Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Normal Immunoglobulin (human)

Proprietary Product Name: Gamunex

Sponsor: Talecris Biotherapeutics Pty Ltd

December 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission: Extension of Indications and New Route of Administration

Decision:	Approved
Date of decision:	17 October 2011
Active ingredient:	Normal Immunoglobulin (Human)
Product name:	Gamunex
Sponsor's name and address:	Talecris Biotherapeutics Pty Ltd 120 Collins St, Melbourne VIC 3000
Dose form:	Solution for Injection
Strengths:	10% solution for Injection; 1g/10 mL, 2.5g /25 mL, 5g/ 50 mL, 10g/ 100 mL and 20g/ 200 mL
Containers:	Single Use Glass vials
Approved therapeutic use:	*Replacement therapy* in: · Primary Immunodeficiency (PI) Diseases. · Symptomatic Hypogammaglobulinaemia secondary to underlying disease or treatment. *Immunomodulation* in: · Idiopathic Thrombocytopaenic Purpura (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count. · Guillain Barré Syndrome (GBS). · Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). · Kawasaki disease.
Routes of administration:	Intravenous (IV) or subcutaneous (SC) infusion (latter in PI disease only).
Dosage:	2 g/kg for ITP and 2 g/kg loading dose and 1 g/kg maintenance dose in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).
ARTG numbers:	117237, 117238, 117239, 117240 and 116689

Product background

Gamunex is a ready to use sterile solution of human normal immunoglobulin 10% solution for intravenous (IV) use which was first registered in Australia in April 2006 (AUST R 116689, 117237, 117238, 117239 and 117240).

This AusPAR describes an application by the sponsor for an extension of indications and for a new route of administration of Gamunex with the following details:

· subcutaneous (SC) infusion for the treatment of Primary Immune Deficiency (PID)

· an extension of indications to include Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and the treatment for

- Congenital hypogammaglobulinaemia,
- Multiple myeloma (MM)
- Chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections,
- Children with congenital AIDS[1] and recurrent severe bacterial infections,
- Guillian Barré Syndrome (GBS),
- Kawasaki disease (KD),
- Allogeneic bone marrow transplantation (BMT).

The sponsor also proposes to update the manufacturing process, that is, to change the Gamunex final container (low pH) incubation time from 21 to 28 days to 14 to28 days.

Gamunex is a commercially available intravenous (IV) IgG product in a number of countries for the treatment of PID.

The sponsor's rationale for the change in the route of administration was that for SC infusions of immunoglobulins:

· replacement venous access is not required,

· patient tolerance is acceptable, and

· in home or self administration are facilitated.

There has been renewed interest over the last few years in the SC delivery of IgG, especially when administered in the home setting for the treatment of PID.

The sponsor withdrew a proposal for a higher IV infusion rate for Gamunex.

The maximum clinical IV dose of 600 mg/kg (6 mL/kg) every 3 to 4 weeks for Primary Humoral Immunodeficiency is to remain. However, the proposed weekly SC dose for replacement therapy in primary humoral immunodeficiencies will be calculated "by multiplying the IV Gamunex dose by 1.37, then dividing this dose into weekly doses based on the subject's previous IV Gamunex treatment interval."

Regulatory status

The overseas regulatory status for Gamunex is summarised in Table 1.

[1] Acquired Immune Deficiency Syndrome

Table 1. Overseas Regulatory Status.

Country where similar submission made for the additional well established indications	Registration/ Approval Dates	Comments
Sweden	15/06/2007	
United Kingdom	27/07/2006	
Canada	11/08/2003	
Country where similar submission made for the CIDP indication		
EU (via Mutual Recognition procedure (MRP) with Germany as the Reference Member State)	12/06/2009	
Canada	03/02/2009	
United States of America	09/12/2008	Orphan Designation
Country where similar submission made for subcutaneous infusion for the Primary Humoral Immunodeficiency indication		
Canada	13/05/2010	
United States of America	13/10/2010	

Subcutaneous infusion has been approved by the FDA and Health Canada for use in PID patients. The CIDP indication has also been approved by the FDA (September 2009), Health Canada and some the EU countries including the UK, Sweden and the Netherlands. The higher infusion rate has been approved for Gamunex marketed in Canada and the 16 EU countries including the UK, Sweden and the Netherlands.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Update to manufacturing process

The manufacturer proposes to change the manufacturing process by reducing the final container (low pH) incubation time.

Currently, Gamunex is incubated in the final container at a pH of 4.0 to 4.3 and at a temperature of 23°C to 27°C for between 21 and 28 days. Based on data from current viral validation studies, the sponsor proposes that the time of incubation can be changed from 21-28 days to 14-21 days.

This step in the manufacturing process is one of the key steps for viral inactivation and has been validated for the reduction of viruses. In particular, this step in the process targets enveloped viruses. Validation studies have been performed using a final container of Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified (IGIV-C; Gamunex) spiked with enveloped virus (3.2.A.2).

With regards to this change, the following is a summary of the outcomes of the quality evaluation process which are noteworthy:

- The sponsor (Talecris) confirmed that six final container lots of Gamunex that were incubated for less than 21 days (the new manufacturing procedure) has been placed in the stability program under licensed storage conditions. These lots will be continuously monitored on stability through shelf life. Talecris commits to inform TGA of any stability excursions for these lots.
- The company was questioned about the impact that the decreased final container (low pH) incubation time might have on thromboembolic adverse events (TAE) associated with the use of an IVIG preparation. Talecris responded to this by indicating that batches of Gamunex Drug Substance (initial sterile bulk) subjected to thrombin generation test (TGT) and non-activated partial thromboplastin time (na-PTT) test adapted from European Pharmacopiea (Ph. Eur. 2.6.22) all showed no response above baseline or were comparable to buffer control. Further, testing on 15 consecutive lots of Drug Products did not show pro coagulation activity by TGT.
- The applicant confirmed that 'no other aspects of the quality information have been changed, including procedures and equipment, raw material, and finished product specification other than the change submitted to shorten the low pH incubation time from 21 days to 14 days'.
- The TGA Pathogen Safety evaluation has been completed and there are no outstanding issues.
- Generally, the labelling and packaging are considered acceptable. An issue raised in the labelling evaluation (the way in which the IgG content was presented) is considered minor and discretionary and is unlikely to affect the information conveyed about the quality of the product.

There were no other outstanding quality issues that need to be addressed.

The Pharmaceutical Subcommittee (PSC) was asked to review the quality evaluation report(s) and to advise the TGA if there were any outstanding issues.

III. Nonclinical findings

Introduction

Nonclinical references referred to in this AusPAR are listed at the end of the document under *Nonclinical References*.

Several published scientific papers were submitted, in which it was shown that subcutaneous administration of IgG was safe and effective (Berger, 2004; Chapel *et al*., 2000; Gaspar *et al*., 1998; Nicolay *et al*., 2006; Ochs *et al*., 2006; Smith *et al*., 1972; Waniewski *et al*., 1994), even during pregnancy (Berger *et al*., 1982) and in children (Gardulf *et al*., 2006) with primary immunodeficiencies. Reviews of immunodeficiency diseases (IUIS Scientific Group) and IgG replacement therapies (Gelfland *et al*., 2003) were also submitted by the sponsor.

The maximum amount of IgG given in these studies was 20 mL/day, in a pregnant woman (Berger *et al*., 1982).

Other Normal Immunoglobulin products are approved for deep intramuscular (IM) and IV administration but not for SC administration. The sponsor provided a kinetics study in which the area under the plasma concentration time curve (AUC) after SC administration of Gamunex to rabbits was compared with SC administration of Gamunex and Vivaglobin

(SC normal IgG not approved in Australia). The study showed that SC administration of Gamunex at doses between 1.2 and 1.5 times the IV dose maintained blood levels of IgG that were comparable to those achieved by IV administration.

The maximum clinical IV dose of 600 mg/kg (6 mL/kg) every 3 to 4 weeks for Primary Humoral Immunodeficiency is to remain, however the proposed weekly SC dose for replacement therapy in primary humoral immunodeficiencies will be calculated "by multiplying the IV Gamunex dose by 1.37, then dividing this dose into weekly doses based on the subject's previous IV Gamunex treatment interval." This proposed method to calculate the SC dose is supported by the results of the rabbit kinetics study in which there were no significant differences in the plasma kinetic profiles between application of 100% of the approved dose IV and application of 137% of the dose SC. Although the rabbit data is not directly representative of human kinetics, the comparison provides some supporting evidence for the higher dose by the SC route.

The pharmacokinetic study was not Good Laboratory practice (GLP) compliant. The infusion rate, the weights of the animals, the manufacturing process for the test article (current or proposed), and description of any local adverse reaction observed were not provided in the report.

Although a high proportion (up to 92%) of new SC IgG (Vivaglobin® 16% IgG) patients in a study (Ochs *et al*., 2006) were found to experience mild to moderate local reactions (local swelling, soreness, redness, and induration), the sponsor did not provide a nonclinical local toxicity study in support of the proposed SC route of administration.

No efficacy, safety pharmacology, acute or repeat-dose toxicity or local tolerance studies by the proposed SC route were submitted for Gamunex. The sponsor justified the lack of new studies on the basis of:

1. prior toxicity studies by the IV route, and
2. claims a lack of toxicological effects in clinical studies and postmarketing use (sponsors Nonclinical Overview). Nonetheless, it is considered that such nonclinical studies were technically feasible.

The lack of carcinogenicity, genotoxicity and reproductive and developmental toxicity studies may be justified on several grounds:

- the active ingredient is a naturally-occurring plasma protein intended for replacement therapy;
- it has known pharmacological properties;
- it is in current clinical use; and
- repeated dosing in laboratory animal species would result in the induction of antibodies against the human proteins, making interpretation of the results difficult.

There are no nonclinical data in young animals to support the use of the product in paediatric patients. The approval of use in paediatric patients would have to rely on clinical experience with other normal immunoglobulin products as well as clinical data submitted for Gamunex.

Nonclinical summary and conclusions

1. The sponsor provided a kinetics study of SC Gamunex and another immunoglobulin in rabbits. The plasma bioavailability of Gamunex administered SC was similar to IV when administered at 120% to 150% of the IV dose. It was not stated in the study report if the tests had been carried out with a formulation including the proposed manufacturing process changes. No histopathology of the local injection sites was

conducted. The study resulted in single dose exposure margins of less than 0.1 fold for the immunoglobulins at the recommended dose for humans, both SC and IV.

2. No nonclinical efficacy, safety pharmacology, acute or repeat-dose toxicity or local tolerance studies by the proposed SC route were submitted. The sponsor justified the lack of new studies on the basis of (i) prior toxicity studies by the IV route, and (ii) claimed lack of toxicological effects in clinical studies and post-marketing use (sponsor's Nonclinical Overview). Nonetheless, such studies were technically feasible.
3. There were no genotoxicity, carcinogenicity or reproductive toxicity studies for Gamunex. This is acceptable given the human source of the active ingredient. There is no nonclinical data to support the use of the product in paediatric patients. The approval of use in paediatric patients would have to rely on clinical data.

Conclusions and recommendations

New nonclinical data consisted only of a single dose kinetics (bioavalability) study in rabbits which supported the proposed increase in SC dose, that is, 137% of the current IV dose.

No nonclinical efficacy, safety pharmacology, acute or repeat-dose toxicity or local tolerance studies by the proposed SC route were submitted. The sponsor justified the lack of new studies (see above). Nonetheless, such nonclinical studies were feasible. There were no nonclinical studies in young animals to support use in children.

In view of the very limited nonclinical testing of the proposed changes, demonstration of safety and efficacy will depend almost entirely on clinical data.

IV. Clinical findings

Introduction

Five clinical studies are included in the current submission: one study for subcutaneous infusion, one study for CIDP treatment, and three studies assessing rapid infusion rates. These five studies are listed below:

1. *Study 060001* evaluated the subcutaneous administration of Gamunex.
2. *Study 100538* assessed the use of Gamunex in the treatment of CIDP patients.
3. *Study 100213* assessed 3 infusion rates (0.08, 0.11, and 0.14 mL/kg/min) in ITP subjects
4. *Study 100422* evaluated two infusion rates (0.08, 0.14 mL/kg/min) in ITP subjects
5. *Study 100348* evaluated two infusion rates (0.08 and 0.14 mL/kg/min) in PID subjects.

The preparation of the protocol and the execution of each study were carried out following the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and any applicable regulations and local laws.

Pharmacokinetics

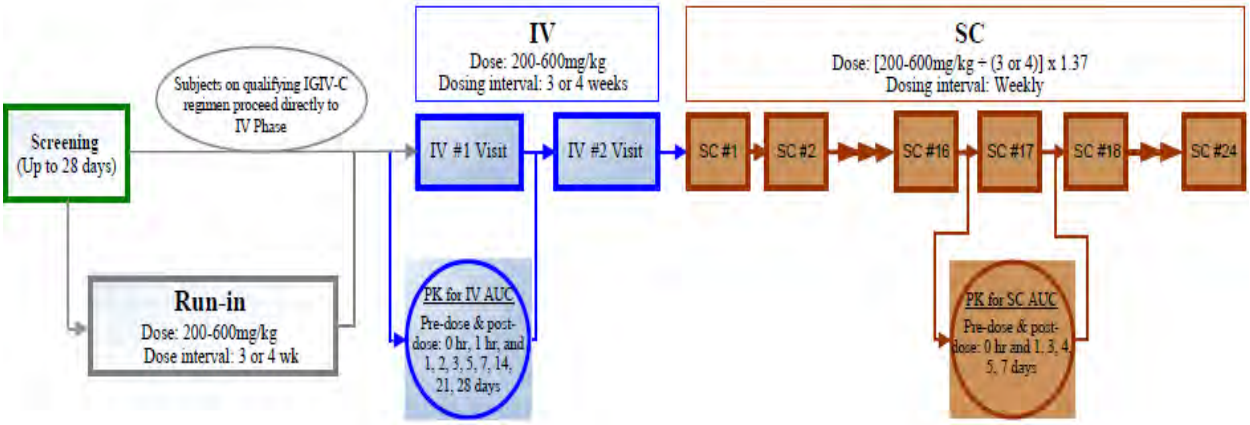
One clinical study (Study 060001) was provided to support the change to SC administration of Gamunex in patients with PID. It was an open-label, multi-center, single-

sequence, cross-over, pharmacokinetic (PK), safety and tolerability study of Gamunex administered SC in subjects with PID.

Study 060001

This study consisted of two PK phases: an IV phase followed by a SC phase. In addition, certain subjects were required to enter a Run-in phase prior to the IV phase in order to ensure that all subjects were at approximate steady state prior to entering the IV phase where PK parameters were to be measured. The primary PK objective was to determine a dose of weekly SC administration that produces a steady state AUC of plasma IgG that is non inferior to that of the regularly administered IV dose of Gamunex. The subject dosing and PK sampling schedules for both the IV and SC phases are shown in Figure 1 below.

Figure 1. Subject dosing and PK sampling in Study 060001.



Primary PK endpoint

- AUC in the IV phase: Steady state AUC of plasma total IgG administered IV over a regular dosing interval (τ), either every 3 weeks or every 4 weeks (that is, $AUC_{0\text{-}\tau\ IV}$; or $AUC_{0\text{-}21\ days\ IV}$ or $AUC_{0\text{-}28\ days\ IV}$, respectively)
- AUC in the SC phase: Steady state AUC of plasma total IgG over a weekly SC dosing interval (τ) (that is, $AUC_{0\text{-}\tau\ SC}$ or $AUC_{0\text{-}7\ days\ SC}$)

The PK population

The PK Population consisted of all subjects who received study medication and had sufficient and valid plasma total IgG concentration versus time data for either the IV or SC phase to allow calculation of $AUC_{0\text{-}\tau,\ SC}$ or $AUC_{0\text{-}\tau,\ IV}$ (Primary PK endpoint). The PK Population was used for the analyses of the Primary PK endpoint.

Statistical analysis

The IV phase was considered as the Reference phase and the SC phase as the Test phase. Any administration effect between SC and IV routes was assessed by exponentiation of the difference in least squares means (LSM) between the phases (Test minus Reference) and the corresponding 90% confidence interval (CI) for the geometric LSM ratio between study phases (Test/Reference) for AUC. The Test (SC) was to be considered non-inferior to Reference (IV) if the lower bound of 90% CIs for the geometric LSM ratios of AUC between the Test and Reference was above 0.80.

Disposition of study subjects

A total of 32 subjects completed the IV phase and had valid PK data for PK analysis. All 32 subjects then entered the SC phase. Seven subjects discontinued the SC phase, however, a total of 26 subjects had valid PK data in the SC phase for PK analysis. In the PK population,

78% (25/32) were women. The average age was 42.5 years. Three adolescents (one aged 13 and two aged 15) were included in the PK population. Two of them contributed to the PK data for calculating AUC for both IV and SC phases. One subject (a 15 year old) discontinued the study during the SC phase and thus only had IV PK data for calculating AUC_{IV}. Four elderly subjects (65 - 68 years) contributed both IV and SC data of plasma total IgG for PK analysis. The demographics for a subset of the PK population (subjects who had a PK profile in both the IV and SC phases) were similar to those of the total PK population.

Steady-state plasma concentrations of total IgG

The mean steady state concentration of total IgG versus time curves following both IV and SC administration of Gamunex are presented in Figure 2 below.

Figure 2. Mean steady state plasma total IgG concentration versus time curves following IV or SC administration (PK Population)

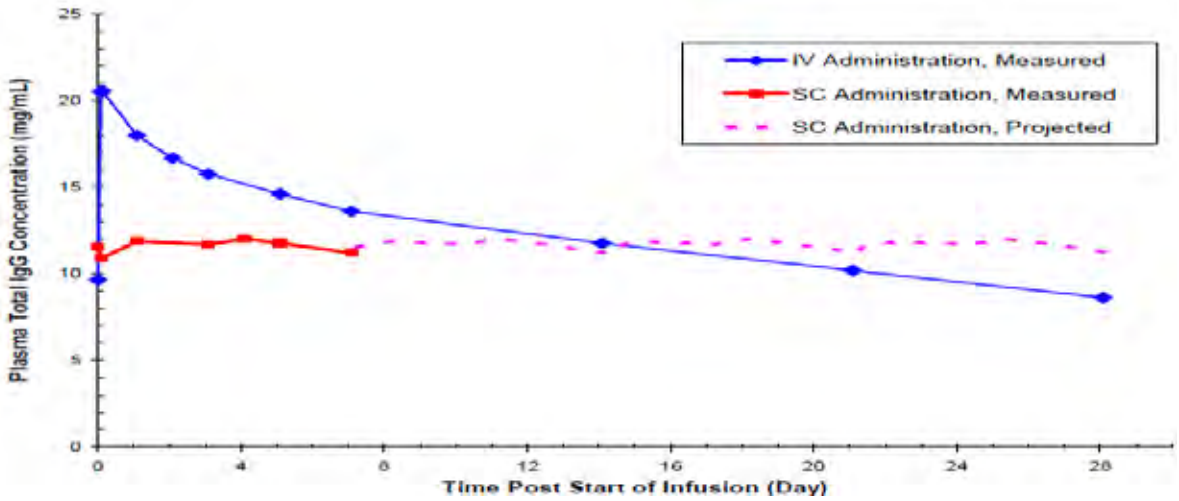


Figure 2 showed that weekly SC administration provided relatively constant steady state plasma concentrations of total IgG.

The results of the primary PK endpoint of plasma total IgG at steady state following IV or SC administration is summarized in Table 2 below.

Table 2. Summary of primary PK endpoint of plasma total IgG at steady state following IV or SC administration (PK Population)

Route of Administration	Statistics	$AUC_{0-\tau,IV}$ (mg*h/mL)	$AUC_{0-\tau,SC}$ (mg*h/mL)	Adj._$AUC_{0-\tau,SC}$[a] (mg*h/mL)
IV (n = 32)	Mean	7640	NA	NA
	%CV	15.9		
	Range	5616-10400		
SC (n = 26)	Mean	NA	1947	6858
	%CV		20.4	18.1
	Range		1300-2758	5169-10364

NA = not applicable; %CV = percent coefficient of variation.

[a] Adj._ $AUC_{0-\tau,SC}$: Adjusted $AUC_{0-\tau}$ after SC dosing, which is equivalent to $AUC_{0-\tau,SC}$ multiplied by 3 or 4 depending on the IV dosing frequency

The IV administration of Gamunex every 3 or every 4 weeks produced similar mean $AUC_{0-\tau,IV}$ values of 7448 and 7741 mg.h/mL in 11 and 21 subjects, respectively. The overall mean of $AUC_{0-\tau\ IV}$, regardless of the IV dosing schedule, was 7640 mg.h/mL in the 32 subjects. The weekly SC infusion (where SC doses were calculated using a conversion factor of 1.37 from the IV dose) produced a mean $AUC_{0-\tau\ SC}$ value of 1947 mg.h/mL (over a

7 day interval) which translated to a mean adjusted $AUC_{0-\tau\ SC}$ value of 6858 mg.h/mL over a 21 day or 28 day period (to compare to the regular IV dosing schedule).

The primary PK endpoint of plasma total IgG showed relatively small variability among subjects following either IV or SC administration as reflected by the %CV values for $AUC_{0-\tau IV}$ and $AUC_{0-\tau\ SC}$ of 16-20%. The conversion factor of 1.37 is adequate to produce these results.

Bioequivalence - statistical analysis of primary PK endpoint

Thirty-two subjects from the IV phase and 26 subjects from the SC phase provided the PK data for the PK endpoint analysis using analysis of variance (ANOVA). The ANOVA results are provided in Table 3.

Table 3. Statistical analysis of primary PK endpoint of plasma total IgG (PK Population)

Route	Primary PK Endpoint	Geometric Least-Squares Mean	Geometric LSM Ratio, SC/IV	
			Point Estimate	90% Confidence Interval
SC	Adj_$AUC_{0-\tau,SC}$[a]	6706	0.888	(0.861, 0.917)
IV	$AUC_{0-\tau,IV}$	7549		

LSM = Least square means

[a] Adj._ $AUC_{0-\tau,SC}$: Adjusted $AUC_{0-\tau}$ after SC dosing, which is equivalent to $AUC_{0-\tau,SC}$ multiplied by 3 or 4 depending on the IV dosing frequency

The results showed that the lower bound of the 90% CI for the geometric LSM ratio, SC/IV, of the primary PK endpoint of $AUC_{0-\tau}$ is above 0.80, indicating that the SC dose determined from the IV dose based on a conversion factor of 1.37 produces an AUC of plasma total IgG that is non inferior to that produced by an IV dose over an equal dosing interval. In addition, the overall 90% CI falls within the range of 0.80-1.25, an accepted criterion for "bioequivalence" between the two treatments. Therefore, the primary PK objective of this study was achieved by demonstrating that a conversion factor of 1.37 is appropriate when determining a SC dose from the IV dose of Gamunex.

Plasma trough concentration of total IgG

The average steady state mean through plasma level (C_{trough}) of total IgG determined across Week 13 to Week 21 of the SC phase in all subjects was 11.4 mg/mL (range: 8.10-16.2 mg/mL), which was 19% higher than the mean Ctrough of 9.58 mg/mL following the regular IV dosing of Gamunex. Weekly SC infusion of Gamunex provided relatively constant steady state plasma concentrations of total IgG. The IV administration of Gamunex resulted in steady state plasma total IgG levels fluctuating between 9.6 and 21.2 mg/mL, that is, a more than 2 fold range over a 3- or 4-week period.

It is important to note that the plasma C_{trough} values of total IgG in all subjects measured at each visit throughout the entire SC Phase were higher than the desired target therapeutic trough concentration of 5 mg/mL. In fact, all C_{trough} values in all subjects were 7.1 mg/mL or higher following SC administration, that is, the lowest measured C_{trough} for any individual SC visit during the study was 7.1 mg/mL.

Serum trough IgG subclasses concentrations

The serum trough concentrations of four IgG subclasses (IgG1, IgG2, IgG 3 and IgG4) were measured in both the IV and SC Phases. After the subjects were switched from IV to SC administration, the levels of all IgG subclasses were increased at Week 5 of SC infusion (when they were first measured). The increases were maintained throughout the SC Phase. The increases in average serum trough concentrations in the SC Phase as compared with the IV phase were 20.2% for IgG1, 15.2% for IgG2, 12.3% for IgG3 and 11.1% for IgG4. No preferential absorption or loss of IgG subclasses (IgG1, IgG2, IgG3, and IgG4) was

observed when Gamunex was administered by SC infusion. Proportions of the levels of IgG subclasses were consistent with a physiologic distribution pattern.

Serum trough antibacterial antibody concentrations

After the subjects switched from IV to SC administration, there was an average increase in antibody titers (for *Haemophilus influenzae* (*H. influenzae*) and *Streptococcus pneumoniae (S. pneumoniae*)) at SC Week 5 (the first measurement in the SC phase). These increased levels were maintained throughout the SC phase. The increase in the antibody titers ranged from 31.1 to 66.9%.

Pharmacodynamics

A pharmacodynamics (PD) study is not formally required for this type of product and no PD data have been submitted for Gamunex.

The PK results of Study 060001 showed that a weekly SC Gamunex dose calculated based on a conversion factor of 1.37 from the IV Gamunex dose (with adjustment of dosing interval) provides comparable overall SC plasma concentrations of total IgG, as determined by steady state AUC, to those IV plasma concentrations produced by the IV dose. The point estimate and 90% CI of the geometric LMS ratio for the steady state AUC demonstrates non inferiority of a SC infusion and bioequivalence between SC and IV infusions of Gamunex. The study also showed that the weekly SC infusion of Gamunex resulted in relatively constant steady state plasma levels of total IgG while the steady state IgG level with IV infusion fluctuations more than 2 fold (peak 21.2 mg/mL to trough 9.6 mg/mL) and the steady state mean C_{trough} of total IgG after weekly SC Gamunex dosing was 19% higher than the steady state mean C_{trough} after regular IV dosing. The trough concentrations of total IgG in all subjects at each visit throughout both the IV and SC phases were all above 6.3 and 7.1 mg/mL, respectively, and greater than the commonly accepted protective trough concentration of ≥ 5 mg/mL. The major determinant of the prevention of infections in PID patients is believed to be the maintenance of a minimum trough IgG level of ≥ 5 mg/mL.

The EU Guideline for SC IgG products[2] which has been adopted by the TGA requires PK and efficacy data to be collected from no less than 10 children and all patients should be followed over 6 months. Study 060001 included only three adolescents (13 to15 years old). This number was too small for a separate evaluation of paediatric PK and safety and it was not possible to determine whether paediatric and adult responses to Gamunex are different. The efficacy and safety of the SC route in paediatric patients have therefore not been established.

Efficacy

Introduction

One study (Study 100538) was submitted and evaluated for the efficacy and safety of Gamunex for the treatment of CIDP.

[2] Note for guidance on the clinical investigation of human normal immunoglobulin for subcutaneous and intramuscular use. EMEA/CPMP/BPWG/283/00. <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004255.pdf>

Study 100538

This was a multicenter, double-blind, placebo-controlled study with two randomisations and two periods of study. The study consisted of two randomizations: a 24 week Efficacy period and a 24 week Randomized Withdrawal Period.

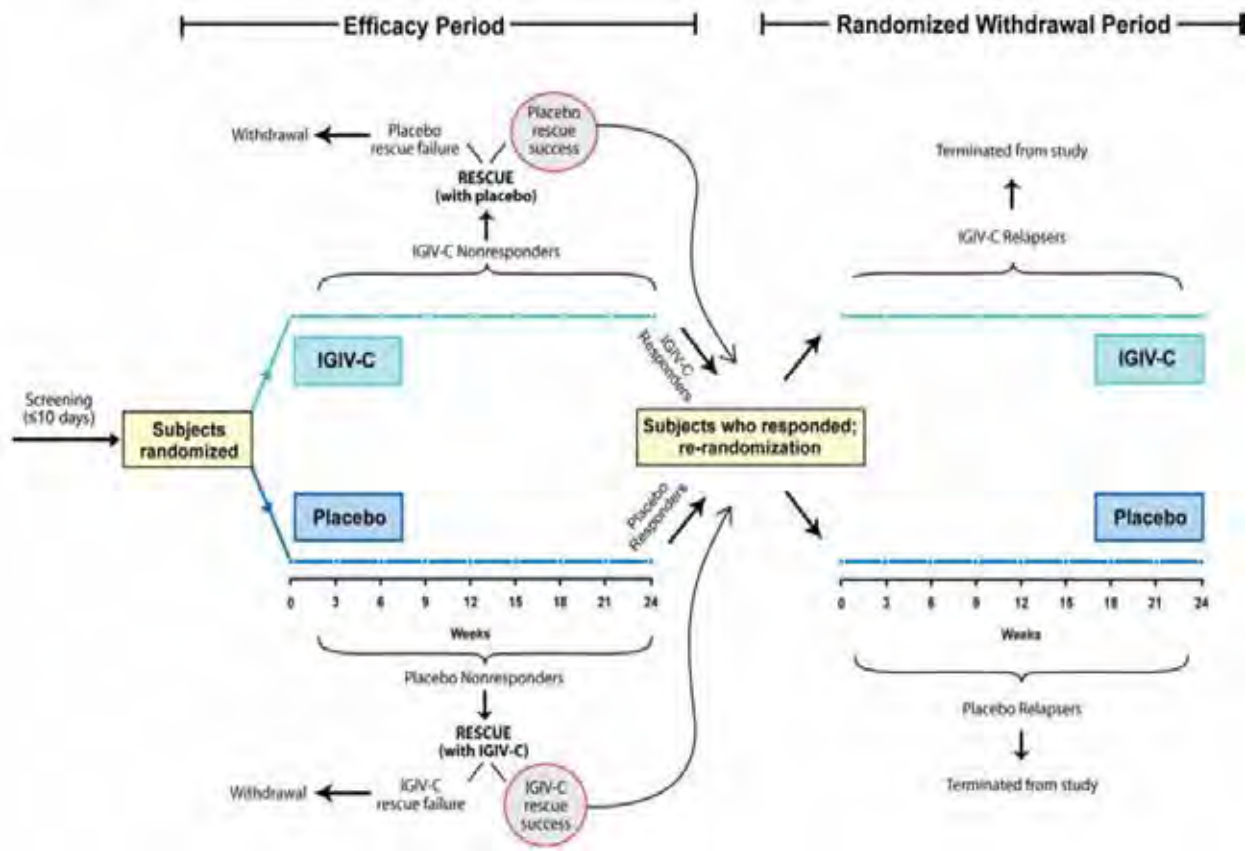
The two randomisation periods were included in order to address two separate questions.

1. The Efficacy Period aimed to answer whether Gamunex was more effective than Placebo for the treatment of CIDP. As CIDP is a disease that can go into remission and all Efficacy Period Responders must have had improvement by Week 3, there was concern that Responders might have gone into remission after their first two infusions of Gamunex. If these subjects were in remission, then the continued administration of Gamunex might have been unnecessary.
2. The second question was whether long term administration of Gamunex was necessary for long term benefit. Therefore, the Randomized Withdrawal Period evaluated the effect of withdrawing Gamunex from subjects who had improved during the treatment. If subjects who improved while taking Gamunex were in remission then there might be no effect from withdrawing Gamunex. This would suggest that long term administration was not necessary for long term benefit.

Hence, by including two randomizations in two separate study periods, the study assessed (in the Efficacy Period) the ability of Gamunex to produce the benefit and also the importance of long term administration for the maintenance of that benefit (in the Randomized Withdrawal Period).

An Efficacy Period Responder was defined as a subject with ≥ 1 point improvement in the adjusted European INCAT scale (Inflammatory Neuropathy Cause and Treatment scale), with the improvement maintained through the end of Week 24 in the Efficacy Period. If an INCAT scale score worsened by ≥ 1 point between Day 16 and Month 6, the subject crossed over to the other treatment (Blinded Rescue Treatment) for 6 months. Subjects with an unchanged INCAT score after Week 6 could also be crossed over to the other study drug at the study investigator's discretion. The subject flow into Efficacy Period and Randomized Withdrawal Period is presented in Figure 3 below.

Figure 3: Subject Flow into Efficacy Period and Randomized Withdrawal Period



Entry into the Randomized Withdrawal Period was only allowed for Efficacy Period Responders and Blinded Rescue Treatment successes. These subjects were randomised a second time to enter the blinded Randomized Withdrawal Period. A subject remained in the Randomized Withdrawal Period until relapse or for a maximum of six months (whichever came first). There was a requirement that a patient was to be removed from the Randomized Withdrawal Period when a worsening in the adjusted INCAT score relative to the baseline score at entry into this arm occurred.

Study participants

Adult subjects with a documented diagnosis of CIDP were enrolled. The diagnosis had to be made by a neurologist based on:

1. progressive or relapsing motor and sensory dysfunction of more than one limb resulting from neuropathy over the last two months, and
2. cerebro-spinal fluid (CSF) with less than 50 white cells/µl since CIDP diagnosis (CSF testing was not mandatory).

Eligible subjects had to fulfil the INCAT neurophysiological criteria for focal demyelinating polyradiculoneuropathy, an overall INCAT score between 2-9 and significant disability in upper or lower limb function in at least two limbs (an INCAT score of 2 had to be exclusively from leg disability to qualify).

Treatments

The test product was 10% Gamunex, the 10% Intravenous Human Immune Globulin manufactured using chromatography, supplied as liquid preparation in 50 mL (5.0 g) vials.

The Efficacy Period and the Rescue Treatment started with a loading dose of 2 g/kg body weight (bw) over 2 to 4 consecutive days. All other infusions (including the first infusion of the Randomized Withdrawal Period) were given as maintenance doses of 1 g/kg bw at

intervals of three weeks. The maximum dose was 80 g Gamunex per infusion day, even for subjects whose body weight exceeded 80 kg. The initial infusion rate was 0.02 mL/kg/min for the first 15 min. If there was no evidence of a hypersensitivity reaction, the infusion was given at a slowly increasing rate over the next 30 minutes up to a maximum allowable rate of 0.08 mL/kg/min.

Placebo was albumin (human) at a final concentration of 0.1% administered IV. According to the double-blind character of the study, the volume and mode of placebo infusion was identical to that of Gamunex.

If the adjusted INCAT score had deteriorated by ≥ 1 point after Day 15 the subject was entered into Rescue treatment with the alternate study drug. If the adjusted INCAT score was unchanged at Week 6, the subject was entered into the Rescue Treatment with the alternate study drug. A complete End of Treatment evaluation was required before the infusion of the alternate drug.

Primary efficacy endpoint

The primary efficacy endpoint was the adjusted INCAT score in the Efficacy Period. In 2003 when Study 100538 was being planned, the INCAT 10 point scale was a globally accepted disability scale used in studies of treatment in CIDP. The adjusted INCAT score is based on the 10 point INCAT scale measured at each study visit and is the primary outcome measure to determine if a subject is an Efficacy Period Responder. The adjustment was that an improvement in the 10 point INCAT score by only 1 point, due only to a change in the upper extremity score from 1 to 0, was deemed to be a Non Responder in the Efficacy Period by the adjusted INCAT score.

Endpoint for subjects who dropped out (did not enter Rescue Treatment) or for subjects who entered Rescue Treatment is the last INCAT assessment (after initiation of study drug infusion). Any subject who dropped out or entered Rescue Treatment was considered a Non Responder.

A Responder was a subject in the Efficacy Period who:

1. was not deteriorating at the Day 16 or Week 3 visit;
2. was improved (by ≥1 point on the adjusted INCAT score, relative to baseline) by Week 6; or
3. c) maintained a greater than1 point improvement through all visits, including the last visit at Week 24.

Secondary efficacy endpoints:

- Mean change (from baseline to endpoint) in amplitude in the most severely affected motor nerve during the *Efficacy Period*;
- Mean change (from baseline to endpoint) in grip strength during the Efficacy Period;
- The time to relapse for the Gamunex Efficacy Period Responders and Rescue Treatment successes who were then again randomised into the *Randomized Withdrawal Period*.

Sample size

The sample size estimation was conducted for the primary efficacy comparison of the blinded 6 month Efficacy Period. Assuming a response rate of 15% in the Placebo group and of 40% in the Gamunex group and a 5% two-sided alpha, a sample size of 49 subjects per group was required to show efficacy with 80% power by a Chi-square test. Assuming a dropout rate of 10%, 55 subjects per treatment group or a total of 110 subjects were planned to be enrolled in this study.

Statistical methods

The primary efficacy analysis was the comparison of the Responder rates in the Intention to Treat (ITT) population. The ITT population was defined as all randomised patients. Treatment group differences were tested by a Chi-square test. Subjects who did not complete the 24 week Efficacy Period and entered Rescue treatment with the alternative treatment were counted as Non responders. A supportive analysis using a Cochran Mantel Haenszel test (CMH test) adjusted for regions was conducted.

For secondary efficacy endpoints, analysis of covariance was used to compare the treatment differences for change from baseline in amplitude of the most severely affected motor nerve and change from baseline in grip strength. Kaplan-Meier estimates and log rank test were used to compare the treatment difference for time to relapse in the Randomized Withdrawal Period.

Results

A total of 117 subjects were randomised to either Gamunex (n = 59) or Placebo (n = 58) in the Efficacy Period. Of the 117 randomised subjects, 77 (66%) were men. Participants were aged between 18 and 83 years (mean age: 51.6 ± 16.5 years). The vast majority (91%) were Caucasians. Fifty of the 77 men (65 %) and 35 of the 40 women (88 %) were < 65 years of age.

An overview of the number of subjects in the different study periods and their distribution between the two groups are presented in Table 4 below:

Table 4. Number of randomised subjects in the Efficacy Period (Study 100538).

	Total N	IGIV-C N	Placebo N
Randomized	117	59	58
Efficacy Period	117	59	58
Rescue treatment	68	45	23
Randomized Withdrawal Period	73	43	31

Subject disposition across all periods

A summary of the subject disposition by study period is shown in Table 5 below. At the start of the Efficacy Period, the mean baseline INCAT score in the ITT population was 4.2 ± 1.4 points. The range extended from 2 to 9 points (consistent with the inclusion criteria), covering a wide range of functional disability. Both for the INCAT sub scores (upper and lower extremity scores) and for the INCAT total score, the mean values in the two treatment groups were comparable at study entry.

Table 5. Study 100538:S ubject disposition (all randomised subjects)

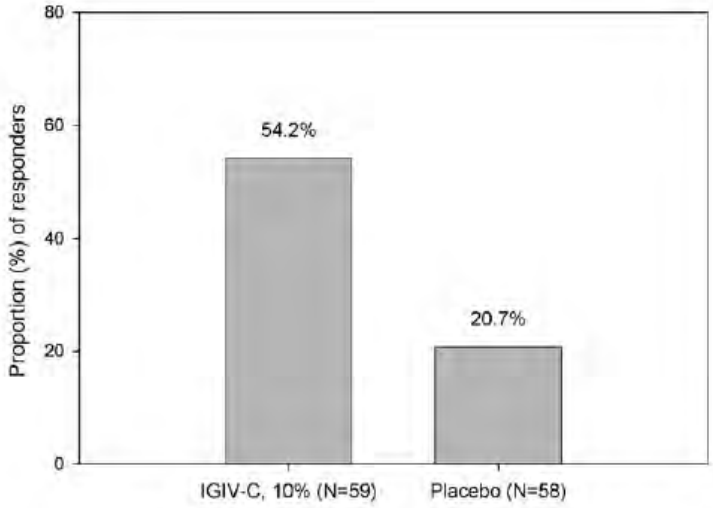
Phase	Status	N (%)	N (%)
Efficacy Period		IGIV-C	Placebo
	Enrolled and randomized	59 (100)	58 (100)
	Completed	33 (56)	12 (21)
	Responder	32 (54)	12 (21)
	Non-responder (at last visit)	1 (2)	0
	Not completed	26 (44)	46 (79)
	Reason for discontinuation		
	- INCAT failure (→ entered Rescue treatment)	23 (39)	45 (78)
	- Adverse event	1 (2)	1 (2)
	- Consent withdrawn	1 (2)	0
	- Protocol violation	1 (2)	0
Rescue treatment		IGIV-C	Placebo
	Entered	23 (100)	45 (100)
	Completed	5 (22)	26 (58)
	Success	5 (22)	26 (58)
	Non-Success (at last visit)	0	0
	Not completed	18 (78)	19 (42)
	Reason for discontinuation		
	- INCAT failure	16 (70)	16 (36)
	- Adverse event	0	2 (4)
	- Consent withdrawn	2 (9)	0
	- Lost to follow-up	0	1 (2)
Randomized Withdrawal Period		IGIV-C	Placebo
		(Treatment as responder)	
	Responder at the end of the Efficacy Period or Rescue treatment Success	58 (100)	17 (100)
	Entered	56 (97)	17 (100)
	Not entered	2 (3)	0
	Reason for not entering the Randomized Withdrawal Period		
	- Consent withdrawn	1 (2)	0
	- Insufficient therapeutic effect	1 (2)	0
		IGIV-C	Placebo
	No. of subjects treated after re-randomization [a]	43 (100)	31 (100)
	Completed	37 (86)	16 (52)
	Not completed	6 (14)	15 (48)
	Reason for discontinuation		
	- INCAT failure (relapse)	6 (14)	11 (35)
	- Adverse event	0	1 (3)
	- Non-compliance	0	1 (3)
	- Insufficient therapeutic effect (without relapse)	0	1 (3)
	- Lost to follow-up	0	1 (3)

[a]Subject no. 804001 completed the study in the IGIV-C group as Non-responder and entered the Randomized Withdrawal Period in error (re-randomized to the Placebo group).

Outcomes and estimation

The primary efficacy analysis was a comparison of Responder rates in the Gamunex and Placebo groups. In the ITT population, 32 (54.2%) of the 59 subjects in the Gamunex group and 12 (20.7%) of the 58 subjects in the Placebo group fulfilled the above criteria for a Responder, that is, they had an improvement in adjusted INCAT score by at least 1 point. The absolute difference in Responder rates between the two treatment groups was 33.5% (95% CI: 15.4% to 51.7%) in favour of the Gamunex treatment. This translates to a number needed to treat of 3 (95% CI of 2 to 7) in order to produce one Responder. The relative increase in Responder rate (difference in Responder rate between Gamunex and Placebo/Responder rate to Placebo) in the Gamunex group, compared to the Placebo group, was 162% (95% CI of 74% to 250%). The treatment difference was highly statistically significant ($p<0.001$; Chi-square test and CMH adjusted for region). In addition, the odds ratio was 4.53 (95% CI: 2.01 to 10.28) without any adjustment for baseline and demographic characteristics. The responder rates for subjects in the Gamunex and Placebo groups are presented in Figure 4 below.

Figure 4. Responder rates a in the adjusted INCAT score during the Efficacy Period (ITT population)



[a]Responder was a subject in the Efficacy Period who: a) was not deteriorating at the Day 16 or Week 3 visit; and b) improved (by ≥ 1 point on the adjusted INCAT score, relative to baseline) by Week 6 ; and c) maintained ≥ 1 point improvement through all visits, including the last visit at Week 24.

A summary of sensitivity analyses of the primary endpoint is shown for the ITT population in Table 6. Sensitivity analyses were performed using four pre specified alternative definitions of a Responder. The better efficacy of Gamunex was confirmatory ($p < 0.001$) for three of the four definitions.

Table 6. Responder analysis for the Efficacy Period (ITT population)

Analysis	IGIV-C (N=59) n (%)	Placebo (N=58) n (%)	Difference [a] (%)	95% CI for the difference	p-value [b]
Primary analysis	32 (54.2)	12 (20.7)	33.5	[15.4; 51.7]	<0.001 (<0.001)
Sensitivity analyses [c]:					
Conservative	16 (27.1)	8 (13.8)	13.3	[-2.8; 29.4]	0.074 (0.082)
LOCF at Week 6	32 (54.2)	12 (20.7)	33.5	[15.4; 51.7]	<0.001 (<0.001)
Worst case	32 (54.2)	13 (22.4)	31.8	[13.5; 50.2]	<0.001 (<0.001)
Best case	35 (59.3)	12 (20.7)	38.6	[20.6; 56.6]	<0.001 (<0.001)

[a]IGIV-C minus Placebo
[b]Chi-square test not in brackets; CMH test adjusted for region in brackets.

Subgroup analyses of the primary endpoint

A trial of 117 subjects with a rare disease was not designed to have statistical power in subgroups. The objective of the subgroup analyses was to look for consistency in trends. Despite the relatively small number of subjects enrolled, subgroup analyses for the primary endpoint were consistent with regard to the benefit of Gamunex over Placebo. The results in the protocol pre specified and post hoc subgroups were as follows:

1. Country: Treatment difference favoured Gamunex over Placebo in 9 of 10 countries, with no difference between groups in one country (Canada, which had only one subject in each group).

2. Baseline INCAT score: Treatment difference favoured Gamunex for 5 of the 8 baseline INCAT score groups, with no difference between study groups in the other three baseline score groups (each of which contained only one to four subjects).
3. Gender: Treatment difference favoured Gamunex in males (p =0.003) and females (p = 0.062),
4. Age: Treatment difference favoured Gamunex in subjects < 65 years old (p <0.001), but slightly favoured Placebo for subjects ≥ 65 years old (p = 0.782),
5. Previous exposure to any intravenous IG (IVIG): Treatment difference favoured Gamunex in IVIG experienced subjects (p < 0.001) and IVIG naïve subjects (p = 0.024).

Secondary endpoints

Three secondary endpoints (not powered) were assessed:

1. *Mean change in amplitude in the most severely affected motor nerve in the Efficacy Period.*

Results are shown in Table 7. Comparison of the treatment groups with regard to mean changes in amplitude showed a larger improvement in the Gamunex group than in the Placebo group but the difference between mean changes in the two groups of 0.24 mV was not statistically significant. The trial was not powered to detect a statistically significant difference in this endpoint. However, the trend in favour of Gamunex compared to Placebo is consistent with the results of the other primary and secondary endpoints.

Table 7. Mean changes in amplitude [mV] measured at most proximal site in the most severely affected motor nerve from baseline to endpoint during the Efficacy Period (ITT population)

Parameter	Visit / Time of change from Baseline	IGIV-C N	IGIV-C mean ± SD	Placebo N	Placebo mean ± SD
Most severely affected motor nerve	Baseline	59	1.29 ± 1.39	58	1.82 ± 1.99
	Endpoint	59	1.98 ± 2.24	58	2.29 ± 2.94
	Change at Endpoint	59	0.69 ± 1.86	58	0.47 ± 2.29
ANCOVA [a]: Point estimate for the contrast [b] [95% CI]: 0.24 mV [-0.53; 1.00] p-value: 0.542					

[a]The main effect ANCOVA model includes the change from baseline to endpoint (LOCF) in the Efficacy Period as dependent variable, treatment and region as fixed factors, and baseline value as covariate.
[b]IGIV-C minus Placebo

2. *Mean change in grip strength during the Efficacy Period*

In both groups, the mean grip strength for both the dominant and the non dominant hand increased during the Efficacy Period and at all time points (every study visit after baseline) the increases were much more pronounced in the Gamunex group. The treatment effect was analysed by different analysis of co variance (ANCOVA) models (reduced model, main effect model, and saturated model). The main effect model was the pre specified model used in the primary endpoint analysis (other models were for sensitivity analyses). At endpoint, a strong effect of the Gamunex treatment regarding the least square mean changes in grip strength was seen in the pre specified ANCOVA primary analysis (p values of the comparisons for both hands ≤ 0.005).The changes in grip strength from baseline to endpoint of the Efficacy Period, together with the results of the ANCOVA (main effect model) are presented in Table 8 below. The treatment difference favoured IGIV-C over Placebo for the dominant hand (p < 0.001) and the non dominant hand (p = 0.005).

Table 8. Changes in grip strength from baseline to endpoint in Efficacy Period (ITT population)

Parameter	Visit / Time of change from Baseline	IGIV-C N	IGIV-C mean ± SD	Placebo N	Placebo mean ± SD
Dominant hand	Baseline	57	48.2 ± 23.6	58	52.1 ± 23.3
	Endpoint	58	60.9 ± 25.0	58	53.6 ± 25.8
	Change at endpoint	57	13.2 ± 19.3	58	1.5 ± 15.6
ANCOVA[a]:	Point estimate for the contrast[b] [95% CI]:		10.94 kPa [4.65; 17.22]		
	p-value:		<0.001		
Non-dominant hand	Baseline	58	47.0 ± 25.1	58	50.2 ± 22.8
	Endpoint	58	60.3 ± 26.5	58	54.5 ± 28.9
	Change at endpoint	58	13.3 ± 17.4	58	4.3 ± 14.9
ANCOVA[a]:	Point estimate for the contrast[b] [95% CI]:		8.63 kPa [2.62; 14.64]		
	p-value:		0.005		

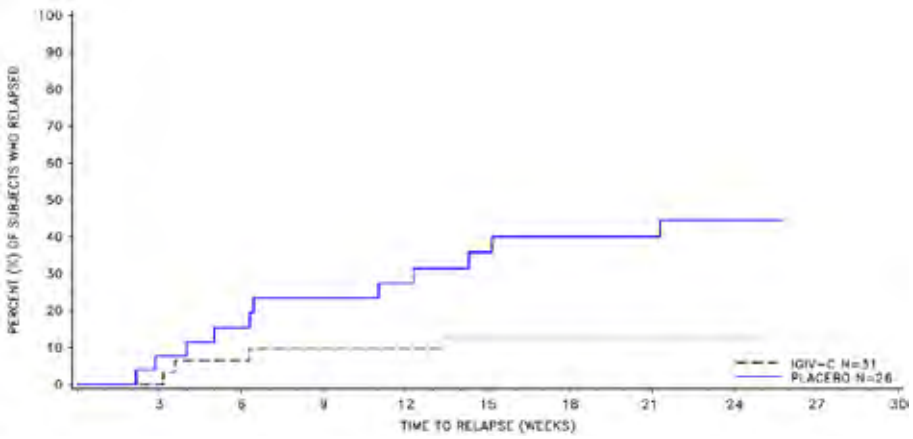
[a]The main effect ANCOVA model includes the change from baseline to endpoint (LOCF) in the Efficacy Period as dependent variable, treatment and region as fixed factors, and baseline value as covariate.
[b]IGIV-C minus Placebo

3. Time to Relapse during Randomised Withdrawal Period

Although 74 subjects entered into the Randomized Withdrawal Period, the pre specified analysis of this secondary endpoint included only the 57 subjects who were either Efficacy Period Responders to Gamunex or Gamunex Rescue Treatment successes. In other words, this analysis did not include the Placebo Efficacy Period Responders and Placebo Rescue Treatment successes who were entered into this Randomized Withdrawal Period. Placebo Responders and successes had been randomised into this period solely to maintain the blind. The only pre specified secondary endpoint for the Randomized Withdrawal Period was time to relapse. Relapse was defined as a deterioration of ≥ 1 point on the adjusted INCAT score.

Of the 57 subjects who entered into the Randomized Withdrawal Period, 31 were again randomised to the Gamunex group, and 26 were again randomised to the Placebo group. Subjects who continued to receive Gamunex experienced a longer time to relapse compared to subjects treated with Placebo (p=0.011). Overall, four of the 31 subjects who were again randomised to Gamunex and 11 of the 26 subjects who were again randomised to Placebo experienced a relapse. Comparison of the Kaplan-Meier curves (Figure 4) by a log rank test resulted in p = 0.011, indicating that the time to relapse was markedly shorter in subjects treated with Placebo. The probability of a relapse during the 6 month Randomized Withdrawal Period was 12.9% during Gamunex treatment and 44.7% during Placebo treatment (Kaplan-Meier estimates). Correspondingly, the hazard ratio (Gamunex versus Placebo) for a relapse was 0.19 (95% CI: 0.05 to 0.70; Cox proportional hazard model) in favour of the Gamunex treatment. The hazard ratio of 0.19 indicates that the hazard of relapse for subjects receiving Gamunex is only 19% of the hazard for subjects receiving Placebo, controlling for the Region effect. Inverting the hazard ratio results in an estimate of 5.26 (95% CI: 1.43 to 20.0), which means that the subjects receiving Placebo have a 5.26 times higher risk of relapse compared to subjects receiving Gamunex.

Figure 4. Kaplan-Meier curve for the time to relapse (ITT population of previous Gamunex Responders and Gamunex Successes) who entered into the Randomized Withdrawal Period



[a]Including a subject who entered into the Randomised Withdrawal period (Extension period) as a Non responder.

Exploratory endpoints

There were numerous exploratory pre specified endpoints and post hoc analyses.

Thirty-six of 74 (49%) exploratory endpoint analyses were statistically significant for the Gamunex group at $p < 0.050$. Nineteen of the remaining 74 analyses (26%) favoured the Gamunex group at $p < 0.200$. Two hundred and forty of the 326 nerve conduction study comparisons (74%) favoured Gamunex. Some 36 of the 80 (49%) exploratory endpoint analyses were statistically significant for the Gamunex group at $p < 0.050$. Twenty of the remaining 80 analyses (26%) favoured the Gamunex group at $p < 0.200$. Two hundred and forty-eight of the 336 nerve conduction comparisons (74%) favoured IGIV-C.

In the Efficacy Period and Rescue Treatment Period, muscle strength (MRC), sensory impairments (ISS), average amplitude of all motor neurons and quality of life (as assessed by the SF-36[3]) were all markedly improved by Gamunex treatment as compared to Placebo.

While exploratory endpoints are not intended to provide substantial confirmatory evidence in a Phase III study, the consistency of the results in favour of Gamunex over Placebo provide supportive evidence of the benefit of Gamunex in CIDP.

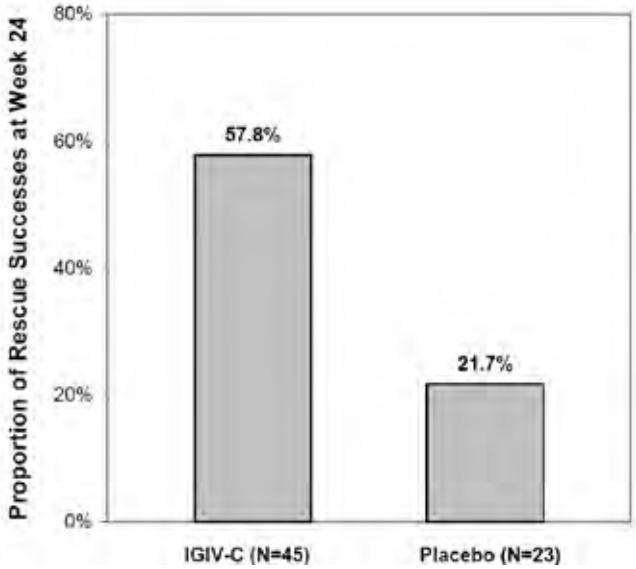
Success Rate in Rescue Treatment

The analyses of the Rescue Treatment are based on the 23 subjects initially allocated to the Gamunex group and the 45 subjects initially allocated to the Placebo group who entered into Rescue Treatment with the alternate treatment. If not otherwise mentioned, the term Rescue "baseline" in this section refers to the last measurement before start of the Rescue treatment. Rescue Treatment success was defined as at least one point improvement in the adjusted INCAT score at Week 24 of the Rescue Treatment Period. Rescue Treatment success occurred in 57.8% of Gamunex group subjects and 21.7% of

[3] The SF-36 is a multipurpose, short form health survey with only 36 questions. It yields an 8 scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4 week recall) and acute (1 week recall).

Placebo group subjects. The difference in success rates was 36% (95% CI: 10.6% to 61.5%), with p-values of 0.005 (Chi-square test) and 0.005 (CMH adjusted for region). The results were consistent across regions.

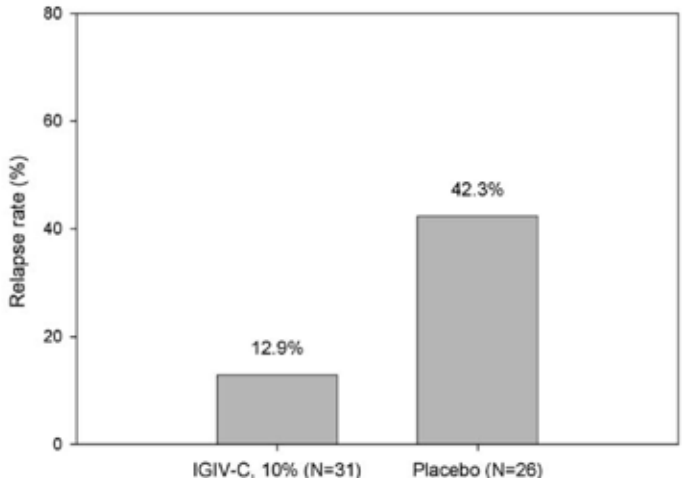
Figure 5: Success rate (%) in the Rescue treatment (ITT population - Rescue treatment)



Relapse rate in randomized withdrawal period

As shown in Figure 6 in subjects who had previously improved from Gamunex treatment (n = 57; including the subject who was not a Responder and entered into the Randomized Withdrawal Period in error), the relapse rate was 13% (4 of 31 subjects) in subjects re randomised to the Gamunex group and 42% (11 of 26 subjects) in subjects re randomised to the Placebo group. Comparison of the relapse rates resulted in an absolute difference (Placebo minus Gamunex) of 29.4% (95% CI: 3.5% to 55.3%) in favour of the Gamunex treatment (p=0.006; CMH adjusted for region).

Figure 6. Relapse rate in Randomized Withdrawal Period (Efficacy Responders and Gamunex Rescue Treatment Successes-ITT population)



The treatment difference of 29.4% in the Randomized Withdrawal Period is very similar to the treatment difference of 33.5% in the Efficacy Period (Figure 4), and the treatment difference of 36% in the Rescue treatment (see Figure 5). For each of these analyses, the number of subjects needed to treat with Gamunex in order to have one subject with a favourable effect on disability (that is, either a Responder during the Efficacy Period, a

Rescue Treatment success or a subject who did not relapse during the Randomized Withdrawal Period) is approximately three. This consistency of the magnitude of the treatment effect in these three different segments of the study serves as internal (within the same study) confirmation (and re confirmation) of the benefit of Gamunex on disability.

Evaluator's overall conclusions on clinical efficacy

Study 060001 assessed the SC administration of Gamunex but this study did not include any efficacy variables as primary endpoints. The rate of serious bacterial infections and any infections as well as febrile episodes were assessed as safety variables (see *Safety* section below). As discussed in the *Pharmacology* section, the study showed that the trough concentrations of total IgG at any SC visit for all subjects were 7.1 mg/mL or higher and a maintenance of trough IgG level ≥ 5 mg/mL is considered as a major determinant for the prevention of infections in PID patients.

Study 100538 assessed the efficacy of Gamunex treatment in CIDP patients. No guidelines are currently available with regard to the requirement of clinical trials investigating the role of IVIG for the treatment of CIDP. Study 100538 was a well designed and adequately powered study with longer term (48 weeks) follow-up, and the blinding was maintained throughout the 24 weeks of Efficacy Period and the 24 weeks Randomised Withdrawal Periods. The INCAT scale for the assessment of CIDP is considered to be a well developed and validated score and it is a simple, reliable, and responsive scale that has been used previously in clinical studies to assess disease activity. The choice of the primary endpoint was clinically meaningful and the choice of Gamunex dose is in keeping with doses used in other immunomodulatory conditions. The primary efficacy analysis was a comparison of responder rates in the Gamunex group and the Placebo group during the Efficacy Period. The primary efficacy results demonstrated statistically significant higher responder rates in the Gamunex group and therefore provided evidence of the benefit of Gamunex for the treatment of CIDP. The study also showed that there was a significant improvement in mean grip strength of subjects treated with Gamunex as well as a longer time to relapse with lower probability of relapse in subjects who continued to receive Gamunex in the Randomised Withdrawal Period. It is noted that the efficacy data is not available for paediatric patients with CIDP.

Safety

Introduction

Safety of Gamunex was evaluated in Study 060001 with regard to the SC infusion, in Study 100538 with regard to the CIDP treatment and in three studies (Studies 100213, 100422 and 100348) relating to rapid infusion rate. The safety data from these five studies are discussed separately below.

Study 060001

The safety and tolerability of patients to SC administration of Gamunex were assessed by analysing adverse events (AEs) and clinical laboratory parameters. The incidence of serious bacterial infections, any infections, concomitant medications and vital signs were also evaluated.

A summary of the drug exposure is presented in Table 9 below. A total of 32 subjects were infused with Gamunex by both IV and SC administration. There were 77 IV infusions during the Run in Phase, 64 IV infusions during the IV Phase, and 725 SC infusions in the SC Phase. The mean duration of subject exposure to Gamunex was 13.0 weeks for the Run-

in Phase, 5.0 weeks for the IV Phase, and 22.8 weeks for the SC Phase. The total subject exposure to the study drug in the Run-in, IV and SC Phases were 272 weeks, 160 weeks, and 728 weeks, respectively.

It should be noted that the difference in length of exposure time and number of infusions for IV and SC administration make direct comparisons of the rates of the Treatment Emergent Adverse Events (TEAEs) difficult to interpret.

Table 9. Exposure to treatment drug during the study phases (safety population)

Parameter	Study Phase		
	Run-in (N = 21) Mean ± SD Median [range]	IV (N = 32) Mean ± SD Median [range]	SC (N = 32) Mean ± SD Median [range]
Duration of exposure per subject (weeks)	13.0 ± 4.2 12.3 [3.3; 18.6]	5.0 ± 0.6 5.1 [4.0; 6.3]	22.8 ± 8.6 24.0 [2.0; 40.7]
Total duration of subject exposure (weeks)[a]	272.0	159.7	728.0
Total volume infused (mL)	1389.0 ± 901.6 1225.0 [200; 4500]	709.6 ± 226.18 620.0 [400; 1600]	3210.2 ± 1869.36 3126.9 [202; 8745]
No. of infusions per subject[b]	3.7 ± 1.4 4.0 [1; 6]	2.0 ± 0.0 2 [2; 2]	22.7 ± 8.5 24.0 [2; 41]
Total number of infusions	77	64	725

[a] Total duration is a summation of duration of exposure of all subjects during each study phase.

[b] Each weekly infusion is counted once regardless of number of SC infusion sites used during each infusion.

Treatment emergent adverse events (TEAEs)

The most frequent TEAE during the Run-in and IV Phases was headache. In the SC Phase, 93.8% of subjects (30/32) experienced TEAEs including both local infusion site reactions and non infusion site TEAEs. Some 25 to 41 % of SC subjects had infusion site erythema, pain, swelling, extravasation and/or pruritus. A total of 27 subjects in the SC phase (84.4%) reported non infusion site TEAEs. The most frequent non infusion site TEAEs that occurred in 10% of or more subjects in the SC phase were sinusitis, upper respiratory tract infection, headache, diarrhoea, fatigue and nausea (see Table 10 below).

Table 10. TEAEs by preferred term irrespective of relationship to study drug during the study phases (Safety Population) (≥ 5% of subjects)

Preferred term[a]	Study Phase				
	Run-in (N=21) N (%)	IV (N=32) N (%)	SC (N = 32) N (%)		
			Non-infusion Site TEAEs	Local Infusion Site Reactions	Total in SC Phase
No. of TEAEs	48	16	171	427	598
No. of subjects with at least one TEAE	16 (76.2)	11 (34.4)	27 (84.4)	24 (75.0)	30 (93.8)
Infusion site erythema	0	0	0	13 (40.6)	13 (40.6)
Infusion site pain	0	0	0	13 (40.6)	13 (40.6)
Infusion site swelling	0	0	0	11 (34.4)	11 (34.4)
Sinusitis	2 (9.5)	0	8 (25.0)	NA	8 (25.0)
Infusion site extravasation	0	0	0	8 (25.0)	8 (25.0)
Infusion site pruritus	0	0	0	8 (25.0)	8 (25.0)
Infusion site bruising	0	0	0	7 (21.9)	7 (21.9)
Upper respiratory tract infection	0	2 (6.3)	7 (21.9)	NA	7 (21.9)
Headache	4 (19.0)	1 (3.1)	6 (18.8)	NA	6 (18.8)
Diarrhoea	0	2 (6.3)	5 (15.6)	NA	5 (15.6)
Fatigue	0	0	5 (15.6)	NA	5 (15.6)
Infusion site haemorrhage	0	0	0	5 (15.6)	5 (15.6)
Infusion site oedema	0	0	0	4 (12.5)	4 (12.5)
Nausea	1 (4.8)	1 (3.1)	4 (12.5)	NA	4 (12.5)
Insomnia	2 (9.5)	0	1 (3.1)	NA	1 (3.1)
Pneumonia	2 (9.5)	0	0	NA	0
Dizziness	1 (4.8)	2 (6.3)	0	NA	0
Toothache	0	2 (6.3)	0	NA	0

NA, not applicable.

[a] At each level of summation (preferred term), subjects were only counted once.

Drug related TEAEs

TEAE results are shown in Table 11. There were seven drug related TEAEs reported during the Run-in Phase and one TEAE reported during the IV Phase. All seven were mild or moderate in severity. The most frequent drug related TEAE that occurred in 5% or more subjects in the Run-in and IV Phases was headache.

The SC Phase had a much longer duration of study drug exposure (24 weeks in SC as compared to 5 weeks in the IV Phase and 16 weeks in the Run-in Phase). For the 39 drug related non infusion site TEAEs that were reported in 21.9% (7/32) of the subjects in the SC Phase, the majority (87.2% [34/39]) were mild or moderate in severity. The most frequent drug related non infusion site TEAEs that were reported in 5% or more of subjects were headache, fatigue, arthralgia and pyrexia. Local infusion site reactions that occurred in two or more subjects and were considered drug related included infusion site erythema, pain, swelling, extravasation, pruritus, bruising, haemorrhage, oedema, rash, urticaria and induration (Table 11 below).

Table 11. Drug-related TEAEs by preferred term during the study phases (Safety population) (≥ 5% of subjects)

TEAEs (Preferred Term)	Study Phase				
	Run-in (N = 21) N (%)	IV (N = 32) N (%)	SC (N = 32) N (%)		
			Non-infusion Site TEAEs	Local Infusion Site Reactions	Total in SC Phase
No. of drug-related TEAEs	7	1	39	427	466
No. of subject with at least one drug-related TEAE	4 (19.0)	1 (3.1)	7 (21.9)	24 (75.0)	25 (78.1)
Infusion site erythema	0	0	NA	13 (40.6)	13 (40.6)
Infusion site pain	0	0		13 (40.6)	13 (40.6)
Infusion site swelling	0	0		11 (34.4)	11 (34.4)
Infusion site extravasation	0	0		8 (25.0)	8 (25.0)
Infusion site pruritus	0	0		8 (25.0)	8 (25.0)
Infusion site bruising	0	0		7 (21.9)	7 (21.9)
Infusion site haemorrhage	0	0		5 (15.6)	5 (15.6)
Infusion site oedema	0	0		4 (12.5)	4 (12.5)
Headache	2 (9.5)	1 (3.1)	4 (12.5)	NA	4 (12.5)
Fatigue	0	0	2 (6.3)		2 (6.3)
Arthralgia	0	0	2 (6.3)		2 (6.3)
Infusion site rash	0	0	NA	2 (6.3)	2 (6.3)
Infusion site urticaria	0	0		2 (6.3)	2 (6.3)
Infusion site induration	0	0		2 (6.3)	2 (6.3)
Pyrexia	0	0	2 (6.3)	NA	2 (6.3)

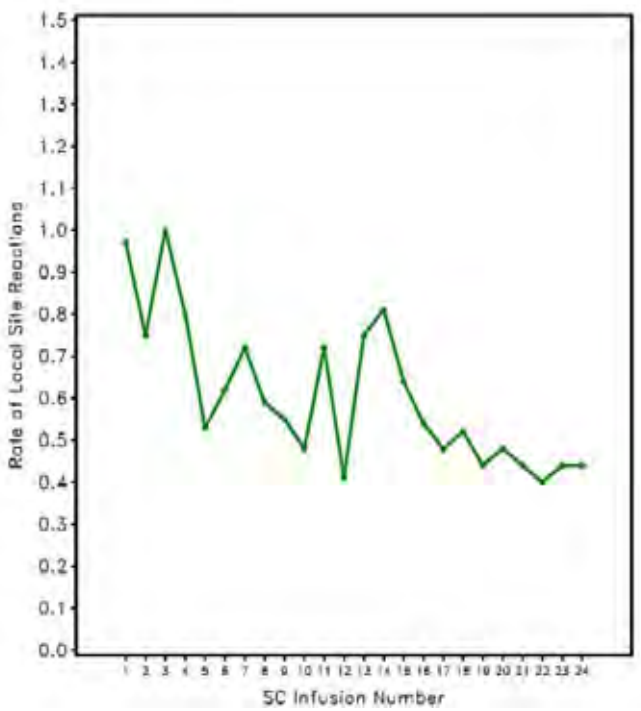
NA, not applicable

Local infusion site reactions during the SC phase

During the SC Phase, the most frequent TEAEs were local infusion site reactions (75% of subjects). These local infusion site reactions mainly consisted of mild and moderate swelling, redness and site pain. No serious local infusion site reactions occurred. The majority of local infusion site reactions resolved within three days. Most local infusion site reactions occurred during or within 24 hours of treatment and relatively few additional reactions occurred subsequently (during or within 72 hours). Non infusion site TEAEs were distributed throughout the study phase period and not concentrated within the initial 24 or 72 hour period following infusion.

The analysis of rates of local infusion site reactions per infusion showed that there was a decrease in these following repeated SC infusions (Figure 7 below). During the first few infusions, a rate of approximately one local infusion site reaction per infusion was reported. A gradual decrease in the rate of local infusion site reactions was observed after repeated weekly SC infusions. At the end of the SC phase (24 infusions for this analysis), less than 0.5 local infusion site reactions per infusion was reported, that is, the rate of local infusion site reactions was reduced by almost 50%.

Figure 7: Rate of local infusion site reactions after repeated infusions during the SC phase (Safety population)



Non infusion site TEAEs

During the SC Phase, non infusion site TEAEs that occurred in ≥ 5% of the subjects included sinusitis (25%), upper respiratory tract infection (21.9%), headache (18.8%), diarrhoea (15.6%), fatigue (15.6%) and nausea (12.5%). Only a small percentage of non infusion site TEAEs were reported as severe (9.4%, 16/171), consistent with the percentages observed in the IV Phase (12.5%, 2/16) and the Run-in Phase (10.4%, 5/48). There were 39 drug related non infusion site TEAEs during the SC Phase and most were mild or moderate in severity. Only five (12.8% of 39) drug related TEAEs occurring in two subjects were severe (one subject experienced four episodes of severe headache and another subject experienced severe arthralgia). These TEAEs were expected in association with Gamunex therapy.

Deaths and serious adverse events (SAEs)

Results are shown in Table 12. No death was reported and a total of six SAEs were reported in three subjects. During the Run-in Phase, three severe SAEs (pneumonia, sepsis syndrome and respiratory failure) occurred in one subject and two moderate SAEs in another subject (two incidences of incisional hernia subsequent to elective surgeries). There was no SAE reported during the IV Phase. During the SC Phase, only one subject had a moderate SAE; a drug dependence to Xanax® (alprazolam). All six SAEs were considered as not related to drug treatment. All SAEs were resolved. The subject with three severe SAEs was withdrawn from the study after one infusion during the Run-in Phase. The other two subjects completed the study.

Table 12. Listing of all SAEs (Safety Population)

Subject	Study Phase	Preferred Term	Severity	Relationship to Study Drug	Action Taken/Outcome of Event
0040001	Run-in	Pneumonia	Severe	Unlikely	Study med discontinued; other actions: treated with conmed including IV antibiotics/ Resolved
		Sepsis Syndrome	Severe	Unlikely	Study med discontinued; other actions: treated with conmed including IV antibiotics & oxygen/ Resolved
		Respiratory failure	Severe	Unlikely	Study med discontinued; other actions: treated with conmed including IV antibiotics/ Resolved
0120001	Run-in	Incisional hernia	Moderate	Not related	None taken with study drug; other action: surgery/ Resolved
		Incisional hernia	Moderate	Not related	None taken with study drug; other action: surgery/ Resolved
0110002	SC	Drug dependence	Moderate	Not related	None taken with study drug; other action: Rehab for Xanax® (alprazolam) dependency; Subject voluntarily went to rehabilitation/ Resolved with sequelae

Serious bacterial infections

The annual rate of serious bacterial infections defined as bacteraemia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, pneumonia and visceral abscess was evaluated as a safety variable. All serious bacterial infections have already been counted and analysed as TEAEs in the previous sections. No serious bacterial infection was reported during either the IV or the SC Phase. During the Run-in Phase, two serious bacterial infections occurred in one subject (4.8%, 1/21 subjects) and the annual infection rate was therefore 0.272. The infection rate per person year was 0.37. However, these results should be viewed with caution because they were extrapolated from a very short duration (a Run-in Phase mean duration of 13 weeks) and small population (21 subjects). These two serious bacterial infections were reported as SAEs. Details of the two cases of serious bacterial infections are provided in Table 13 below.

Table 13. Serious bacterial infections by subjects during the study phases (safety population)

Serious Bacterial Infections (Preferred Term[a])		Study Phase: Run-in (N=21) N (%)	IV (N=32) N (%)	SC (N=32) N (%)
No. of serious bacterial infections		2	0	0
No. of subjects with at least one serious bacterial infection		1 (4.8)	0	0
Pneumonia		1 (4.8)	0	0
Sepsis Syndrome		1 (4.8)	0	0
Summary				
Total no. of person-year[b]		5.4	3.1	14.5
Serious bacterial infection rate per person-year[c]		0.37	0	0
Annual serious bacterial infection rate[d]	Mean±SD	0.272±1.246	0	0
	98% CI	[0.12, 0.42]		

CI: Confidence interval; SD: standard deviation

[a] At each level of summation per study phase, subjects are counted only once.

[b] Person-year is the summation of duration of drug exposure in years for all subjects in a study phase.

[c] Infection rate per person-year is calculated by the total number of serious bacterial infections for all subjects divided by the total number of person-years.

[d] Annual serious bacterial infection rate is calculated by the total number of serious bacterial infections divided by the duration of each study phase for each subject.

Non serious infections

All reported infections that were not serious, including signs and symptoms of possible infections, are summarized in Table 14 below. There were fourteen TEAEs in the Run-in Phase, six in the IV Phase, and sixty in the SC Phase that were considered as infections or possible signs and symptoms of infections. The overall annualized non serious infection rate of any infections during the SC phase was found to be 4.3 per subject in this study (Table 14). The annualized infection rate for the Run-in Phase was 2.7 as compared to 1.9 in the IV Phase. In the current study, which evaluated 5293 subject days (14.5 person years) in a SC Gamunex weekly administration regimen, there were no reported hospitalisations due to an infection. The annualised rate of infection observed in the SC Phase was higher than that in the IV phase. This was likely to be related to the longer duration of the SC Phase and the seasonal timing of the SC Phase (the majority (70%) of infections in the SC Phase occurred during the autumn or winter season when subjects may be more susceptible to infection, in particular respiratory infections).

In the current study there were no serious bacterial infections during the SC Phase or the IV Phase. One subject who received one Run-in Phase infusion experienced one serious bacterial infection which was related to a single episode of pneumonia with sepsis syndrome. It is clinically relevant to note that this subject had an ongoing pneumonitis at the time of study entry. The overall annualised infection rate of any infections was 4.3 per patient which is similar to the reported infection rate of another SC administered IgG (SCIG) product (Vivaglobin, the only other SCIG product marketed in the USA).

Table 14. Non serious infections or signs and symptoms of possible infections by study phase (Safety Population) (≥5% of subjects)

TEAEs (Preferred Term[a])	Study Phase		
	Run-in (N = 21)	IV (N = 32)	SC (N = 32)
No. of TEAEs (other reported infections or signs and symptoms of possible infections)	14	6	60
No. of subject with at least one TEAE (N [%])	9 (42.9)	5 (15.6)	24 (75.0)
Sinusitis (N [%])	2 (9.5)	0	8 (25.0)
Upper respiratory tract infection (N [%])	1 (4.8)	2 (6.3)	7 (21.9)
Diarrhoea (N [%])	0	2 (6.3)	5 (15.6)
Bronchitis (N [%])	0	0	3 (9.4)
Pharyngolaryngeal pain (N [%])	0	0	3 (9.4)
Acute sinusitis (N [%])	0	0	2 (6.3)
Ear infection (N [%])	1 (4.8)	0	2 (6.3)
Nasopharyngitis (N [%])	1 (4.8)	0	2 (6.3)
Urinary tract infection (N [%])	1 (4.8)	0	2 (6.3)
Pyrexia (N [%])	0	0	2 (6.3)
Viral infection (N [%])	1 (4.8)	0	2 (6.3)
Summary			
Total no. of person-years[b]	5.4	3.1	14.5
Infection rate per person-year[c]	2.57	1.95	4.14
Annual infection rate[d] (Mean ± SD)	2.68 ± 3.81	1.90 ± 4.65	4.34 ± 4.44

[a] At each level of summation per study phase, subjects are counted only once.

[b] Person-year is the summation of duration of drug exposure in years for all subjects in a study phase.

[c] Infection rate per person-year is calculated by the total number of infections for all subjects divided by the total number of person-years.

[d] Annual infection rate is calculated by the total number of infections divided by the duration of the each study phase for each subject.

Study 100538

Extent of exposure

A summary of the total exposure to Gamunex and Placebo is shown in Table 15. As a result of higher rates of exit from the Efficacy Period and discontinuation from Rescue Treatment for Placebo treated subjects, the mean duration subjects remained on Placebo treatment was about half that of Gamunex (14.1 ± 12.0 weeks as compared to 23.8 ± 16.4 weeks). Also the mean number of infusions received by each subject was 6.1 ± 4.6 infusions in the Placebo group as compared to 9.7 ± 6.5 infusions in the Gamunex group.

Table 15. Summary of exposure to Gamunex (IGIV-C) and placebo

Parameter	IGIV-C (N=113) mean ± SD median [range]	Placebo (N=95) mean ± SD median [range]
Duration of exposure per subject [weeks]	23.8 ± 16.4 24.1 [0.1; 50.1][d]	14.1 ± 12.0 7.6 [2.0; 49.7][d]
Number of treatment courses received per subject[a]	7.8 ± 5.4 8.0 [1; 16]	4.6 ± 4.0 2.0 [1; 16]
Number of infusions administered per subject	9.7 ± 6.5 9.0 [1; 32]	6.1 ± 4.6 4.0 [2; 22]
Total volume infused per subject [mL]	6253 ± 3987 5910.0 [750; 13600]	3921 ± 2828 2400.0 [760; 13600]
Total number of infusions administered [b]	1096	575
Number of infusions administered as loading dose [b, c]	227	182
Number of infusions administered as maintenance dose [b]	869	393

[a]One course corresponds to 1 total dose (2 g/kg for loading dose and 1 g/kg for maintenance dose) administered, irrespective of the total number of infusion days. The loading dose (2 g/kg) was allowed to be given over up to 4 days, and the maintenance dose (1 g/kg) over up to 2 days, depending on the subject's tolerance.
[b]Refers to single doses, i.e., if a dose was given over 2 (or more) days, this was counted as 2 (or more) infusions.
[c]Loading doses were only administered at start of the Efficacy Period and Rescue treatment, but not at start of the Randomized Withdrawal Period.
[d]The duration was > 48 weeks due to scheduling of visits.

A total of 113 subjects were exposed to Gamunex and 95 subjects were exposed to Placebo. TEAEs and exposure to study drug during the whole study are presented in the Table 16 for the safety population.

Table 16. TEAEs and exposure to study drug during the whole study (Safety Population)

Parameter	IGIV-C n or n (%)	Placebo n or n (%)
Number of subjects exposed	113 (100)	95 (100)
Total no. of infusions [a]	1096	575
No. of subjects with TEAEs	85 (75)	45 (47)
Total no. of TEAEs	377	120
No. of TEAEs per infusion	0.344	0.209
No. of subjects with drug-related TEAEs	62 (55)	16 (17)
Total no. of drug-related TEAEs	194	25
No. of drug-related TEAEs per infusion	0.177	0.043
No. of subjects with SAEs	6 (5)	8 (8)
Total no. of SAEs	9	11
No. of SAEs per infusion	0.008	0.019
No. of subjects with drug-related SAEs	3 (3)	3 (3)
Total no. of drug-related SAEs	5	4
No. of drug-related SAEs per infusion	0.005	0.007
No. of subjects withdrawn due to TEAEs	3 (3)	2 (2)

[a]Refers to single daily doses, *i.e.*, if a dose was given over 2 (or more) days, this was counted as 2 (or more) infusions.

During the entire study (all study periods/treatments combined), a total of 377 TEAEs occurred in 85 (75%) of 113 subjects receiving Gamunex treatment. Some120 TEAEs occurred in 45 (47%) of 95 subjects while receiving Placebo treatment. The exposure to Gamunex was about twice as long as the exposure to Placebo, which is reflected in the higher incidence of TEAEs during Gamunex treatment. Comparison of the numbers of TEAEs per infusion also shows an increase in the incidence density during Gamunex treatment as compared to Placebo treatment (0.344 versus 0.209), respectively, which was due to a higher incidence density of drug related TEAEs during Gamunex therapy as compared to Placebo treatment(0.177 versus 0.043), respectively.

An overview of the most frequent TEAEs, that is, TEAEs that were reported in at least four (4%) subjects is given in Table 17 below. The most common AE in the Gamunex group was headache (32%) followed by pyrexia, dizziness, asthenia, chills, back pain, arthralgia, nausea or abdominal pain.

Table 17. Most frequent TEAEs (cut-off point: 4%) for all study periods combined (Safety Population)

MedDRA preferred term	IGIV-C (N=113)			Placebo (N=95)		
	n_{Sub} (%)	n_{TEAE}	Incidence density[a]	n_{Sub} (%)	n_{TEAE}	Incidence density[a]
Any TEAE	85 (75)	377	0.344	45 (47)	120	0.209
Headache	36 (32)	57	0.052	8 (8)	15	0.026
Pyrexia	15 (13)	27	0.025	0	0	0
Hypertension	10 (9)	20	0.018	4 (4)	6	0.010
Asthenia	9 (8)	10	0.009	3 (3)	4	0.007
Chills	9 (8)	10	0.009	0	0	0
Back pain	9 (8)	10	0.009	3 (3)	3	0.005
Arthralgia	8 (7)	11	0.010	1 (1)	1	0.002
Rash	8 (7)	13	0.012	1 (1)	1	0.002
Nausea	7 (6)	9	0.008	3 (3)	3	0.005
Dizziness	7 (6)	3	0.006	1 (1)	1	0.002
Influenza	6 (5)	6	0.005	2 (2)	2	0.003
Influenza like illness	5 (4)	13	0.012	0	0	0
Pain in extremity	5 (4)	8	0.007	0	0	0
Dermatitis allergic	5 (4)	5	0.005	0	0	0
Urticaria	5 (4)	6	0.005	0	0	0
Myalgia	4 (4)	4	0.004	4 (4)	4	0.007
Abdominal pain	4 (4)	4	0.004	0	0	0
Nasopharyngitis	4 (4)	4	0.004	4 (4)	4	0.007
Urinary tract infection	4 (4)	5	0.005	2 (2)	3	0.005

[a]Calculated by the total number of TEAEs divided by the number of infusions received (1096 for IGIV-C and 575 for Placebo).

Deaths and SAEs

One subject died during the study. This subject was briefly treated with Gamunex during the Efficacy Period, crossed over to Placebo during the Rescue Treatment and had a relapse of CIDP symptoms which led to her discontinuation from the study as per protocol. The subject developed fatal sepsis three months after she had been withdrawn from the study due to insufficient therapeutic effect. The development of sepsis in this subject was not considered as drug related.

A total of 20 SAEs occurred in 13 subjects. All SAEs that occurred during the study are listed by subject and treatment at the start of the SAE in the Table 18.

Table 18. Listing of all serious adverse events (Safety Population)

Subject no.	Treatment at start of SAE	MedDRA preferred term	Severity	Drug-related yes / no	Outcome
302001	IGIV-C	Pulmonary embolism	moderate	yes	resolved
304005	IGIV-C	Dizziness	moderate	no	resolved
	IGIV-C	Palpitations	moderate	no	resolved
352004	IGIV-C	Pyrexia	moderate	yes	resolved
	IGIV-C	Headache	moderate	yes	resolved
352006	IGIV-C	Dyspnea	mild	no	resolved
352011	IGIV-C	Headache	moderate	yes	resolved
	IGIV-C	Vomiting	moderate	yes	resolved
805005	IGIV-C	Bronchopneumonia	moderate	no	unchanged
	Placebo	Myalgia	moderate	no	resolved
304001	Placebo	Demyelinating polyneuropathy	severe	no	improved
304006	Placebo	Back pain	severe	no	resolved
352010	Placebo	Asthma	severe	yes	resolved
	Placebo	Medical observation (for asthma)	mild	yes	resolved
	Placebo	Gastroenteritis viral	mild	no	resolved
402001	Placebo	Cerebrovascular accident	moderate	yes	resolved
501003	Placebo	Deep vein thrombosis	moderate	yes	resolved
806002	Placebo	Pregnancy	mild	no	resolved
351004	Placebo	CIDP (relapse)	severe	no	Death
	N/A[a]	Sepsis	severe	no	(unchanged death

[a] developed sepsis about 3 months after withdrawal from the study.

Nine SAEs occurred in six (5%; incidence density: 0.008) subjects during Gamunex treatment and this included one AE of pulmonary embolism. Eleven SAEs occurred in eight subjects (8%; incidence density: 0.019) during Placebo treatment. One subject experienced an SAE under both Gamunex and Placebo treatment. Another subject had a relapse of CIDP symptoms under Placebo treatment and three months after withdrawal from the study the subject developed a sepsis which resulted in death. With the exception of two SAEs (moderate bronchopneumonia and severe relapse of CIDP symptoms), all SAEs had resolved by the end of the observation period.

Withdrawals due to TEAEs

A total of five subjects (3 during Gamunex treatment and 2 during Placebo treatment) prematurely discontinued the study due to TEAEs. Three of the five subjects (1 during Gamunex treatment and 2 during Placebo treatment) were withdrawn because of SAEs. The remaining two subjects (both in the Gamunex group) were withdrawn because of non serious TEAEs. All TEAEs leading to premature termination of the study are listed by treatment at the start of the TEAE in Table 19 below.

Table 19. Listing of all TEAEs leading to premature discontinuation from the study (safety population)

Subject no.	Treatment Period	Treatment at start of TEAE	MedDRA preferred term	Serious yes / no	Severity	Drug-related Yes / no	Outcome
401003	Efficacy	IGIV-C	Urticaria	no	moderate	yes	resolved
804003	Rescue	IGIV-C	Dyspnea	no	mild	yes	unchanged
805005	Rescue	IGIV-C	Bronchopneumonia	yes	moderate	no	unchanged
402001	Efficacy	Placebo	Cerebrovascular accident	yes	moderate	yes	resolved
501003	Efficacy	Placebo	Deep vein thrombosis	yes	moderate	yes	resolved

Laboratory findings

No new safety issues arose from the various haematological, chemistry or urine microscopic examination tests. After normalisation of the incidence rates of high or low

laboratory values by the number of infusions, there was little difference between the incidence densities of liver enzyme elevations between the Gamunex and Placebo groups. A listing of all TEAEs related to clinical chemistry findings are shown in Table 20. Some transient small decreases in white blood cells (WBCs) occurred immediately post-infusion but these levels were considered to be normal when assessed prior to the next infusion. The effect seems to be recurrent in individual patients and occurs with different formulations of intravenous Ig formulations (IVIG). While there was a slightly greater mean decrease in some haematology parameters in the Gamunex group immediately post infusion, there was no evidence of increased incidence densities of plasma free haemoglobin, lactate dehydrogenase (LDH), potassium or bilirubin, suggesting that there was no clinically important hemolysis. Clinically important changes that were reported as TEAEs occurred only when subjects were receiving Gamunex. These include reports of elevated creatine kinase (CK) (three subjects; one assessed as drug related), hypokalaemia (one subject), increased creatinine (one subject), increased urea nitrogen (one subject), and increased hepatic enzymes (one subject). Eight subjects had elevated CK levels that were ≥ 3 x upper limit of normal (ULN) during the study. There were no contributory medical conditions or concomitant medications that could explain the CK elevations of >3 x ULN.

Table 20. Listing of all TEAEs related to parameters of clinical chemistry that occurred under Gamunex treatment (Safety Population)

Subject no.	Time	Parameter	Normal range	Value at date of report	Severity	Drug-related yes / no	Outcome
103001	EP W6	CK	24-204 U/L	491 U/L	moderate	no	Resolved
501002	EP W3	CK	24-204 U/L	444 U/L	moderate	yes	Improved
352009[b]	EP W24	CK	24-204 U/L	1172 U/L	mild	no	Resolved
006-001	EP W6	Creatinine	0.5-1.5 mg/dL	1.6 mg/dL	mild	yes	unchanged
	RW W6	BUN	5-26 mg/dL	30 mg/dL	mild	yes	unchanged
806004	RW W8	Potassium	N/D	N/D	moderate	no	Resolved
352004	EP D2	ALT/AST [a]	0-40 U/L	72/82 U/L	mild	yes	Resolved

[a]Reported as "liver enzymes increased".
[b]Subject no. 352009 had the CK elevation actually occur while receiving Placebo, but it was not reported until the subject began receiving IGIV-C
N/D = not documented, EP = Efficacy Period, RW = Randomized Withdrawal Period, D = Day, W = Week.

The Direct Coombs test was positive in 17 (17%) of the 101 subjects tested while receiving Gamunex and in one (1%) of the 88 subjects tested while receiving Placebo. In none of the subjects was a positive Coombs test associated with signs of hemolysis. There were no elevations in mean LDH levels during the study, suggesting that there was no clinically important hemolysis.

In summary, the safety profile of Gamunex in the CIDP treatment trial is consistent with the safety profile of Gamunex in other clinical trials and no major new safety concerns arose.

Study 100422

This study was a randomised, controlled, open label study conducted in patients with ITP. The objective of the study was to determine if the safety and tolerability of Gamunex is similar when infused at two different infusion rates and whether different infusion rates affect hemolysis (as described below). The latter objective was the primary objective.

Patients must have been diagnosed with ITP as defined by the ITP Practice Guidelines Committee of the American Society of Haematology:

1. Thrombocytopenia without associated leukocyte abnormalities or anaemia (unless due to bleeding or a concomitant benign haematological condition, such as thalassaemia trait)

2. No diseases(s) associated with immune thrombocytopenia such as collagen vascular disease or lymphoproliferative disease.

All adult patients (age ≥18 years) must have been diagnosed with either acute or chronic (for at least 2 months) ITP. All children (ages 12-17 years) must have a diagnosis of chronic ITP for at least 6 months (platelet counts < 50 Giga/L which recovers >50 Giga/L upon a treatment course of IGIV-C (1-2 g/kg given over 1-5 days) or corticosteroids).

A total of eight patients were enrolled and randomised. These patients ranged in age from 26 to 65 years (mean age was 47.6 years). There were seven women and one man randomised. Eligible patients were randomised into one of two crossover groups. Patients randomised to Group 1 were to receive their first Gamunex infusion at a rate of 0.08 mL/kg/min and their second infusion at a rate of 0.14 mL/kg/min. Conversely patients randomised to Group 2 were to receive their first Gamunex infusion at a rate of 0.14 mL/kg/min and their second infusion at a rate of 0.08 mL/kg/min. All patients were to receive maximal target rates of 0.08 and 0.14 mL/kg/min Gamunex (if tolerated) on two separate occasions but all infusions of Gamunex must commence at an initial rate of 0.02 mL/kg/min with the rates increased to these target rates according to the following stepwise scheme.

Target Infusion Rate = 0.08 mL/kg/min.

Step 1:	First 15 minutes rate = 0.02 mL/kg/min (if tolerated go to step 2)
Step 2:	Increase the rate to 0.04 mL/kg/min and run at this rate for 15 minutes (if tolerated go to step 3)
Step 3:	Increase the rate to 0.08 mL/kg/min and run at this rate until the infusion is complete

Target Infusion Rate = 0.14 mL/kg/min.

Step 1:	First 15 minutes rate = 0.02 mL/kg/min (if tolerated go to step 2)
Step 2:	Increase the rate to 0.04 mL/kg/min and run at this rate for 15 minutes (if tolerated go to step 3)
Step 3:	Increase the rate to 0.08 mL/kg/min and run at this rate for 15 minutes (if tolerated go to step 4)
Step 4:	Increase the rate to 0.14 mL/kg/min and run at this rate until the infusion is complete

The criteria for safety evaluation were the number and character of clinical and laboratory abnormalities or AEs occurring during treatment with Gamunex when administered at a rate of 0.08 mL/kg/min versus a rate of 0.14 mL/kg/min.

Results

All eight subjects were evaluated for safety. Except for one patient who received one infusion, all patients received two infusions. The patient who only received one infusion had platelet levels that did not drop low enough to require a second infusion during the timeframe of this study. The volumes infused for each patient was the same for Infusion 1 and Infusion 2.

The mean duration of study drug infusion was 146.25 minutes (n=8) when given slowly versus 97.86 minutes (n = 7) when given rapidly, resulting in approximately a savings of 1/3 of the infusion time (48.39 minutes) when the drug was given rapidly versus slow.

The incidence rates of TEAEs are shown in Table 21. All patients experienced at least one AE for each infusion given, irrespective of whether the infusion was given at the rapid or slow rate. The most frequently reported event was headache.

Table 21. Incidence Rates of TEAEs Occurring in Any Treatment Group

	Slow (N=8)	Rapid (N=7)
Diarrhea	1	0
Abdominal distension	1	0
Arthralgia	2	1
Dizziness	0	1
Headache	5	4
Pharyngeal pain	1	1
Upper Respiratory tract infection	1	0
Rash	2	1
Urticaria	2	2

No patient prematurely discontinued the study due to an AE and there were no deaths or SAEs. Most events where mild in severity (no severe events occurred). All infusions were administered at the required target speed with no requirement for interruptions or temporary reduction in infusion speed. The rates of infusion were ramped up according to the protocol. In some cases for the rapid infusion, the rates were increased faster than described in the protocol. Infusion related AEs included headache and urticaria which occurred with a similar frequency between the two rates of infusion.

The AEs that occurred in the slow or rapid infusion groups were similar in terms of type of event and their incidence. Only the incidences of headaches and urticaria (with the same frequency in the two groups; Table 21) were deemed to be drug related by the study investigators. All the TEAEs listed in Table 21 were followed until a final outcome of resolution. None of the TEAEs were severe. In fact most of the AEs were mild, with only one headache in the slow infusion group listed as of moderate intensity. One headache and two incidences of urticaria in the rapid infusion group were also listed as of moderate intensity.

The analysis of laboratory abnormalities did not reveal any clinically important findings to distinguish the standard from the rapid infusion rate. There were no laboratory signs of hemolysis and despite some patients showing a positive Direct Antiglobin tests (DAT, or direct Coombs tests) post infusion; free haemoglobin levels potassium, bilirubin and LDH levels remained unchanged. There were few changes in plasma free haemoglobin, haptoglobin, and mean alkaline phosphatase just prior to or immediately post infusion or at 1 and 7 days post infusion.

Overall, in this study, the nature and frequency of all AEs, including the subset of infusion related AEs, were similar between the two infusion rates (0.8 and 0.14 mL/kg/min). There were no laboratory or clinical finding suggestive of hemolysis.

Study 100213

This study was a multicenter, unblinded, randomised, cross over trial conducted in patients with chronic ITP. The primary objective of this study was to determine the safety and tolerability of Gamunex administered at infusion rates of 0.11 and 0.14 ml/kg/min relative to the currently approved rate of 0.08 ml/kg/min. As this was a safety and tolerability study there was no determination of efficacy.

Gamunex at a dose of 1,000 mg/kg was given on three occasions as a single daily infusion, as needed, at maximum intervals of six weeks. The three different infusion rates were applied to each patient at random sequences. Each patient received all three dose rates in one of six random sequences.

Patients were closely monitored throughout the infusion with frequent checks of vital sign. Each infusion was initiated at a rate of 0.01 ml/kg/min and increased to 0.08

ml/kg/min within 30 minutes. If no adverse events occurred, it was increased to the target rate over the next 30 minutes as tolerated. The infusion was completed at the target rate if no adverse events occurred.

All patients enrolled had been diagnosed with chronic ITP defined as isolated thrombocytopenia with no other clinically apparent associated conditions or factors that were known to cause thrombocytopenia. Chronic ITP was further defined as thrombocytopenia of <100 ^{6}/L for at least 6 months. All enrolled patients had an entry platelet count of 20-40 ^{6}/L with the exception of patients who were previously enrolled in another Bayer protocol (100176) and they were enrolled and treated at any platelet count <40 ^{6}/L (or higher if clinically indicated).

Subject disposition

A total of 28 patients with chronic ITP were randomised and evaluable for safety analysis. Some 61% of patients were female and 71% were Caucasian. Table 22 summarises the premature discontinuations from this study. Seven patients were prematurely discontinued: five patients did not require all three infusions (4 were classified as protocol violations and 1 as lost to follow up), one was terminated because of non compliance (demanding a prohibited premedication) and one patient withdrew because of an AE (hives). Twenty-one patients received the three planned infusions of Gamunex.

Table 22. Premature Discontinuations

	0.08 then 0.11 then 0.14 (n=4)	0.11 then 0.14 then 0.08 (n=4)	0.14 then 0.08 then 0.11 (n=7)	0.08 then 0.14 then 0.11 (n=4)	0.11 then 0.08 then 0.14 (n=4)	0.14 then 0.11 then 0.08 (n=5)
Any reason	1 (25%)	0 (0%)	2 (29%)	1 (25%)	1 (25%)	2 (40%)
Adverse event	0 (0%)	0 (0%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)
Patient non-compliance	1 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Additional treatment not required*	0 (0%)	0 (0%)	1 (14%)	1 (25%)	1 (25%)	2 (40%)

*four coded as protocol violations and one coded as lost to follow up.

The overall mean age was 50 years and was similar among the infusion rate sequence groups. The patients ranged in age from 15 years to 88 years.

The criteria for safety evaluation were the frequency, nature and severity of all AEs, their relationship to infusion rates of study drug, their course and resolution, in addition to clinically significant changes in vital signs.

Table 23 below summarises the number of infusions for each of the assigned rates. It is noted that some of the patients did not receive some rates while others had multiple infusions at the same rate.

Table 23. Infusion summary

Rate (ml/kg/min)	0.08	0.11	0.14
number	27	24	24
mean dose (mg)	983	970	970
mean volume (ml)	729	710	726
mean infusion time (hrs)	2.7	2.4	2.2

Safety results

The number of patients who experienced at least one AE for the 0.08, 0.11, and 0.14 ml/kg/min infusions was 12 (46%), 13 (59%), and 11 (46%), respectively. Table 24 below summarises the overall AE experience of this study population.

Table 24. Overall Adverse Event Summary

Patients who experienced:	0.08 ml/kg/min (N=26)	0.11 ml/kg/min (N=22)	0.14 ml/kg/min (N=24)
Any adverse event	12 (46%)	13 (59%)	11 (46%)
Any drug-related adverse event	6 (23%)	8 (36%)	8 (33%)
Any serious adverse event	1 (4%)	0 (0%)	1 (4%)
Discontinuations due to adverse events	1 (4%)	0 (0%)	0 (0%)

The AEs occurring in at least 10% of any infusion rate group are shown in Table 25 below.

Table 25: Incidence Rates of AEs Occurring in at Least 10% of Any Infusion Group

Adverse Event	0.08 ml/kg/min (N=26)	0.11 ml/kg/min (N=22)	0.14 ml/kg/min (N=24)
Any event	12 (46%)	13 (59%)	11 (46%)
Headache	1 (4%)	5 (23%)	3 (13%)
Ecchymosis	2 (8%)	4 (18%)	1 (4%)
Petechiae	1 (4%)	4 (18%)	1 (4%)

Analysis of AEs

The most commonly reported AE was headache, which occurred more frequently at the higher infusion rates (4% at 0.08 ml/kg/min versus 23% at 0.11 ml/kg/min versus 13% at 0.14 ml/kg/min). A similar pattern of drug related headaches AEs was also observed (4%, 18% and 13%, respectively). All of the headaches were rated as mild except for a single severe headache in a patient infused at the 0.08 rate. The incidence rates of AEs and drug related AEs were otherwise generally similar among the three infusion groups.

After detailed review of published experience with IVIG, the clinicians from Bayer selected the AEs that were deemed most likely to truly result from a high rate of IVIG infusion. With the exception of mild headache, there is no evidence that the event rates differ for the infusion related AEs. The rate of such events (excluding mild headache) was 23% at 0.08 mg/kg/min, 23% at the 0.11 ml/kg/min rate and 25% at the 0.14 ml/kg/min rate. When such events (excluding mild headache) were restricted to the day of infusion, the respective rates were 12%, 23% and 21% (see the Table 26 below).

Table 26. Incidence Rates of Selected AEs That Occurred Only on the Day of Infusion Deemed Most Likely to Result from Infusion

Adverse Event	0.08 ml/kg/min (N=26)	0.11 ml/kg/min (N=22)	0.14 ml/kg/min (N=24)
Any "infusion related" event on day of infusion	3 (12%)	8 (36%)	7 (29%)
Any "infusion related" event on day of infusion excluding mild headache	3 (12%)	5 (23%)	5 (21%)
Headache	1 (4%)	4 (18%)	2 (8%)
Headache excluding mild events	1 (4%)	0 (0%)	0 (0%)
Hypertension	1 (4%)	2 (9%)	1 (4%)
Urticaria	1 (4%)	1 (5%)	2 (8%)
Rash	1 (4%)	0 (0%)	2 (8%)
Hypotension	0 (0%)	2 (9%)	0 (0%)
Nausea	1 (4%)	0 (0%)	0 (0%)
Vomiting	0 (0%)	0 (0%)	0 (0%)
Asthma	0 (0%)	0 (0%)	1 (4%)
Injection site reaction	0 (0%)	1 (5%)	0 (0%)
Dyspnea	0 (0%)	0 (0%)	0 (0%)

SAEs are listed in Table 27 below. There was one drug related severe event (headache) in one patient in the 0.08 ml/kg/min infusion rate group and one severe event that was not drug related (meningioma) in one patient in the 0.14 ml/kg/min infusion rate group.

Table 27. Severe Adverse Events at infusion rates of 0.08 and 0.14 mL/kg/min

SEVERE ADVERSE EVENTS
POPULATION: ALL PATIENTS VALID FOR SAFETY

INFUSION RATE=0.08 ML/KG/MIN

OBS	Patient	Rel. Day to Start of Prev. IgIV Infusion	Adverse Event (COSTART Term)	Adverse Event (Investigator Term)	Serious?	Relation to Drug	Action(s) Taken
1	9002	1	HEADACHE	HEADACHE	NO	PROBABLE	REMEDIAL DRUG THERAPY

INFUSION RATE=0.14 ML/KG/MIN

OBS	Patient	Rel. Day to Start of Prev. IgIV Infusion	Adverse Event (COSTART Term)	Adverse Event (Investigator Term)	Serious?	Relation to Drug	Action(s) Taken
2	9003	6	NEOPLASM	MENINGIOMA (BENIGN)	YES	NONE	HOSPITAL (REQ. OR PROLONGED)

All three infusion rate groups appeared similar with no notable changes (compared to pre infusion) in vital signs (including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature) other than a slightly decreased heart rate at all time points after infusion at all rates.

Study 100348

This was a prospective, single blind, randomised, multi center cross over study conducted in patients with PID. The primary objective of the study was to compare the incidence and severity of infusion related AEs when Gamunex was administered at a rate of 0.14 mL/kg/min compared to a rate of 0.08 mL/kg/min as a single daily infusion.

Patients with a confirmed diagnosis of PID were to be treated with two infusions given 3-4 weeks apart at the fixed individual dose regimen (400-600 mg/kg) established prior to entry into the study. Any subject with an established dose in the range of 200-399 mg/kg was to be assigned to receive 400 mg/kg during the course of the study at the same dosing schedule as that established prior to entry into the study.

After a screening period, patients were to be randomised into one of two cross over groups. Patients randomised to Group 1 received their first Gamunex dose at a rate of 0.08 mL/kg/min and their second infusion at a rate of 0.14 mL/kg/min 3-4 weeks later. Patients randomised to Group 2 received Gamunex at a rate of 0.14 mL/kg/min on the first infusion day and then 0.08 mL/kg/min for their the second infusion 3-4 weeks later. Just prior to each Gamunex infusion all patients were to receive the same volume of 5% dextrose as calculated for their Gamunex infusion for blinding purposes.

All patients entered must have had a confirmed chronic PID as defined by the World health organization (WHO) Scientific Group on Immunodeficiency and must have received stable IVIG replacement therapy in the range of 200-600 mg/kg every 3-4 weeks. These include primarily (but not limited to) patients with:

- Congenital agammaglobulinaemia or hypogammaglobulinaemia including X-linked and autosomal forms
- Common variable immunodeficiency
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome

A total of 100 patients were randomised of whom 97 were valid for safety assessment. Forty-nine were infused with a slow followed by a rapid infusion and 51 patients were infused with a rapid infusion followed by a slow infusion. The 97 patients ranged in age from 17 to 79 years (mean age was 43.6 years) and 59 of them were male.

Criteria for evaluation of safety were the number and type of clinical (including vital signs) and laboratory abnormalities or AEs occurring during treatment with Gamunex when administered at a rate of 0.08mL/kg/min versus a rate of 0.14 mL/kg/min.

All 97 subjects received both study drug infusions. No patient prematurely discontinued the study due to an AE. There were no deaths and only two SAEs were reported after the study drug was given (angina and appendicitis). None were considered as drug related. Most events where mild in severity (4 severe events occurred; abdominal pain, appendicitis and increased blood creatine phosphokinase when Gamunex was given at the slow rate and unstable angina at the rapid rate). All Gamunex infusions reached the required target speed. Only two AEs caused a temporary interruption in an infusion. One patient experienced nausea when the rate was initially increased to 0.04 mL/kg/min and the rate was therefore decreased to 0.02 mL/kg/ and then successfully ramped up to 0.14 mL/kg/min without further problems. Another patient experienced itching at the site of infusion and the 0.14 mL/kg/min the infusion was therefore interrupted for 5 minutes.

Brief summary of adverse events

All 97 patients were evaluated for safety. Approximately one-third of all patients reported at least one AE after being treated either at the slow or rapid rates of Gamunex (Table 28).

Table 28. Overall Treatment Emergent Adverse Events Summary

Patients who experienced:	Slow Rate (N=97)	Rapid Rate (N=97)
Any adverse event	31 (32.0 %)	36 (37.1 %)
Any drug-related adverse event	8 (8.2 %)	17 (17.5 %)
Any serious adverse event	1 (1.0 %)	2 (2.1 %)
Discontinuations due to adverse events	0 (0.0 %)	0 (0.0 %)

Table 29 below lists all AEs that were deemed to be drug related by the investigator.

Table 29. Incidence Rates of Treatment Emergent Drug Related AEs Occurring at Any Infusion Rate

Patients who experienced:	Slow (N=97)	Rapid (N=97)
Headache	3(3.1%)	7 (7.2%)
Fatigue	4(4.1%)	4(4.1%)
Nausea	1 (1.0%)	2(2.1%)
Infusion site reaction	0	1(1.0%)
Injection site pruritus	0	1(1.0%)
Infusion site pain	0	1(1.0%)
Infusion site burning	0	1(1.0%)
Pain	0	1(1.0%)
Pyrexia	0	1(1.0%)
CPK Increase	1(1.0%)	1(1.0%)
Back pain	0	1(1.0%)
Muscle Cramp	0	1(1.0%)
Myalgia	0	2(2.1%)
Pain in Extremity	1(1.0%)	0
Dizziness	0	1(1.0%)
Irritability	1(1.0%)	0
Pollakiuria	0	1(1.0%)
Total	**8(8.2%)**	**17(17.5%)**

None of the drug related TEAEs were severe and the majority of the AEs were mild. More patients experienced a drug related TEAEs (as deemed by the investigator) during the rapid IGIV-C infusion compared to the slow infusion. However, this discrepancy is at least to some degree related to injection site reactions and headaches.

The study was considered to have had a negative outcome if the infusion rate of 0.14 mL/kg/min resulted in at least 25% more infusion related AEs compared to the slower infusion rate of 0.08 mL/kg/min. Based on this single criterion the study outcome was negative; there were three infusion related AEs in the slow group and five in the rapid group. However, as the overall number of AEs was so low (and the only difference between the two rates of infusion was two infusion related events), it seems that both rates of infusion were safe, well tolerated and not different with respect to the incidence of infusion related AEs. The analysis of laboratory assessed abnormalities did not reveal any clinically important findings to distinguish standard, or slow rate, from the rapid rate of infusion. There were no laboratory signs of haemolysis reported.

Postmarketing experience

The Product Safety Update Reports (PSURs) for the period of September 2006 to August 2009 were submitted. Events of haemolytic and thromboembolic nature continue to be events that requiring ongoing surveillance, as are those suggestive of transfusion related acute lung injury (TRALI). It is noted that haemolytic type events may have an association with patients who possess blood group A allele (Type A or AB) and who receive IVIG dosing greater than 2g/kg. The sponsor plans to monitor this group of patients as a subpopulation and to investigate this relationship as a potential safety signal.

Evaluator's overall conclusions on clinical safety

Study 060001 assessed the safety of SC administration of Gamunex in 32 PID patients followed for 24 weeks (a total of 725 SC infusions). The result showed a relatively low incidence of systemic adverse events, with tolerable local infusion site reactions that

improve over time with repeated infusions. The study concluded that SC administration of Gamunex is well tolerated with the overall safety profile similar to that of other SC IgGs.

Study 100538 was conducted in CIDP patients (113 subjects were exposed to Gamunex; number of Gamunex infusion = 1096). No new safety issues occurred during this study when assessing the adverse events, laboratory parameters (including hematological, serum chemistry and urinalysis), or vital signs. Overall, despite the high doses used and the long exposure time (48 weeks) in this study, Gamunex was well tolerated and the safety profile of Gamunex was similar to previous Gamunex studies.

Three studies assess rapid infusion rates.

Study 100422 was conducted in eight ITP patients. The nature and frequency of all AEs and the subset of infusion related AEs were similar between the two infusion rates (0.8 and 0.14 mL/kg/min) in this study. There were no laboratory or clinical findings suggestive of hemolysis.

Study 100213 enrolled 28 patients with CITP. The study demonstrated a reasonable tolerability of infusion rates up to 0.14 ml/kg/min. No patients experienced a drug related SAE and only a single patient withdrew due to an AE of hives at the lowest infusion rate. Except for 'mild headache' occurring more frequently at the higher infusion rates, the overall rates of AE appeared to be comparable across the three infusion rates.

Study 100348 was conducted in 100 PID patients. It was noted that twice as many drug related AEs occurred during the rapid infusion rate (0.14 mL/kg/min) as compared to the lower infusion rate (0.08 mL/kg/min). This discrepancy was largely due to infusion site reactions and mild/moderate headaches. It should be noted that these studies were conducted in a limited number of subjects (a total of 136 patients from three studies) and the study subjects may not include patients with other co morbidities, such as those with renal insufficiency or those at high risk of thrombo embolic events.

Clinical summary and conclusions

SC infusion for PID subjects

According to the relevant EU guideline[4], it is important to assess the PK behaviour of the IgG product and its ability to maintain plasma IgG levels in the therapeutic range for the PID indication. Study 060001 demonstrated that Gamunex was able to maintain the plasma IgG level above the target range (4-6 g/L) in all subjects at each visit throughout both the IV and SC Phases; the trough concentrations of total IgG were above 6.3 and 7.1 mg/mL for IV and SC infusion, respectively. Study 060001 also demonstrated that weekly SC Gamunex dose calculated based on a conversion factor of 1.37 from the IV Gamunex dose provides comparable overall SC plasma concentrations of total IgG (as determined by steady state AUC) to plasma concentrations produced by an IV dose; the point estimate and 90% CI of the geometric LMS ratio (SC versus IV) for steady state AUC shows non inferiority of the SC route and bioequivalence between SC and IV administration of Gamunex. The study also showed that the weekly SC administration of Gamunex resulted in relatively constant steady state plasma levels of total IgG. In contrast, IV administration caused steady state fluctuations of more than 2 fold. The steady state mean C_{trough} of total IgG after weekly SC dosing was also 19% higher than the steady state mean C_{trough} after regular IV Gamunex dosing.

[4] CPMP/BPWG/859/95 rev.2. Guideline on core SmPC for human normal immunoglobulin for intravenous administration IVIg.
<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003567.pdf>

The safety profile of Gamunex SC infusions was assessed in Study 060001. The study showed a relatively low incidence of systemic AEs and tolerable local infusion site reactions which improved significantly over time with repeated infusions. The SC Gamunex infusion was considered well tolerated and the overall safety profile was similar to that of other SC IgG products.

It is noted that Study 060001 included only three adolescents subjects aged between 13 and15 years. This number was too small for a separate evaluation of PK and safety in this population and it was not possible to determine whether this group responds differently to adults. Therefore, the efficacy and safety of the SC route in paediatric patients have not been established. The sponsor needs to collect PK and efficacy safety data in paediatric subjects with primary immunodeficiency (PI) post-approval. There are no efficacy variables for this study. Serious bacterial infections and any infections as well as febrile episodes were evaluated as safety variables. There were no serious bacterial infections in the SC phase of the PK/Safety study.

Extension of indications

Gamunex has been approved for the treatment of PID and ITP based on the efficacy and safety data for these two indications respectively. The EU guideline[5] adopted in Australia allows for extrapolation to the following "well established" indications (Table 30) on the basis of the efficacy and safety data from PID and ITP subjects:

Table 30: The "well established" indications for immunoglobulin products

Replacement therapy in:	Immunomodulation:
Primary Immunodeficiency Syndromes such as: Congenital agammaglobulinemia and hypogammaglobulinemia Common variable Immunodeficiency Severe combined immunodeficiency Wiskott Aldrich Syndrome	Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding prior to surgery to correct the platelet count.
Secondary states such as: Myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections. Children with congenital AIDS and recurrent infections.	Guillain Barre Syndrome. Kawasaki disease.
Allogenic bone marrow transplantation.	

The EU guideline[4] also allows extrapolation to use of IVIg in allogenic bone marrow transplantation based on studies in PID and ITP as both substitution and immune regulation mechanism are thought to be involved. Similar data have been accepted by the

[5] CPMP/BPWG/388/95 rev 2. Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004768.pdf>

TGA in the past. Therefore, the clinical evaluator considers it is appropriate to approve the following indications based on previous data on PID and ITP patients:

- Congenital hypogammaglobunaemia,
- Multiple myeloma,
- Chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemiaand recurrent infections,
- Children with congenital AIDS and recurrent severe bacterial infections,
- Guillain Barré Syndrome,
- Kawasaki disease,
- Allogeneic bone marrow transplantation

The European regulatory authority has produced a guideline[3] to standardise the content of the SPC for IVIG products marketed in and this guideline also sets out standard dosage regimens for each of the indications that can be approved for such products. It is noted that the proposed dosage regimens for each of the above indications for Gamunex in Australia are consistent with this guideline.

It should be noted that for other auto immune disorders, in particular multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyneuropathy (CIDP), myasthenia gravis exacerbations, confirmatory clinical data are required by the same EU guideline.

The sponsor conformed to this requirement and a clinical study, Study 100538, was conducted to evaluate the short and longer term efficacy and safety of Gamunex in the treatment of CIDP subjects. Study 100538 was a large, optimally powered study with 48 weeks of follow up. The study was well designed and the blind was maintained throughout the efficacy and randomised withdrawal periods. The INCAT scale for the assessment of CIDP is considered to be a well developed and validated score to use. The choice of the primary endpoint is clinically relevant and the choice of Gamunex dose was in keeping with doses used in other immunomodulatory conditions. The primary efficacy analysis was a comparison of the responder rates in the Gamunex group to the placebo group during the 24 weeks efficacy period. The results demonstrated a statistically significant higher responder rates in the Gamunex group and provided the evidence of the benefit of Gamunex in the treatment of CIDP. The results of the secondary endpoints further supported the benefit of Gamunex for CIDP patients. There were no new drug related AEs or changes in laboratory parameters or vital signs reported during the study. Generally, the reports were consistent with the known safety profile of Gamunex. It should be noted that the efficacy and safety of Gamunex has not been evaluated in paediatric patients with CIDP.

Rapid infusion rates

The clinical safety of IV Gamunex administered at rapid infusion rates was evaluated in two studies in ITP patients and one study in PID patients.

Study100422 in eight ITP patients showed that the nature and frequency of all AEs and the subset of infusion related AEs were similar between the two infusion rates (0.08 and 0.14 mL/kg/min).

Study 100213 in 28 ITP patients demonstrated the three infusion rates (0.08, 0.11, and 0.14 ml/kg/min) were generally comparable in terms of overall adverse event rates but that 'mild headache' was more frequent at the higher infusion rates.

Study 100348 in 100 PID patients did not show any unexpected safety findings. The drug related AEs were approximately twice as common at the rapid infusion rate as compared with the slow infusion rate but this was largely due to infusion site reactions and mild/moderate headaches.

As discussed previously, these studies were conducted in a limited number of subjects (a total of 136 patients from three studies) and the study subjects may not include patients with other co-morbidities such as those with renal insufficiency or those at risk of thrombo-embolic events or aseptic meningitis.

Benefits and risks assessment

Benefits

SC administration

SC administration of immunoglobulin has certain advantages over IV administration of immunoglobulin. The relevant EU guideline[1] has summarised the advantages of SC immunoglobulin therapy: "Subcutaneous home therapy presents a well tolerated treatment, an increase in health-related quality of life for the patients and reduces the costs in the healthcare sector. In addition, compared to the intravenous route very few adverse systemic reactions have occurred; the need for venipuncture is circumvented and the efficacy in maintaining normal range serum IgG levels has been demonstrated in various studies".

Treatment of CIDP

The short term (24 weeks) and longer term (48 weeks) benefits of Gamunex infusion for the treatment of CIDP patients were demonstrated in a well designed and adequately powered study (Study 100538). This study was discussed in the Efficacy section of this report.

Rapid infusion rate

The proposed faster infusion rate would reduce the infusion time, nursing time and medical cost. A faster infusion rate would also be more convenient for patients and their quality of life.

Risks

The risks associated with the SC administration in PID patients are considered minimal and mainly consists of injection site reactions. As mentioned, SC administration is not suitable for ITP patients due to risk of hematoma.

Study 100538 conducted in CIDP patients did not reveal any unexpected safety signals and the safety profile was consistent with that of other clinical studies conducted with Gamunex.

The risks associated with rapid infusion rate include increased frequency of mild headache and infusion site reactions. The approved Gamunex Product Information states aseptic meningitis (ASM) may occur more frequently in association with rapid infusion rate. In addition, rapid rate of infusion is not considered appropriate for patients with high risk of renal impairment and in patients with high risk of embolic events.

Balance between benefits and risks

The benefit and risk balance is considered positive in the following situations;

- SC administration in adult patients with PID
- Treatment of adults patients with CIDP

For the rapid infusion rates, in view of the increased frequency of infusion site reactions and mild headache observed in the submitted studies and taking into account of the potential risks of increased frequency of aseptic meningitis and patients with higher risk of renal insufficiency and thromboembolic events (see the approved Gamunex PI), the clinical evaluator considers that the benefits/risks balance of rapid infusion rates is inconclusive at this stage. Larger studies are required to clarify this.

Recommendation regarding registration

Subject to the recommendations of the quality evaluators, the clinical evaluator recommended that the product be approved for the following:

- An extension of indication to include the treatment of CIDP.
- An extension of indication to include congenital hypogammaglobinaemia, multiple myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections, Children with congenital AIDS and recurrent severe bacterial infections, Guillain Barré Syndrome, Kawasaki disease and Allogeneic bone marrow transplantation
- SC infusion for the treatment of Primary Immune Deficiency.

The dosing regimens included in the PI are based on EU guidance documents and are same as previously for the IVIG. These are therefore supported.

Recommended conditions of registration

The following conditions of registration approval were suggested:

- To comply with the pharmacovigilance requirement as assessed by the Office of Product Review, TGA
- To amend the Product Information to the satisfaction of the TGA.

V. Pharmacovigilance findings

The Office of Product Review (OPR) at TGA reviewed the sponsors Risk Management Plan (RMP). Table 31 summarises the Ongoing Safety Concerns and the proposed Risk Minimisation Activities proposed by the sponsor.

Table 31. Summary of Ongoing Safety Concerns and Proposed Risk Minimisation Activities.

Safety concern	Proposed PhV[6]	Proposed risk minimisation activities[7]
Haemolysis (Class IVIg effect) as an important	Routine.	Product labelling.

[6] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[7] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Safety concern	Proposed PhV[6]	Proposed risk minimisation activities[7]
potential risk.		

PhV=Pharmacovigilance

The Office of Product review made the following recommendations regarding the conditions of registration for this submission with respect to the Risk Minimisation Plan:

The full implementation of the RMP Version AUS-1.0 with:

1. the following RMP revisions to be provided within 90 days of approval:
   - The RMP is to include documentation on the epidemiology of the indications, potential for overdose, misuse for illegal purposes, potential for off-label use and potential for off-label paediatric use.
   - The RMP is to include the following as Ongoing Safety Concerns requiring further characterisation and evaluation along with corresponding pharmacovigilance actions, milestones for reporting and risk minimisation activities:

     Hypersensitivity and anaphylactic reactions.

     Thromboembolic events.

     Aseptic meningitis syndrome.

     Transmission of infective agents.

     Transfusion-related acute –lung injury (TRALI).

     Experience in patients with renal impairment.

     Experience in patients with cardiac disease.

     Experience in pregnancy/lactation

     Experience in paediatric patients.(≤ 16 years).

     Experience in elderly patients (≥ 65 years).

     Long term safety of subcutaneous administration.
2. The following additional risk minimisation activities:
   - To provide subcutaneous self administration and dose calculation aids for healthcare providers in Australia concurrent with product distribution. This material should be provided to the TGA for review and acceptance.
   - To provide an intravenous administration dosing chart for healthcare providers. This material should be provided to the TGA for review and acceptance.
   - To provide the consumer medicine information within the medicine package.

The sponsor has responded to the evaluator's recommendations and the OPR evaluator considered that the sponsor's responses were acceptable. The sponsor has given an undertaking to revise the RMP accordingly.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The sponsor proposes to change the manufacturing process by reducing the final container low pH incubation time. This step is one of the key viral inactivation steps. There were no objections on Viral/transmissible spongiform encephalopathy (TSE) safety grounds to approval of the change.

The sponsor was questioned about the potential for the manufacture change to impact on thromboembolic adverse events. Batches of initial sterile bulk are subjected to thrombin generation test (TGT) and non activated partial thromboplastin time test and these show no response above baseline or buffer control. Testing of 15 consecutive lots of drug products did not show procoagulant activity by TGT.

There are no outstanding quality issues after the quality evaluation. The quality evaluation was considered by the PSC.

Nonclinical

The change to manufacture process was considered unlikely to be of toxicological concern. The sponsor provided a single dose PK study in rabbits relevant to SC administration. The plasma bioavailability of Gamunex administered SC was similar to IV when the administered SC dose was 120% to 150% of the IV dose. No nonclinical efficacy, safety pharmacology, acute or repeat dose toxicity or local tolerability studies by the proposed SC route were submitted. There were no nonclinical studies in young animals to support use in children. No nonclinical studies were submitted to support the proposed increase in IV infusion rate.

In view of the limited nonclinical testing of changes related to SC route of administration, demonstration of safety and efficacy will depend almost entirely on clinical data.

Clinical

The current submission contains one study which evaluated SC administration of Gamunex (Study 060001), one study which evaluated Gamunex in treatment of CIDP patients (Study 100538) and three studies which assessed several infusion rates of Gamunex (Studies 100213, 100422 and 100348).

The clinical evaluator supported registration of Gamunex administration by SC infusion for replacement therapy in PID. In adult PID subjects, weekly SC Gamunex dose calculated based on a conversion factor of 1.37 from the IV Gamunex dose (with adjustment of dosing interval) provides comparable overall SC plasma concentrations of total IgG, as determined by steady state AUC, to plasma concentrations produced by the IV dose. The trough concentrations of total IgG in all subjects at each visit throughout both the IV and SC phases were all above 6.3 and 7.1 mg/mL, respectively, and greater than the commonly accepted protective trough concentration of ≥ 5 mg/mL. SC administration was associated with low incidence of non infusion site adverse events, comparable to the incidence with IV administration. Local infusion site reactions were tolerated and the frequency of these was reduced over time with repeated infusions. The EU Guideline for Immunoglobulin for SC use[2] has a requirement for at least 10 children to be included, a criteria which was not met in the study.

The clinical evaluator supported registration of the extension of Gamunex indications to include “Immunomodulatory effect in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)”. Study 100538 was a large, well-designed study with 48 weeks of follow up. The study blind was maintained throughout the Efficacy and Randomised Withdrawal Periods. The INCAT scale used in this study for the assessment of CIDP is considered a well developed and validated score. The choice of the primary endpoint is

clinically relevant. The primary efficacy analysis was a comparison of the responder rates in the Gamunex group to the Placebo group during the 24 weeks efficacy period. The results demonstrated a statistically significant higher responder rates in the Gamunex group and provided evidence of the benefit of Gamunex in the treatment of CIDP. The results of the secondary endpoints further supported the benefit of Gamunex for CIDP patients. There were no drug related adverse events or changes in laboratory parameters or vital signs reported during the study that are not consistent with the known safety profile of Gamunex. Submission of confirmatory data with the applicants IVIG is recommended for "other auto-immune disorders" including CIDP in EU Guidelines (discussed under *Clinical Summary and Conclusions* above).

The clinical evaluator supported registration of the extension of Gamunex indications to include "well established" indications identified in the relevant EU guideline[5] and which this guideline allows by extrapolation of data from PID and ITP studies.

The clinical evaluator considered that the benefit/risks balance of rapid IV infusion rates was inconclusive. The clinical evaluator noted that the three studies of rapid IV infusion rate involved small patient numbers. Study 10348 was the largest study which demonstrated that drug related AE were more frequent (2 fold) with a faster infusion rate than the currently recommended maximum rate. The studies did not include subjects with comorbidities. The sponsor has submitted a revised PI document accepting the clinical evaluator's recommendation.

Risk management plan

The Office of Product review made several recommendations regarding the conditions of registration for this submission with respect to the Risk Minimisation Plan (see *Section V*. above).

Risk-benefit analysis

Delegate considerations

The proposed extension of indications for CIDP is considered to be supported by a well designed and conducted study. The clinical evaluator commented that the choice of Gamunex dose in Study 100538 was is in keeping with doses used in other immunomodulatory conditions. The 2 g/kg (loading dose) and 1 g/kg doses are high dose regimens for immunomodulatory indications and repeat dosing every 3 weeks for an indefinite period is recommended. Although the proposed dose for Gamunex for CIDP appears to be tolerated up to 48 weeks it may not be the minimum effective dose. Published reports[8] for various IVIg products report that lower maintenance doses (as low as 0.4 g/kg with doses repeated every 2 to 6 weeks) have demonstrated efficacy.

The TGA has adopted EU Guidelines[4] which describes the extrapolation of "well established" indications for IVIg. The EU currently has a replacement guideline[9] discussing the clinical investigation of human normal immunoglobulin products which has included some revisions to the "well established indications". This includes a change from "Allogeneic bone marrow transplantation" under "Immunomodulation" to "Replacement

[8] Eftimov F, Winer JB, Vermeulen M, de Haan R, van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001797. DOI: 10.1002/14651858.CD001797.pub2

[9] EMA/CHMP/BPWP/94033/2007 rev 2. Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500078472.pdf>

therapy- Hypogammaglobulinaemia in patients after allogeneic haemopoietic stem cell transplantation". Although the TGA has not yet formally adopted this guideline, the sponsor is requested to consider amendment of "well established" indications with the amendment of dosage recommendations for Gamunex under the Allogeneic bone marrow transplantation subheading.

ACPM are requested to comment on the appropriateness of amended "well established" indications in the relevant EU guideline.[8]

Another EU guideline[10] provides relevant dosage recommendation for:

"Hypogammaglobulinaemia in patients after allogenic haemopoietic stem cell transplantation".

A European Medicines Agency (EMA) concept paper[11] discusses revision of the existing guideline to focus on clinical trial requirements in PID patients and the requirements necessary for immunomodulatory indications.

The clinical evaluator considered that the benefit/risks balance of rapid IV infusion rates was inconclusive. The sponsor has subsequently submitted a revised PI document accepting this recommendation (a recommended maximum IV infusion rate of 0.8 mL/kg per minute).

Delegate' proposed action

The Delegate proposed to approve the extension of indications for Gamunex to include immunodulatory effect in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). The Delegate also proposed to approve an extension of indications to include:

- immunodulatory effect in Guillain Barré Syndrome (GBS) and
- Kawasaki disease (KD) (in conjunction with acetylsalicylic acid)

and replacement therapy in

- hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed;
- hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma (MM) patients who have failed to respond to pneumococcal immunisation,
- hypogammaglobulinaemia in patients after allogeneic haemopoietic stem cell transplantation (HSCT) and children and adolescents with congenital AIDS and recurrent bacterial infections.

The Delegate also proposed to approve administration of Gamunex by the SC route for replacement therapy of primary immunodeficiency syndromes.

The advice of the Advisory Committee for Prescription Medicines (ACPM) was requested.

[10] EMA/CHMP/BPWP/94038/2007 rev 3. Guideline of core SmPC for human normal immunoglobulin for intravenous administration(IVIg)

[11] EMA/CHMP/BPWP/761007/2010 Concept paper on revision of: Note for Guidance on the Clinical investigation of human normal immunoglobulin for subcutaneous and intramuscular use (CPMP/BPWG/283/00). and Core SPC for human normal immunoglobulin for subcutaneous and intramuscular use (CPMP/BPWG/282/00). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/12/WC500099995.pdf>

Response from Sponsor

The sponsor welcomed the opportunity to comment on the Delegate's request for ACPM advice regarding the extension of indications, new route of administration and update of the manufacturing process sought for Gamunex. Overall, the sponsor agreed with the Delegate's comments on the quality, nonclinical and clinical evaluators' reports.

The sponsor would like to mention that the higher IV infusion rate proposed for Gamunex has been deleted from the proposed Australian PI document.

The sponsor noted the recommendations made by the OPR evaluator for the risk minimisation plan and commits to provide a revised RMP to the TGA within 90 days of the approval of this application.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

In expressing its view that this submission for Normal Immunoglobulin (Human) (Gamunex) solution 1 g/10 mL; 2.5 g /25 mL; 5 g/ 50 mL; 10 g/ 100 mL & 20 g/ 200 mL was suitable to be considered for approval, the ACPM agreed with the Delegate that the overall risk-benefit profile for this product was positive. The ACPM considered the following matters:

The ACPM noted that changes to the manufacturing process in the application included a step that is one of the key viral inactivation steps. It was also noted that the reduction in non enveloped virus titres was less than expected but within required limits. The testing of procoagulant activity was reassuring and quality control aspects of the application were considered adequate.

Efficacy

The ACPM noted the absence of data generated using modified product. Nonetheless, the evidence of efficacy in CIDP was found to be adequate and equivalent to the Cochrane findings in terms of number needed to treat. The subcutaneous route had advantages for patients both in terms of convenience and more even tissue levels. It would also have the advantage of reduced use of hospital resources.

The ACPM queried the validity of calculating the dosage by multiplying by 1.37 and suggested evidence be provided for this factor.

Safety

There were no new safety signals apparent. Injection site reactions were reported but these appeared to diminish over time.

The ACPM agreed with the Delegate that there were insufficient data submitted on the higher infusion rate but encouraged the sponsor to submit further data as this is an individualised treatment and some patients may be able to accommodate the higher rate.

The ACPM noted that there were clearly insufficient numbers in the paediatric range in the trial to conform to the current EMA guidelines. However, there were significant safety data with the currently registered product and the individualised nature of this treatment would allow extrapolation to this group.

The ACPM supported extending the immunomodulatory indications to CIDP, GBS and KD (omitting the specification of aspirin use) but were not supportive of the indication for allogenic BMT. The replacement indications were all supported except that the committee considered the term "congenital AIDS" inaccurate and suggested "symptomatic HIV in

children" as a possible alternative. However, IVIG is no longer used in paediatric HIV infection and this indication is of historical interest only. The ACPM was of the view that it would be advantageous for the statement of indications to conform to the current therapeutic criteria.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Gamunex containing normal immunoglobulin (Human) 10% solution for Injection (1g/10 mL, 2.5g /25 mL, 5g/ 50 mL, 10g/ 100 mL and 20g/ 200 mL) for the following:

1. New indications:

   Immunomodulation in Guillain Barré Syndrome (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), and Kawasaki disease – and amendment of the Replacement indications.

2. An additional route of administration:

   Subcutaneous infusion in connection with *Replacement therapy in Primary Immunodeficiency [PI] Diseases* only.

   and

3. An update to the manufacturing process:

   A reduction in the duration of the viral inactivation process.

Nonclinical references

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Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au