Application Type	Efficacy Supplement
STN	125046/1325
CBER Received Date	February 4, 2015
PDUFA Goal Date	December 5, 2015
Division / Office	DHCR /OBRR
Priority Review	No
Reviewer Name(s)	Daniela J. Vanco, M.D. Victor C. Baum, M.D.
Review Completion Date / Stamped Date	November 24, 2015
Supervisory Concurrence	Mitchell Frost, M.D.
Applicant	Grifols Therapeutics Inc.
Established Name	Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified
(Proposed) Trade Name	Gamunex®-C, Gammaked™
Pharmacologic Class	Immune Sera and Immune Globulins
Formulation(s), including Adjuvants, etc	Liquid Solution Containing 10% IgG
Dosage Form(s) and Route(s) of Administration	Liquid Solution for Subcutaneous (SC) Administration
Dosing Regimen	Weekly, 1.37xcurrent IV dose (0.3g – 0.6g/kg) in grams/IV dose interval in weeks
Indication(s) and Intended Population(s)	Primary Humoral Immunodeficiency (PI) in patients two years of age and older
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
BLA	biologics license application
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMV	cytomegalovirus
eCTD	electronic Common Technical Document
ELISA	Enzyme-Linked Immunosorbent Assay
FDAAA	Food and Drug Administration Amendments Act of 2007
GRMP	good review management principles
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ISE	integrated summary of efficacy
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
OBE	Office of Biostatistics and Epidemiology
OCOD	Office of Communication Outreach and Development (CBER)
PD	pharmacodynamics
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PSA	prostate-specific antigen
SAE	serious adverse event

GLOSSARY

AE	adverse event(s)
AESI	adverse event(s) of special interest
AUC	area under the curve
BMT	bone marrow transplant
CIDP	chronic inflammatory demyelinating polyneuropathy
IG	immune globulins
IgG	immunoglobulin G
IgIV	intravenous immunoglobulin
IRB	institutional review board
ITP	idiopathic thrombocytopenic purpura
IR	information request(s)
IV	intravenous
PeRC	Pediatric Review Committee
PI	primary immunodeficient/immunodeficiency
PMR	postmarketing requirement
SC	subcutaneous(ly)
SAE	serious adverse event(s)
SCID	severe combined immunodeficiency
TEAE	treatment-emergent adverse event(s)

1. Executive Summary

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

Gamunex (also distributed by Kedrion as "Gammaked"), is a ready-to-use sterile, non-pyrogenic solution of human immune globulin protein for intravenous (IV) and SC administration for PI. Gamunex consists of 9%–11% protein in 0.16–0.24 M glycine. Not less than 98% of the protein has the electrophoretic mobility of gamma globulin.

Gamunex received licensure for SC administration on October 13, 2010, for the indication of treatment of PI (BLS 125046/619). At the time of approval, the pediatric study requirement for patients 0 to <2 years of age was waived because the necessary studies were impossible or highly impractical. The pediatric PMR study for patients ≥2 to 16 years of age was agreed upon.

The deferred pediatric PMR clinical trial is the subject of this submission. T5004-401 was a phase 4, multi-center, open-label, single-sequence, crossover trial to evaluate the

pharmacokinetics (PK), safety and tolerability of SC-administered Gamunex in pediatric PI subjects ages 2-16.

The trial was conducted to determine if weekly SC administration of Gamunex, at a dose 1.37 times the prior IV dose, would provide a steady-state area under the curve (AUC) 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).

Subjects received Gamunex 200-600 mg/kg IV every 3-4 weeks for at least 3 months, at which time they entered the IV phase of the study. Subjects were crossed over to weekly SC infusions. The weekly SC dose was determined by multiplying the IV dose by 1.37 and dividing the resulting new total dose by 3 or 4 depending on the previous IV dosing interval.

The trial showed that PK of Gamunex is comparable between adults and children 6 years of age and older. No conclusion can be drawn for children 2-5 years of age due to small sample size (n =1). Weekly SC administration of Gamunex 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 after IV administration of Gamunex (997 mg/dL). The AUC ratio of IV and SC administration is similar across the 2-16 year age range.

There were no deaths in the trial. There was one serious adverse event (SAE) lower extremity fracture, which was unrelated to the treatment. The most frequent adverse reactions (AR) were local infusion site reactions that were generally mild to moderate in severity.

The revised final label (received October 30, 2015) is acceptable, and approval of the efficacy supplement is recommended.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

T5004-401 evaluated PK, safety and tolerability of SC administered Gamunex in 12 pediatric subjects 2-16 years old; all 12 were Caucasian with 7 males and 5 females. The small number of subjects in the study precludes a meaningful subset analysis.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

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. Pathologies include, but are not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiency (SCID). IG replacement therapy has been the standard treatment for PI since the early 1950s.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Treatments for PI involve treating infections, generally with antibiotics, and preventing infections. Antibiotics may also be used to prevent infections in PI; however, the mainstay of prevention lies in correcting the immunodeficiency. Bone marrow transplantation (BMT) can be used, particularly in life-threatening immunodeficiency, and can be curative. BMT is not always successful and requires a donor who is a suitable tissue match to the recipient. Post-transplant BMT clinical management requires immunosuppressive therapy and runs the risk of graft vs. host disease. Enzyme replacement with adenosine deaminase is another option, but is only useful in patients who lack this enzyme.

Current treatment of PI is replacement therapy with human IG products, usually administered IV every 3-4 weeks, in a dose range of 300 to 600mg/kg body weight. There are four marketed products in the United States that are approved for SC route of administration: Hizentra (CSL-Behring), Gamunex-C (Grifols), Gammagard Liquid (Baxalta) and Hyqvia (Baxalta). The recommended dosing schedule for weekly SC administration of these products is identical to that in this protocol, namely (previous intravenous dose /number of weeks between doses) x 1.37.[1]

2.3 Safety and Efficacy of Pharmacologically Related Products

Safety and effectiveness of human IG products for replacement therapy of PI in adults and pediatric patients have been well established. The administration routes have evolved from intramuscular to IV to SC. In general, the systemic adverse event (AE) rate of SC infusions is lower than that of IG administered IV, without compromising efficacy.[2] This is likely due to the slower infusion and uptake than intravenous infusion.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Gamunex, initially approved in the United States in 2003 for PI, is currently approved for PI, idiopathic thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The proposed pediatric PMR was reviewed by the Pediatric Review Committee (PeRC). The committee agreed with DHCR's recommendations and on March 10, 2010. Studies for age group two years of age 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 (IND 13120/32 and BLA 125046/1204). In an August 1, 2013 telephone conference, FDA agreed to plans for termination of further enrollment in that age group.

1 Hyqvia does not have a weekly dosing recommendation.
2 http://primaryimmune.org/treatment-information/immunoglobulin-therapy/ (Accessed November 17, 2015)

- 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 (STN 125046/1280).

2.6 Other Relevant Background Information

Two protocol amendments were implemented following the original submission. Main provisions of these were:

- Amendment 1 (May 10, 2011)
  - Additional study visit for AUC sampling
  - Homecare nurse required for all SC infusions done away from the study site
  - Added AUC as a key variable and removed steady-state trough IgG concentration as the sole primary endpoint
- Amendment 2 (October 24, 2011)
  - Modified inclusion and exclusion criteria and clarified premedication use

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This supplement has been submitted electronically in compliance with *Guidance for Industry: Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications*. The submission is also compliant with ICH guideline M4E, *Common Technical Document for the Registration of Pharmaceuticals for Human Use*, using appropriate numbering within the Modules. The index provides links to the relevant sections.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The submission is adequately organized and integrated to accommodate the conduct of a complete clinical review. Additional clarification of the PK portion of the study was received via information requests (IR).

3.3 Financial Disclosures

The Applicant adequately disclosed financial arrangements with clinical investigators as recommended in the FDA Guidance for Industry- Financial Disclosure by Clinical Investigators.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Gamunex is a ready-to-use sterile, non-pyrogenic solution of human immune globulin protein for IV and SC (PI indication only) administration, at pH 4.0-4.3. GAMUNEX-C consists of 9%–11% protein in 0.16–0.24 M glycine. Not less than 98% of the protein has the electrophoretic mobility of gamma globulin.

There are no new chemistry, manufacturing, and controls data in the submission.

4.3 Nonclinical Pharmacology/Toxicology

There are no new nonclinical pharmacology/toxicology data in the submission.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Gamunex acts through a broad spectrum of opsonic and neutralizing IgG antibodies against pathogens and their toxins involving antigen binding and effector functions.

4.4.2 Human Pharmacodynamics (PD)

Based on Grifols' trial 060001in an adult and adolescent population, a conversion of 1.37 times the intravenous dose was shown to be appropriate for SC dosing, providing comparable total IgG (AUC).

4.4.3 Human Pharmacokinetics (PK)

The primary efficacy endpoints of the trial were to evaluate the steady-state AUC and mean trough level of serum total IgG for SC- administered Gamunex compared to that of the regular IV administered dose in pediatric subjects, and to evaluate the safety and tolerability of SC-administered Gamunex in pediatric subjects.

4.5 Statistical

Both efficacy analyses and safety analyses in the submission were verified to support the claim for the use of Gamunex via SC route in pediatric subjects with PI, and no statistical issues were identified.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

All documents submitted in the supplement were reviewed. IR and labeling revisions were sent to the applicant as necessary until the subjects of the IR were clarified and agreement was reached on the labeling.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

BLA 125046/0
BLS 125046/619
STN 125046/1280
IND 13120

5.3 Table of Studies/Clinical Trials

There was one clinical trial submitted in this supplement.

5.4 Consultations

Not applicable.

5.4.1 Advisory Committee Meeting (if applicable)

Not applicable.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Clinical Trial T5004-401

T5004-401: An Open-label, Single-sequence, Crossover Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Subcutaneous Gamunex in Pediatric Subjects with Primary Immunodeficiency.

6.1.1 Objectives (Primary, Secondary, etc)

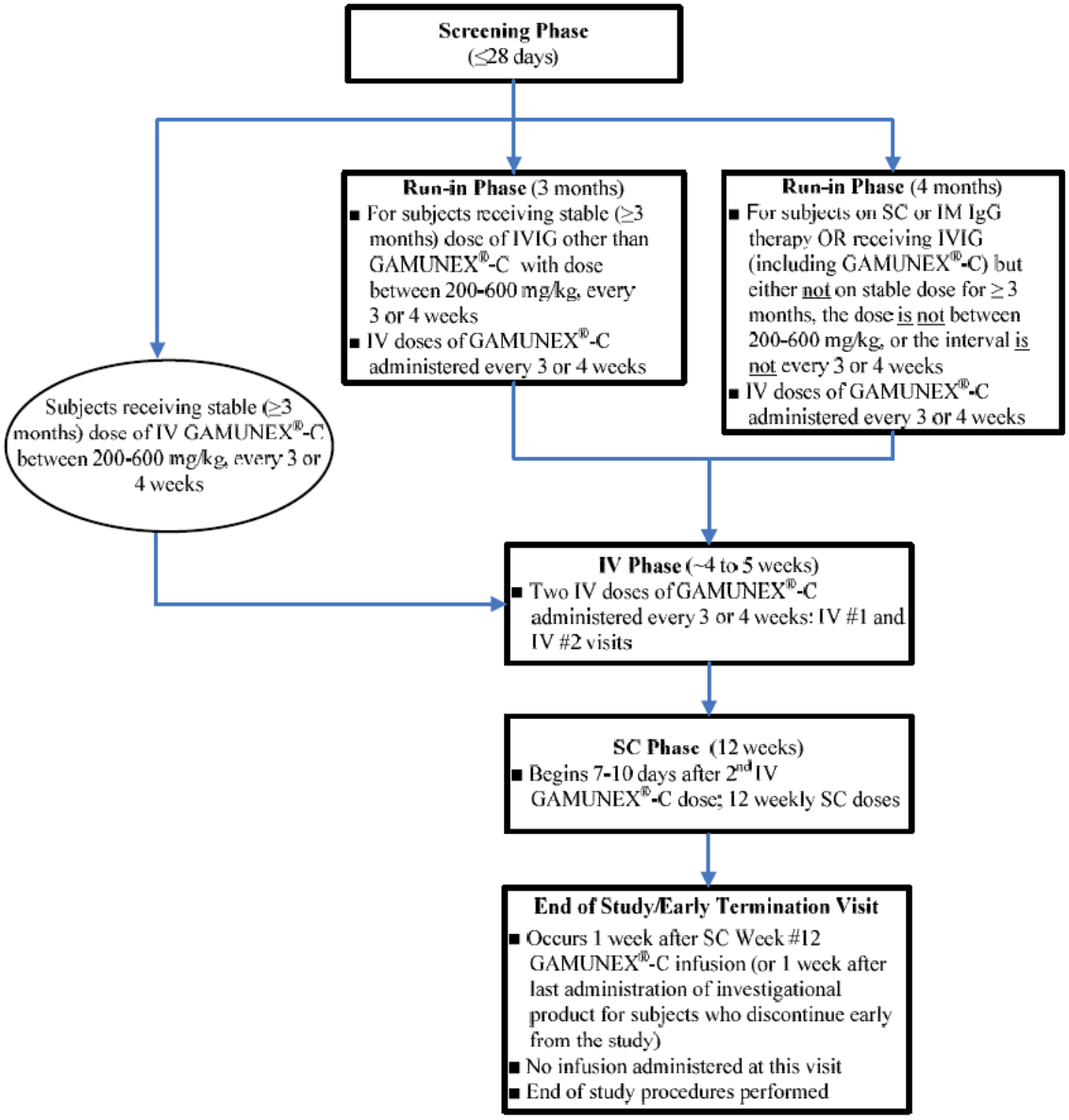
Objectives:

- PK: steady-state AUC and mean trough of serum total IgG for SC-administered Gamunex compared to that of the regular IV administered dose in pediatric subjects (ages 2-16).
- Safety and tolerability of SC-administered Gamunex in pediatric subjects (ages 2-16).

6.1.2 Design Overview

This was a multi-center, open-label, single-sequence, crossover trial to evaluate the PK, safety and tolerability of SC-administered Gamunex in pediatric PI subjects (ages 2-16). The trial consisted of a Screening Phase, two Treatment Phases (an IV phase and a SC phase), and an End of Study/Early Termination (EOS/ET) visit. See the Figure 1, trial schema, below:

Figure 1. Trial Schema



Source: Clinical Study Report Body page 15 o5 93.

6.1.3 Population

Key Inclusion Criteria:

- Age 2-16 years old at the time of screening, inclusive.
- Documented and confirmed pre-existing diagnosis of PI with features of hypogammaglobulinemia requiring immunoglobulin replacement that included, but was not limited to, humoral-based immunodeficiency syndromes (e.g., X-linked agammaglobulinemia, common variable immunodeficiency), disorders of innate immunity (e.g., NF-kappa-B essential modulator; WHIM [Warts, Hypogammaglobulinemia, Infections and Myelokathexis] syndrome), and combined immunodeficiency syndromes (e.g., SCID, hyper-IgM immunodeficiency syndrome).

- Currently receiving IgG replacement therapy with a serum IgG trough concentration of ≥ 500 mg/dL at the Screening Phase Visit.
- Adequate normal skin to allow for SC infusions.
- The subject signed an assent form (if applicable per Institutional Review Board [IRB] requirements). A parent or legal guardian must have signed an informed consent form.
- If a subject was a female of childbearing potential, she must have had a negative result on an approved urine pregnancy test at the time of screening, and must have practiced, based on the clinical judgment and assessment of the Investigator, an effective form of contraception (which may have included abstinence) for the duration of the study.

Key Exclusion Criteria:

- History of anaphylaxis or severe systemic response to an immunoglobulin or blood product.
- A specific antibody deficiency disorder, IgG subclass deficiency, or transient hypogammaglobulinemia of infancy
- Significant proteinuria and/or a history of acute renal failure and/or severe renal impairment (serum creatinine more than 2.5 times the upper limit of normal for age and gender) and/or on dialysis.
- History or current diagnosis of thrombotic episodes (e.g., deep vein thrombosis, myocardial infarction, cerebrovascular accident); subjects with a venous thrombus that occurred in association with a medical device (e.g., PORT-A-CATH®, HICKMAN® catheter) in the past 2 years.
- Currently receiving anti-coagulation therapy.
- Received systemic corticosteroids, immunosuppressants or immunomodulants.
- History of Kawasaki disease.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Following are the dose and mode of administration:

- Run-in phase: IV administration of Gamunex, 200-600 mg/kg body weight
- IV phase: IV administration of Gamunex, 200-600 mg/kg body weight
- SC phase: Weekly SC administration of Gamunex
    - For subjects on an every-4-week IV dosing - 1/4 of the current IV dose multiplied by 1.37
    - For subjects on an every-3-week IV dosing - 1/3 of the current IV dose multiplied by 1.37

Reviewer comment: *A single lot of Gamunex was used in the study.*

6.1.6 Sites and Centers

Five U.S. centers (California, Iowa, Pennsylvania, Florida, Colorado)

6.1.8 Endpoints and Criteria for Study Success

PK Endpoints:

- Steady-state AUC for serum total IgG
- Mean trough serum total IgG

Exploratory Endpoint:

- Trough measles antibody titers (functional assay) were measured as an exploratory variable in this study for informational purposes only.

Safety Endpoints:

- AEs included infections, local infusion site reactions, SAEs, and discontinuations due to AEs and SAEs
- Physical Examination (excluded breast, genitourinary, and rectal exam)
- Vital signs (heart rate, blood pressure, respiratory rate, and temperature)
- Clinical laboratory parameters included:
    - Hematology
    - Chemistry
    - Urinalysis
    - Concomitant medications
    - Serious Bacterial Infections (SBI)[3]

6.1.9 Statistical Considerations & Statistical Analysis Plan

6.1.10 Study Population ***and Disposition***

- Safety Population: all subjects who received any amount of Gamunex
- IgG Population: all subjects who received any amount of Gamunex and had any serum total IgG concentration data.
- PK Population: all subjects who received any amount of Gamunex and had sufficient and valid serum total IgG concentration data to facilitate calculation of AUC.

6.1.10.1 Populations Enrolled/Analyzed

Safety analysis was performed on the safety population and summarized in descriptive statistics by study phase. A total of 11 subjects during the IV phase and 10 subjects during the SC phase were included in the PK analysis for serum total IgG, and analyses on PK parameters were summarized by descriptive statistics by trial phase. The ratio between the weekly SC AUC and the adjusted weekly IV AUC was also summarized.

6.1.10.1.1 Demographics

[3] Serious bacterial infections were defined as per "*FDA Guidance for Industry - Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*" issued June 2008. These include bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and visceral abscess.

A total of 18 to 20 eligible pediatric PI subjects 2-16 years of age were originally planned for enrollment in this study, ensuring at least 4 subjects in each of the following 3 age ranges: 2 to 5 years old, 6 to 11 years old, and 12 to 16 years old. The requirement for subjects 2 to 5 years old was later lifted by FDA (see section 2.5).

Twelve subjects were enrolled in the study and analyzed for safety. All 12 were Caucasian; there were 7 males and 5 females. Following is the distribution of the subjects by the age groups:
Age 2-5: 1 subject
Age 6-11: 5 subjects
Age 12-15: 6 subjects

Reviewer Comment: *The small number of subjects in the study precludes meaningful subset analyses.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

6.1.10.1.3 Subject Disposition
Subject disposition is shown by phase of trial in Table 1.

Table1. Subject Disposition

Phase	Status	N (%[a])
Run-in	Entered	11
	Completed	10 (90.9)
	Subjects who prematurely discontinued	1 (9.1)
	Protocol violation (Subject (b) (6) use of methotrexate, an exclusionary medication)	1 (9.1)
IV	Entered	11
	Completed	11 (100)
	Subjects valid for safety analysis	11 (100)
	Subjects valid for IgG concentration	11 (100)
	Subjects valid for PK analysis	11 (100)
	Subjects who prematurely discontinued	0
SC	Entered	11
	Completed	10 (90.9)
	Subjects valid for safety analysis	11 (100)
	Subjects valid for IgG concentration	11 (100)
	Subjects valid for PK analysis	10 (90.9)
	Subjects who prematurely discontinued	1 (9.1)
	Other, withdrew due to pain at injection site (Subject (b) (6)	1 (9.1)

[a] Percentages are based on the number of subjects treated (Safety Population) within each phase

Source: Post-text Tables 14.1.1/1.1 and Listings 16.2.1/1 and 16.2.1/2.

6.1.11 Efficacy Analyses

The primary efficacy endpoint was PK.

6.1.11.1 Analyses of Primary Endpoint(s)

AUC of total IgG following IV and SC administration is summarized in Table 2 below:

Table 2. AUC of IV and SC Routes of 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

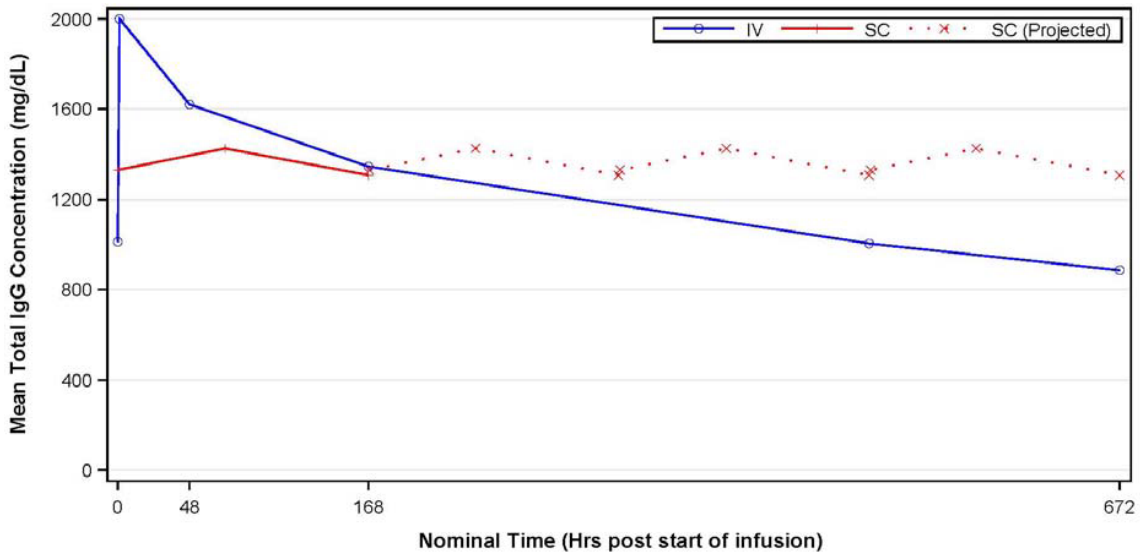
[a] Adj._ $AUC_{0-\tau,IV}$: Adjusted weekly IV $AUC_{(0-7\ days)}$ is calculated as $AUC_{(0-21\ days)}/3$ or $AUC_{(0-28\ days)}/4$.

CV = coefficient of variance, NC = not calculated

Source: Post-text Table 14.2.1/2

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 2, below:

Figure 2. Mean Steady State Plasma IgG Concentrations



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

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

6.1.11.3 Subpopulation Analyses

The small number of subjects in the study precludes meaningful subset analyses and interpretation.

6.1.11.4 Dropouts and/or Discontinuations

Data from the subject who withdrew (for injection site pain) were included, where possible, in all summaries and analyses. All summaries and analyses were based on observed data. No imputation was performed for missing data.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety analyses were done on the safety population. The safety population was defined as all subjects who received any amount of Gamunex.

The mean durations of subject exposure to Gamunex for all age groups combined during the study was 14.2 weeks for the Run-in phase, 4.5 weeks for the IV phase, and 11.0 weeks for the SC phase. The mean number of infusions per subject for all age groups combined was 4.5 during the Run-in phase, 2.0 in the IV phase, and 11.0 in the SC phase. Accordingly, the total numbers of infusions for all age groups combined were 50, 22 and

121, respectively, as shown in Table 3, below. The mean SC duration was shorter than 12 weeks and the mean number of infusions in the SC phase was less than 12 infusions due to a single subject discontinuing in the first week of the SC phase.

Table 3. Exposure to Gamunex During the Study Phases (Safety Population)

Parameters	Study Phase		
	Run-in Mean ± SD [range]	**IV Mean ± SD [range]**	**SC Mean ± SD [range]**
Age Group: Overall	**N = 11**	**N = 11**	**N = 11**
Duration of exposure per subject (weeks)	14.20 ± 2.064 [9.6, 16.1]	4.50 ± 0.542 [4.0, 5.6]	11.03 ± 3.326 [1.0, 12.1]
Total volume infused (mL)	1124.70 ± 754.548 [337.8, 2982.6]	455.65 ± 313.227 [138.6, 1215.6]	1214.63 ± 652.568 [337.0, 2392.0]
No. of infusions per subject[a]	4.5± 0.82 [3, 5]	2.0 ± 0.00 [2, 2]	11.0 ± 3.32 [1, 12]
Total number of infusions	50	22	121
Age Group: 2-5 year olds	-	**N = 1**	**N = 1**
Duration of exposure per subject (weeks)	-	5.10	12.00
Total volume infused (mL)	-	160.00	337.00
No. of infusions per subject[a]	-	2.0	12.0
Total number of infusions	-	2	12
Age Group: 6-11 year olds	**N = 5**	**N = 5**	**N = 5**
Duration of exposure per subject (weeks)	14.84 ± 1.726 [11.9, 16.1]	4.26 ± 0.261 [4.1, 4.7]	9.86 ± 4.953 [1.0, 12.1]
Total volume infused (mL)	643.78 ± 238.934 [337.8, 961.0]	273.46 ± 96.689 [138.6, 381.6]	865.25 ± 202.952 [595.0, 1083.0]
No. of infusions per subject[a]	4.8± 0.45 [4, 5]	2.0 ± 0.00 [2, 2]	9.8 ± 4.92 [1, 12]
Total number of infusions	24	10	49
Age Group: 12-16 year olds	**N = 6**	**N = 5**	**N = 5**
Duration of exposure per subject (weeks)	13.67 ± 2.321 [9.6, 15.1]	4.62 ± 0.698 [4.0, 5.6]	12.00 ± 0.071 [11.9, 12.1]
Total volume infused (mL)	1525.47 ± 817.920 [720.2, 2982.6]	696.96 ± 315.907 [443.4, 1215.6]	1669.66 ± 594.827 [1034.0, 2392.0]
No. of infusions per subject[a]	4.3± 1.03 [3, 5]	2.0 ± 0.00 [2, 2]	12.0 ± 0.00 [12, 12]
Total number of infusions	26	10	60

[a] During the SC phase, each weekly infusion is counted once regardless of number of infusion sites used during each infusion

Source: Post-text Table 14.1.5/1, 14.3.1/5.2, and 14.3.1/5.3

6.1.12.2 Overview of Adverse Events

The most frequent ARs, observed in ≥ 5% of subjects, were local infusion site reactions that were generally mild to moderate in severity.

- During the Run-in and IV phases, 10/12 subjects (83.3%) developed treatment-emergent AEs (TEAEs). These included fatigue, headache and pain.
- In the SC phase 11/11 subjects experienced TEAEs. Infusion site reactions that occurred in >50% of subjects included infusion site erythema, pain and pruritis. Non-infusion site TEAEs included dyspnea (1 subject) and pain (1 subject).

The frequency of TEAEs was generally consistent across the age groups.
In the SC phase 91/96 (94.8%) of TEAEs were mild or moderate.

No TEAE was considered by the investigator or this reviewer to be drug related during the Run-in or IV phases.

There were 69 drug related TEAEs reported in 11/11 subjects during the SC phase. Most (67/69) were mild or moderate in severity. The two severe drug-related TEAEs that were severe were one severe infusion site pain in an 8 year old female (Subject [redacted] who developed infusion site pain on two occasions that led to discontinuation, and one severe headache during the SC phase in a 13 year old male (Subject [redacted]) who continued participation. The majority were local infusion site reactions (Table 4).

Table 4. Drug-related TEAEs

TEAEs (Preferred Term)	Study Phase SC N (%)
Age Group: Overall	N=11
No. of drug-related TEAEs	69
No. of subjects with at least one drug-related TEAE	11 (100.0)
Infusion site erythema	7 (63.6)
Infusion site pain	6 (54.5)
Infusion site pruritus	6 (54.5)
Infusion site discomfort	3 (27.3)
Infusion site haematoma	2 (18.2)
Infusion site swelling	2 (18.2)
Infusion site extravasation	1 (9.1)
Infusion site induration	1 (9.1)
Infusion site inflammation	1 (9.1)
Infusion site warmth	1 (9.1)
Influenza	1 (9.1)
Headache	1 (9.1)

Note: At each level of summation (PT) per study phase, subjects are counted only once.

Source: Post-text Table 14.3.1/4.1

6.1.12.3 Deaths

There were no deaths reported in the clinical trial.

6.1.12.4 Nonfatal Serious Adverse Events

There was a single severe TEAE in each of the Run-in and IV phases, several of which were unrelated to Gamunex-C administration.

- Run-in: rheumatoid arthritis
  - Subject [redacted], 15 year old female
- IV: joint sprain

- Subject , 8 year old female

Four subjects in the in the SC phase reported six severe TEAEs.

- Age 6-11: pain in extremity, infusion site pain (2)
  - pain in extremity, subject , 10 year old male
  - infusion site pain, subject , 8 year old female
  - infusion site pain, subject , 8 year old female
- Age 12-16: lower limb fracture, headache, drug hypersensitivity (to cefdinir, an antibiotic)
  - lower limb fracture, subject , 14 year old male
  - headache, subject , 13 year old male
  - drug sensitivity, subject , 15 year old male

6.1.12.5 Adverse Events of Special Interest (AESI)

No serious bacterial infections were reported during any phase of the study. No thromboembolic events, included in a boxed warning in this class of products, were reported in the study. No hemolytic events were reported.

6.1.12.6 Clinical Test Results

Results of hematology, chemistry and urinalysis testing did not suggest evidence of hemolysis or thrombotic events, immunogenicity, or any other safety signals.
No subject tested positive for hepatitis B surface antigen, hepatitis C virus, or HIV.

6.1.12.7 Dropouts and/or Discontinuations

Two subjects prematurely discontinued participation in the trial.

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

6.1.13 Study Summary and Conclusions

Gamunex-C given SC, provided adequate pharmacologic equivalence with IV dosing and showed adequate evidence of clinical efficacy in children. There were no new safety signals in this pediatric population. No direct conclusions can be drawn about children 2-5 years of age due to small sample size (N= 1).

7. INTEGRATED OVERVIEW OF EFFICACY

Data from a single clinical trial was submitted in support of this efficacy supplement.

8. INTEGRATED OVERVIEW OF SAFETY

Data from a single clinical trial was submitted in support of this efficacy supplement.

8.5 Additional Safety Evaluations

Not applicable.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

This trial only evaluated children and adolescents.

9.1.1 Human Reproduction and Pregnancy Data

This trial was performed only in children and non-pregnant adolescents. The current Gamunex-C label indicates that "animal reproduction studies have not been conducted with GAMUNEX-C. It is not known whether GAMUNEX-C can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMUNEX-C should be given to a pregnant woman only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation."

9.1.2 Use During Lactation

This trial only included children and nulliparous adolescents. Gamunex has not been evaluated in nursing mothers.

9.1.3 Pediatric Use and PREA Considerations

The pediatric assessment in this submission and the associated labeling changes were presented to the PeRC on October 7, 2015. The PeRC agreed that the PREA PMR has been fulfilled by the current efficacy supplement, and found the pediatric population adequately addressed in the proposed language of the package insert.

10. CONCLUSIONS

- Grifols has fulfilled the PREA PMR with submission of the clinical study report for T5004-401, which included a pediatric assessment in 12 pediatric subjects.
- Grifols has previously received a PREA waiver for submission of pediatric assessment in pediatric patients two years of age and younger.
- Grifols has updated the package insert for Gamunex to incorporate the pediatric findings, and revised it with FDA recommendations in BLA 125046/1325.4.

11BENEFIT-RISK CONSIDERATIONS AND RECOMMENDATIONS

11.1 Benefit-Risk Considerations

. Safety and effectiveness of human IG products given SC for replacement therapy of PI in adult and pediatric patients have been well established. Thromboembolic events and hemolysis in predisposed patients have been described after the administration of IGSCs. Measures to mitigate the risk of thromboembolic events following use of Gamunex-C are highlighted in the label as a boxed warning and the risk of hemolysis is described in the

current PI under Warnings and Precautions. In general, the systemic AE rate of SC infusions is lower than that of IG administered IV, without compromising efficacy.

This clinical trial demonstrated that weekly SC administration of Gamunex-C in pediatric subjects resulted in relatively constant steady-state trough serum concentration of total IgG. The AUC ratio of IV and SC administration is similar across the 2-16 year age range. The trial indicates that the PK and safety of Gamunex 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).

As for all age groups, dosing for pediatric subjects is based on body weight and the labeling clearly instructs dosing to be titrated to patients' clinical responses. No pediatric-specific dose requirements are necessary to achieve the desired serum IgG levels.

- 11.4 Recommendations on Regulatory Actions

Approval of this efficacy supplement is recommended.

11.5 Labeling Review and Recommendations

The final labeling was agreed upon and was submitted in the amendment 1325.4.

11.6 Recommendations on Postmarketing Actions

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

3.