

**FINAL REVIEW MEMO OF ORIGINAL BLA EFFICACY SUPPLEMENT
SEEKING A NEW INDICATION – CHRONIC ITP**

Application Type	Efficacy Supplement
STN	125329/55
CBER Received Date	May 9, 2012
PDUFA Goal Date	March 9, 2013
Division / Office	DH /OBRR
Priority Review	No
Reviewer Name(s)	L. Ross Pierce, M.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Bio Products Laboratory
Established Name	Immune Globulin Intravenous (Human)
(Proposed) Trade Name	Gammaplex
Pharmacologic Class	Immunoglobulin (polyclonal)
Formulation(s), including Adjuvants, etc	Liquid ----(b)(4)----- total protein of which (b)(4) 95% IgG; excipients include NaCl, glycine, -(b)(4)-, sorbitol ((b)(4) g/L), and Polysorbate 80 ((b)(4) mcg/mL)
Dosage Form(s) and Route(s) of Administration	IV
Dosing Regimen	1.0 g/kg IV on each of 2 consecutive days
Indication(s) and Intended Population(s)	For the treatment of adults with chronic idiopathic thrombocytopenic purpura

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RECOMMENDATION:

A Complete Response letter is recommended because the sponsor has not as of this date provided an acceptable draft package insert. See letter-ready comments below regarding outstanding labeling issues. The efficacy supplement is otherwise approvable for the new indication for the treatment of chronic idiopathic thrombocytopenic purpura in adults

The product has orphan status for this indication and thereby does not trigger PREA.

LETTER-READY COMMENTS:

Please provide the following additional revisions to the package insert:

1. Use the following cross reference format in the FPI: use bracket then parentheses. For example, [see Warnings and Precautions (5.2)] in FPI.
2. Please identify at the beginning of section 6 (ADVERSE REACTIONS) the most clinically significant ARs and direct practitioners to more detailed information about those reactions, if any. For example, the section should first identify and cross-reference all serious and otherwise potentially important ARs which have occurred with your product, described in greater detail in other labeling sections, especially BOXED WARNING or WARNINGS AND PRECAUTIONS. For example:

“The following potential serious adverse reactions are described below and/or elsewhere in the labeling:

- Thrombotic Events [See Warnings and Precautions (5.2)]
- Hemolysis [See Warnings and Precautions (5.6)]

[Note to sponsor: Do not include here ARs that have not been reported following administration of Gammaplex.]

Next, in section 6, please list the most frequent adverse reactions reported during clinical trials in PI and ITP separately as follows:

“The most common ARs observed in the PI clinical trial were headache (18 subjects, 36%), fatigue (6 subjects, 12%), nausea (6 subjects, 12%), pyrexia (6 subjects, 12%), hypertension (3 subjects, 6%), chills (3 subjects, 6%), myalgia (3 subjects, 6%), pain (4 subjects, 8%), and vomiting (3 subjects, 6%).”

“The most common ARs observed in the Chronic Immune Thrombocytopenia clinical trial were headache (12 subjects, 34%), followed by vomiting (8 subjects, 23%), nausea (5 subjects, 14%), pyrexia (5 subjects, 14%), pruritis (2 subjects, 6%), and arthralgia (2 subjects, 6%).”

[Note to sponsor: Please do not express percentages as decimals when discussing AR incidence by subjects in section 6 and subsection 6.1. (Decimals may be retained when expressing AR incidence per infusion.)]

3. Please revise the title of Table 4, pharmacokinetic (PK) parameters, to indicate that the values have been corrected by subtracting the baseline concentrations.
4. In section 14 CLINICAL STUDIES please change
 - a. the tense of the following phrase to read “...which met the *a priori* success criterion that required it to be greater than 60%.”
 - b. The following sentence to read “At Day 32, the median (\pm SD) platelet count ($24 (\pm 90) \times 10^9/L$) was still higher than the baseline value...”
5. In subsection 6.1 Clinical Trials Experience, under the header “Treatment of Chronic Immune Thrombocytopenic Purpura,” please strike the bracketed message to you, “[Note to sponsor: this was subject -(b)(6)-.]”

Please include in your response both a red-line strike out and clean copy of the revised package insert in WORD format.

GLOSSARY

ITP – Immune Thrombocytopenic Purpura, also Idiopathic Thrombocytopenic Purpura

PI: primary humoral immunodeficiency; also package insert.

SAE – Serious Adverse Event

SUAR - Suspected Adverse Reaction

SUSAR – Suspected Serious Adverse Reaction

TRALI – Transfusion Related Acute Lung Injury

1. EXECUTIVE SUMMARY

The sponsor has submitted the study report for a single phase 3 IND clinical trial, protocol GMX02, to provide substantial evidence of efficacy and safety of the Gammaplex (Immune Globulin Intravenous (Human)) for a new indication, adult chronic immune thrombocytopenic purpura (ITP). The outcomes of the study provide substantial evidence of efficacy in that the study met its primary efficacy endpoint, the percentage of subjects in the intent-to-treat (ITT) population whose platelet counts rose by study day 9 to $\geq 50 \times 10^9/L$, with the lower bound of the 95% and 97.5% confidence intervals (CIs) exceeding the pre-specified success threshold of 60%.

Twenty-nine of 35 subjects (82.9%, lower bound of 97.5% one-sided CI = 66.4%) were responders in the primary efficacy analysis in the intent-to-treat (ITT) population. The results of the two secondary efficacy endpoints and exploratory descriptive endpoints also support efficacy. The protocol and final statistical analysis plan (SAP) do not agree as to whether the 95% confidence interval for the primary endpoint analysis was to be a one-sided or two-sided confidence interval. Regardless of which analysis approach is used, the *a priori* success criterion for the primary efficacy endpoint was met.

It is noteworthy that the median duration of efficacy in terms of maintaining platelets $\geq 50 \times 10^9/L$ (one of 2 secondary efficacy endpoints) was only 10 days. In the context of a chronic disease which has already persisted for a minimum of 6 months, this duration may be regarded as less than impressive.

The safety profile of the product at the recommended dose of 1g/kg per day x 2 consecutive days appears acceptable. The medical literature suggests that the low dose IGIV regimen for ITP, which consists of 5 consecutive days of 400 mg/kg/day IV infusions, which has not been studied by this

sponsor for this product, may be better tolerated than the proposed dosing regimen (Bernesch et al. *J Pediatr Hematol Oncol* 2003;10:797-800). The key safety finding in the phase 3 clinical trial is hemolysis. Drops in hemoglobin (Hb) by > 2.0 g/dL in temporal association with study product infusion(s) and at least one other biochemical abnormality consistent with hemolysis were observed for 4/35 subjects (11%). The total number of subjects with Hb drops of > 1.0 g/dL for whom the sponsor was unable to exclude at least mild treatment-emergent hemolysis was 11/35 = 31%. Most cases of possible hemolysis were mild and may have represented extravascular hemolysis but two subjects had findings consistent with possible intravascular hemolysis in the sponsor's analysis. One of these two subjects was blood group O negative, however, had a maximum fall in Hb of 1.5 g/dL, negative DAT, negative urine hemosiderin, normal LDH, and had a delayed fall in Haptoglobin on day 16, so the evidence of intravascular hemolysis in this subject was suspect in the opinion of this reviewer. Five subjects experienced low serum haptoglobin levels – a finding seen in intravascular hemolysis. Only three of 35 subjects (8.6%) were reported to have developed treatment-emergent anemia reported as an adverse event (AE). It is noteworthy that new class labeling for IGIV products, recently approved for Privigen, warns prescribers that the benefits and risks of the high dose regimen for ITP (i.e., the only regimen studied in the data submitted in this BLA supplement) should be carefully weighed in patients at risk of hemolysis. The following risk factors may be associated with the development of hemolysis following IGIV administration: high doses (e.g., ≥ 2 g/kg), given either as a single administration or divided over several days, and non-O blood group.[Ref: Kahwaji J, Barker E, Pepkowitz S, et al. Acute Hemolysis After High-Dose Intravenous Immunoglobulin Therapy in Highly HLA Sensitized Patients. *Clin J Am Soc Nephrol* 2009;4:1993-1997].

I recommend going forward that FDA give consideration to requiring sponsors who seek the indication for chronic ITP to study both the high and low dose regimens. For this and other sponsors whose IGIV product have been approved for chronic ITP based solely on having studied the high dose regimen, consideration could be given to requiring post-marketing requirement studies to characterize the risks (including hemolysis) and efficacy using the low dose regimen in either all or only non-O blood group adult subjects with chronic ITP. However at this time I recommend an alternative approach of requesting the sponsors of such products add the following statement to their package inserts in the DOSAGE AND

ADMINISTRATION section: “Adequate and well-controlled data on the platelet response to the low dose regimen (e.g., 400 mg/kg per day for 5 consecutive days) are not available for [sponsor to insert product name].”

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Immune Thrombocytopenia is a diagnosis of exclusion. The 2011 Clinical Practice Guideline on the Evaluation and Management of Immune Thrombocytopenia (ITP) recommends the following essential elements for the evaluation of patients for ITP:

- History: Isolated bleeding symptoms consistent with thrombocytopenia without constitutional symptoms
- (e.g. significant weight loss, bone pain, night sweats).
- Physical examination: Bleeding symptoms in the absence of hepatosplenomegaly, lymphadenopathy, or stigmata of congenital conditions.
- Complete blood count: Isolated thrombocytopenia (platelet count $<100 \times 10^9/L$). Anemia only if due to significant bleeding otherwise normal red cell indices, white blood cell count and differential.
- Peripheral blood smear: Identified platelets should be normal to large in size. Red and white blood cell morphology should be normal.
- All adult patients with newly diagnosed ITP should undergo testing for HIV and HCV.

The presence of abnormalities in the history, physical examination, or the complete blood count and peripheral blood smear should be further investigated, e.g. with a bone marrow examination or other appropriate investigations, before the diagnosis of ITP is made. Bone marrow examination is not needed in patients with typical features of ITP. There is insufficient evidence to support the routine measurement of anti-platelet antibodies in the evaluation of patients suspected of ITP.

Secondary causes of isolated thrombocytopenia (as opposed to pancytopenia) include:

- HIV
- HCV
- H. pylori in adults
- Mumps, Measles, and Rubella (MMR) vaccine related in children

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

WinRho SDF (Rh₀(D) Immune Globulin Intravenous (Human) is licensed for ITP as follows:

Raising platelet counts in Rh₀(D) positive, non-splenectomized:

- Children with chronic or acute ITP
- Adults with chronic ITP and
- Children and adults with ITP secondary to HIV infection

Rhophylac is licensed for chronic ITP.

Dexamethasone is approved for treatment of ITP in adults.

Thrombopoietin receptor agonists are approved in adults with chronic ITP who have insufficient response to corticosteroids, immunoglobulins, or splenectomy.

2.3 Safety and Efficacy of Pharmacologically Related Products

Some other IGIVs, including Gamunex and Carimune NF are indicated for ITP/chronic ITP.

Serious adverse reactions of IGIV products include:

- Acute renal insufficiency (especially sucrose-containing products)
- Thrombosis
- Hemolysis

- Aseptic Meningitis
- Hypersensitivity
- Volume Overload
- Transfusion Related Acute Lung Injury (TRALI)

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

The U.K. package insert for Gammaplex includes a contraindication that is currently not present in the US PI: hereditary fructose intolerance and in infants not yet exposed to sucrose. See labeling review memo.

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

The cover letter of the original supplement make no mention of any pre-BLA supplement meeting with the agency or the fact that the pivotal trial in the indication being sought under this supplement was conducted under US IND. It does state that the product was granted orphan status by FDA (Designation Request 11 3352).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

Submission quality is acceptable after the sponsor submitted a correctly annotated draft package insert by amendment. Cover letters and responses to FDA queries in earlier amendments were sometimes incomplete and did not always specifically reference previous submissions where appropriate, necessitating further information requests. The original submission lacked electronic datasets, which were provided by amendment.

3.2 Compliance with Good Clinical Practices and Submission Integrity

In order to assess compliance with GCPs and to verify the key submitted efficacy data against source documents for a sampling of study sites of the pivotal chronic ITP study, three Bioresearch Monitoring inspections were requested as follows:

Study Site Number	Study Site	Location	Number of Subjects
001	Oregon Health and Science University	Portland, Oregon	2
024	Center for Cancer and Blood Disorders, PC	Bethesda, Maryland	3
209	Hemato-Oncology Clinic, Vedanta	Navrangpura, Ahmedabad Gurarat, India	6

Sponsor-Identified Protocol Violations/Deviations

Twenty of 35 subjects had at least one protocol deviation/violation.

While many of the protocol violations, such as missing vital sign data at selected visits, reduced the quality of the study data, overall they did not invalidate the study conclusions.

3.3 Financial Disclosures

The table of contents in Module 1 of the original submission lacked the required section for financial disclosures. This was submitted at FDA request and did not indicate significant financial conflict of interest among investigators of the chronic ITP study.

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

None

4.1 Chemistry, Manufacturing, and Controls

Selected Specifications for Gammaplex Drug Product Limits Compliance Ref.

Excipients	-(b)(4)-, mmol/L	-(b)(4)-	(b)(4)
	-(b)(4)-, mmol/L	-(b)(4)-	(b)(4)
	Glycine, mmol/L	-(b)(4)-	(b)(4)
	-(b)(4)-, mmol/L	-(b)(4)-	(b)(4)
	Sorbitol, g/L	-(b)(4)-	(b)(4)
	Polysorbate 80, mcg/mL	-(b)(4)-	(b)(4)

Test		Limits	Compliance Reference
Impurities	Anti-A, Anti-B Haemagglutins ---(b)(4)---	------(b)(4)----- -----	-(b)(4)-

Test		Limits	Compliance Reference
	Anti-D	------(b)(4)----- -----	--(b)(4)--
	IgA, -----(b)(4)-----	-(b)(4)-	(b)(4)
	-----(b)(4)-----	-(b)(4)-	(b)(4)
	------(b)(4)----- -----	-(b)(4)-	----- -(b)(4)-
	------(b)(4)-----	-(b)(4)-	-(b)(4)-

Five batches of the product were used in the pivotal ITP study.

4.3 Nonclinical Pharmacology/Toxicology

Not included in BLA supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

IGIVs are known to have immunomodulatory properties in several autoimmune conditions, but the exact mechanism(s) of action are not well established.

4.4.2 Human Pharmacodynamics (PD)

The onset of action in raising platelet counts in chronic ITP with IGIV is rapid, often evident within a few days of the initial infusion.

4.4.3 Human Pharmacokinetics (PK)

See Table 4 in subsection 12.3 of the draft package insert, which in the submission dated 30 October 2013 did not reflect correction for baseline IgG levels. The sponsor has been asked to use baseline correction for PK parameters for both PI and ITP subjects in the package insert.

4.5 Statistical

The FDA biostatistician verified that the primary efficacy endpoint was met. The biostatistician requested the sponsor submit key safety and efficacy analyses by geographic region, the results of which are discussed in the Appendix to this review memo.

4.6 Pharmacovigilance

The OBE PVP review memo by Dr. Winiecki concludes that routine

Pharmacovigilance is an acceptable strategy for the identified and potential safety issues included in the sponsor's Risk Management Plan for this product.

A Postmarketing Safety Report for Gammaplex 5% Liquid IGIV covering the period 17 Sept 2009 (Int'l Birth Date of Product) to 31 May 2012 was included in the sponsor's 28 June 2012 amendment 05.

The product was first licensed by the U.S. on 17 Sept 2009, then in the UK on 05 Oct 2009, then in Israel on 13 Feb 2011.

The sponsor issued ~ --(b)(4)-- of Gammaplex during this period, equivalent to ~ --(b)(4)-- infusions.

During the reporting period, 40 spontaneous adverse reaction reports considered by the sponsor to be product related were received. In addition one spontaneous ADR report considered non-serious and classified by the sponsor as unrelated to Gammaplex was received.

Of the 40 ADR reports considered related by the sponsor, 12 were classified as serious. These included 3 serious unexpected ADRs:

- Extreme fatigue
- Bone pain
- Possible interaction with Warfarin: Lower than anticipated INR

Expected ADRs reported in postmarketing experience include:

- Myocardial Infarction (MI)
- Pulmonary Embolus (PE)
- Urticaria

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

5.1 Review Strategy

This review focuses on the single phase 3 single arm open label prospective safety and efficacy IND study in adults and children with chronic ITP, study

GMX02. In addition the submitted postmarketing data are reviewed. This is not a SDTM submission and no electronic datasets were supplied with the original submission, however these were later provided in an amendment for the pivotal chronic ITP study in response to an FDA information request.

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

Study report for chronic ITP study GMX02 and clinical BLA supplement amendments.

5.3 Table of Studies/Clinical Trials

Protocol No.	Indication/Study Population	Phase/Design	Number of Subjects Enrolled / Completed	Primary Endpoint
GMX02	Chronic ITP	3/Open label, Single Cohort, Prospective	35	Percentage of Subjects with Rise in Platelets to $\geq 50 \times 10^9/L$ by day 9

The sponsor states in the postmarketing safety report in amendment 5 that 20 pediatric PI subjects have received a total of 183 infusions of the product in a study of PI in children, conducted under IND 12569.

5.4 Consultations

Not applicable.

5.4.1 Advisory Committee Meeting: **Not applicable.**

5.4.2 External Consults/Collaborations: **Not applicable.**

5.5 Literature Reviewed

A limited number of published studies have compared higher vs. lower dose regimens of IGIV for ITP:

- Bernesch et al. studied 34 consecutive children with acute ITP (a condition which is generally self-limited) and a platelet count $< 20 \times 10^9/L$, randomizing them into a group receiving 1 g/kg daily x 2 days or 300 mg/kg daily x 2 days. Fifteen of 17 subjects (88%) in the high

dose group and 13 of 17 subjects(76.5%) in the lower dose group achieved a platelet count $> 20 \times 10^9/L$ within 72 hours. “Side effects of IGIV administration were more common in the high-dose group.”
Ref: J Pediatr Hematol Oncol 2003;10:797-800.

- Warrier et al. pooled data from 2 multicenter randomized studies with a total of 24 pediatric ITP subjects, which compared various lower dose regimens (250 mg/kg/day, 400 mg/kg/day, or 500 mg/kg/day) given for 2 consecutive days to 1 g IGIV/kg/day x 2 consecutive days. IGIV was considered effective in 16 of 17 (94%) of subjects in the low dose groups. By 48 hours, platelet counts ranged from $32 \times 10^9/L$ to $256 \times 10^9/L$ and peak platelet counts ranged from $38 \times 10^9/L$ to $551 \times 10^9/L$. There were 2 SAEs in the study: a subject receiving 400 mg/kg/day had an anaphylactoid reaction and a subject in the high dose group had aseptic meningitis. Ref: J Pediatr Hematol Oncol 1997;3:197-201.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The pivotal phase 3 study GMX02 was a single-arm pivotal study in adults with chronic ITP. The primary efficacy endpoint was increased platelet count to $\geq 50 \times 10^9/L$ from a baseline of $< 20 \times 10^9/L$ by day 9 and the success criterion was defined such that the lower bound of the 95% confidence interval of the percentage of subject responders was required to exceed a pre-specified threshold (of $\sim 60\%$). This definition took into account the historical observation that only 5% or less of chronic ITP patients with a ≥ 6 month history of thrombocytopenia were observed to achieve spontaneous remission.

6.1 Trial #1

IND Protocol GMX02

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective:

To determine if GAMMAPLEX (BPL) raises the platelet count of subjects with chronic ITP to a threshold of $50 \times 10^9/L$, similar to that of an historical control.

- Secondary Objectives:

- To determine the safety of GAMMAPLEX at the dosage used in this study
- To determine if GAMMAPLEX maintains platelet counts of $> 50 \times 10^9/L$ in subjects with chronic ITP for a period of time similar to that of an historical control.

6.1.2 Design Overview

The study was a multicenter, prospective, open-label study of safety and efficacy of GAMMAPLEX IGIV. Eligible subjects with chronic ITP (of ≥ 6 months duration) received 1.0 g/kg on days 1 and 2 and returned for clinical assessments on days 3, 5, 9, 14, 21, 32, and 90. At the discretion of the investigator and subject or his/her legally authorized representative (LAR), up to 2 additional 1.0 g/day x 2 day courses of GAMMUNEX were permitted within 32 to 90 days after the initial course. Subjects who had additional courses were followed as per the schedule of the first course such that their total period of f/u was extended accordingly.

6.1.3 Population

Inclusion criteria

- Males and Females age 6 – 70 years (revised to age 18 to 70 years in protocol amendment 7).
- Confirmed diagnosis of chronic ITP of at least 6 months duration
- Platelet Count $\leq 20 \times 10^9/L$ at enrollment (by local lab just prior to first infusion of Gammaplex).
- Absence of other conditions that, in the opinion of the investigator, could cause thrombocytopenia
- If treated with corticosteroids, the regimen/dose was to have been stable for a minimum of 2 weeks before day 1 and should have remained constant until day 32.
- If treated with cyclophosphamide, azathioprine, or attenuated androgens, the regimen and dose were to have remained stable for a minimum of 2 months before day 1 and should have remained constant until day 32.
- Splenectomized subjects and both RhD positive and RhD negative subjects were included.

Exclusion criteria

- Any severe or anaphylactic reaction to blood or any blood-derived product, or any severe reaction to immunoglobulin intravenous or another other IgG preparation.
- Intolerant to any component of the Investigational Product (IP)
- Received any live virus vaccine within previous 3 months
- Received IGIV within 1 month before day 1.
- Currently receiving or had received any investigational agent within 1 month before day 1
- Received any blood, blood product, or blood derivative within 1 month before day 1.
- Received Rituximab within 3 months before day 1.
- Pregnant or nursing
- Positive at screening for any of: HBsAg, NAT for HCV or HIV, Abs to HCV or HIV 1 or 2.
- Screening AST or ALT > 2.5x ULN
- Severe renal impairment (serum creatinine > 2x ULN or BUN > 2.5x ULN; subject on dialysis; history of acute renal failure
- History of DVT or thrombotic complications of IGIV therapy
- Any history or sign of hyperviscosity, TIA, CVA, or other thrombotic event or unstable angina.
- Suffered from any acute or chronic medical conditions (renal disease or predisposing conditions for renal disease, coronary artery disease, or protein losing enteropathy that, in the opinion of the investigator may have interfered with the conduct of the study
- An acquired medical condition such as CLL, lymphoma, multiple myeloma, chronic or recurrent neutropenia (abs neutrophils < 1 x 10⁹/L).
- Htn with BP > 160 systolic and/or diastolic > 90 mm Hg.
- Anemia at screening (Hb < 10 g/dL)

6.1.4 Study Treatments or Agents Mandated by the Protocol

Gammaflex was administered at the dose of 1.0 g/kg IV on each of 2 consecutive days starting on day 1. Up to 3 courses of this 2-day dose regimen could be administered if required to maintain platelet response.

6.1.5 Directions for Use

An initial infusion rate for ITP of 0.5 mg/kg/min for 15 minute with increase to 4 mg/kg/min if tolerated, is recommended. [This is the same infusion rate as listed in the approved PI for primary humoral immune deficiency.]

6.1.6 Sites and Centers

Sites in the U.S., India, and Argentina

6.1.7 Surveillance/Monitoring

Subjects returned for clinical assessments on days 3, 5, 9, 14, 21, 32, and 90.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint:

- The percentage of subjects attaining a platelet count of $\geq 50 \times 10^9/L$ by day 9 (7th day after completion of 2nd I.P. infusion)

Secondary Efficacy Variables

- Duration of time for which the platelet count remained of $\geq 50 \times 10^9/L$ following the first treatment course of I.P.
- Changes in the signs of any bleeding/hemorrhage up to day 32

Safety Endpoints

- Adverse Events (AEs)
- Vital signs
- Clinical laboratory tests, including CBC, serum haptoglobin, LDH, ALT
- Direct Coomb's test (DCT)
- Transmission of viruses
- Physical examination

6.1.9 Statistical Considerations & Statistical Analysis Plan

- Should the lower bound of the one-sided 95% confidence interval (CI) for the proportion of subjects attaining a platelet count of $> 50 \times 10^9/L$ on or before day 9 exceed 60%, Gammplex would be declared effective for the treatment of chronic ITP. The lower CI was

calculated using the normal approximation to the binomial distribution.

- assumptions used to calculate the sample size (percent power, magnitude of effect (i.e., point estimate of efficacy), lower bound of confidence interval)
- pre-specified methods of handling missing data
- statistical methodology used to adjust for multiplicity: none.
- The primary efficacy data were analyzed using the ITT population
- Duration of platelet count response was calculated as date of last sample [with platelet count $> 50 \times 10^9/L$] minus date of first sample [with platelet count $> 50 \times 10^9/L$] + 1
- Kaplan-Meier Plots were used to depict the distribution of time duration for which platelet counts remained $> 50 \times 10^9/L$.
- Descriptive statistics were used for platelet counts at each visit through visit 32 as well as for maximum platelet count.
- Each bleeding/hemorrhage event was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V 3.0 and analyzed using descriptive statistics.
- Results of vital testing were only provided for subjects age 12 to 70 years.

6.1.10 Study Population and Disposition

The planned study population was 31 evaluable subjects. Thirty-five subjects were enrolled in the study, were treated, and were included in safety and ITT study populations. However, the sponsor's definition of "enrolled" required that the subject received investigational (medicinal) product (IMP, IP). Eight subjects (22.9%) discontinued the study prematurely. Five subjects discontinued after 2 IMP infusions and 2 discontinued after a total of four IMP infusions.

Twenty-seven (77%) subjects completed the study. One subject discontinued prematurely after a single infusion due to an adverse event (AE, severe headache). Five subjects, 14.3% were lost to follow-up. One subject (-)(b)(6)- withdrew consent and one subject discontinued prematurely because another therapeutic intervention for thrombocytopenia was required.

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Demographic Characteristics (ITT Population)

Mean Age +/- SD (years)	36.3 +/- 18.3
Median Age (range, years)	32.0 (6 – 69)
Age 6-11 years (number of subjects)	2
Age 12-17 years (number of subjects)	1
Age 18 – 70 years (number of subjects)	32
Males (number, (%))	9 (26%)
Females (number, (%))	26 (74%)
African-American (number, (%))	0
Asian (number, (%))	22 (63%)
Caucasian (number, (%))	10 (29%)
Hispanic (number, (%))	8 (23%)
Height (mean +/- SD (cm))	156.2 +/- 13.6
Weight (mean, median, (range))	64.6, 65.0 (17.4 – 133.0)

Adapted from Table 11-1 of study report

6.1.10.1.2 Medical Characterization of the Enrolled Population

Baseline Disease Characteristics

Mean Elapsed time since diagnosis of ITP (months, (range))	61.9 (6 – 567)
Median Platelet Count at Diagnosis (range) (x 10 ⁹ /L)	10.0 (2 – 86)
History of Splenectomy (number (%))	7 (20%)
Normal Megakaryocytes on Bone Marrow	8 (23%)
Increased Megakaryocytes on Bone Marrow	22 (63%)
Had prior treatment with IGIV for ITP	7 (20%)

Five subjects had unknown or missing bone marrow megakaryocytes results

6.1.10.1.3 Subject Disposition

All 35 enrolled subjects received at least one infusion of Gammaplex. One subject did not complete the first course of treatment.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Twenty-nine of 35 subjects (82.9%) in the ITT population were considered responders in that their platelet count rose to $> 50 \times 10^9/L$ on or before day 9. The lower one-sided 95% CI for the percentage of responders was 68.9%, which met the pre-specified minimum success threshold of 60%.

An additional robustness analysis was performed in which subjects whose baseline local platelet counts were $> 20 \times 10^9/L$ were excluded from the analysis. The response rate in this subpopulation was 28/34 (82.4%) with a lower bound of the 95% one-sided C.I. of 68.1%.

6.1.11.2 Analyses of Secondary Endpoints

Duration of response

The median duration of platelet count response to a level of $> 50 \times 10^9/L$ response for responders was 10 days.

Prevalence of Bleeding

Prevalence of Bleeding on Various Study Days (n (%))

Type of Bleeding	Screening	Day 9	Day 90
Petechiae	24 (69%)	1 (3%)	6 (17%)
Hematoma	7 (20%)	2 (6%)	5 (14%)
Genitourinary	7 (20%)	1 (3%)	
GI	5 (14%)	1 (3%)	
Other	4 (11%)	1 (3%)	

During the period from days 2-32, 2 CTCAE grade 3 bleeding/hemorrhage events were reported.

As seen in the table above, the prevalence of petechiae, hematoma, and other evidence of bleeding fell over the course of the study, which tends to support the efficacy of the product.

6.1.11.3 Subpopulation Analyses

A subgroup analysis of adults age 18 years and above resulted in a response rate of 25/31 subjects (80.6%) with a lower bound of the 95% one-sided C.I.

of 65.3%. Thus, the subgroup of subjects of age ≥ 18 also met the primary efficacy endpoint success criterion.

Subgroup analyses by race and sex were missing, but were submitted in the 9 Nov 2013 amendment as per FDA request. Efficacy and safety results were generally similar in race and sex subgroups.

6.1.11.4 Dropouts and/or Discontinuations

All 35 enrolled subjects received at least one infusion of Gammaplex. One subject did not complete the first course of treatment. Five subjects were lost to follow-up.

6.1.11.5 Exploratory and Post Hoc Analyses

Mean platelet count by study day

Study Day	Baseline 1	2	9	14	21	32
Platelet Count (mean x 10⁹/L)	13.2	52.4	158.3	70.2	55.2	61.1

The standard deviation was 6.0 at baseline and 201.3 on day 9

Median maximum platelet count was 160.0 x 10⁹/L (range 5 to 1373 x 10⁹/L).

Median maximum change from baseline platelet count was 141.0 x 10⁹/L (range minus14 to 1370 x 10⁹/L).

Eleven of 33 subjects (33.3%) continued to have platelet counts $> 50 \times 10^9/L$ on day 32.

The median duration of platelet count response to a level of $> 50 \times 10^9/L$ response for responders was 10.0 days.

Eleven subjects (31.4%) received a 2nd course of treatment and two subjects (5.7%) began a 3rd course of treatment.

6.1.12 Safety Analyses

Exposure to Gammaplex

Gammaplex IGIV doses ranged from approximately 480 to 1150mg/kg per infusion. Because repeated treatment courses were allowed by the protocol after a pre-specified waiting period following the initial treatment course, a total of 94 infusions were given during the study period. One subject received a single infusion. Twenty-three subjects received a total of 2 infusions. Eleven subjects received 4-6 infusions. The 2nd treatment course began on median day 36.

6.1.12.1 Methods

At each visit the following were performed:

- Medication history recorded
- AEs assessed
- Vital signs 10 minutes prior to treatment and again at 10 minutes after start of infusion, 10 minutes after each rate increase, 10 and 30 minutes after the maximum rate was achieved, every 60 minutes until the infusion was completed, and at 15 and 30 minutes post infusion on infusion days.
- Physical Examination
- In addition to viral testing, blood for bilirubin, serum creatinine, BUN, ALT, and AST were obtained at screening and on days 1, 3, 9, 32, and 90.
- CBC with white cell differential and platelet count were obtained at screening and on days 1, 3, and 9.
- Serum IgG levels were obtained at all visits. IgA and IgM were obtained at screening and end of study visit.

Diary cards were to be completed daily from day 1 until day 32 describing any adverse events (AEs) and concomitant medications, as well as any bleeding episodes.

Safety Monitoring:

Laboratory Evaluation

Viral serologies were drawn at screening and following Gammaplex dosing on day 9 (B19 only), 32 (age 12 to 70years only), and day 90.

- HBsAg
- Anti-HCV
- Anti-HIV 1 & 2

Nucleic Acid Testing (NAT) for viral pathogens was also performed for the following viruses at the above time points.

- HIV NAT
- HCV NAT
- Parvovirus B19

6.1.12.2 Overview of Adverse Events

No deaths were reported during the study.

Twenty-five subjects (71%) reported at least one TEAE (herein after called AE). The most common AEs were headache in 13/35 subjects (37%), vomiting in 9 subjects (26%), nausea in 7 subjects (20%), and petechiae in 7 subjects, (20%).

Fifteen subjects (42.9%) had suspected (causally-related) adverse reactions (SUARs). The most common SUARs were headache (n = 10), vomiting (n = 7) and pyrexia (n = 5).

Four subjects experienced a total of 8 reported SAEs, of which 5 were considered SUARs.

One subject discontinued the study due to severe headache considered an SAE and SUAR.

AEs reported to be severe in intensity were as follows:

- Headache (3 subjects, 9%)
- Vomiting (2 subjects, 6%)
- Anemia (1 subject, 3%)
- Tachycardia (1 subject, 3%)
- Pneumonia (1 subject, 3%)
- Sepsis (1 subject, 3%)
- Dehydration (1 subject, 3%)
- Hypokalemia (1 subject, 3%)
- Cough (1 subject, 3%)
- Ecchymosis (1 subject, 3%)

Twenty-four subjects (68.6%) reported 88 AEs which began during or up to 72 hours after the infusion of Gammaplex. Of these 88, 51 were reported by 19 subjects on the day of infusion and 75 were reported by 23 subjects during or within 24 hours of the infusion. Only 2 subjects reported AEs at infusion rates up to 0.06 mL/kg/min. At the maximum rate of 0.08 mL/kg/min a total of 19 of 35 subjects reported AEs during the infusion. This suggests that the tolerability of the product worsens at the maximum infusion rate of 0.08 mL/kg/min.

6.1.12.3 Deaths

No subjects died during the study.

6.1.12.4 Nonfatal Serious Adverse Events

SAEs were reported as follows in study GMX02 (Safety Population):

Subject	SAE	Relationship to Product (according to investigator)
--(b)(6)--	Vomiting	Definitely
--(b)(6)--	Dehydration	Definitely
--(b)(6)--	Headache	Definitely
--(b)(4)--	Headache	Probably
--(b)(6)--	Diarrhea	Not Related
--(b)(6)--	Pneumonia	Not Related
--(b)(6)--	Sepsis	Not Related
--(b)(6)--	Headache	Possibly

Adapted from Sponsor's Table 12-7 of Study Report

See also Pharmacovigilance review memo for analysis of SAEs.

6.1.12.5 Adverse Events of Special Interest (AESI)

Hemolysis

A total of 11 subjects may have experienced hemolysis, mostly mild, in an analysis the sponsor performed at FDA request. See item 5 from the sponsor's 30 October 2012 response to FDA Information Request dated 18 October 2012 in the Appendix to this memo for details. FDA requested the following: "Please state the number of subjects you consider to have experienced treatment-emergent hemolysis and provide the criteria you use to make this assessment."

Sponsor Response [excerpt]:

The data from all subjects has been examined with the starting point as the decrease in haemoglobin (Hb). The data was extracted from Listing 24.2 for each subject. Added to these data were results of haptoglobin, LDH, direct Coombs' test (Direct Antibody Test, DAT) and urine haemosiderin. All these data are displayed by subject (one per page) in Appendix 2 to this summary of the reply to the RFI. A commentary was written for each subject based essentially on these aggregated data and supplemented, as appropriate, with selected data from Listings 4, 17, 24.1 and 24.2 to identify any potentially relevant clinical features. For each case a conclusion was drawn based on these data.

Broadly the criteria used were as follows:

DAT is generally positive in cases of extravascular haemolysis, but usually negative in the presence of intravascular haemolysis;

Urine haemosiderin is usually absent in extravascular haemolysis but present with intravascular haemolysis;

Haptoglobin decrease with both intra- and extra-vascular haemolysis but the decrease is usually greater with intravascular haemolysis; is absent in severe intravascular haemolysis;

LDH is of lesser help because it can increase with both intra- and extra-vascular haemolysis.

Table 1 summarises the conclusions with regard to possible haemolysis. Overall, there were 23 cases without evidence of haemolysis, 6 with possible extravascular haemolysis, one with possible intravascular haemolysis, one with possible combined intra- and extra-vascular haemolysis, two with possible haemolysis but without clear evidence of site(s). There were two unassessable cases. Table 2 presents the

commentaries for each case extracted from the Appendix which includes the relevant data from the key Listings in the CSR.

Subject number	Overall conclusion
--(b)(6)--	Possible intravascular haemolysis
--(b)(6)--	None
--(b)(6)--	Possible mixture of intra- and extra-vascular haemolysis
--(b)(6)--	None
--(b)(6)--	None
--(b)(6)--	Haemolysis possible but ongoing bleeding likely
--(b)(6)--	None
--(b)(6)--	Slow mild extravascular haemolysis possible
--(b)(6)--	Unassessable
--(b)(6)--	Possible haemolysis
--(b)(6)--	None
--(b)(6)--	None
--(b)(6)--	Unassessable
--(b)(6)--	Possible extravascular haemolysis with bleeding
--(b)(6)--	None

Subject number	Overall conclusion
--(b)(6)--	Possible extravascular haemolysis
--(b)(6)--	Possible extravascular haemolysis
--(b)(6)--	None
--(b)(6)--	None
--(b)(6)--	Possible extravascular haemolysis
--(b)(6)--	None
--(b)(6)--	Possible extravascular haemolysis
--(b)(6)--	None
--(b)(6)--	None
--(b)(6)--	Possible extravascular haemolysis
--(b)(6)--	None

The sponsor's analysis of possible hemolysis cases focused on subjects who had a fall in Hb by > 1 g/dL and also on subjects with elevations in LDH, and was limited somewhat by the lack of baseline haptoglobin and baseline LDH measurements.

The sponsor's table 1 lists subject --(b)(6)-- as having had possible intravascular hemolysis. This subject had Hb decreases of up to 1.5 g/dL on each of 2 occasions in temporal association with Gammaplex infusion courses (nadir Hb values on days 2 and 40, in each case corresponding to infusion day 2). Haptoglobin was substantially reduced below normal and from the day 5 value (which was normal at 0.6 g/L) on days 16 (value 0.1 g/L, LLN 0.34 g/L) and 43 (value 0.34). DAT, urine hemosiderin, and LDH were negative. The subject had apparently minor epistaxis and then rectal bleeding on days 4 and 21, respectively, which the sponsor concluded were unlikely to have affected the observed drops in Hb. The sponsor concluded that the pathogenesis of the drops in Hb were uncertain but may have represented mild intravascular hemolysis insufficient to completely deplete haptoglobin. Of note, this subject is blood group O negative, which is quite uncommon among hemolysis cases following IGIV presented at the CBER Blood Safety Team meeting in 2012. Nevertheless, no completely satisfactory alternative explanation for the repeated Drops in Hb after the first day of each course of therapy is apparent. It is unclear why the hemolysis did not progress after the 2nd infusion of each course, however. Also, it is noted that haptoglobin was much lower on day 14 than it was on day 5, at which time it was normal and by which time the Hb had risen by 1 g/dL from its initial nadir on day 2. Thus the probability of product-induced hemolysis may be modest, but I agree with the sponsor that it cannot be excluded.

Subject --(b)(6)-- was concluded by the sponsor as having a possible mixture of intra- and extra-vascular hemolysis. This subject's Hb fell from 13.2 g/dL at screening to 12.8 g/dL on day 1 (pre-treatment), to 11.8 g/dL on day 3 (delta – 1.4 g/dL from the mean of screening and day 1 values) to a nadir of 10.2 on day 10 (unscheduled draw, delta – 2.8 g/dL from the mean of screening and day 1 Hb values). This subject was blood group A+ and had treatment emergent positive DAT on day 4, positive urine hemosiderin on day 4 which had reverted to negative on day 14, borderline haptoglobin of 0.35 g/dL on day 5 and abnormally low haptoglobin of 0.276 on day 14 (LLN = 0.34 g/L), and normal LDH on days 5 and 14. The initial drop in

Hb on day 3 may have been reduced from what it otherwise would have been due to hemoconcentration from severe vomiting and volume depletion. I consider hemolysis in this subject to be unequivocal and likely intravascular with a plausible extravascular component. Serum haptoglobin may have had time to recover from the time of its initial measurement on day 5.

Subject -----(b)(6)----- was concluded by the sponsor as having a possible extravascular hemolysis following each of 2 courses of infusion with test product. This subject's Hb rose from a value of 14.7 at screening to 15.1 prior to infusion on day 1, then fell to 13.8 on day 2, 13.6 on days 3 and 5 and reached an initial nadir of 13.3 on day 10. It then rose to 14.9 by day 32, but fell again to 13.0 on day 86 after infusion 4 (treatment course 2). The maximum drops in Hb from baseline were thus 1.8 and 2.1 g/L respectively. It then rose to 15.3 by day 180. Serum haptoglobin was low all 3 times it was measured on days 5, 14 and day 90 (values of 0.14, 0.31, and 0.37 g/L, respectively (LLN = 0.4 g/L).

Subject -----(b)(6)----- was concluded by the sponsor as having a possible extravascular hemolysis. This subject had a screening Hb of 12.6 which rose to 13.1 on day 1 prior to the initial Gammaplex infusion. Hb fell to 13.3 on days 2 and 3 and fell progressively to a nadir of 6.5 at end of study. Haptoglobin was reduced to 0.06 g/L on day 5 and rose to a still low 0.25 on day 14 (LLN = 0.4 g/L), but serum total bilirubin remained normal. LDH was elevated on day is 5 and 14. Direct Coombs was negative on days 1, 6, and 14, and urine hemosiderin was negative on days 6 and 14. The subject reported menorrhagia on days 5, 11, and 76, and also had petechiae on day 15. While bleeding probably contributed to the progressive anemia, the rapid fall in Hb with the first infusion and the low haptoglobin values in conjunction with the elevated LDH are consistent with hemolysis.

Subject -----(b)(6)----- was concluded by the sponsor as having a possible extravascular hemolysis. This subject had a screening Hb of 121, which rose to 128 on day 1 prior to administration of test product. On day 2 Hb fell to 11.4. Hb drifted down to 10.6 by day 21 and rose to 11.6 on day 91. The maximum fall from baseline was thus 2.2 g/dL. LDH was abnormal on day 5 and normalized by day 14. DAT was negative on days 1, 5 and 14. Haptoglobin was well within the normal range on days 5 and 14, and urine hemosiderin was negative on those days. I agree that with the rapid Hb fall after the first infusion with an elevation of LDH on day 5 that normalized by day 14 the possibility of some extravascular hemolysis cannot be excluded, given the lack of evidence of visible bleeding in this subject. LDH was elevated all 3 times it was measured, with a maximum value on day 5 of 347 (ULN = 209 IU/L). Direct Coombs was negative and urine hemosiderin was negative on days 5, 145, and 90. The subject did not have visible bleeding during the trial.

A total of 5 subjects had low haptoglobin levels during the study. LDH elevations were commonly observed in subjects with mostly mild drops in hemoglobin shortly after infusion of test product.

Anemia

Three subjects had treatment-emergent anemia reported as an AE, of whom one also had a concomitant elevation in WBC count. One subject's urine was positive for hemosiderin. No hemoglobinuria or other urinalysis abnormalities were observed.

Skin Reaction

One case of erythema multiforme was observed.

Liver Dysfunction

One subject experienced a treatment-emergent worsening of AST which was abnormal at baseline (from 88 U/L, reference range < 46 U/L, up to 128 U/L (2.8x ULN) on day 9. At the day 90 visit, the subject's AST was 63 U/L.

Three subjects had treatment-emergent anemia reported as an AE, of whom one also had a concomitant elevation in WBC count. One subject's urine

was positive for hemosiderin. No hemoglobinuria or other urinalysis abnormalities were observed.

6.1.12.6 Clinical Test Results

Median serum IgG levels increased from 11.1 g/L at baseline to 41.9 g/L on day 3. On day 9 the median level was 28.2 g/L. On day 32 it was 15.1 g/L and on day 90 it was similar to baseline at 11.8 g/L.

One subject had a worsening of AST, abnormal at baseline, to 2.8 x ULN, as noted above.

There was no evidence of viral transmission.

Four subjects (12%) had positive direct Coomb's test on day 5 and one had positive urine hemosiderin. On day 14, 3 (9%) had positive DCT but none had urine hemosiderin.

One subject experienced > 30% increase in systolic BP. Four subjects had > 30% increases in diastolic BP. There were no decreases in systolic BP by > 25%, whereas 4 subjects had noted decreases in diastolic BP by >25%.

Two subjects had increases in heart rate > 1.6 x baseline which were temporally associated with an infusion.

Five subjects had reports of mild pyrexia considered product-related.

6.1.12.7 Dropouts and/or Discontinuations

One subject discontinued the study prematurely due to severe headache considered an SAE and SUAR.

7. INTEGRATED OVERVIEW OF EFFICACY: NOT APPLICABLE.

8. Integrated Overview of Safety: not applicable, as only a single phase 3 IND study GMX02 was submitted and evaluated for safety in chronic ITP.

8.6 Safety Conclusions

The safety profile is acceptable for chronic ITP.

9. ADDITIONAL CLINICAL ISSUES

No discussion of the actual use of concomitant medications was located in the study report. Inspection of sponsor data listing 12.2, Concomitant Medications, reveals:

<u>Subject</u>	<u>Medication</u>
----------------	-------------------

- | | |
|----------|---|
| -(b)(6)- | Methyl Prednisolone 50 mg IV pre-medication on day 1 |
| -(b)(6)- | Cyclosporin 50 mg BID ongoing |
| -(b)(6)- | Prednisone 10 mg QOD from pre-study through day 64 |
| -(b)(6)- | Medrol 4 mg p.o. QD for pruritis days 17 to 22 |
| -(b)(6)- | Amicar 2 g p.o. for bleeding prophylaxis on day 31. |
| -(b)(6)- | Prednisone 10 mg p.o. QD for ITP ongoing |
| -(b)(6)- | “Cellrept” (immunosuppressive) 500 mg p.o. BID ongoing |
| -(b)(6)- | “IVIG” 30 g IV prn on day 67 |
| -(b)(6)- | Aranesp (anti-anemic) 200 mcg SC prn anemia on day 36 |
| -(b)(6)- | T. Azathioprine 50 + 25 mg mg P.O. QD for ITP ongoing |
| -(b)(6)- | T. Methylprednisolone 16 mg P.O. QD for ITP ongoing. |
| -(b)(6)- | Methylprednisolone 10 + 15 mg P.O. BID for ITP from pre-study to day 21 |
| -(b)(6)- | Xamic (antifibrinolytic) 500 mg p.o. prn from day 21 to day 116. |

- (b)(6)- Dexamethasone 40 mg QD for ITP from day 56 through day 59
- (b)(6)- Tranexa (antifibrinolytic) 500 mg p.o. TID to prevent menorrhagia ongoing
- (b)(6)- Prednisolone 10 mg p.o. QD for ITP from pre-study to day 43
- (b)(6)- Tranexamic Acid) 500 mg p.o. TID to prevent menorrhagia ongoing
- (b)(6)- Tranexa 500 mg p.o. TID to prevent menorrhagia days 6 to 27
- (b)(6)- Wysolone (corticosteroid) 10 mg p.o. QD for ITP days 2 to 43
- (b)(6)- Tranexa 500 mg p.o. QID prn bleeding from pre-study to day 6, days 21-28
- (b)(6)-- Azoran (immunosuppressive) 100 mg p.o. QD for ITP ongoing**
- (b)(6)-- Danazol 200 mg p.o. BID for ITP ongoing**
- (b)(6)-- Prednisone 40 mg po q.d. for ITP days 21-32
- (b)(6)-- Tranexamic [acid] 500 mg po. TID to prevent bleeding days 1-5, 21 – 37
- (b)(6)-- Wysolone (glucocorticoid) 10 mg p.o. qd for ITP ongoing
- (b)(6)-- Wysolone (glucocorticoid) 5 mg p.o. qd for ITP pre-study to day 32
- (b)(6)-- Methyl Prednisona 10 mg p.o. QD for ITP pre-study to day 49

The list above shows that 4 subjects received 5 androgens or immunosuppressives other than glucocorticoids. Their doses were stable during the period of the trial used for the primary endpoint efficacy analysis. Eleven subjects took glucocorticoids during the study.

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

None contained in the submission from clinical trials.

9.1.2 Use During Lactation

9.1.3 Pediatric Use and PREA Considerations

The product, having orphan designation, is exempt from PREA.

Study GMX02 had 3 pediatric subjects, which, as stated in the draft package insert, is insufficient to characterize its efficacy and safety in the various pediatric subpopulations.

9.1.4 Immunocompromised Patients

Seven subjects in study GMX02 had undergone splenectomy. Stable doses of corticosteroids and/or other immunosuppressives were permitted under the protocol. Four subjects took immunosuppressives for ITP other than glucocorticoids. Their doses were stable during the period of the trial used for the primary endpoint efficacy analysis. Eleven subjects took glucocorticoids during the study.

9.1.5 Geriatric Use

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. CONCLUSIONS

The efficacy and safety of GAMMAPLEX has been established in the single pivotal phase 3 IND clinical trial, GMX02. The product met its primary endpoint. Both secondary endpoints were suggestive of benefit:

- The median duration of platelet count response to a level of $> 50 \times 10^9/L$ response for responders was 10.0 days.
- The prevalence of all categories of bleeding was substantially reduced from baseline to day 9.

The data from the study suggest a potential for product-induced hemolysis. Most drops in Hb were mild and those few that were more substantial were confounded by bleeding. Risk factors for hemolysis deduced from the literature and from CBER's OBE analysis of data from various IGIVs include non-O blood group and doses ≥ 2 g/kg (whether split among several days or given in a single infusion)

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

Data from completed phase 3 study GMX02 indicate that in chronic ITP patients with a platelet count $< 20 \times 10^9/L$ the benefits outweigh the risks of therapy with Gammaplex in the dose of 1.0g/kg daily x 2. Substantial evidence of efficacy and safety for the requested indication for the treatment of adults with chronic ITP have been demonstrated.

The efficacy supplement is approvable, but a complete response letter is recommended because the sponsor has not responded to a request for numerous further changes to the draft package insert. Data regarding adverse reactions in the submitted draft package insert and inaccurate and misleading.

Going forward, I recommend FDA consider requiring sponsors designing trials of IGIVs in chronic ITP to study the low dose regimen. Analysis of hemolysis cases following IGIV administration for the entire class of U.S.-licensed products has been by CBER's Office of Biostatistics and Epidemiology and suggests that doses of 2g/kg (whether single or divided among different days) may be associated with a greater risk of clinically significant hemolysis. The literature suggests that the high dose regimen for ITP is associated with a higher incidence of AEs but is approximately as effective as the high dose regimen. The latter may offer greater patient and HC provider convenience, however.

11.2 Risk-Benefit Summary and Assessment

See above section 11.1.

11.3 Discussion of Regulatory Options

See section 11.

11.4 Recommendations on Regulatory Actions

I recommend the sponsor be sent a complete response letter listing the outstanding changes to the package insert that FDA has requested/is requesting. The application is otherwise approvable from the medical perspective and from the perspective of all relevant reviewing disciplines.

11.5 Labeling Review and Recommendations

See separate labeling review memo and letter-ready comments under RECOMMENDATIONS.

11.6 Recommendations on Postmarketing Actions

None.

AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMV	cytomegalovirus
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
DIS	Division of Inspections and Surveillance
eCTD	electronic Common Technical Document
-(b)(4)-	------(b)(4)-----
ES	Executive Summary
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
NDA	new drug application
NME	new molecular entity
OBE	Office of Biostatistics and Epidemiology
OCOD	Office of Communication Outreach and Development (CBER)
OSE	Office of Surveillance and Epidemiology
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
REMS	risk evaluation and mitigation strategy
RMS/BLA	regulatory management system for the biologics license application
RTF	refuse to file
SAE	serious adverse event

APPENDICES

FDA Information Requests - Clinical and Statistical – With Sponsor Responses Dated 14 June 2012 (Amendment 03) and 28 June 2012 (Amendment 5)

05 June 2012 – With Sponsor Responses Dated 28 June 2012 (Amendment 5)

1. The submitted draft hard copy annotated package insert (PI) is unsatisfactory because it does not highlight all new additions and changes to the PI. For example, the new indication is not highlighted. Please correct this and also submit a copy of the currently approved PI.

Sponsor Reply:

[Amend 05] We have now supplied clean copy of the draft PI which includes all new additions and indications.

Reviewer Comment:

Regarding your 28 June 2012 hard copy response to item 1 of our 05 June 2012 information request, we note that all new (compared to currently approved labeling) additions and changes to the PI are still not highlighted in either the “Draft PI” or the “Draft PI with Changes.” Please submit an electronic version of the draft annotated package insert in Microsoft Word which highlights all new (compared to currently approved labeling) proposed additions and changes to the PI and which contains annotations providing the location of data supporting the proposed additions.

2. Please submit electronic versions of the clean and annotated redline/strikeout versions of the draft PI.

Sponsor Reply:

We have provided clean copy of the currently approved PI and a redline//strikeout versions [sic] of the draft PI.

Reviewer Comment:

There is no submission in the EDR under this STN corresponding to the sponsor's 28 June hard copy submission received 29 June 2012. Rather, there are electronic folders received 09 May 2012 with an 08 May 2012 (original submission) cover letter stating that BPL had been granted orphan status for the new ITP indication and therefore did not need to submit a pediatric waiver request. Another folder under this date is labeled "PI-draft-4.1-dated-23Mar12-Annotated rev CHD 22Mar12 FINAL.doc," which fails to highlight or annotate the new ITP indication either in HIGHLIGHTS or in the full prescribing information. A 14 May submission folder contains only a cover letter of the same date in 2012 which states they are submitting an amendment in response to a request to resubmit the form 3674, as well as the completed form, which cites NCT # 00504075 for the ClinicalTrials.gov data bank entry.

3. Please submit electronic SAS transport files for the clinical data for the study supporting the new indication with a document giving expanded definitions of the field names.

Sponsor Reply:

[Amendment 05] Not addressed.

Reviewer Comment:

The sponsor skips over this question in its point-by-point response letter dated 11 June 2012 included with its 28 June 2012 Amendment 05.

4. Please revise the draft PI, taking into account postmarketing ADR experience to date. Please submit a supporting postmarketing ADR report and line listings of all postmarketing ADRs received since marketing inception, organized by body system and including both verbatim terms and coding dictionary terms.

Sponsor Reply:

[Note: The sponsor requested and received an extension to respond until 30 June 2012.]

5. Please correct the indications listed in the PI to reflect the fact that the primary humoral immunodeficiency indication is limited to adults and that the new indication would be limited to adults, give the paucity of pediatric subjects in your studies.

Sponsor Reply:

[Amendment 03]

With regard to question 5 relating to limiting Primary immunodeficiency (PID) and the new indication (i.e. ITP) to adults. The current Prescribing Information (covering the licensed indication of Primary Immunodeficiency, PID) was approved by FDA with no specific request to limit the original indication (i.e. PID) to adults (see attached version of the current approved Prescribing Information). We are unsure why this position should be altered now, particularly as we have in excess of 2 years post-marketing experience with the product and we are also running a post-marketing study in children with PID.

Additionally, we have extended the text in section 8.4 to cover pediatric use in the ITP indication. This is to be consistent with the current approved wording for pediatric use in PID, which was already present in this section.

[Amendment 05] Not addressed.

Reviewer Comment:

The sponsor skips over this question in its point-by-point response letter dated 11 June 2012 included with its 28 June 2012 Amendment 05.

22 June 2012

1. According to your study protocol, you planned to conduct an interim analysis when 27 evaluable patients have completed Day 9 evaluation. But there seems to be no interim study report in the submission. Please clarify if you had conducted the interim analysis or not and if so, please submit your interim analysis results.

06 July 2012 – With Sponsor Responses dated 11 July 2012 (Amendment 07):

“As communicated to you by email on June 5, 2012:

1. Please correct the indications listed in the PI to reflect the fact that the primary humoral immunodeficiency indication is limited to adults and that the new indication would be limited to adults, give the paucity of pediatric subjects in your studies. Please make these changes notwithstanding the foreign marketing experience of this product.

Sponsor Reply:

BPL submitted a response to this question on 28 June 2012.

With respect to the small number of pediatric patients, BPL provided a response on 14 June 2012: The current Prescribing Information (covering the licensed indication of Primary Immunodeficiency, PID) was approved by FDA with no specific request to limit the original indication (i.e. PID) to adults (see attached version of the current approved Prescribing Information). We are unsure why this position should be altered now, particularly as we have in excess of 2 years post-marketing experience with the product and we are also running a post-marketing study in children with PID.

Additionally, we have extended the text in section 8.4 to cover pediatric use in the ITP population. This is to be consistent with the current approved wording for pediatric use in PID, which was already present in this section.

Reviewer Comment:

Dr. Jain has agreed to my request to hold a teleconference with the sponsor to inform them of the need to restrict the existing PI and new ITP indication to adults, given the paucity of pediatric data, in order to conform to CRB current thinking for this class of products.

2. Please revise the draft PI, taking into account postmarketing ADR experience to date. Please submit a supporting postmarketing ADR report and line listings of all postmarketing ADRs received since marketing inception, organized by body system and including both verbatim terms and coding dictionary terms.

Sponsor Reply:

BPL submitted a response to this question on 28 June 2012.

Reviewer Comment:

A Postmarketing Safety Report for Gammaplex 5% Liquid IGIV covering the period 17 Sept 2009 (Int'l Birth Date of Product) to 31 May 2012 was included in the sponsor's 28 June 2012 amendment 05.

3. Please provide the location in the BLA of the report for the interim analysis for the chronic ITP study. According to the protocol, you had planned to conduct one interim analysis when 27 evaluable patients had completed Day 9. This analysis was to have been used to re-estimate the sample size.

Sponsor Reply:

The interim analysis gave the same conclusion as the final study report. Our US agent submitted the interim analysis on 10 July 2012.

23 July 2012

1. Please make the following additional changes to the draft package insert:
 - a. In HIGHLIGHTS, WARNINGS AND PRECAUTIONS:
 - i. Please move the bullet regarding thrombotic events to just above the bullet which begins "Hyperproteinemia..." and reword as follows: "Thrombotic events may occur. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity (5.3)."
 - ii. Please reword the bullet concerning hemolysis to read "Hemolysis that is either intravascular or due to enhanced red blood cell sequestration can develop subsequent to Gammaplex treatments. Risk factors for hemolysis include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia (5.6)."

- iii. Please add the following new bullet following the one above concerning hemolysis: “Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload (5.8).”

b. In the FULL PRESCRIBING INFORMATION section:

- i. Reverse the order of the “Thrombotic Events” and Hyperproteinemia...” subsections of WARNINGS AND PRECAUTIONS sections and their respective entries in the Contents listing.
- ii. Revise the 2nd sentence in subsection 2.2.2 of DOSAGE AND ADMINISTRATION to read “Carefully consider the relative risks and benefits before prescribing the high dose regimen (e.g., 1 g/kg/day for 2 days) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload (see Warnings and Precautions [5.8])” and place it as a separate paragraph.
- iii. Revise the first sentence of the 2nd paragraph of the Thrombotic Events subsection of WARNINGS AND PRECAUTIONS to read “Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.”
- iv. Under the Hemolysis subsection of WARNINGS AND PRECAUTIONS:
 - 1. Please revise the first paragraph to read “Gammaplex may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin test (DAT) (Coombs’ test) result and hemolysis.⁵⁻⁷ Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.⁸ Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of IGIV.”
 - 2. Please insert a new paragraph following the above paragraph which reads ”The following risk factors

may be associated with the development of hemolysis following IGIV administration: high doses (e.g., ≥ 2 g/kg), given either as a single administration or divided over several days, and non-O blood group.[Ref: Kahwaji J, Barker E, Pepkowitz S, et al. Acute Hemolysis After High-Dose Intravenous Immunoglobulin Therapy in Highly HLA Sensitized Patients. *Clin J Am Soc Nephrol* 2009;4:1993-1997. Other individual patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV, [Ref: Daw Z, Padmore R, Neurath D, et al. Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: A case series analysis. *Transfusion* 2008;48:1598-1601.] but their role is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP and PI.⁷

3. Please revise the third paragraph to read “Closely monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform additional confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

- v. Add a new subsection entitled "Volume Overload" under WARNINGS AND PRECAUTIONS just above the "Transmissible Infectious Agents" subsection which reads "Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload."
- vi. Please change the pH range in draft package insert (PI) section 11 (DESCRIPTION) as following from 4.8 - 5.1 to --(b)(4)--:

"Gammaplex is a ready to use sterile solution of polyclonal human Immunoglobulin G for IV administration that contains sorbitol, glycine and polysorbate 80 as stabilizers. Specifically, Gammaplex contains approximately 5 g normal human immunoglobulin and 5 g D-sorbitol in 100 mL of buffer solution containing: 0.6 g glycine, 0.2 g sodium acetate, 0.3 g sodium chloride, and ~5 mg polysorbate 80. Immunoglobulin G purity is > 95%, the pH is in the range of 4.8 to 5.1 (b)(4), and osmolality is not less than 240 mOsmol/kg (typically 420 to 500 mOsmol/kg)...."

Sponsor Response of 31 July 2012:

(Excerpt)

"Implementing this change will require revision to the current license specification and also put at risk a small number of batches which may not comply with the proposed -(b)(4)- pH specification. BPL is unclear why this change is necessary and requests that FDA consider retaining the current specification range for pH, which will then require no further change to section 11 (Description) of the PI."

2. Viral clearance capacity of canine parvovirus (CPV) (overall value of 4.6) in the manufacturing process is proposed in the log reduction factor (LRF) table (Table 3) in the PI draft section 11. Please provide supporting information regarding CPV LRF, including relevant supplements' STN numbers.

Sponsor Response of 31 July 2012:

Please find attached dossier section including the associated appendices.

M3-2-P-3-5-24 Viral adventitious agents (page 13-14)
App 7 V856 Study report (Gammaplex DV20)
App 8 V885 Study Report (Gammaplex DV20 ---(b)(4)---)
App 11 V801 Study report (Gammaplex low pH)

The data required for this supporting information is detailed in section M3-2-P-3-5-24 as submitted with the BLA, and supporting data is provided in the associated appendices.

27 Aug 2012

1. According to your protocol you may analyze the data when at least 27 evaluable subjects have completed Day 9, and the observed response rate would be estimated and compared with the historical control to re-estimate the sample size. But there seems to be no such analysis report in the submission. Please clarify if you have conducted this analysis or not and if so whether you have adjusted your sample size based on this interim result and what sample size re-estimation method you used. Please submit related analysis report if you conducted such analysis.

FDA Information requested dated 18 October 2012 with sponsor responses dated 30 October 2012 (received 02 November 2012) and 08 Nov 2012, together with Reviewer Comments

1. Please correct the indications listed in the PI to reflect the fact that the primary humoral immunodeficiency indication is limited to adults and that the new indication would be limited to adults, give the paucity of pediatric subjects in your studies.

Sponsor Response:

The Prescribing Information has now been corrected.

NB. BPL has data on 17 pediatric [Primary Immunodeficiency] subjects and is hoping to discuss this further with FDA regarding retaining the original pediatric indication.

Reviewer Comment:

Noted. The sponsor has not limited the PI and new ITP indications to adults as requested. Dr. Jain asked the sponsor to submit interim pediatric data in primary humoral immunodeficiency from the ongoing PMC pediatric phase 4 study under a separate STN as a final study report, describing efforts to recruit subjects into the lowest age stratum which remains not fully enrolled. Submission of pediatric data from that study will likely be classified as an efficacy supplement if it contains substantial clinical data not limited to PK data, which would trigger a user fee. Such data should not be submitted under this STN for the new chronic ITP indication.

2. Please adequately disclose financial arrangements with clinical investigators of study GMX02 as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. Please submit completed Form 3454 under Module 1.3.4 of the electronic Common Technical Document (eCTD) structure.

Sponsor Response:

Form 3454 was omitted from the original submission package in error. Please find the completed and signed form 3454 along with a table of investigators and sub-investigators who participated in this study (See Appendix 1). Please note, due to an oversight during the study the details for two investigators and 3 sub investigators were not submitted as an IND amendment (highlighted in red in the table). We have also submitted the CVs and the 1572 forms for the two missing investigators.

Reviewer Comment:

Form 3454 is included in this amendment. Box 1 is checked, suggesting on substantial financial conflict of interest on the part of the investigators listed on the form, which go up to site 315.

3. Regarding your 28 June 2012 responses to our 05 June 2012 information request,

a. [Re: items 1 and 2] We note that all new (compared to currently approved labeling) additions and changes to the PI are still not highlighted in either the hard copy “Draft PI” or the hard copy “Draft PI with Changes.” Although your PDF file, “02 – Package Insert – Annotated.PDF” from your subsequent 31 July 2012 amendment received 02 August 23012 does highlight changes to the currently approved PI, it does not contain annotations which show the location in the supplement of data to support the proposed changes. Please submit an electronic version of the draft annotated package insert in Microsoft Word which highlights all new (compared to currently approved labeling) proposed additions and changes to the PI and also which provides annotations indicating the location in the application of data to support the requested changes.

Sponsor Response:

An electronic version of the draft annotated package insert in Microsoft Word highlighting the new proposed additions and changes to the PI and also with annotations indicating the location in the application of data to support the requested changes has now been provided.

Reviewer Comment:

Noted. The revised draft package insert requires numerous changes and is being reviewed under a separate labeling review memo.

4. Although page 7 of the study report states that 5 subjects had reports of pyrexia considered product-related, page 8 of the report states that “No severe or moderate changes in temperature were observed.” Please reconcile this apparent discrepancy.

Sponsor Response:

Of the 5 subjects where pyrexia was considered product-related all of these episodes were mild in severity (see below for the specific episodes of pyrexia for the 5 subjects extracted from data listing 17 (“All Adverse Events”). Therefore the statements on pages 7 and 8 are both correct.

Reviewer Comment:

Noted. The sponsor also included a table showing that all reported fevers were rated as mild in severity.

5. Please state the number of subjects you consider to have experienced treatment-emergent hemolysis and provide the criteria you use to make this assessment.

Sponsor Response:

See section 6.1.12.5 Adverse Reactions of Special Interest of this review for the sponsor’s narrative response.

Table 1 summarises the conclusions with regard to possible haemolysis. Overall, there were 23 cases without evidence of haemolysis, 6 with possible extravascular haemolysis, one with possible intravascular haemolysis, one with possible combined intra- and extra-vascular haemolysis, two with possible haemolysis but without clear evidence of site(s). There were two unassessable cases. Table 2 presents the commentaries for each case extracted from the Appendix which includes the relevant data from the key Listings in the CSR.

Subject number	Overall conclusion
--(b)(6)--	Possible intravascular haemolysis
--(b)(6)--	None
--(b)(6)--	Possible mixture of intra- and extra-vascular haemolysis
--(b)(6)--	None
--(b)(6)--	None
--(b)(6)--	Haemolysis possible but ongoing bleeding likely
--(b)(6)--	None
--(b)(6)--	Slow mild extravascular haemolysis possible
--(b)(6)--	Unassessable
--(b)(6)--	Possible haemolysis
--(b)(6)--	None
--(b)(6)--	None
--(b)(6)--	Unassessable
--(b)(6)--	Possible extravascular haemolysis with bleeding
--(b)(6)--	None

Subject number	Overall conclusion
--(b)(6)--	Possible extravascular haemolysis
--(b)(6)--	Possible extravascular haemolysis
--(b)(6)--	None
--(b)(6)--	None
--(b)(6)--	Possible extravascular haemolysis
--(b)(6)--	None
--(b)(6)--	Possible extravascular haemolysis
--(b)(6)--	None
--(b)(6)--	None
--(b)(6)--	Possible extravascular haemolysis
--(b)(6)--	None

Subject number	Overall conclusion
--(b)(6)--	<u>Commentary</u> This subject (blood group O -, see Listing 4 in CSR) had a decrease in Hb of >1g/dL coincident with each of two courses of Gammaplex. DAT remained negative throughout as was urinary haemosiderin. LDH remained in the normal range with no appreciable variation after the two courses of Gammaplex. There was a delayed reduction in haptoglobin (Day 16) which was also below the normal range on Day 43 after the second course of Gammaplex, but DAT remained negative as did LDH. This is a complex haematological picture which does not clearly indicate either intravascular or extravascular haemolysis. The subject had an epistaxis on 07Feb2008 (Day 4, see Listing 17 in CSR) and rectal bleed on 24Feb2008 (Day 21, see Listing 17 in CSR) which do not seem likely to have affected the changes recorded. The pathogenesis of the decrease in Hb on the two occasions is uncertain but may represent mild intravascular haemolysis insufficient to deplete haptoglobin.
--(b)(6)--	<u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) did not have a decrease in Hb of >1 g/dL and the tests do not support potential haemolysis. The subject had bruising of back and arm on Day 29 (15Jul2009, see Listing 17 in CSR), which may have been the cause of the late decrease in Hb on that day (Day 29).
--(b)(6)--	<u>Commentary</u> This subject (blood group A+, see Listing 4 in CSR) had a decrease in Hb of 1 g/dl on Day 3 and the following day was found to have a positive DAT and urine was positive for haemosiderin. Haptoglobin was marginally below the normal range on Day 14, coincident with a decrease in Hb of 2.6 g/dL. This large decrease in Hb followed shortly after the subject had severe vomiting and dehydration (on 27/28 Mar2008, see Listing 17 in CSR). It is possible that this subject had a mixture of intravascular and extravascular haemolysis, although LDH

Subject number	Overall conclusion
	was well within the normal range on both occasions it was measured.
--(b)(6)--	<p><u>Commentary</u> This subject (blood group O-, see Listing 4 in CSR) did not have a decrease in Hb of ≥ 1g/dL and the haematological parameters did not indicate any potential haemolysis; the only abnormality was a very marginal increase in LDH above the normal range on Day 7 (to 210 IU/L) but ALT, AST and bilirubin were all normal throughout (see Listing 24.1 in CSR).</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) had a decrease in Hb of 1.5 g/dL (Day 3). All DATs were positive including the two before administration of Gammaplex. LDH was raised to a similar low level on both occasions it was measured (Days 5 and 17), but this subject had raised AST and ALT from screening virtually throughout the period of observation but bilirubin was consistently normal (see Listing 24.1 of CSR). The separate isoenzymes comprising LDH were not assayed so the change in total LDH, at least in this case is likely to be a result of hepatic dysfunction rather than red cell destruction. In conclusion, because of the consistently positive DAT even well before the administration of Gammaplex, with the normal haptoglobin, negative urine haemosiderin and only marginally high LDH associated with ‘transaminasaemia’, there is no clear evidence that Gammaplex administration led to haemolysis.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group B+, see Listing 4 of CSR) had a decrease in Hb after the first dose of Gammaplex reaching a maximum decrease of 1.0 g/dL on Day 14. DAT was positive on Days 6 and 14 but urine haemosiderin was negative on Day 14 and LDH was within the normal range – at the top end on Day 14. The subject also developed petechiae on Day 6 (28Apr2008, see Listing 17 in CSR) and had gingival bleeding on Day 14 (06May2008, see Listing 17 in CSR), which suggests some ongoing bleeding – the subject did not respond to Gammaplex (Listing 24.2 of CSR). These results suggest some ongoing bleeding, but the possibility that haemolysis had taken place during the 14 days after infusion of Gammaplex cannot be ruled out.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group O+, see Listing 4 of CSR) had a decrease in Hb after the first dose of Gammaplex reaching a maximum decrease of 1.5 g/dL on Day 11. A decrease did not occur immediately after the second course of Gammaplex (Days 49/50) but was delayed until Day 53. DAT, haptoglobin, urine haemosiderin and LDH were all normal. This subject had a platelet response to Gammaplex after both courses, but had gingival bleeding on Day 23 (30Jul2008, see Listing 17 of CSR) and one week of abdominal pain from Days 32-39 (08-15Aug2008, see Listing 17 of CSR) which could have been the source of blood loss although no overt loss was reported. There was no evidence of haemolysis in this patient so it is possible that the decreases in Hb were related to the incidences of bleeding when platelets were low.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group A+, see Listing 4 in CSR) did not have had a decrease in Hb of > 1 g/dL. However, DAT was positive on four occasions after Gammaplex although haptoglobin and LDH were within the normal range throughout. Urine was positive for haemosiderin on Day 38 coincident with a positive DAT. The subject entered the study with bruising (21-25Jul2008) which recurred on 12-29Aug2008 (see Listing 17 in CSR) when there had been decreases in Hb. In conclusion, this subject may have had a slow mild extravascular haemolysis accompanied by some bleeding.</p>

Subject number	Overall conclusion
--(b)(6)--	<p><u>Commentary</u> This subject (blood group A+, see Listing 4 in CSR) did not have had a decrease in Hb of >1 g/dL, although follow-up was too short to make any definitive comments. The subject had entered the study with a gastrointestinal bleed on Days 1-2 (12-13May2008, see Listing 17 in CSR) and had bruising on Day 2 (see Listing 17 in CSR). The GI bleed may have been the reason for the decrease in Hb (0.3 g/dL).</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) entered the study with a low Hb but had a decrease of >1 g/dL on Day 2. At no times were DAT or urine haemosiderin positive, and haptoglobin remained within the normal range. LDH was marginally raised on both occasions it was measured, although ALT, AST and bilirubin were normal throughout (see Listing 24.1 in CSR). Although it is possible that there was some haemolysis in this subject, the supporting information is limited and the subject had anaemia pre-study.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group A+, see Listing 4 in CSR) entered the study with a low Hb (118 g/L) but did not have a decrease of >1 g/dL (there was an increase on Day 2). Although haptoglobin decreased to just below the normal range on Day 14, there had not been a clinically important decrease in Hb (118 to 116 g/L) and all other tests for potential haemolysis were normal. In conclusion, there is no evidence of haemolysis in this subject.</p>
--(b)(6)--	<p><u>Commentary</u> Although this subject (blood group O+, see Listing 4 in CSR) had a decrease of >1 g/dL on Day 5 (26Mar2010), all tests of possible haemolysis were normal. Therefore, there is no evidence to indicate a haemolytic process in this subject.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) had a decrease of >1 g/dL on Day 2 (25May2010) but had experienced abdominal pain on that day (Day 2, see Listing 17 in CSR) but there is no evidence of a GI bleed. No tests to assess possible haemolysis were conducted in this subject after the start of Gammaplex. This case is unassessable.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group A+, see Listing 4 in CSR) had a decrease of >1 g/dL on Day 2 reaching a maximum decrease on Day 10 (07Aug2010) but with a secondary decrease, maximum on Day 86, (the day after the first infusion of Gammaplex of the subject's second course). DAT and urine haemosiderin were negative but haptoglobin was lower than the normal range and LDH was above the normal range on all three occasions. ALT and AST were normal throughout but bilirubin was raised, including at screening (see Listing 24.1 in CSR). The subject had a good but brief response to Gammaplex after both courses but platelets were very low from 11Aug2012 to 21Oct2010 (Days 14-85, see Listing 24.2 in CSR) suggesting there may have been some occult bleeding around this time when there was a decrease in Hb. In conclusion, it is possible there was some extravascular haemolysis in this subject, together with some occult bleeding.</p>

Subject number	Overall conclusion
--(b)(6)--	<u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) had a decrease of 1 g/dL on Day 87, the day of the second infusion of Gammaplex in this subject's second course. There were small decreases in Hb after the first course (Day 2 – 14) but the only abnormal result of the tests for possible haemolysis was a slightly raised LDH on Day 6 (ALT, AST and bilirubin were normal throughout, see Listing 24.1 in CSR). In conclusion, clinically significant haemolysis is unlikely in this subject.
--(b)(6)--	<u>Commentary</u> This subject (blood group B+, see Listing 4 in CSR) had a decrease of >1 g/dL on Day 2 reaching a maximum decrease on Day 6 (21Mar2011). DAT and urine haemosiderin were negative throughout but LDH was marginally raised on Day 14; ALT, AST and bilirubin were normal throughout (see Listing 24.1). In this subject it is possible there was some extravascular

Overall conclusion

--(b)(6)--	<p><u>Commentary</u> This subject (blood group A+) had a decrease of Hb of >1 g/dL after each of the three courses. DAT and urine haemosiderin were negative throughout, but LDH was raised on Days 4, 14 and 36 (this day was day 6 after the start of the second course). On Day 9 ALT and AST were raised but these were isolated abnormal values. Bilirubin was intermittently raised including at screening (see Listing 24.1 in CSR). In conclusion, it is possible that there was some extravascular haemolysis in this subject.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) had anaemia on entry to the study but had no significant decrease of Hb. LDH was raised on Days 6, 14 and 39 (day 5 after the start of the second course of Gammaplex). ALT, AST and bilirubin were all normal except for an isolated high bilirubin on Day 126 (06Jul2010, see Listing 24.1 in CSR) which is remote from the infusions of Gammaplex. In conclusion, it is unlikely that there was any haemolysis in this subject.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group O-, see Listing 4 in CSR) did not have a decrease in Hb of >1 g/dL but had an isolated marginally raised LDH on Day 6. ALT, AST and bilirubin were all normal except for a marginally isolated increase in AST (47.0 IU/L) on Day 9 (29Apr2010, see Listing 24.1 in CSR). In conclusion, there is no evidence to indicate haemolysis in this subject.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) had a decrease in Hb of >1 g/dL on Day 2; Hb thereafter continued to decrease; this subject did not respond to Gammaplex and platelet remained consistently $<8 \times 10^9/L$ (see Listing 24.2 in CSR). DAT and urine haemosiderin were negative but haptoglobin was reduced on Days 6 and 14 with increased LDH on these days, too (ALT, AST and bilirubin remained within their normal ranges, see Listing 24.1 in CSR). On Day 5 (13Jun2010), the subject had menorrhagia and on Day 11 (19Jun2010) further vaginal bleeding. On Day 15 (23Jun2010), she reported petechiae. She had further menorrhagia on Day 76 (23Aug2010, see Listing 17 in CSR). The occurrence of the bleeding episodes likely account for a high proportion of the decreases in Hb. However, it is possible there was also a haemolytic component because of the reduced haptoglobin and raised LDH, probably extravascular.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group B+, see Listing 4 in CSR) had a decrease in Hb of >1 g/dL on Day 9 (28Aug2010) and had a marginally increased haptoglobin on Day 6 (25Aug2010) coincident with diarrhea (see Listing 17 in CSR). LDH was also slightly elevated on Day 6, but ALT, AST and bilirubin were normal throughout (see Listing 24.1 of CSR). DAT and urine haemosiderin were negative. The subject reported ecchymosis from 06Aug2010 (i.e. before Gammaplex) to Day 9 (28Aug2010, see Listing 17 in CSR). There had been a platelet response between Days 6 and 15 (see Listing 24.2 in CSR). In conclusion, there is little evidence that there was a significant haemolysis in this subject.</p>

--(b)(6)--	<p><u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) had a decrease in Hb of >1 g/dL on Day 2 (11Dec2010) and a second decrease on Day 9. There was also a decrease on Day 21 which was day 5 of the second course of Gammaplex. This subject had bruising on Day 2 (11Dec2010), haemorrhoidal pain on Day 7 (16Dec2010), epistaxis on Day 13 (22Dec2010) and repeated bleeding manifestations between Days 12 and 23 (21Dec2010 and 01Jan2011; see Listing 17 in CSR). AST was raised on Day 3 (12Dec2010; see Listing 24.1 in CSR) but this was an isolated increase before the noted raised LDH on Day 5. Despite the raised LDH on</p>
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Subject number	Overall conclusion
	Day 5 after the first course of Gammaplex, LDH was not raised on day 5 after the second course of Gammaplex (30Dec2010). Haptoglobin was normal throughout and DAT and urine haemosiderin were negative. In conclusion, there is no evidence that this subject is susceptible to haemolysis associated with Gammaplex. The decreases in Hb are more likely to be related to the repeated haemorrhagic episodes.
--(b)(6)--	<p><u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) had a decrease in Hb of >1 g/dL but not until Day 22 (21Mar2011), which is when the subject had pneumonia and sepsis (see later and Listing 17 in CSR). DAT and urine haemosiderin were negative and haptoglobin was well within the normal range. AST was raised before the study and was intermittently raised during; ALT was raised on Day 34 (02Apr2011) but bilirubin was negative throughout (see Listing 24.1 in CSR). LDH was raised on both occasions it was measured. The patient had diarrhoea (17-30Mar2011), fever (18Mar2011 to 02Apr2011), pneumonia and sepsis (21-31Mar2011), and hypokalaemia between 21 and 24 March 2011 (see Listing 17 of CSR). Although these various infections occurred after the period when LDH was raised, it is possible that the development of these pathologies played a role. In conclusion, it is unlikely that haemolysis was the cause of the decreases in Hb.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group A+, see Listing 4 in CSR) had a decrease in Hb of >1 g/dL but only after the second course of Gammaplex on Day 37 (13May2010). DAT and urine haemosiderin were negative and haptoglobin values were within the normal range even on Day 39, two days after the decrease in Hb, when LDH was also normal. LDH was raised on Days 6 and 14 and ALT was also raised on Day 9 (15Apr2010), although AST was normal throughout and bilirubin was normal on all occasions after Gammaplex; it was also raised at screening (see Listing 24.1 in CSR). In conclusion, there is no convincing evidence to suggest a consistent haemolytic process to account for the changes in Hb in this subject.</p>
--(b)(6)--	<p><u>Commentary</u> This subject (blood group B-, see Listing 4 in CSR) had a decrease in Hb of >1 g/dL on Day 3 (29Apr2010) and LDH was raised on Days 4 and 14 (ALT, AST and bilirubin were all normal throughout, see Listing 24.1 in CSR); haptoglobin was within the normal range and DAT and urine haemosiderin were negative. It is possible the raised LDH was a result of some haemolysis, but the pre-treatment value to assess whether the high values were increased after the infusions is not known. Therefore, in conclusion the possibility of some, possibly extravascular, haemolysis cannot be excluded.</p>

Subject number	Overall conclusion
--(b)(6)--	<u>Commentary</u> This subject (blood group A+, see Listing 4 in CSR) had a decrease in Hb of >1 g/dL on Day 8 (16Aug2010) which continued to be less than the baseline until and including the end of study (EOS) assessment. There were no positive markers suggestive of haemolysis. There was a history of bleeding <i>per vaginam</i> from 24Aug2010 until 02Sep2010 (see Listing 17 of CSR), at the time the subject had a very low platelet count (see Listing 24.2 in CSR), which may have been the cause of at least some of the decreases in Hb. In conclusion, there is no positive evidence to suggest haemolysis in this subject.
--(b)(6)--	<u>Commentary</u> This subject (blood group B+, see Listing 4 in CSR) did not have a decrease in Hb of >1 g/dL during the study. The only abnormality was a raised LDH on Day 14 when the Hb had hardly moved from the baseline. There is no evidence of haemolysis in this subject.
--(b)(6)--	<u>Commentary</u> This subject (blood group B+, see Listing 4 in CSR) had a decrease in Hb of >1 g/dL on Day 2 (24Nov2010) which reached a maximum decrease on Day 19 (11Dec2010), but DAT and

<p>haemosiderin were negative and haptoglobin values were within the normal range. LDH was above the upper limit of the normal range on Day 5 and at the top of the normal range on Day 14 (ALT was raised at screening and at all other times except end of study, EOS); AST was raised on Days 1, pre-Gammaplex, and Day 9; bilirubin values were all normal throughout, see Listing 24.1 in CSR). It is possible the raised LDH was a result of some haemolysis, but the pre-treatment value to assess whether the high values were increased after the infusions is not known. Therefore, in conclusion the possibility of some, possibly extravascular, haemolysis cannot be excluded.</p>	
<p>--(b)(6)--</p>	<p><u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) did not have a decrease in Hb of >1 g/dL until Day 35, which is not close to any infusion. DAT and urine haemosiderin were negative and haptoglobin increased on Day 14 (25Mar2011); the subject had had fever on 12Mar2011 followed by vomiting and dehydration from Days 3-7 (14 -17Mar2011, see Listing 17 in CSR), so the increase may have been a result of its role as an acute phase protein. The raised LDH on Days 5 and 14 are not readily explicable as ALT, AST and bilirubin were normal at these times (see Listing 24.1 in CSR). In conclusion, there is no evidence of a clinically significant haemolysis in this subject.</p>
<p>--(b)(6)--</p>	<p><u>Commentary</u> This subject (blood group B+, see Listing 4 in CSR) did not have a decrease in Hb of >1 g/dL at any time in the study. However, LDH was slightly increased on Day 5 (17Apr2011), but was within the normal range by Day 14. All other markers of potential hemolysis were normal. This subject did not respond to Gammaplex (see Listing 24.2 in CSR). In conclusion, it is unlikely that there was any clinically relevant haemolysis in this subject.</p>
<p>--(b)(6)--</p>	<p><u>Commentary</u> This subject (blood group B+, see Listing 4 of CSR) appeared to have a decrease in Hb of 3.9 g/dL on Day 3 but Hb had recovered by Day 5. There was a secondary decrease of 1.6 g/dL (from baseline) on Day 15, although Hb values were fluctuating for much of the study. All markers of potential haemolysis were normal. In conclusion, there is no evidence to suggest haemolysis in this subject.</p>
<p>--(b)(6)--</p>	<p><u>Commentary</u> This subject (blood group A+, see Listing 4 in CSR) had a decrease in Hb of >1 g/dL on Day 3 (25Aug2010) which reached a maximum decrease on Day 5. All markers of potential haemolysis were normal. In conclusion, there is no evidence to suggest haemolysis in this subject.</p>
<p>--(b)(6)--</p>	<p><u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) had a decrease in Hb of >1 g/dL on Day 33 (14May2010) which was the second day of the second course of Gammaplex. After the first course, the Hb decreased by a maximum of 0.9 g/dL on Day</p>

	2 without any positive evidence from the markers of potential haemolysis. In conclusion, there is no evidence to suggest haemolysis in this subject.
--(b)(6)--	<u>Commentary</u> This subject (blood group O+, see Listing 4 in CSR) did not have a decrease in Hb of >1 g/dL at any time, nor were the markers of potential haemolysis positive. In conclusion, there is no evidence to suggest haemolysis in this subject.
--(b)(6)--	ALT was increased on Days 3 and 9 (see Listing 24.1 in CSR). All the other markers of potential haemolysis were normal. In conclusion, because of the gynaecological bleed close to the start of Gammaplex, there is no substantial evidence to suggest haemolysis.

[The sponsor also submitted an appendix which contains line listings of pertinent laboratory data by date for the above cases to support their conclusions regarding possible hemolysis cases.]

Reviewer Comment:

Letter-ready comment:

- a. Please include a sentence in this [ADVERSE REACTIONS] section indicating that, based on a review of clinical and laboratory data, 4/35 subjects (11%) with drops in hemoglobin exceeding 2g/dL following administration of Gammaplex were considered to have experienced suspected treatment-emergent hemolysis. Milder treatment-emergent hemolysis could not be excluded for an additional 7 subjects, giving a total of 11 of 35 subjects (31%) for whom hemolysis could not be excluded (not including an additional two subjects WHO lacked follow-up testing for hemolysis, so their hemolysis status was considered unassessable). Data for two subjects were consistent with possible intravascular hemolysis, including one subject who may also have had an element of extravascular hemolysis. Nine of the possible hemolysis cases were mild and appeared consistent with possible extravascular hemolysis.

6. Please modify the CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections of the draft package insert to add a contraindication for patients with hereditary fructose intolerance and for infants and neonates for whom sucrose or fructose tolerance has not been established.

7. *Sponsor Response:*

The sponsor added this in the draft PI submitted 30 Oct 2012.

Reviewer Comment:

See separate labeling review memo.

7. Please describe in detail efforts made to contact the 5 subjects (14%) who were lost to follow-up in the comparatively short duration chronic ITP study, GMX02.

Sponsor Response:

A total of 35 subjects were enrolled and treated with study drug. All of the subjects were included in the safety and ITT populations. Twenty-seven subjects (77.1%) completed the study, and eight subjects (22.9%) discontinued from the study prematurely.

One subject discontinued after the first infusion because of an AE of severe headache (Subject --(b)(6)--). Five subjects discontinued after two infusions, of whom three were lost to follow-up (Subject --(b)(6)-- -----, Subject --(b)(6)-- and Subject --(b)(6)--), one withdrew consent (Subject --(b)(6)--) and one required other therapeutic intervention for thrombocytopenia (Subject --(b)(6)--). Two subjects discontinued after four infusions, both of whom were lost to follow-up (Subject --(b)(6)-- and Subject --(b)(6)--).

[The sponsor also included a table detailing efforts to contact subjects lost to f/u.]

Reviewer Comment:

Review of the table detailing efforts to contact subjects lost to f/u reveals that, for subject --(b)(6)--, no letter was sent to the subject to attempt follow-up, however the subject missed 2 visits and was not reachable by phone on one occasion to confirm the day 90 f/u visit. Subject --(b)(6)-- also evidently was not sent a letter in an effort to f/u with the subject regarding the missed day 90 visit, although telephone contact was attempted.

8. Please provide the location in the submission where you report the results of subgroup analyses of the primary and secondary efficacy endpoints by sex and by race. Please submit the results of these analyses if they have not been submitted previously.

Sponsor Response:

[The sponsor provided appropriate subgroup analyses by sex and by race for the primary efficacy endpoint, for TEAEs, SAEs, related AEs, discontinuations due to AE, AEs which began during or within 72 hours of an infusion, and the most common temporally associated AEs.

Reviewer Comment:

Noted. For the primary efficacy endpoint, the observed response rate was 88.9% for men (LL 95% CI: 68.9%) and 80.8% for women (LL 95% CI: 63.7%).

The percentage of male subjects reporting TEAEs was 67% vs. 73% for women.

The percentage of male subjects reporting TEAEs considered product related by the investigator was 56% vs. 38% for women.

Two males (22%) and 2 females (8%) reported SAEs of which 2 among males (22%) and one among females (4%) were considered product related by the investigator.

One male (11%) and zero females discontinued due to an AE. Six males (67%) and 18 females (69%) reported AEs that began during or within 782 hours of infusion.

The most common AEs considered product related by the investigator that began during or within 72 hours of an infusion were headache, reported for 4 males (44%) and 5 females (19%), vomiting, reported for 2 males (22%) and 3 females (12%), and nausea, reported for zero males and 3 females (12%).

The primary endpoint response rate was similar among Caucasians (8/10 = 80%), Hispanics (3/3 = 100%), and Asians (18/22 = 82%).

No SAEs were reported among Caucasians, 1 (33%) was reported among Hispanics, and 3 (14%) were reported among Asians.

No Caucasians, no Hispanics, and 1 Asian (4%) discontinued prematurely due to an AE.

AEs which began during or within 72 hours of an infusion of study product were reported for 7 Caucasians (70%), 3 Hispanics (100%), and 14 Asians (64%).

Headache considered product related was reported less frequently among Caucasians (10%) than among Hispanics (33%) or Asians (32%), but the small size of the subgroups precludes definite conclusions in this regard.

2. You stated that study GMX02 is an international trial and the study sites are in the United States, India and Argentina. Please conduct a subgroup analysis by region for the primary efficacy endpoint and key safety endpoints to assess if the results are consistent across region.

Sponsor Response:

Primary efficacy endpoint:

A subgroup analysis by country was conducted using the Clopper-Pearson method. The observed response rate at a 95% lower one-sided CI was calculated (Table 2 below), and compared to the observed response for “All Subjects” in the study.

Table 2 Response Rate for All Subjects and by Country (Intent-to-treat Population)

Platelet Count $\geq 50 \times 10^9/L$

Response Rate

**95%
Lower 1-Sided**

On or Before Day 9

n

Observed

All Subjects ^b	35		
Confidence Limit^a			
Yes	29	82.9%	
No	6		
USA ^c	9		
Yes	8	88.9%	57.1%
No	1		
India ^c	21		
Yes	17	81.0%	
61.6% No	4		
Argentina ^c	5		
Yes	4	80.0%	
No	1		

a Calculated using the Clopper-Pearson exact method.

b Table 9 dated 09Dec11 (supplied in the original submission, section 14.2). Cross reference Listing 13. c Table 9 dated 26Oct12. Cross reference Listing 13.

The study was not powered for a sub group analysis by country. The observed response rate was highest in the USA (88.9%) with India and Argentina showing responses of 81% and 80% respectively. These differences are not significantly different. The observed response rates for each country compare favorably to the response rate for “All Subjects” thus suggesting there was little variation between regions. However, due to the small number of subjects with consequential lack of power for the sub group analysis, the lower bound of the 95% confidence limits cannot be relied upon to form any meaningful conclusion on efficacy.

Key safety endpoints:

A summary of adverse events by country was used to compare variations between regions (See Table 3 below).

Table 3 Overview of Adverse Events for All Subjects and by Country (Safety

Populations)		
All Sub	N = 35	
ects with TEAEs	n (%)	Confidence Interval^a
	25 (71.4)	53.7, 85.4
USA	8 (88.9)	51.8, 99.7
India	15 (71.4)	47.8, 88.7
Argentina	2 (40.0)	5.3, 85.3
All Subjects with no TEAEs	10 (28.6)	
14.6, 46.3		
USA	1 (11.1)	0.3, 48.2
India	6 (28.6)	11.3, 52.2
Argentina	3 (60.0)	14.7, 94.7
All Subjects with product-related TEAEs (i.e. ADRs) ^b	15 (42.9)	26.3, 60.6
USA	4 (44.4)	13.7, 78.8
India	10 (47.6)	25.7, 70.2
Argentina	1 (20.0)	0.5, 71.6
All Subjects with TEAEs unrelated to product	10 (28.6)	14.6, 46.3
USA	4 (44.4)	13.7, 78.8
India	5 (23.8)	8.2, 47.2
Argentina	1 (20.0)	0.5, 71.6
All Subjects with SAEs	4 (11.4)	3.2, 26.7
USA	1 (11.1)	0.3, 48.2
India	3 (14.3)	3.0, 36.3
Argentina	0	
0.0, 52.2		
All Subjects with product-related SAEs (i.e. serious ADRs) ^c	3 (8.6)	1.8, 23.1
USA	1 (11.1)	0.3, 48.2
India	2 (9.5)	1.2, 30.4
Argentina	0	0.0, 52.2
All Subjects with SAEs unrelated to product	1 (2.9)	0.1, 14.9
USA	0	0.0, 33.6
India	1 (4.8)	0.1, 23.8
Argentina	0	0.0, 52.2
All Subjects discontinued because of AEs	1 (2.9)	0.1, 14.9
USA	0	0.0, 33.6
India	1 (4.8)	0.1, 23.8
Argentina	0	0, 52.2

Abbreviations: ADR, adverse drug reaction; AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Note: Only AEs with onset between first infusion date and 30 days after the last infusion are included.

a Two-sided 95% confidence interval of percent (exact method).

b Includes all AEs (and SAEs) that were possibly, probably or definitely related to product.

c Includes all SAEs that were possibly, probably or definitely related to product.

Source: Cross reference listing 17 of the CSR. See Table 15 Sub group Analysis Summary of Adverse Events by Region dated 07Nov1212. Also Table 15 dated 09 Dec11 (supplied in the original submission, Section 14.3).

Regional variation in adverse events suggested that Argentina generally reported less treatment emergent adverse events (TEAEs), i.e. in 40% (2/5) of subjects, compared to USA and India, who reported in 88.9% and 71.4% of subjects respectively. India reported product-related TEAEs (ADRs) in 10 subjects, (47.6%), which was higher than in both the USA (4 subjects, 44.4%) and Argentina (1 subject, 20%). However, all the confidence intervals were wide with appreciable overlap, suggesting there were no significant differences between regions with regard to reporting either TEAEs or product-related TEAEs.

The majority of SAEs reported in the study were in India, with the exception of one product-related SAE in the USA. As these are very small numbers no conclusion can be drawn.

A regional analysis was conducted for the number and percent of subjects with and adverse events and with product-related adverse events as a function of time after infusion (See Table 4 below and Appendix, Table 24x dated 26Oct12).

Table 4 Number and Percent of Subjects with Any Adverse Events and Product-related Adverse Events within 72 hours of Infusion by Country - Safety population (N=35)

Country	Any AEs			
	Product-Related AEs		Within 72 hours	
	Subjects n (%)	Events n	Subjects n (%)	Events n
USA	9 (100.0)	33	5 (55.6)	14
India	13 (61.9)	52	10 (47.6)	34
Argentina	2 (40.0)	3	1 (20.0)	1

Derived from Table 24 dated 26Oct12 and Table 24x dated 26Oct12

The highest proportion of subjects reporting any adverse event within 72 hours was in the USA, i.e. all nine subjects (100%), this compares to 13 subjects (61.9%) in India and 2 subjects (40%) in Argentina. The number of events reported per subject in this period was between 3 and 4 except in Argentina where it was 1.5 (3/2) but because of the small number of subjects the difference is not clinically significant.

Five subjects in the USA reported 14 product-related adverse events (ADRs) within 72 hours after an infusion (Table 4), i.e. a mean of 2.8 per subject which was similar to the subjects in India (3.4 [34/10] per subject). The small number of subjects in Argentina makes comparison with this country inappropriate. These analyses, therefore, do not suggest any appreciable regional variation in adverse event reporting. They also suggest there is little difference between the subjects in India and those in the USA with the tolerability of Gammaplex.

The most common product-related AEs within 72 hours of infusion by region were analysed (see Table 5 below).

Table 5 Most Common Product-Related Adverse Events within 72 hours of Infusion by Region - Safety population (N=35)

Adverse Event Preferred Term	USA		India		Argentina	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Headache	2 (22.2)	4	7 (33.3)	12	N/A	N/A
Vomiting	1 (11.1)	1	4 (19.0)	6	N/A	N/A
Pyrexia	1 (11.1)	1	4 (19.0)	5	N/A	N/A
Nausea	N/A	N/A	3 (14.3)	3	N/A	N/A
Pruritus	2 (22.2)	2	N/A	N/A	N/A	N/A

Derived from Table 24x dated 26Oct12

The commonest AE reported within the 72 hours after infusions in both USA and India was headache (4 events in 2 [22.2%] subjects and 12 events in 7 [33.3%] subjects respectively). However, none of the five subjects in Argentina reported headache during this 72 hours period. The next most common AE differed between the regions with pruritus in USA and vomiting in India. There is reasonable consistency between the regions considering the small number of subjects, especially in Argentina.

Reviewer Comment:

Noted. The results of the primary efficacy endpoint were similar across geographic regions. I agree with the sponsor's analysis that safety parameters appear to be generally similar across regions, but with a trend toward more frequent temporally associated AE reporting in the US than in India and more AE reporting in India than in Argentina.

Reviewer Comment:

1. In Section 11.4.1.1 of your clinical study report you stated that "Response to treatment on or before Day 9, as determined by a platelet count of $50 \times 10^9/L$ or greater in the ITT population, was achieved by 29 of 35 subjects (82.9%), with a 95% lower one-sided confidence limit of 68.9%". Please calculate and report the one-sided 97.5% Clopper Pearson lower confidence limit.

Sponsor Response:

The lower bound of the 97.5% one-sided CI for the primary endpoint = 66.4%.

Reviewer Comment:

The sponsor's result was verified by the FDA statistician. This meets the success criterion for the primary endpoint as stated in the Statistical Analysis Plan for the lower bound to be > 60%.

Discussion of Other Clinical Trials which Supported Approval of Other IGIV Products for Chronic ITP in Relation to Gammaplex Study GMX02

The pivotal Gammaplex study GMX02 was a single-arm phase 3 study in adults (and 3 children) with chronic ITP. The primary efficacy endpoint was increased platelet count by day 9 and the success criterion was defined

as the lower bound of the 95% or 97.5% confidence interval of the percentage of subject responders who exceeded a pre-specified threshold (of ~ 60%), which took into account the historical observation that only 5% or less of chronic ITP patients with a ≥ 6 month history of thrombocytopenia were observed to achieve spontaneous remission. Recent IGIV approvals for chronic ITP have been based on similar single-arm studies using an historical control. Such studies have generally enrolled subjects with chronic ITP whose baseline platelet counts were $< 20 \times 10^9/L$ and the primary endpoint has been defined as the proportion of subjects whose platelet counts rise to $> 50 \times 10^9/L$ within a specified time frame of approximately 7 days, depending on the particular trial.

Prior to the recent single-arm studies, Bayer (acquired by Talecris and now Grifols) had performed a double-blind, randomized, parallel clinical trial with 97 ITP subjects having baseline platelet counts $< 20 \times 10^9/L$ comparing Gamunex (now Gamunex-C) against a previously marketed IGIV, Gamimune N, 10%. Both products were administered at 1.0 g/kg on each of 2 consecutive days. In that trial, which enrolled 97 ITP subjects (24% pediatric (age ≤ 16 years) and 76% adults), 35/39 (90%) of subjects in the per-protocol analysis in the Gamunex-C group achieved an increase to $> 50 \times 10^9/L$ in platelet count within 7 days of treatment and 29/39 (74%) of subjects had a sustained platelet response to $> 50 \times 10^9/L$ for 7 days. For Gamimune N subjects, responders in the per-protocol analysis were 35/42 (83%) by day 7 and 25/42 (60%) for subjects having a sustained platelet count for 7 days.