Summary Basis for Regulatory Action Template

Date: November 9, 2015

From: Victor C. Baum, M.D., Clinical Reviewer

BLA/ STN#: 125046/1325

Applicant Name: Grifols Therapeutics, Inc.

Date of Submission: February 4, 2015

PDUFA Goal Date: December 5, 2015

Proprietary Name/ Established Name: Gamunex®-C, Gammaked™ / Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified

Indication: Primary Humeral Immunodeficiency (PI) in patients two years of age and older

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority:
Paul Mintz, M.D., Director
Division of Hematology Clinical Review, Office of Blood Research and Review

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Material Reviewed/ Consulted Reviewer Name – Document(s) Date	**Specific documentation used in developing the SBRA**
Clinical Review	Victor C. Baum, M.D.
Clinical Pharmacology Review	Iftekhar Mahmood, Ph.D.
Statistical Review	N/A
CMC Review	N/A
Pharmacology/ Toxicology Review	N/A
Bioresearch Monitoring Review	Bioresearch monitoring inspections were not conducted for this BLA efficacy supplement
Establishment Inspection Report	N/A
Advisory Committee Transcript	N/A
Other	Package Insert

1. Introduction

On February 4, 2015, Grifols Therapeutics Inc. (hereafter Grifols) submitted an efficacy supplement to Biologics License Application STN 125046/1325 for Gamunex-C, Gammaked, Immune Globulin Intravenous (Human), 5% Liquid administered subcutaneously, to include revisions to the package insert that reflect the primary immune deficient pediatric population evaluated in postmarketing requirement study (PMR) T5004-401 in accordance with Section 505B(d)(1) of the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

Gamunex-C was licensed for subcutaneous (SC) use in the United States on October 13, 2010 for the indication of treatment of primary humoral immunodeficiency (PI). At the time of approval, the PMR for subjects 0 to <2 years of age was waived and for subjects ≥2 to 16 years of age was deferred. The deferred pediatric PMR under PREA, required under 505B(a) of the Federal Food, Drug, and Cosmetic Act, is the subject of this submission.

T5004-401 was a phase 4, multi-center, open-label, single-sequence, crossover clinical trial to evaluate the pharmacokinetics (PK), safety, and tolerability of SC-administered Gamunex-C in pediatric PI subjects ages 2 to 16 years. The trial was conducted to determine if weekly SC administration of Gamunex-C, at a dose 1.37 times the prior intravenous (IV) dose would provide a steady-state area under the curve (AUC), and mean trough levels of plasma total immunoglobulin (IgG) level that is non-inferior to that provided by the subject's previous IV infusion regimen (every 3 or 4 weeks).

The results of the clinical trial indicate that weekly SC administration of Gamunex-C at a dose 1.37 times the IV dose provides comparable mean total IgG serum concentrations in subjects 2-16 years old as demonstrated by steady-state AUC values (the mean of the ratios of SC AUC vs. IV
AUC was 1.05±0.10446). The steady-state trough serum concentration of total IgG (1325 mg/dL) was relatively constant, and averaged 31% higher than the steady-state trough concentration of total IgG after IV administration of Gamunex-C (997 mg/dL).

There were no deaths in the trial or serious adverse events (SAE) related to the drug. An impact of subjects' gender and race could not be established due to the limited sample size.

The revised final label is acceptable, and approval of the efficacy supplement is recommended.

2. Background

PI is a spectrum of intrinsic defects in humoral and cellular immune function that can cause aberrations in immune globulins (IG), rendering subjects more susceptible to infections. IG replacement therapy has been the standard treatment for PI since the early 1950s.

Gamunex-C, initially approved for PI in the United States in 2003, is approved for idiopathic thrombocytopenic purpura, and chronic inflammatory demyelinating polyneuropathy.

The proposed pediatric PMR and the recommendations made by the Division of Hematology Clinical Review (DHCR) were reviewed by the Pediatric Review Committee (PeRC) on March 10, 2010. The PeRC agreed with DHCR's recommendations. Pediatric studies in ages two years and younger were waived.

- On June 18, 2013, Grifols submitted a request to terminate enrollment due to the difficulty in enrolling pediatric subjects in the 2-5 year old range. In an August 1, 2013 telephone conference, FDA agreed to plans for termination of further enrollment in that age group.
- On November 12, 2013, Grifols requested a deferral extension to the commitment date for trial completion and final report submission. FDA granted the deferral extension. The trial completion date was changed from August 13, 2013 to January 13, 2014 and the final report submission date from February 13, 2014 to June 30, 2014. FDA indicated that 10 pediatric subjects, along with supplemental safety data from the literature would suffice for fulfillment of the PMR.
- The last patient / last visit occurred on October 30, 2013, the database was locked on January 6, 2014, meeting the commitment date of January 13, 2014. The clinical study report was submitted on the commitment date of June 30, 2014.

3. Chemistry Manufacturing and Controls (CMC)

Gamunex- C is a ready-to-use sterile, non-pyrogenic solution of human IG protein for IV and SC (PI indication only) administration.

No additional CMC data were submitted in this efficacy supplement.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology data submitted in this efficacy supplement.

5. Clinical Pharmacology

Trial T54004-401was a multi-center, open-label, single-sequence, crossover trial, to evaluate the PK, safety and tolerability of SC-administered Gamunex-C in children 2-16 years of age with PI. A total of 14 subjects during the IV phase, and 10 subjects during the SC phase were included in the PK analysis for total IgG. There was 1 subject in the 2-5 years of age group, 5 subjects in the 6-11 years of age group, and 8 subjects in the 12-16 years of age group.

The Gamunex-C IV dose (200-600 mg/kg per infusion) and dosing interval (every 3-4 weeks) used for each subject was based on each subject's previous IgG treatment regimen, and the investigator's best clinical judgment. All subjects switched to the SC Phase upon completion of the IV Phase; approximately one week (7 to 10 days) after the IV #2 visit. Dosing in the SC Phase continued for 12 weeks. To adjust for bioavailability, the SC dose was 1.37 times the IV dose.

During the SC phase, SC Gamunex-C was administered weekly. For subjects on an every-4-week IV dosing - 1/4 of the IV dose was multiplied by 1.37, and for subjects on an every-3-week IV dosing - 1/3 of the IV dose was multiplied by 1.37.

For the PK analysis, blood samples were taken prior to infusion, 1 hour, 2 days, 7 days, and 21 or 28 days post infusion. Steady-state AUC for SC-administered Gamunex-C was determined by collection of three serial blood samples for total serum IgG concentration obtained at pre-infusion (trough), and at weeks 5, 9, and 12. The PK parameters of Gamunex-C following IV administration are shown in Table 1. In Table 2, a comparison between $AUC_{(0\text{-}tau)}$ and $AUC_{(0\text{-}7)}$ following SC and IV administration of Gamunex-C is shown. The results and conclusions of the study are as follows:

- The study indicates that the PK of Gamunex-C is comparable between adults and children 6 years and older. No conclusion can be drawn for children 2-5 years of age due to small sample size (n =1) (Table 1).
- Weekly SC administration of Gamunex-C in pediatric subjects resulted in relatively constant steady-state trough serum concentration of total IgG (1325 mg/dL), which averaged 31% higher than the steady-state trough concentration of total IgG (997 mg/dL) after IV administration of Gamunex-C.
- The AUC ratio of IV and SC administration is similar across 2-16 years of age (Table 2).

Table 1: PK parameters following IV administration of Gamunex-C by age

Age Category	Statistics	$t_{1/2}$ (hr)	AUC(0-t) (hr*mg/mL)	AUC(0-tau) (hr*mg/mL)	CL(0-t) (mL/hr/kg)	Vss (mL/kg)
2 – 5 years	N	1	1	1	1	1
	Mean	1038.50	7479.0	7499.0	0.05430	82.040
	SD	N/A	N/A	N/A	N/A	N/A
6 – 11 years	N	5	5	5	5	5
	Mean	758.52	5953.6	6052.6	0.09128	94.784
	SD	137.989	1573.84	1333.59	0.027465	17.6773
12 – 16 years	N	8	8	8	8	8
	Mean	717.90	8131.9	8009.5	0.07029	73.303
	SD	170.141	1173.38	1358.76	0.015912	17.2204
≥ 17 years	N	29	29	29	29	29
	Mean	720.62	7564.9	7524.8	0.06243	65.494
	SD	130.864	1190.68	1183.05	0.015547	18.7172

SD = standard deviation; N/A = not applicable.

Table 2: Summary of AUC of serum total IgG at steady state following IV or SC administration

Route of Administration	IV (N = 11)			SC (N = 10)	AUC Ratio, SC/IV
Statistics	$AUC_{0-\tau,IV}$ (h*mg/dL) (0-21 days)	$AUC_{0-\tau,IV}$ (h*mg/dL) (0-28 days)	Adj._$AUC_{0-\tau,IV}$[a] (h*mg/dL) (0-7 days)	$AUC_{0-\tau,SC}$ (mg*h/mL) (0-7 days)	
All Subjects (N)	9	2	11	10	10
Mean	661851.9	800112.0	216873.7	230830.0	1.05
%CV	22%	9%	21%	17%	-
Range	486832.0 – 875356.0	749868.0 - 850356.0	162277.0 - 291785.0	187577.0 - 303913.0	0.86 – 1.21
Age Group: 2-5 years (N)		1	1	1	1
Mean	NC	749868.0	187467.0	202298.0	1.08
%CV	NC	NC	NC	NC	-
Range	NC	NC	NC	NC	NC
Age Group: 6-11 years (N)	5		5	4	4
Mean	605265.4	NC	201755.0	238921.3	1.14
%CV	22	NC	22	19	-
Range	486832.0 - 830830.0	NC	162277.0 - 276943.0	197074.0 - 303913.0	1.10 - 1.21
Age Group: 12-16 years (N)	4	1	5	5	5
Mean	732585.0	850356.0	237873.8	230063.4	0.98
%CV	20	NC	19	17	-
Range	527066.0 - 875356.0	NC	175689.0 - 291785.0	187577.0 - 267197.0	0.86 - 1.07

[a] Adj._ $AUC_{0-\tau,IV}$: Adjusted weekly IV $AUC_{(0-7\ days)}$ is calculated as $AUC_{(0-21\ days)}/3$ or $AUC_{(0-28\ days)}/4$.

CV = coefficient of variance, NC = not calculated

Source: Post-text Table 14.2.1/2

6. Clinical/ Statistical

a) Clinical Program

"An Open-label, Single-sequence, Crossover Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Subcutaneous Gamunex-C in Pediatric Subjects with Primary Immunodeficiency", a phase 4 trial, included a PK evaluation in both the children (2 to 11 years of age), and adolescent (12 to 16 years of age) age groups. Twelve subjects entered the trial and 10 completed the trial (1 subject 2-5 years of age, 5 subjects 6 to 11 years of age and 6 subjects 12 to 15 years of age) in 5 investigational centers in the United States. There were seven males and five females, and all were Caucasian. The limited number of subjects precludes meaningful subpopulation analysis.

Subjects were administered Gamunex-C at the same IV dose that they had previously been maintained on of either Gamunex-C or another IGIV, and at the same 21 or 28 day interval. The trial consisted of three phases:

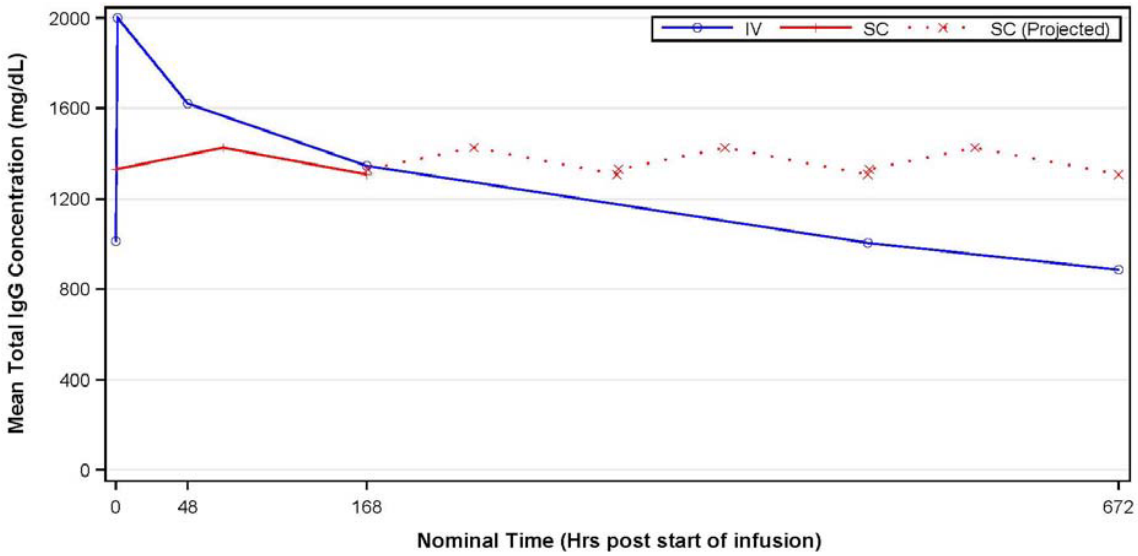
- Run-in phase (3 to 4 months): For subjects receiving stable (≥3 months) dose of IGIV other than Gamunex-C with dose between 200-600 mg/kg every 3 or 4 weeks, IV Gamunex-C was administered at 200-600 mg/kg body weight
- IV phase (4 to 5 weeks): IV administration of Gamunex-C, 200-600 mg/kg body weight
- SC phase (12 weeks): Weekly SC administration of Gamunex-C

- For subjects who had been on an every-4-week IV dosing - 1/4 of the current IV dose was multiplied by 1.37
- For subjects who had been on an every-3-week IV dosing - 1/3 of the current IV dose was multiplied by 1.37

There were two PK primary endpoints. They were the equivalence in steady-state AUC for serum total IgG and mean trough serum total IgG for SC versus IV modes of administration. The results of the AUC analysis are shown in Table 2 and indicate that the AUC ratio of IV and SC administration is similar across subjects 2-16 years of age(ratio SC:IV range 0.86 to 1.21, mean 1.05 for all subjects).

Mean steady state plasma total IgG concentration vs. time curves following IV administration or weekly SC administration in adults and adolescents is shown in Figure 1. Figure 1 shows a steady mean trough level after SC administration) Gamunex-C would be re-administered at day 8).

Figure 1. Mean Steady State Plasma IgG Concentrations



Source: Study Report Body Figure 11-1, p 53 of 93

Table 2 and Figure 1 fulfill the efficacy requirements for non-inferiority of AUC and mean steady state plasma concentrations for SC versus IV routes of administration.

b) Pediatrics

The pediatric assessment in this submission and the associated labeling changes were presented to the PREA Subcommittee [Pediatric Review Committee (PeRC)] on October 7, 2015. The PeRC agreed with DHCR's recommendation that the PMR for PREA deferral has

been fulfilled by the current efficacy supplement, and found the pediatric population adequately addressed in the proposed language of the package insert.

c. Other Special Populations

This trial was limited to pediatric subjects.

d. Overall Comparability Assessment

Gamunex-C for subcutaneous administration has been studied in adult subjects. The pharmacokinetic results in this pediatric population are equivalent to results in adults receiving SC Gamunex-C.

7. Safety

Two subjects prematurely discontinued participation in the study.

- Subject [redacted]. This 8 year old female discontinued due to two AE of infusion site pain at two separate infusion sites, possibly related to Gamunex-C, during the SC phase, which resolved.
- Subject [redacted]. This 15 year old female with pre-existing rheumatoid arthritis had an adverse event of rheumatoid arthritis in the Run-in phase, and one month later this subject was discontinued due to a protocol violation (received methotrexate, a prohibited medication).

There were no deaths in this trial. No serious bacterial infections were reported during any phase of the study. No thromboembolic events or renal dysfunctions, which have a boxed warning in this class of products, were reported in the study. No hemolytic events were reported.

Eight nonfatal SAE were reported in six subjects.

- Run-in: rheumatoid arthritis
- IV: joint sprain
- SC: Four subjects in the in the SC phase reported six severe treatment-emergent AEs.
    - Age 6-11: pain in extremity, infusion site pain (2)
    - Age 12-16: lower limb fracture, headache, drug hypersensitivity (to an antibiotic)

8. Advisory Committee Meeting

There were no issues for the Blood Products Advisory Committee to address.

9. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

10. Labeling

The final labeling was negotiated and agreed upon.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The clinical reviewer recommends approval of 125046/1325

b) Benefit/Risk Assessment

Benefits

There are currently no concerns regarding the benefit-risk ratio. Safety and effectiveness of human IG products for replacement therapy of PI in adult and pediatric patients have been well established.

The clinical study showed that the product develops equivalent blood levels with SC and IV dosing in the pediatric population. As for all age groups, dosing for pediatric subjects is based on body weight. No pediatric-specific dose requirements are necessary to achieve the desired serum IgG levels.

Risks

No serious drug-related serious adverse events were reported and no serious bacterial infections or deaths were reported. Thromboembolic events and renal dysfunction in predisposed patients have been described after the administration of IGIVs. Measures to mitigate the risk of thromboembolic events and renal dysfunction following use of Gamunex-C are highlighted in the label as a boxed warning. In general the systemic AE rate of SC infusions is lower than that of IV administered IV, without compromising efficacy. This is likely due to the slower infusion and uptake than intravenous infusion.

c) Recommendation for Postmarketing Risk Management Activities

This submission fulfills the PMR. No further postmarketing clinical studies are needed at this time.