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Proposed indication(s): Treatment of Primary Immunodeficiency Disease

Applicant: Grifols

Product: XEMBIFY®, Immune Globulin Subcutaneous (Human) (IGSC),
20%

Subject: Preclinical Pharm-Tox Review

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Brief Description

This BLA seeks approval for XEMBIFY®, a liquid formulation of 20% human Immune Globulin for subcutaneous administration (IGSC 20%) for Primary Immunodeficiency in patients 2 years of age or older. XEMBIFY is meant to be administered at regular intervals, from daily to every 2 weeks at doses that are individualized based on prior IGIV dosing and the desired dosing regimen. Based on the formula, a potential weekly high dose would be $1.37 \times 800 \text{ g/kg} \div 3 = 365 \text{ mg/kg}$ or a nominal dose volume 1.83 mL/kg ; the highest dose administered during the clinical trial was 276 mg/kg .

XEMBIFY is formulated with glycine and polysorbate 80 (PS80), at pH 4.1–4.8; its ingredients and final specification ranges are shown in Table 1.

Table 1: Composition of XEMBIFY®

Component	Function	Dosage
Human Immunoglobulin	Active Ingredient	18 to 22%
Glycine	Excipient	0.16 to 0.26 mM
Polysorbate 80	Excipient	10 to 40 $\mu\text{g/mL}$

The nonclinical package to support approval for XEMBIFY included single (PRD-14-125) and repeat dose (PRD-14-126) pharmacokinetic studies, single (PRD-14-119) and repeat dose (PRD-12-120) safety and local tolerance studies, and a local tolerance study following improper route of administration (PRD-14-124) in New Zealand White rabbits.

Main Findings

The toxicities observed in the single and repeated dose studies were consistent with hemolysis and local site and systemic inflammation related to self- *versus* foreign- immune reactions. These toxicities are expected in animals receiving human IG preparations and are not predictive of human reactions.

Local injection site swelling was observed in XEMBIFY but not in the comparator (Gamunex-C) groups following single and repeated dosing. The sign was correlated with findings of subcutaneous and cutaneous inflammation upon microscopic examination. The findings were of higher severity in the XEMBIFY groups compared to Gamunex-C due to higher total protein administered in one single site. The local irritation following improper administration of XEMBIFY and Gamunex-C comparator was of similar incidence and severity.

The formulation of XEMBIFY does not raise toxicologic concerns.

Conclusion

There are no animal pharmacology and toxicology issues that would prevent this application from being approved.

Complete Review

Pharmacokinetics

Study Number: PRD-14-125

Title: A Single Dose Subcutaneous Injection Pharmacokinetics Study of IGSC 20% in the New Zealand White Rabbit

Performing laboratory: (b) (4)

Final Report Issue Date: 23 February 2015; study initiated 23 September 2014

Aim: A GLP study to determine the pharmacokinetic properties of IGSC 20% when administered by a single subcutaneous (SC) injection to New Zealand White rabbits; one IV injection of Gamunex-C (IVIG-C 10%) was used as a comparator.

Study design: n=5 male rabbits/group aged 4-5 months old and weighing between 2.4 to 3.3 kg received one of the five test articles shown in Table 2 either IV in auricular vein or SC in interscapular area.

Outcome measures: Animals were observed for signs of toxicity through daily cageside observations and weekly clinical assessments, weekly body weight and food consumption assessments, clinical pathology parameters (hematology, coagulation, clinical chemistry) on day 10 and urinalysis on day 11, organ weights at necropsy (day 11); pharmacokinetic samples were collected at time 0, 1 min, 4 hr, 8 hr, and daily from Day 2-11, plasma human IgG concentration was measured using a validated nephelometry method and PK parameters were determined using (b) (4) PK software.

ANOVA with post-hoc pairwise comparisons was used to assess the differences between the experimental groups.

Table 2. Experimental Design, Study PRD-14-125

Group No.	Test Material	Route of Administration	Dose Level (mg/kg)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Male Nos.
1	Gamunex	IV	100	1.0	100	1001-1005
2	IGSC 20%	SC	100	0.5	200	2001-2005
3	IGSC 20%	SC	115	0.575		3001-3005
4	IGSC 20%	SC	130	0.65		4001-4005
5	IGSC 20%	SC	150	0.75		5001-5005

Results: There was no difference between the test article and the Gamunex-C comparator in all the toxicologic outcome measures assessed.

A summary of the PK parameters and fractional plasma availability (Fp) is shown in Table 3. The exposure (AUC) to human IgG after SC administration increased proportionally with dose. There was no difference in AUC between one single IV dose of 100 mg/kg Gamunex-C and either 130 or 150 mg/kg SC XEMBIFY dose, whereas single SC 100 and 115 mg/kg doses resulted in AUC that were statistically different from the IV control ($p < 0.05$, analysis performed by this reviewer, using (b) (4) software). However, the SD for AUC was significantly different between the groups.

Table 3. Summary Mean (\pm SD) Total Human IgG Pharmacokinetic Parameters, Study PRD-14-125

Dose (mg/kg)	Route	T _{max} ^a (hr)	C _{max} (g/L)	AUC _(0-t) (g•hr/L)	T _{1/2} (hr)	Fp ^b (%)
100	IV	0.0170 (0.0170 - 4.00)	3.00 ± 0.499	254 ± 15.1	90.0 ± ID	N/A
100	SC	96.0 (72.0 - 96.0)	1.01 ± 0.236	187 ± 46.1	NC	74
115	SC	72.0 (72.0 - 96.0)	1.14 ± 0.0733	202 ± 5.85	79.2 ± ID	80
130	SC	72.0 (72.0 - 120)	1.24 ± 0.0791	226 ± 16.5	76.2 ± ID	89
150	SC	96.0 (72.0 - 96.0)	1.35 ± 0.0598	241 ± 6.73	NC	95

^a Median (Min - Max)

^b Fp = (IGSC 20 % AUC_(0-t) / IVIG-C 10% AUC_(0-t)) x 100

NC = Not Calculated

ID = Insufficient Data

N/A = Not Applicable

Study Number: PRD-14-126

Title: A 4-Day Repeat Dose Subcutaneous Injection Pharmacokinetics Study of IGSC 20% in the New Zealand White Rabbit

Performing laboratory: (b) (4)

Final Report Issue Date: 23 February 2015; study initiated on 16 September 2014

Aim: A GLP study to determine the pharmacokinetic properties of IGSC 20% when administered by repeated subcutaneous (SC) administrations to New Zealand White rabbits; one IV injection of Gamunex-C was used as a comparator.

Study design: n=5 male rabbits/group aged 5 months old and weighing between 2.4 to 3.1 kg received either a single dose of 400 mg/kg Gamunex-C IV in a marginal ear vein or four daily doses of 100, 115, 130 and 150 mg/kg SC, respectively in different injection sites in the back of the animal (Table 4).

Outcome measures: Animals were observed for signs of toxicity through daily cageside observations and weekly clinical assessments, weekly body weight and food consumption assessments, clinical pathology parameters (hematology, coagulation, clinical chemistry) on day 14 and urinalysis on day 15, necropsy; pharmacokinetic samples were collected at appropriate time-points up to day 15, plasma human IgG concentration was measured using a validated nephelometry method and PK parameters were determined using (b) (4) PK software. ANOVA with post-hoc pairwise comparisons as appropriate was used to assess the differences between the experimental groups.

Table 4. Experimental Design, Study PRD-14126

Group No.	Test Material	Route of Administration	Dose Level (mg/kg/day)	Dose Volume (mL/kg/day)	Dose Conc. (mg/mL)	Total No. of Doses	No. of Males
1	IGIV-C	IV	400*	4.0	100	1	5
2	IGSC 20%	SC	100**	0.5		4	5

3	IGSC 20%	SC	115**	0.575	200	4	5
4	IGSC 20%	SC	130**	0.65		4	5
5	IGSC 20%	SC	150**	0.75		4	5

IV: Intravenous injection; SC: Subcutaneous injection

*Single injection on Day 1

**Daily injections Days 1-4

Results: There were no test article related toxicities observed.

A summary of the PK parameters and fractional plasma availability (Fp) is shown in Table 5. The exposure (AUC) to human IgG after repeated SC administration increased proportionally with dose. There was no difference in AUC between one single IV dose of 400 mg/kg Gamunex-C and four 130 or 150 mg/kg SC XEMBIFY doses, whereas four repeated SC 100 and 115 mg/kg doses resulted in AUC that were statistically different from the IV control ($p < 0.05$, analysis performed by this reviewer using (b) (4) software).

Table 5. Summary Mean (\pm SD) Total Human IgG Pharmacokinetic Parameters, Study PRD-14-126

Material	Day	Route	Dose (mg/kg)	T _{max} ^a (hr)	C _{max} (g/L)	AUC ₍₀₋₂₆₄₎ (g•hr/L)	AUC ₍₀₋₃₃₆₎ (g•hr/L)	AUC _(0-inf) (g•hr/L)	T _{1/2} (hr)	Fp ^b (%)
IVIG-C 10%	1	IV	400	0.02 (0.02 - 0.02)	11.4 \pm 0.841	1010 \pm 120	1140 \pm 157	964 \pm ID	75.9 \pm ID	N/A
IGSC 20%	4	SC	100	48.0 (48.0 - 72.0)	3.52 \pm 0.396	656 \pm 94.9	N/A	559 \pm ID	21.3 \pm ID	65
IGSC 20%	4	SC	115	48.0 (48.0 - 48.0)	4.01 \pm 0.307	792 \pm 68.3	N/A	NC	NC	78
IGSC 20%	4	SC	130	48.0 (48.0 - 96.0)	4.38 \pm 0.362	897 \pm 70.1	N/A	NC	NC	89
IGSC 20%	4	SC	150	48.0 (48.0 - 72.0)	4.64 \pm 0.448	935 \pm 135	N/A	NC	NC	93

^a Median (Min - Max)

^b Fp = (IGSC 20 % AUC₍₀₋₂₆₄₎ / IVIG-C 10% AUC₍₀₋₂₆₄₎) x 100

ID = Insufficient Data

NC = Not Calculated

N/A = Not Applicable

Toxicology

Study Number: PRD-14-119

Title: A Single Dose Subcutaneous Injection Toxicity and Local Tolerance Study of IGSC 20% in the New Zealand White Rabbit with a 14 Day Recovery Period

Performing Laboratory: (b) (4)

Date: 24 Feb 2015, study initiation 19 Aug 2014

Aim: To assess systemic toxicity and local tolerance of IGSC 20% when administered as a single subcutaneous injection to male New Zealand White rabbits with observation to 14 days.

Study Design: In this GLP study, 5-10 male New Zealand rabbits/group aged 4-5 months old and weighing 2.1 - 2.8 kg received 500, 1000 or 1500 mg/kg XEMBIFY or 1500 mg/kg Gamunex-C by SC administration to the right scapular and mid-dorsal areas; same volume of normal saline was administered to the left side. Gamunex-C was administered in two boluses, one on each side. 5 animals/group were sacrificed on day 3, and 5 remaining animals/high dose and control groups on day 15 (recovery animals). Groups and administration details are shown in table 6.

Table 6. Study PRD 14-119

Experimental Design

Group No.	Test Material	Dose Level (mg/kg)	Dose Volume (mL/kg)	No. of Animals (Males)	
				Main	Recovery
1	IVIG-C 10%	1500	15	5	5
2	IGSC 20%/Saline	500	2.5	5	-
3	IGSC 20%/Saline	1000	5	5	-
4	IGSC 20%/Saline	1500	7.5	5	5

Outcome measures:

Cage-side observations daily; weekly detailed clinical observations, body weight and food consumption; hematology, coagulation and clinical chemistry on day 3 and 15 (recovery animals), urinalysis on day 15. Upon necropsy organs were collected, weighed and sites of gross lesions and injection sites were assessed histopathologically.

Results:

Increases in the number of neutrophils (dose-dependent) and monocytes (middle dose and Gamunex groups) and increased fibrinogen levels; these changes are likely related to subcutaneous and/or skin hemorrhage and swelling/mixed cell inflammation at injection sites. Decreases in lymphocyte and red blood cell parameters were seen in the reference, mid and high dose groups; these were associated with increases in reticulocyte counts, indicating recovery. Increases in creatine kinase activity were observed in the mid and high dose test item suggestive of muscular damage. These changes were mild.

Mild to moderate increases in total bilirubin were observed in all groups; although no reason was given for the change, it is likely due to RBC hemolysis and hemoglobin metabolism.

Subcutaneous swelling was seen at some injection sites for XEMBIFY, but not the saline or Gamunex injection sites. Minimal to mild subcutaneous and/or dermal mixed cell inflammation and hemorrhage at the injection site was seen in all the groups. The severity was higher for XEMBIFY compared to Gamunex.

Changes in urinalysis at the end of the recovery period included red urine in 2/5 animal per recovery group. Changes are consistent with hemolysis.

Recovery or improvement in most, but not all parameters was seen on day 15 consistent with long half-life of XEMBIFY in this species. A new finding in recovery animals - minimal subcutaneous chronic inflammation with fibrosis – was seen in both XEMBIFY and Gamunex and it is likely related to immune reaction to the administered foreign protein.

Conclusion: The toxicities observed in the study, mainly hemolysis and local site and systemic immune response are expected effects of human IgG preparations. Hemolysis seen is a species-related effect due to anti- α -galactosyl (α -gal) antibodies present in these products and their recognition of terminal α -gal epitope present in rabbit RBCs. Although hemolysis is a recognized adverse effect in patients, the etiology of the sign in the clinic is different from what is seen in this species, because human cells do not contain α -gal glycans. (Note: the major glycolipids in rabbit RBCs have terminal α -gal glycans [1].)

Study Number PRD-15-120

Title: A 5-Day Repeat Dose Subcutaneous Injection Toxicity and Local Tolerance Study of IGSC 20% in New Zealand White Rabbit with a 14-Day Recovery Period

Performing Laboratory: (b) (4)

Date: 25 Feb 2015, study initiation 25 Aug 2014

Aim: To assess the potential toxicity and local tolerance of IGSC 20% when administered by subcutaneous injection to New Zealand White rabbits for 5 consecutive days and to evaluate the potential reversibility of any findings 14-days post last dose.

Study Design: In this GLP study, XEMBIFY was administered as 5 consecutive once daily subcutaneous injections in the dorsal (right) area at dose levels of 500, 1000, and 1500 mg/kg in 5 rabbits/group; 5 additional rabbits in the high dose group were used to assess recovery. 1500 mg/kg Gamunex-C was used as the control and administered SC. Animals receiving test item also received a subcutaneous injection of 0.9% sodium chloride on the contralateral side (left), at the same dose volume as used for the test item. Main study and recovery animals were necropsied on Day 7 and 19, respectively.

The study design is shown in table 7.

Table 7. Study PRD 14-120

Experimental Design

Group No.	No. of Males Toxicity (Recovery)	Test Material	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)
1	5 (5)	IVIG-C 10%	1500	100	15
2	5	IGSC 20%	500	200	2.5
3	5	IGSC 20%	1000	200	5
4	5 (5)	IGSC 20%	1500	200	7.5

Outcome measures: Cage-side observations daily; weekly detailed clinical observations, body weight and food consumption; hematology, coagulation and clinical chemistry on day 3 and 15 (recovery animals), urinalysis on day 15. Upon necropsy organs were collected, weighed and sites of gross lesions and injection sites were assessed histopathologically.

Results:

There was mortality in the high dose XEMBIFY and Gamunex-C groups: 5/10 animals receiving the highest dose of XEMBIFY and 7/10 in the Gamunex group died or had to be euthanized for animal welfare reasons within 24 hours of the final dose (days 5 and 6). The animals show signs consistent with immune mediated hemolytic anemia. All animals in these groups had decreased food consumption, clinical pathology, gross and histopathological changes. These changes were similar in incidence and severity between the high dose test and reference item groups thus not considered relevant to humans.

There was no mortality in the low and mid dose XEMBIFY groups.

There were dose related changes in WBC (increase), lymphocytes (decrease), RBC parameters (marked decrease), reticulocyte (increase), increase or decrease in platelets. All these changes are consistent with inflammation and immune mediated hemolysis. Several clinical pathology changes were observed, including increased aspartate aminotransferase (AST) and related transferases, suggestive of hepatocellular and muscular damage due to injection damage and hypoxemia and correlated with histological findings of hepatic centrilobular necrosis observed prematurely terminated animals from both the reference and high dose test item groups. Marked increases in total bilirubin concentrations in both groups of preterminal animals were consistent

with hemolytic hyperbilirubinemia and were associated with moderate bilirubinuria. Decreases in albumin were observed in all animals, possibly related to IgG saturation of albumin rescue receptors (FcRn [2], this reviewer’s conclusion), or inflammation (study pathologist’s conclusion).

Test item-related gross findings included subcutaneous swelling noted at some injection sites which correlated with microscopic findings of minimal to moderate mixed cell inflammation. Swelling was not observed at either the saline or Gamunex injection sites. Microscopically, mild to moderate subcutaneous/cutaneous inflammation at the injection sites was observed in the Gammunex and all XEMBIFY groups; severity was higher in the XEMBIFY groups.

After a 14-day recovery period, partial to complete recovery was observed for the majority of the clinical pathology changes in both the high dose test and reference item groups. Microscopically, the only changes that persisted in both the test and reference item recovery groups were the subcutaneous/cutaneous changes at the injection sites of similar severity between the XEMBIFY and Gamunex groups.

Study Number PRD-14-124

Title: Toxicity and Local Tolerance Following a Single Dose of IGSC 20% Administered By an Improper Route in the New Zealand White Rabbit

Performing Laboratory: (b) (4)

Date: 23 Feb 2015, study initiation 24 Sep 2014

Aim: To determine the potential toxicity and local tolerance of XEMBIFY when administered by improper routes to New Zealand White rabbits

Study Design: In this GLP study, either XEMBIFY or Gamunex-C were administered as a single dose of 100 mg/mL via three improper routes to randomly assigned n=5 male rabbits/group aged 5 months old and weighing 2.4-3.2 kg (Table 8). The sites of administration were: IV via the auricular vein, intra-arterial (IA) via the auricular artery, and perivascular (PV, under anesthesia) in the space between the auricular vein and artery. Animals were monitored for 3 days then terminated.

Table 8. Experimental Design, Study PRD-14-124

Group No.	Test Material	Route	Dose Level (mg/kg)	Dose Volume (mL/kg)	No. of Animals (Males)
					Main
1	IVIG-C 10%	Intravenous injection	100	1	5
2	IVIG-C 10%	Intra-arterial injection	100	1	5
3	IVIG-C 10%	Perivascular injection	100	1	5
4	IGSC 20%	Intravenous injection	100	0.5	5
5	IGSC 20%	Intra-arterial injection	100	0.5	5
6	IGSC 20%	Perivascular injection	100	0.5	5

Outcome measures: clinical signs, body weight, food consumption, clinical pathology parameters at termination (hematology, coagulation, clinical chemistry), gross necropsy findings, organ weights, and histopathologic examinations of injection sites and any gross lesions seen at necropsy.

Results: Discoloration and scabbing of the skin adjacent to the site of administration was seen in all dose groups with, higher incidence in groups receiving XEMBIFY or Gamunex-C by PV route. Edema was also seen in PV dose groups receiving both test and reference items.

Formulation and impurities

XEMBIFY excipients are glycine and Polysorbate 80 at concentrations shown in Table 9. These compounds are present in other IG products at similar levels. There are no expected toxicities from the formulation and impurity profile of XEMBIFY.

Table 9. The composition of XEMBIFY

Component	Highest Concentration	Highest Administered Weekly Dose*	IG Products with Same Excipients
Human Immunoglobulin Proteins	18 to 22%	(b) (4)	
Glycine	NMT 0.26 M	(b) (4)	Gammaflex, Gamunex
Polysorbate 80	NMT 40 µg/mL	(b) (4)	Gammaflex, Cuvitru

*Calculated using the weekly dose volume (b) (4) mL/kg

References

1. Galili U: **Discovery of the natural anti-Gal antibody and its past and future relevance to medicine.** *Xenotransplantation* 2013, **20**:138-147.
2. Pyzik M, Rath T, Kuo TT, Win S, Baker K, Hubbard JJ, Grenha R, Gandhi A, Kramer TD, Mezo AR, et al: **Hepatic FcRn regulates albumin homeostasis and susceptibility to liver injury.** *Proc Natl Acad Sci U S A* 2017, **114**:E2862-E2871.