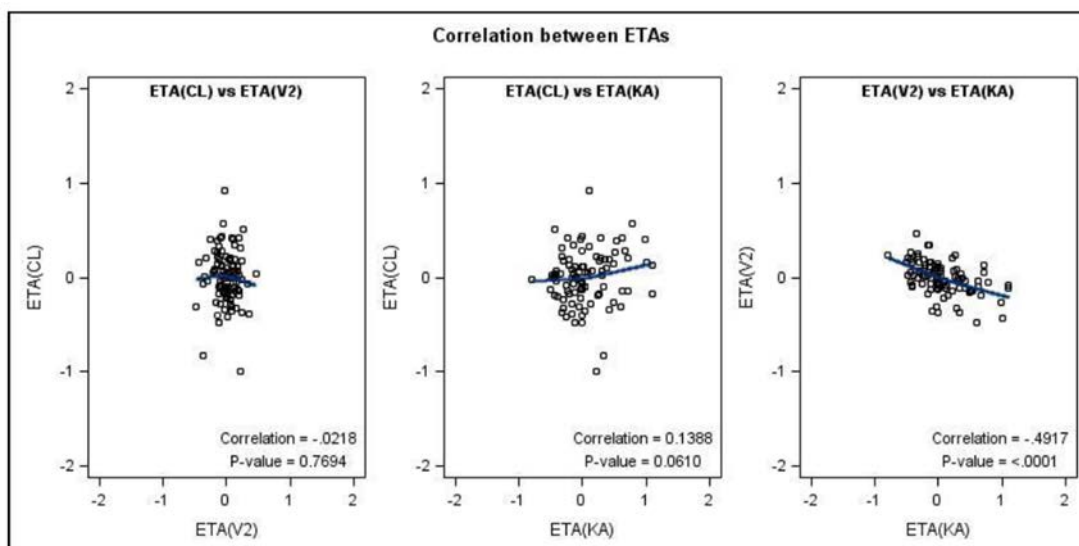
The working group did not express any major concerns in relation to PK modelling and simulation analyses by the sponsor. The working group is of the opinion that the analyses support the proposed dosing recommendations (once weekly, bi-weekly dose at double the weekly dose, and more frequent dosing at the same total weekly dose) in the patient groups (two years and above) analysed in the PK modelling report.

The working group requested the sponsor to address the following questions. The questions and summary of the sponsors response are listed below.

1. In the modelling report, please explain the correlations observed in Figure 1 (shown below).

Could it be because of the different patient population?

Figure 1: Report GRI003 Correlation of random effects included in the final model



ETA: inter-individual variability of the PK parameter

The sponsor believes that this potential correlation between volume of distribution of central compartment (V2) and K_a could be related to body weight, which influenced V2 and probably also on K_a . On the other hand, based on the practically flat PK profile on the immunoglobulin G serum levels obtained after repeated administration of subcutaneous immunoglobulin once a week or once every two weeks, and that the absolute subcutaneous bioavailability would be the same, this potential relationship between V2 and K_a would have a very low clinical significance.

2. Please discuss whether albumin was explored as a covariate during the modelling analysis. Please provide rationale if not explored.

The relationship between albumin and specifically Xembify modelling for immunoglobulin G replacement in congenital primary immunodeficiency does not appear to be sufficiently plausible to include in the model and there was no evident precedent to include in this regard for a non-facilitated subcutaneous immune globulin product. There is no clinical application for dosing of any subcutaneous immune globulin product that is currently commercially available based on host albumin levels; all medically applied dosing paradigms are predicated solely on patient's body weight.

Some additional points for consideration were:

- Formulation, immunoglobulin products are manufactured from the plasma of healthy donors and can be stabilised agents such as human albumin, glycine, polyethylene glycol, or sugars. Some preparations may have as much as 3% albumin, in addition to the immunoglobulin G itself. Notably Cuvitru,⁹ Hizentra,¹⁰ and Xembify contain no albumin in their product formulations.
- Similar distribution/elimination pattern between albumin and immunoglobulin G. Albumin and immunoglobulin G are both plasma proteins that follow similar patterns of distribution and bind with high affinity to neonatal Fc receptor

⁹ Cuvitru was first registered in Australia on 5 October 2017. ARTG number: 282579.

¹⁰ Hizentra was first registered in Australia on 8 May 2014. ARTG number: 207383.

(FcRn), which is a saturable receptor that protects both immunoglobulin G and albumin from intracellular degradation. In PID patients, low serum albumin level was also associated with poor efficiency in patients with intravenous immunoglobulin, but not in patients with subcutaneous immunoglobulin, which could be related to increased catabolism or reduced recycling when high peak immunoglobulin G concentrations are achieved with intravenous infusions in contrast to the more stable levels with more frequent subcutaneous immunoglobulin infusions, since FcRn is a saturable receptor.

3. Please provide the dose adjustment factor and related information when converting from intravenous immunoglobulin to subcutaneous immunoglobulin in the PI.

Additional prescriptive language in the form of a table has been added to the draft Australian labelling.

4. Please provide the impact of missed doses and instructions for clinicians on how to approach in case of a missed dose in the PI.

General instructions have been added to the PI with regard to reinstating therapy as quickly as possible if interrupted or if there is a missing dose.

5. Please provide the dose adjustment guidance either as a descriptive (for example, linear) or detailed information in the PI.

The sponsor has added guidance and a dose adjustment table for target immunoglobulin G trough levels to the revised Australian PI.

6. Please discuss the interchangeability between Xembify and Hizentra (approved CSL product);¹¹ given the potential for it to be initiated in patients already receiving Hizentra.

Based on two clinical trials in treatment experienced patients on pre-existing immunoglobulin G replacement therapy, the transition from previous to a Xembify based regimen should be well tolerated. Patients historically treated with Hizentra, as well as many other brands of immunoglobulin G treatment, were enrolled in both Phase III studies.

Efficacy

Study GTI1503

Study GTI1503 is a multi-centre, open label, single arm Phase III trial to evaluate efficacy, pharmacokinetics, and safety and tolerability of subcutaneous immunoglobulin 20% in subjects with primary immunodeficiency.

The primary efficacy objective was to evaluate whether weekly administered subcutaneous immunoglobulin 20% over a one year period achieved less than one serious bacterial infection per subject per year in PID subjects.

Secondary efficacy objectives included evaluation of all infections of any kind, number of days on antibiotics, number of hospitalisations due to infection and number of days of work/school/daily activities missed per subject year due to infections and related treatment.

Enrolment was planned for approximately 60 subjects.

¹¹ Hizentra human normal immunoglobulin 20% solution for subcutaneous injection; ARTG R: 285344 (5 mL syringe); 285345 (10 mL syringe); 207386 (5 mL vial); 207385 (10 mL vial); 207383 (20 mL vial); 207384 (50 mL vial); CSL Behring Australia Pty Ltd.

The study included three stages: screening/previous regimen phase (up to eight weeks); subcutaneous immunoglobulin 20% treatment Stage 1 (13 times subcutaneous immunoglobulin 20% weekly doses); and subcutaneous immunoglobulin 20% treatment Stage 2 (39 times subcutaneous immunoglobulin 20% weekly doses). The subcutaneous immunoglobulin 20% dose was determined using a previous immunoglobulin G regimen to subcutaneous DAF of 1:1.

Subjects aged 2 to 75 years (inclusive) at screening, with a confirmed pre-existing diagnosis of PID, were included. Treatment naïve subjects who had never received intravenous immunoglobulin or subcutaneous immunoglobulin treatment were not eligible for entry into the study. All measured minimum observed concentration (C_{trough}) levels of immunoglobulin G drawn pre-baseline must have been greater than or equal to 500 mg/dL for the subject to qualify for subsequent treatment with subcutaneous immunoglobulin 20%.

Subcutaneous immunoglobulin 20% treatment Stage 1 involved 13 times subcutaneous immunoglobulin 20% infusions at weekly intervals. In treatment Stage 1 subcutaneous immunoglobulin 20% dose was adjusted if trough level was below 500 mg/dL. Subjects entered subcutaneous immunoglobulin 20% treatment Stage 2 to receive an additional 39 weeks of subcutaneous immunoglobulin 20% therapy.

Of these 68 subjects screened, seven subjects were considered screen failures. Six subjects never received any amount of subcutaneous immunoglobulin 20% and one subject was withdrawn because of a serious adverse event. A total of 61 subjects entered treatment Stage 1 with 60 completing treatment Stage 1. One subject was withdrawn because of an adverse event. Sixty subjects entered treatment stage 2 and 55 (91.7%) completed treatment stage 2. Over the course of the study six subjects withdrew with four subjects withdrawing because of adverse event. Two subjects withdrew due to own decisions. Thirty-two adult subjects (age greater than 16 years) entered and completed subcutaneous immunoglobulin 20% treatment Stage 1. All 32 subjects who completed subcutaneous immunoglobulin 20% treatment Stage 1 entered subcutaneous immunoglobulin 20% treatment Stage 2, and 30 (93.8%) of these subjects completed subcutaneous immunoglobulin 20% treatment Stage 2, 29 paediatric subjects (aged less than 16 years) entered subcutaneous immunoglobulin 20% treatment Stage 1 and 28 (96.6%) of these subjects completed treatment Stage 1 (one subject discontinued due to an adverse event). A total of 28 subjects entered subcutaneous immunoglobulin 20% treatment Stage 2, and 25 (89.3%) completed.

The efficacy evaluable population consisted of all 61 subjects who received subcutaneous immunoglobulin 20%. There were more males (68.9%, 42 out of 61) than females (31.1%, 19 out of 61) in this population. The majority of subjects were White (93.4%, 57 out of 61). Thirty-two (52.5%) subjects were aged greater than 16 years and 29 (47.5%) subjects were aged less than or equal to 16 years. Of the 29 subjects aged less than or equal to 16 years, five (5 out of 61, 8.2%) were aged less than or equal to 2 to less than or equal to 5 years, 14 (14 out of 61, 23.0%) were aged greater than 5 to less than or equal to 12 years, and 10 (10 out of 61, 16.4%) were aged greater than 12 to 16 years.

The mean (SD) time since diagnosis of PID in the efficacy evaluable population (61 subjects) was 8.99 (7.899) years (range: 0.3, 38.9 years). The most common type of PID diagnosed at study entry was common variable immunodeficiency (CVID) (39 out of 61, 63.9%), followed by X-linked agammaglobulinaemia (13 out of 61, 21.3%), primary hypogammaglobulinaemia (8 out of 61, 13.1%), and hyper immunoglobulin M immunodeficiency syndrome (1 out of 61, 1.6%).

Intravenous immunoglobulin treatment was being received by 65.6% (40 out of 61) of subjects and 36.1% (22 out of 61) were receiving subcutaneous treatment. The most

common frequency of immunoglobulin G treatment for the previous 12 months was every four weeks (23 subjects, 37.7%).

Total duration of exposure across all subjects was 15.06 years for subcutaneous immunoglobulin 20% treatment Stage 1, 43.35 years for subcutaneous immunoglobulin 20% treatment Stage 2, and 58.40 years for the overall subcutaneous phase (treatment Stages 1 plus 2). The overall mean annualised serious bacterial infection rate was 0.016 during the entire subcutaneous immunoglobulin 20% subcutaneous phase (0 in treatment Stage 1, 0.022 in treatment Stage 2). The overall rate of serious bacterial infection per person per year in the subcutaneous phase was 0.017 (two sided 98% CI: 0.006, 0.036); (0 in treatment Stage 1; 0.023 (two sided 98% CI: 0.008, 0.049) in treatment Stage 2).

Table 7: Study GTI1503 Summary of serious bacterial infections (efficacy evaluable population)

Serious Bacterial Infection Preferred term	IGSC 20% Treatment Phase		
	Stage 1 (N=61) n (%) ^a	Stage 2 (N=60) n (%) ^a	Overall (N=61) n (%) ^a
Number of Subjects with at least 1 serious bacterial infection	0	1 (1.7)	1 (1.6)
Pneumonia	0	1 (1.7)	1 (1.6)
Total number of events	0	1	1
Summary			
Total duration of exposure (years)	15.06	43.35	58.40
Annualized rate of events ^a			
Mean±SD	0.000±0.0000	0.022±0.1727	0.016±0.1285
Median	0.000	0.000	0.000
Min. Max	0.00, 0.00	0.00, 1.34	0.00, 1.00
Rate of events per person per year ^b	0.000	0.023	0.017
2-sided 98% CI ^c	NA	0.008-0.049	0.006-0.036

Abbreviations: CI = confidence interval; IGSC 20% = immunoglobulin for subcutaneous administration 20%; IV = intravenous; max = maximum; min = minimum; n = number of subjects; NA = not applicable; SD = standard deviation.

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

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

c. Two sided 98% CI is determined from a generalised linear model for Poisson regression for the log transformed duration of exposure in years as an offset variable.

The one-sided 99% upper confidence limit of the serious bacterial infection rate per person per year was less than one and the primary efficacy endpoint was met.

There was only one subject in the efficacy evaluable population with at least one serious bacterial infection. This event was diagnosed as pneumonia in subcutaneous immunoglobulin 20% treatment Stage 2 in a subject aged less than or equal to 16 years. The serious bacterial infection of pneumonia was reported as a serious adverse event not considered by the investigator to be related to the study drug. The event occurred in 10 year old male and was reported 241 days after the start of the infusion. The subject was treated with oral amoxicillin/clavulanic acid (co-amoxiclav) as an outpatient and the event resolved after four days treatment. The event was reported as a serious adverse event and was not considered by the investigator to be related to study drug. There were no serious bacterial infections reported in the greater than 16 years age group, and there were no serious bacterial infection events in subcutaneous immunoglobulin 20% treatment Stage 1.

Across age categories, in the less than or equal to 16 years age group the rate of serious bacterial infection per person per year was 0.037 (two-sided 98% CI: 0.009, 0.096). In the greater than 16 years age group, the rate of serious bacterial infection per person per year was zero.

For other efficacy outcomes, infections of any kind, in the total efficacy evaluable population 73.8% (45 out of 61) of subjects experienced at least one infection. The most frequent infections (incidence greater than or equal to 10%) by Preferred Term were nasopharyngitis (19.7%, 12 out of 61), upper respiratory tract infection (14.8%, 9 out of 61), bronchitis (13.1%, 8 out of 61), and sinusitis (11.5%, 7 out of 61).

The mean (SD) annualised infection rate in the total efficacy evaluable population (n = 61) was 2.327 (2.49), and the rate of all infections per person per year was 2.397 (two sided 95% CI: 1.824, 3.079). The results were generally consistent across the age categories.

In the total efficacy evaluable population (n = 61), in the subcutaneous immunoglobulin 20% subcutaneous phase the total number of days on prophylactic antibiotics overall was 2595 days, the mean (SD) annualised rate of days on prophylactic antibiotics was 42.665 (108.6821), and the rate of days per person per year on prophylactic antibiotics was 44.432 (two sided 95% CI: 26.351, 69.339).

In the total efficacy evaluable population (n = 61), in the subcutaneous immunoglobulin 20% subcutaneous phase the total number of days on therapeutic antibiotics overall was 520 days, the mean (SD) annualised rate of days on therapeutic antibiotics was 8.607 (14.7527), and the rate of days per person per year on therapeutic antibiotics was 8.904 (two sided 95% CI: 5.949, 12.705).

There was one event of hospitalisation due to infection in the overall population subcutaneous immunoglobulin 20% during the subcutaneous phase. The mean (SD) annualised rate of hospitalisations due to infections during the subcutaneous immunoglobulin 20% subcutaneous phase was 0.016 (0.1285), and the rate of hospitalisations due to infections per person per year was 0.017 (two sided 95% CI: 0.008, 0.033). The one subject hospitalised due to infection was a 64-year old White male with a urinary tract infection. The urinary tract infection was reported as a serious adverse event and was not considered by the investigator to be related to the study drug. The infection was treated with antibiotics and resolved after treatment.

In the total efficacy evaluable population (n = 61), in the subcutaneous immunoglobulin 20% subcutaneous phase the overall number of days of work/school/daily activities missed due to infections and related treatment was 291, the overall mean (SD) annualised rate of days missed was 4.84 (13.8489), and the overall rate of days missed per person per year was 4.983 (two sided 95% CI: 3.064, 7.572).

Validated infections documented by positive radiograph, fever (greater than 38°C oral or greater than 39°C rectal), culture, or diagnostic testing for microorganisms (for example, bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test)) were evaluated in this study as an additional efficacy endpoint.

In the total efficacy evaluable population (n = 61), during the subcutaneous immunoglobulin 20% subcutaneous phase there were 36 validated infections. The mean (SD) annualised validated infection rate was 0.597 (1.0926) and the overall rate of validated infections per person per year was 0.616 (two sided 95% CI: 0.401-0.898). Overall, 32.8% (20 out of 61) of subjects experienced at least one validated infection (total of 36 validated infections in 61 subjects). The most frequently reported validated infections (occurring in greater than or equal to two subjects) by Preferred Term were bronchitis (4.9%, 3 out of 61), pyrexia (4.9%, 3 out of 61), upper respiratory tract infection (4.9%, 3 out of 61), gastroenteritis (3.3%, 2 out of 61), influenza (3.3%, 2 out of 61), pneumonia (3.3%, 2 out of 61) and sinusitis (3.3%, 2 out of 61).

Study GTI1502

In Study GTI1502 Serious bacterial infection and other infections were considered to be safety endpoints.

Table 8: Study GTI1502 Serious bacterial infections (safety population)

Serious Bacterial Infection Preferred Term	Study Phase			
	Run-In (N=44) n (%)	IV (N=52) n (%)	Run-in+IV (N=53) n (%)	SC (N=49) n (%)
No. of SBIs	0	2	2	1
Subjects with at least 1 SBI	0	1 (1.9)	1 (1.9)	1 (2.0)
Pneumonia bacterial	0	1 (1.9)	1 (1.9)	0
Sepsis	0	1 (1.9)	1 (1.9)	1 (2.0)
Summary				
Annualized rate of events ^a (mean±SD)	0	0.502±3.6179	0.098±0.7167	0.044±0.3106
Total Duration of Exposure (years)	11.85	4.88	16.73	20.28
SBI rate per person per year ^b	0	0.410	0.120	0.049
95% CI ^c	NA	0.165-0.825	0.051-0.232	0.020-0.098

Note: For incidence, at each level of summation (Preferred Term), subjects are counted only once per study phase.

Abbreviations: CI = confidence interval; IV = intravenous; NA = not applicable; SBI = serious bacterial infection; SC = subcutaneous; SD = standard deviation.

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

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

There were two subjects with a total of three serious bacterial infections in Study GTI1502; in the intravenous phase, one 30-year old male developed bacterial pneumonia four days after entering the intravenous phase following completion of a four month run-in and sepsis developed four days later; serious bacterial infection events of bacterial pneumonia and sepsis were considered to be serious adverse events and were treated and resolved; in the subcutaneous phase, one 54-year old male developed sepsis on Day 140 due to cellulitis associated with a cat bite; the serious bacterial infection event (sepsis) was considered to be a serious adverse event and was treated and resolved.

In the overall population (n = 49), in the subcutaneous immunoglobulin 20% subcutaneous phase 'Infections and Infestations' System Organ Class were reported in 53.1% (n = 26) of subjects, with treatment-emergent adverse events reported in greater than or equal to 5% of subjects being sinusitis (18.4%, nine subjects), upper respiratory tract infection (10.2%, five subjects), bronchitis (6.1%, three subjects), and pharyngitis streptococcal (6.1%, three subjects).

Conclusions on efficacy

It is considered that the totality of the efficacy data for Study GTI1503 supports approval of Xembify for replacement therapy for subjects with PID. The positive efficacy data from Study GTI1503 are supported by the corresponding outcome safety data reported in Study GTI1502.

Safety**Exposure and safety populations**

The safety of Xembify (subcutaneous immunoglobulin 20%) was assessed in subjects with PID in Studies GTI1503 and GTI1502. The safety population in Study GTI1503 included all 61 subjects who received subcutaneous immunoglobulin 20% during the treatment phase.

The safety population in Study GTI1502 included all 53 subjects who received any amount of study medication (either intravenous immunoglobulin 10% or subcutaneous immunoglobulin 20%). In Study GTI1502, 49 of the 53 subjects in the safety population subjects received subcutaneous immunoglobulin 20%. Overall, a total of 110 subjects with PID in the two studies were treated with subcutaneous immunoglobulin 20%.

In Study GT11503, 55 (91.7%) subjects completed the study. Overall, the mean (SD) duration of exposure to subcutaneous immunoglobulin 20% in the subcutaneous phase for all 61 subjects was 49.96 (7.87) weeks. Overall, the mean (SD) total number of infusions was 49.9 (7.86) and the mean (SD) dose per infusion was 125.5 (28.46) mg/kg for all 61 subjects during the subcutaneous phase. In the subcutaneous phase the mean (SD) duration of individual subcutaneous infusions was 1.15 (0.566) hours, and the mean (SD) volume of subcutaneous immunoglobulin 20% per infusion was 37 (17.20) mL. The mean (SD) number of infusion sites used per infusion was 2 (0.75) across all infusions (range: 1, 4 sites). The mean (SD) volume of subcutaneous immunoglobulin 20% infused per site per infusion, was 19.3 (7.64) mL/site. The two most frequently used subcutaneous infusion sites in all subjects were the abdomen (5258 out of 6087 sites, 86.4%) and thigh (462 out of 6087 sites, 7.6%). The mean (SD) infusion rate per site per infusion was 20 (9.29) mL/hr/site and the mean (SD) by subject maximum infusion rate per site per infusion was 25.2 (13.8) mL/hr/site.

Overall, less than 4% of all infusions were interrupted. During the entire subcutaneous immunoglobulin 20% treatment phase, only eight infusion interruptions were potentially due to an adverse event. All eight infusions were resumed and completed, with the exception of one infusion in a subject at subcutaneous Visit 6 which was permanently discontinued due to an AE of anxiety.

In Study GT11502, 42 (79.2%) subjects completed the study, and 11 (20.8%) subjects discontinued the study prematurely. In the subcutaneous phase, 49 subjects were treated with subcutaneous immunoglobulin 20% infusions. In the subcutaneous phase (49 subjects), the mean (SD) duration of subject exposure to subcutaneous immunoglobulin 20% was 21.6 (6.51) weeks, the mean (SD) total volume infused per subject was 1365.4 (798.62) mL, the mean (SD) number of infusions per subject was 21.5 (6.47), the mean (SD) duration of infusions (1049 infusions) was 1.56 (0.843) hours, the mean (SD) volume infused (1053 infusions) was 63.5 (29.5) mL, and the mean (SD) dose per infusion (1053 infusions) was 178.9 (44.98) mg/kg. Most infusions were administered using either four infusion sites (56.2%, 592 out of 1053) or two infusion sites (30.5%, 321 out of 1053). The mean number of infusion sites used per infusion was 3.3 across all infusions. The two most frequently used infusion sites were the abdomen and thigh. Approximately 94% (46 out of 49) of subjects used the abdomen and 38.8% (19 out of 49) of subjects used the thigh for subcutaneous infusion. The mean (SD) volume infused per site per infusion was 20.6 (11.51) mL/site. The mean (SD) infusion rate per site per infusion was 16 (6.9) mL/hour/site. The mean (SD) by subject maximum infusion rate per site per infusion was 17.5 (8.09) mL/hour/site.

Overall, both intravenous and subcutaneous infusions were completed without interruptions in the great majority of cases.

The proportion of subjects treated with subcutaneous immunoglobulin 20% in the subcutaneous phase in Study GTI1503 was 85.2% (52 out of 61) and in Study GTI1502 was 83.7% (41 out of 49).

Any treatment-emergent adverse events

Treatment-emergent adverse events (TEAEs) irrespective of relationship to treatment were reported in greater than or equal to 10% of subjects in Study GTI1503 were nasopharyngitis (19.7%), infusion site erythema (16.4%), cough (14.8%), upper respiratory tract infection (14.8%), bronchitis (13.1%), infusion site pruritus (13.1%),

headache (11.5%), pyrexia (11.5%), rhinitis (11.5%), and sinusitis (11.5%). TEAEs reported in greater than or equal to 10% of subjects in Study GTI1502 were sinusitis (18.4%), infusion site nodule (12.2%) and upper respiratory tract infection (10.2%).

The majority of TEAEs in both studies were mild or moderate in severity. Severe TEAEs were reported in seven (11.5%) subjects in Study GTI1503 (12 out of 411 (2.9%) events) and in three subjects (6.1%) in Study GTI1502 (5 out of 141 (3.5%) events). In Study GTI1503, severe TEAEs were headache (three subjects (4.9%)), infusion site swelling (one subject (1.6%)), urinary tract infection (one subject (1.6%)), pneumonia (one subject (1.6%)), sunburn (one subject (1.6%)), back pain (one subject (1.6%)), neck pain (one subject (1.6%)), and aortic valve incompetence (one subject (1.6%)). In Study GTI1502, severe TEAEs were cellulitis (one subject (2%)), sepsis (one subject (2%)), animal bite (one subject (2%)), neck pain (one subject (2%)), and polymyalgia rheumatic (one subject (2%)).

In Study GT11503 there were 3045 infusions and 441 TEAEs in the subcutaneous immunoglobulin 20% subcutaneous phase, resulting in 0.135 TEAEs per infusion. TEAEs in Study GTI1503 with a rate of greater than or equal to 0.005 per infusion were infusion site erythema (26 events, 0.009), nasopharyngitis (23 events, 0.008), headache (21 events, 0.007), infusion site pruritus (19 events, 0.006), and upper respiratory tract infection (17 events, 0.006).

In Study GT11502 the rate of TEAEs per infusion in the subcutaneous phase was 0.134 (141 TEAEs over a total of 1053 infusions). TEAEs in Study GTI1502 with a rate of greater than or equal to 0.005 per infusion were sinusitis (10 events, 0.009), infusion site nodule (nine events, 0.009), upper respiratory tract infection (six events, 0.006), infusion site rash (five events, 0.005), and infusion site scab (five events, 0.005).

Local infusion site reactions

All local infusion site reactions

The total number of local infusion site reactions irrespective of TEAE event status in Study GTI1503 was 1250 over 3045 infusions (rate per infusion = 0.411).

The total number of localised infusion site reactions in Study GTI1502 was 390 over 1053 infusions (rate per infusion = 0.370).

Treatment-emergent local infusion site reactions

Local infusion site reactions were only considered to be TEAEs if they met the protocol specified criteria. Local infusion site reactions classified as TEAEs in the subcutaneous phase were reported in 21 subjects (34.4%) in Study GTI1503. The rate of local infusion site reactions per infusion considered to be TEAEs in the subcutaneous phase was 0.029 (87 localised infusion site reactions considered to be TEAEs in 3045 infusions). These were infusion site erythema (26 infusions, 0.009 per infusion), infusion site pruritus (19 infusions, 0.006 per infusion), infusion site swelling (11 infusions, 0.004 per infusion), infusion site induration (six infusions, 0.002 per infusion), infusion site pain (five infusions, 0.002 per infusion), and infusion site mass (three infusions, 0.001 per infusion).

Local infusion site reactions classified as TEAEs in the subcutaneous phase were reported in 16 subjects (32.7%) in Study GT11502. The rate of local infusion site reactions per infusion considered to be TEAEs in the subcutaneous phase was 0.039 in Study GTI1502 (41 localised infusion site reactions considered to be TEAEs in 1053 infusions). These were infusion site nodule (nine infusions, 0.009 per infusion), infusion site rash (five infusions, 0.005 per infusion), infusion site scab (five infusions, 0.005 per infusion), infusion site urticaria (four infusions, 0.004 per infusion), infusion site bruising (three infusions, 0.003 per infusion), and infusion site pain (three infusions, 0.003 per infusion).

Non-treatment-emergent local infusion site reactions

Local infusion site reactions not meeting the protocol specified criteria for classification as a TEAE in the subcutaneous phase were reported in 40 (65.5%) subjects in Study GTI1503 (1163 non-TEAE infusion site reactions) and 27 (55.1%) subjects in Study GTI1502 (349 non-TEAE infusion site reactions). The rate of non-TEAE local infusion site reactions per infusion during the subcutaneous phase was similar in the two studies (0.382 in Study GTI1503 and 0.331 in Study GTI1502).

Adverse drug reactions

In the subcutaneous phase, adverse drug reactions were reported in Study GTI1503 in 19 subjects (31.1%). In Study GTI1503, adverse drug reactions reported in greater than or equal to two subjects were infusion site erythema (nine subjects, 14.8%), infusion site pruritus (eight subjects, 13.1%), infusion site pain (four subjects, 6.6%), infusion site swelling (four subjects, 6.6%), infusion site mass (three subjects, 4.9%), infusion site extravasation (two subjects, 3.3%), infusion site induration (two subjects, 3.3%), and blood immunoglobulin G decreased (two subjects, 3.3%).

In the subcutaneous phase, adverse drug reactions were reported in Study GTI1502 in 14 subjects (28.6%). Adverse drug reactions reported in greater than or equal to two subjects were infusion site nodule (five subjects, 10.2%), infusion site bruising (three subjects, 6.1%), infusion site pain (three subjects, 6.1%), infusion site rash (two subjects, 4.1%), and infusion site scab (two subjects, 4.1%).

Serious adverse events

In Study GT11503 in the subcutaneous phase, there were seven (11.5%) subjects with a total of 7 treatment-emergent serious adverse events, all unrelated to study drug. In Study GT11502 in the subcutaneous phase, there were two (4.1%) subjects with 4 serious adverse events, all unrelated to study drug. There were no deaths reported in either Study GT11503 or GT11502.

Discontinuation due to treatment-emergent adverse events

In Study GT11503, four (6.6%) subjects reported a total of four adverse events which led to withdrawal from the study in subcutaneous phase (one subject each with nephrotic syndrome, anxiety, aortic valve incompetence, and infusion site mass). In injection site mass was related to treatment but others considered unrelated to study drug.

In Study GTI1502, TEAEs leading to withdrawal from the study were reported in four (8.2%) subjects in the subcutaneous phase (one subject with infusion site nodule considered definitely related to the study drug; one subject with infusion site discomfort and intentional medical device removal by patient considered definitely related to the study drug; one subject with arthralgia and myalgia considered possibly related to the study drug; one subject with papule and skin plaque considered not related to the study drug).

Any treatment-emergent adverse event during or within 72 hours of drug infusion

In Study GTI1503, there were 45 (73.8%) subjects with at least one TEAE reported during or within 72 hours of a subcutaneous infusion with subcutaneous immunoglobulin 20%. The rate of TEAEs per infusion in this time frame was 0.76. The most frequently reported local infusion site reactions observed in this time frame reported in greater than or equal to 5% of subjects overall were infusion site erythema (16.4%), infusion site pruritus (13.1%), upper respiratory tract infection (eight subjects, 13.1%), nasopharyngitis (seven subjects, 11.5%), cough (six subjects, 9.8%), bronchitis (five subjects, 8.2%), sinusitis (five subjects, 8.2%), rhinitis (four subjects, 6.6%), infusion site pain (6.6%), infusion site swelling (6.6%) and headache (6.6%).

In Study GTI1502, TEAEs reported during or within 72 hours of an infusion occurred in 35 (71.4%) subjects who experienced a total of 92 TEAEs in this timeframe. The most frequent TEAEs were infusion site nodule (10.2%), infusion site bruising (6.1%), infusion site pain (6.1%), sinusitis (6.1%) and upper respiratory tract infection (6.1%).

Infectious adverse events

Any serious bacterial infection

In Study GTI1503, serious bacterial infections were the primary efficacy endpoint. In this study, serious bacterial infections were reported in one (1.6%) subject in the subcutaneous phase (one event of pneumonia). The mean (SD) annualised rate of serious bacterial infections in the subcutaneous phase was 0.016 (0.1285) and the serious bacterial infection rate per person per year was 0.017 (95% CI: 0.006, 0.036).

In Study GTI1502, serious bacterial infections were safety endpoints. In this study, serious bacterial infections were reported in one (2%) subject in the subcutaneous phase (one event of sepsis). The mean (SD) annualised rate of serious bacterial infections was 0.044 (0.3106) and the serious bacterial infection rate per person per year was 0.049 (95% CI: 0.02, 0.098).

Any infection

In Study GTI1503, infections of any kind were a secondary efficacy endpoint. In this study, 140 infections of any kind were reported in 45 (73.8%) subjects in the subcutaneous phase. Infections of any kind reported in greater than or equal to 5% of subjects were nasopharyngitis (12 subjects, 19.7%), upper respiratory tract infection (nine subjects, 14.8%), bronchitis (eight subjects, 13.1%), sinusitis (seven subjects, 11.5%), gastroenteritis (five subjects, 8.2%), lower respiratory tract infection (five subjects, 8.2%), influenzae (four subjects, 6.6%), urinary tract infection (four subjects, 6.6%), and viral infection (four subjects, 6.6%). In the subcutaneous phase, the mean (SD) annualised rate of infections was 2.327 (2.49) and the infection rate per person per year was 2.397 (95% CI: 1.824, 3.079).

In Study GTI1502, infections of any kind were a safety endpoint. In this study, 48 infections of any kind were reported in 26 (53.1%) subjects in the subcutaneous phase. Infections of any kind reported in greater than or equal to 5% of subjects were sinusitis (nine subjects, 18.4%), upper respiratory tract infection (five subjects, 10.2%), bronchitis (three subjects, 6.1%), and pharyngeal streptococcal (three subjects, 6.1%). In the subcutaneous phase, the mean (SD) annualised rate of infections was 2.571 (3.928) and the infection rate per person per year was 2.367 (95% CI: 1.601, 3.345).

Validated infection

In Study GTI1503, validated infections were efficacy endpoints. In this study, 36 validated infections were reported in 20 (32.8%) subjects in the subcutaneous phase. Validated infections reported in greater than or equal to two subjects were bronchitis (three subjects, 4.9%), pyrexia (three subjects, 4.9%), upper respiratory tract infection (three subjects, 4.9%), gastroenteritis (two subjects, 3.3%), influenza (two subjects, 3.3%), pneumonia (two subjects, 3.3%), and sinusitis (two subjects, 3.3%). In the subcutaneous phase, the mean (SD) annualised rate of validated infections was 0.597 (1.0926) and the validated infection rate per person per year was 0.616 (95% CI: 0.401, 0.898).

In Study GTI1502, validated infections were safety endpoints. In this study, 10 validated infections were reported in eight (16.3%) subjects in the subcutaneous phase. Validated infections reported in greater than or equal to two subjects were cellulitis (two subjects, 2.1%), pharyngeal streptococcal (two subjects, 2.1%), and urinary tract infection (two subjects, 2.1%). In the subcutaneous phase, the mean (SD) annualised rate of validated infections was 0.479 (1.168) and the validated infection rate per person per year was 0.493 (95% CI: 0.273, 0.809).

Laboratory abnormalities

Overall, in both studies there were no significant changes in mean values for haematology or clinical chemistry parameters during the subcutaneous phase, with the number of subjects with laboratory values outside the threshold ranges being small.

In Study GTI1503, there were nine individual laboratory abnormalities reported as TEAEs in six subjects in the subcutaneous phase.

In Study GTI1502, there were six individual laboratory abnormalities reported as TEAEs in two subjects in the subcutaneous phase.

Paediatric safety

The safety profiles of subcutaneous immunoglobulin 20% in both studies in children aged greater than or equal to two years and adolescents were generally comparable with the safety profiles of subjects aged greater than 16 years.

Benefit-risk assessment

The clinical evaluation considered the benefit-risk benefit of Xembify for replacement treatment for subjects aged two years or older with PID has been satisfactorily established in the submitted clinical data. Sustained immunoglobulin G trough levels were obtained in both Studies GT11503 and GT11502.

In Study GTI1503, the primary efficacy endpoint analysis demonstrated that rate of SBIs per person per year was 0.017 (98% CI: 0.006, 0.036). The upper 99% confidence limit for the rate was 0.036, which was less than the recommended standard historical rate of one serious bacterial infection per person per year. In the less than or equal to 16 years age group, the rate of SBI per person per year was 0.037 (98% CI: 0.009, 0.096) and in the greater than 16 years age group, the rate of serious bacterial infection per person per year was zero. These results were consistent with the serious bacterial infection rates reported for Xembify in Study GTI1502.

The major risks associated with Xembify are localised infusion site reactions and infections. In Study GTI1503, 21 (34.4%) subjects experienced a total of 87 local ISRs considered to be TEAEs (0.029 events per infusion; 87 events over 3044 total infusions). No infusion site reactions were reported as serious adverse events and treatment discontinuation due to infusion site reactions was reported in only one (1.6%) subject (infusion site mass).

Forty-four (72.1%) subjects experienced a total of 140 infections (2.397 (95% CI: 1.824, 3.079) events per person per year). Only two (3.3%) subjects experienced infections categorised as SAEs (urinary tract infection and pneumonia, both unrelated to treatment) and no infections resulted in treatment discontinuation. Suspected infection adverse drug reasons were reported in six (9.8%) subjects in Study GTI1503, with rhinitis and sinusitis being the only reactions reported in greater than or equal to two subjects and no infections were reported with investigator's causality assessment of 'definite' (that is, as adverse reactions).

The sponsor has provided a comprehensive and satisfactory response to the TGA questions

The sponsor modified the therapeutic indications wording to align with Delegate recommendations and the Australian PI for Gamunex;⁸ as replacement therapy in:

- Primary immunodeficiency diseases (PID).
- Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

The sponsor justified the initially proposed age range of 0 to 18 years. There were no clinical study data in children with primary immunodeficiency less than two years. The sponsor noted a paucity of published data for subcutaneous immunoglobulin administration in infants and toddlers under two years of age but no safety concerns. The sponsor proposes to include the following statement in Section 4.2 (*Dosage and method of administration*) of the Xembify PI:

‘No clinical trials have been conducted with Xembify in children of age 0 to < 2 years. However, experience with immunoglobulins suggests a safety profile similar to that for children of age 2-18 years and adults with Xembify is to be expected’.

The Delegate accepted this response. The addition of information in the PI relating to dosing for patients switching from other subcutaneous immunoglobulin or intravenous immunoglobulin treatments is considered acceptable. No conversion factor is specified for patients switching from intravenous immunoglobulin to subcutaneous immunoglobulin treatment, which was adequately justified.

Following evaluation of the sponsor’s responses to the clinical questions, the assessment of the benefit-risk balance for Xembify by subcutaneous administration remains acceptable as replacement therapy in adult and paediatric patients for primary immunodeficiency diseases and for symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

Risk management plan

The sponsor has submitted European Union (EU) risk management plan (RMP) version 2.0 (24 November 2020; data lock point (DLP) 31 May 2020) and Australia specific annex (ASA) version 1.0 (24 November 2020) in support of this application. Subsequently, the sponsor has submitted ASA version 2.0 (13 December 2021) at second round of RMP evaluation.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 9. Further information regarding the TGA’s risk management approach can be found in [risk management plans for medicines and biologicals](#) and [the TGA's risk management approach](#).

Table 9: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infusion site reactions	✓	-	✓	-
	Hypersensitivity reactions including anaphylactic reactions*	✓	-	✓	-
	Thromboembolic events*	✓	-	✓	-
	Aseptic meningitis*	✓	-	✓	-
	Haemolysis/haemolytic anaemia*	✓	-	✓	-
	Interference with serological testing*	✓	-	✓	-
Important potential risks	Hypersensitivity reactions including anaphylactic reactions†	✓	-	✓	-
	Thromboembolic events†	✓	-	✓	-
	Aseptic meningitis†	✓	-	✓	-
	Theoretical risk of pathogen infection	✓	-	✓	-
	Interaction with live attenuated vaccines	✓	-	✓	-
	Medication errors arising from self-administration	✓	-	✓	-
	Transfusion related acute lung injury (TRALI)*	✓	-	✓	-
Missing information	Use in women who are pregnant or lactating	✓	-	✓	-
	Use in neonates and infants <2 years*	✓	-	✓	-
	Use in patients >65 years*	✓	-	✓	-
	Use in patients with renal or hepatic impairment*	✓	-	✓	-

*ASA only

†EU-RMP only

The sponsor has amended the safety specification as requested by the RMP evaluator. The summary of safety concerns listed in the ASA is now acceptable.

The sponsor has proposed routine pharmacovigilance activities only for all safety concerns which is acceptable.

The sponsor has proposed routine risk minimisation activities only for the safety concerns which consist of the PI and consumer medicine information (CMI). The sponsor has committed to including the CMI, which includes instructions for use, in the packaging of the product. This is acceptable.

Risk-benefit analysis

Delegate's considerations

There are no nonclinical objections to registration.

The pharmacometrics working group considered this submission. The working group did not express any major concerns in relation to PK modelling and simulation analyses by the sponsor. The working group is of the opinion that the analyses support the proposed dosing recommendations.

The working group requested the sponsor to address a number of questions. The Delegate considers the sponsor responses to these questions as being satisfactory.

There are no outstanding RMP evaluation issues.

Proposed action

The Delegate considers the benefit-risk balance for Xembify by subcutaneous administration remains acceptable as replacement therapy in adult and paediatric patients for primary immunodeficiency diseases and for symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

Advisory Committee considerations

The Delegate did not refer this submission to the [Advisory Committee on Medicines \(ACM\)](#) for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Xembify (normal immunoglobulin (human)) 2 g/10 mL (20%), 4 g/20 mL (20%), 1 g/5 mL (20%) and 10 g/50 mL (20%) solution for subcutaneous injection indicated for:

Replacement therapy in adult and paediatric patients for:

- *Primary immunodeficiency diseases (PID)*
- *Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.*

Specific conditions of registration applying to these goods

- Xembify (human normal immunoglobulin) is to be included in the Black Triangle Scheme. The PI and CMI for Xembify must include the black triangle symbol and

mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

- The Xembify EU-RMP (version 2.0, dated 24 November 2020, data lock point 31 May 2020), with ASA (version 2.0, dated 13 December 2021), included with submission PM-2020-06238-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Batch Release Testing & Compliance with Certified Product Details (CPD)

- All batches of Xembify normal immunoglobulin (Human) 20% solution for subcutaneous injection supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results <http://www.tga.gov.au/ws-labs-index> and periodically in testing reports on the TGA website.

Attachment 1. Product Information

The PI for Xembify approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA [PI/CMI search facility](#).

Therapeutic Goods Administration

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