TITLE PAGE

Original Article

Efficacy, Safety, and Pharmacokinetics of a Novel Subcutaneous Immunoglobulin, Evogam[®], in Primary Immunodeficiency

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Running title

Efficacy and safety of Evogam[®] in PID

Abstract

This phase III, open-label, multi-centre study investigated the efficacy, safety, pharmacokinetics, and quality of life impact of Evogam[®], a new chromatographically fractionated 16% subcutaneous immunoglobulin (SCIg), utilising a 1:1 dose transition ratio from previous immunoglobulin therapy. Thirty-five previously treated patients with primary immunodeficiency received weekly Evogam over 36 weeks. Primary endpoints were rate of serious bacterial infections (SBIs), and steady-state serum immunoglobulin G (IgG) trough concentrations. No SBIs were reported during the study. Evogam produced significantly higher mean trough IgG concentrations with 1:1 dose conversion compared to previous immunoglobulin treatment (8.94 versus 8.27 g/L, $p = 0.0063$). Evogam was efficacious in prevention of infections and maintenance of trough levels using a 1:1 dose conversion. It was well tolerated with no withdrawals due to adverse events, and was preferred to IVIg by the majority of patients.

Key words

Immunoglobulin therapy; primary immunodeficiency; subcutaneous immunoglobulin; intravenous immunoglobulin; quality of life.

1 INTRODUCTIONⁱ

Evogam[®] (Human Normal Immunoglobulin 16% (16 g per 100 mL)) is a new liquid immunoglobulin preparation specifically developed for subcutaneous use. The current study evaluated its use as replacement therapy in primary immunodeficiency disorders (PID). There are more than 150 primary immunodeficiency disorders recognised [1], with worldwide prevalence estimates ranging from 4.4 to 83 per 100,000 people [2,3]. The Australasian PID registry reported a prevalence of 5.6 per 100,000 population, with immunoglobulin replacement therapy (IRT) used in 30 separate PID conditions, and 77% of PID patients having predominantly antibody deficiency syndromes [4].

Traditionally IRT has been given intravenously (IV), but subcutaneous (SC) administration is increasingly used. A number of subcutaneous immunoglobulin (SCIg) products are now licensed globally, with differences in concentration, stabiliser, fractionation method and pathogen safety measures. Potential benefits attributed to SCIg include stable trough levels, fewer systemic adverse effects, an alternative to venous access and improved patient autonomy [5]. These factors, in addition to the expansion of options in delivery systems and methods, have facilitated the uptake of SCIg as an alternative modality to intravenous immunoglobulin (IVIg).

ⁱ CHQ PF50[™] - Child Health Questionnaire[™] Parental Form; LQI - Life Quality Index; SF 36v2[™] - Short Form 36-item Health Survey Version

There is lack of consensus on dosing conversions to achieve therapeutic equivalence when transitioning from IV to SC therapy. Strategies focus on attaining either comparable trough levels with 1:1 dosing, an approach used in Europe [6], or comparable total systemic exposure, with dosing ratios of 1:1.37-1.53, as stipulated by the United States Food and Drug Administration (US FDA) [7]. These differences have potential implications for treatment cost, immunoglobulin consumption, and clinical outcomes. A key aspect of the evaluation of safety and efficacy of Evogam in this study, therefore, was the use of equivalent dose in the transition from prior IV therapy.

International policies for plasma product supply vary, with many Asia Pacific countries utilising domestically sourced plasma in preference to imported products to maintain reliability and affordability of supply. CSL Biotherapies (Melbourne, Australia) supplies 6% IVIg and 16% intramuscular immunoglobulin (IMiG) products in these markets. Whilst IMiG is occasionally used off label as SC therapy, no specific SCiG preparation is currently available in the Asia Pacific region under this toll fractionation model. The aim of this study was to assess the efficacy, safety, pharmacokinetics and quality of life impact of Evogam, utilising a 1:1 ratio for dose transition from previous IRT.

2 METHODS

2.1 Patient selection

The study aimed to recruit a minimum of 30 patients overall with at least 20 patients for pharmacokinetic evaluation, in accordance with the European Medicines Agency (EMA) Guidance [6]. Males and females aged three years and above with either X-linked agammaglobinaemia (XLA) or common variable immunodeficiency disorder (CVID) and severe hypogammaglobulinaemia who were maintained on IRT at 0.2-0.6 g/kg/month for the previous six months (IgG trough level ≥ 5 g/L prior to screening) were eligible. Exclusion criteria included PID diagnosis within the six months prior to screening, hypersensitivity or severe side effects from previous IRT, and immunosuppressive therapy (topical, inhaled, or oral low dose steroids permitted, i.e. prednisolone 5-10 mg daily).

Study populations were defined as follows: The Safety Population comprised patients who received at least one dose of Evogam; the Pharmacokinetic (PK) Population were those who reached steady-state on Evogam and could provide adequate blood samples for PK analyses; the Per Protocol (PP) population attended all study visits and had no major protocol violations or deviations; and the Intent-To-Treat (ITT) population included patients who received at least one dose of Evogam and had evaluable trough immunoglobulin G (IgG) levels for current and previous IgG treatment.

2.2 Study design

This phase III, single-arm, open-label, multi-centre study was conducted from April 2007 to October 2009 at nine major hospitals in Australia and New Zealand, in accordance with good clinical practice [8]. Each site was granted ethics approval and all patients provided informed consent prior to being enrolled. Data was managed using Oracle Clinical™ Software which incorporated an electronic audit trail.

The study comprised a Screening Period of up to 42 days, a 12-week Wash-out/Wash-in Period, a 24-week Efficacy Period and an Exit Visit at least 30 days following the last dose (Figure 1).

2.3 Study treatment

Evogam is formulated to 16% w/v protein, pH 6.6, stabilised with 2.25% glycine. The manufacturing process utilises chromatography as the primary fractionation method, which is recognised as a purification technique that delivers high purity products and high yields [9,10]. Pathogen reduction steps include two dedicated processes; pasteurisation and nanofiltration.

The weekly dose of Evogam was calculated as the previous total monthly IVIg dose divided into four or remained unchanged for patients on previous SCIg therapy, with treatment duration of 36 weeks. The first Evogam infusion commenced two weeks after the last infusion of IVIg, or one week post the last SCIg treatment. There were no dose changes permitted during the study.

Evogam was administered subcutaneously by syringe infusion pumps at one or more injection sites, rotated with each treatment. Initial volume per site was 10 mL, administered at 10 mL/hr, with the option to increase to a maximum of 20 mL per site at 20 mL/h, depending on tolerability.

Following training and supervised infusions at visits 1 to 6, patients or guardians administered infusions at home, with details captured in patient diaries. Patients were considered compliant if infusion was within six to eight days of the previous infusion.

2.4 Efficacy and safety assessments

2.4.1 Primary endpoints

The first primary endpoint was the annualised rate of serious bacterial infections (SBIs) per patient occurring during the Efficacy Period. SBIs were defined as bacterial pneumonia, bacteraemia/ septicaemia, osteomyelitis/ septic arthritis, bacterial meningitis and visceral abscess, based on the FDA Guidance for Industry [7]. The second was steady-state serum IgG trough concentrations during the Efficacy Period. These were compared to steady-state trough IgG levels obtained during previous IgG treatment period.

2.4.2 Secondary endpoints

Infection episodes, antibiotic use, days off work or school and days of hospitalisation were recorded during the Efficacy Period.

Blood samples for PK evaluations were collected over a seven day period at Visit 9 (week 24); pre infusion, end of infusion, and at 24, 48, 96 hours and 7 days post infusion.

Generic Health-Related Quality of Life (HRQoL) information was collected at Visits 0, 6 and 12. Adult patients completed the Short Form 36-item Health Survey Version 2 (SF-36v2™) and a treatment satisfaction questionnaire, the Life Quality Index (LQI), at the above visits in addition to a Treatment Comparison Questionnaire at Visits 6 and 12. For paediatric patients, parents or guardians completed the Child Health Questionnaire™ Parental Form (CHQ-PF50™) at Visits 0, 6 and 12. Both the SF-36 and CHQ-PF50 are recognised and validated generic QoL instruments, and the LQI and Treatment Comparison Questionnaire have previously been used to assess treatment satisfaction and patients' preference for home versus clinic infusions [11].

Adverse events (AEs) were recorded throughout the study. Solicited infusion site symptoms of pain/itching/local heat, erythema, and/or induration were assessed in the clinic by the investigator, or at home by the patient, and rated from 0 (none) to 4 (severe). They were considered AEs if they resulted in discontinuation of Evogam, required treatment or impacted adversely on patient wellbeing.

Haematology and biochemistry tests were performed at screening, Visit 1, 4, 6, 9, and Exit Visits. Urinalysis and virology studies were done at screening, with additional virology follow up at Exit Visit, and haemolysis testing performed at screening and Visit 9.

2.5 Statistical analysis

Analysis of efficacy and trough IgG concentration was conducted for the PP and ITT Populations. Poisson regression was used to calculate the SBI rate with one-sided 99% upper confidence interval. Safety variables were assessed using appropriate descriptive variables, the Wilcoxon signed-rank test (non-parametric) or distribution-free methods tests. An analysis of variance model compared profiles between previous IVIg treatment and Evogam, with a 95% CI calculated for the difference between scores for both treatment groups. Statistical Analysis Software, v8.2 was used for analysis. PK variables were calculated and modelled independently using WinNonlin (V5.2, Pharsight Corp., U.S.)

3 RESULTS

3.1 Patient disposition and demographics

A total of 35 patients from nine centres in Australia and New Zealand enrolled in the study and received at least one dose of subcutaneous Evogam (Figure 2). Major protocol violations excluded four patients from the PP population and three patients with insufficiently evaluable blood samples were excluded from the ITT population. All adverse event data was obtained from the Safety Population, whilst analysis of pharmacokinetic data was conducted on the PK Population. CVID was the most common diagnosis (94.3%) (Table I).

3.2 Study drug administration and compliance

A total of 1111 infusions were administered, with a range of 2-36 infusions per patient. The majority of patients received 36 infusions (65.7%), with 17.1% receiving 33-35, 11.4% receiving 13-30, and 5.7% receiving less than 5. Two injection sites were used per infusion in most cases (range 1-5), with infusion duration ranging from 0.8 to 2.7 hours (median 1.48 hours), at a median rate of 28.3mL/hr. Median total dose was 65.6g (range 12-162), with weekly dose ranging from 3-13.5 g (median 6.70 g). The maximum rate achieved was 54mL/hr in two adults, over two to three infusion sites, and for children was 30 mL/hr, with two sites.

Treatment compliance was high (93-100%) at most weeks throughout the study, with the exception of Week 1 (28/35; 80.0% patients), when five patients were one day outside the study protocol time window, and Week 18 (26/30; 86.7% patients). All patients reported at least one concomitant medication, most commonly paracetamol (68.6%) and amoxicillin with potassium clavulanate (37.1%). One patient received prednisolone 5-10mg daily at study entry and throughout the study for pre-existing sarcoidosis. Loratadine or paracetamol was used for pre-medication in 5% of infusions (55 /1111). One patient received ongoing premedication after an AE (moderate infusion site symptoms). A further six patients received premedication at one or more infusions, either as continuation from their prior intravenous therapy (n=3), as prophylaxis commenced at their first subcutaneous infusion (n=2), or following a mild site reaction, not classified as an AE (n=1). Four patients (11.4%; 1 adult, 3 children), used topical local anaesthetic pre infusion at the injection site.

3.3 Primary efficacy assessments

Efficacy assessments were conducted in both the ITT (n=32) and PP populations (n=31) and results were similar for both. Outcomes for the ITT population are reported here.

3.3.1 Serious bacterial infections

The 12-month serious bacterial infection (SBI) rate per patient during the Efficacy Period was 0 (upper 99% CI: 0.33). No SBIs were reported during the entire study period.

3.3.2 Serum IgG trough concentrations

Mean trough IgG concentrations ($C_{\min}$) were significantly higher with Evogam treatment compared to previous IgG treatment (Table II), with a least square mean of 8.27 g/L on previous treatment, and 8.94 g/L on Evogam. There was minimal variation in mean trough

serum IgG concentrations from visit 6 onwards, indicating rapid achievement of steady state, with a relatively flat trough profile over time (Figure 3). No patient had a trough IgG concentration of less than 5 g/L at any time during the study. Paediatric results were consistent with the overall results, with minimal variation in trough levels during the efficacy period, but had no significant change in mean $C_{\min}$ results between Evogam and previous IgG treatment.

3.4 Secondary efficacy endpoints

3.4.1 Infection episodes

Thirty six non-serious infection episodes were reported, with an annualised rate of 2.82 per patient (upper 95% CI: 3.66). Lower and upper respiratory tract infection, sinusitis, rhinitis, and ear infection were the most commonly reported.

3.4.2 Days of hospitalisation due to infection

One patient spent a total of eight days in hospital due to infection, with an annualised rate per patient of 0.56 days.

3.4.3 Days away from work/school

Eleven patients missed work, school, kindergarten or day care for a total of 42 days. The annual rate per patient was 2.97 days (upper 95% CI: 3.82).

3.4.4 Antibiotic usage

Twenty-seven patients (84.4%) spent a total of 1750 days on IV or oral antibiotics during the efficacy period for treatment of infection, prophylaxis or other medical/surgical conditions

(123.57 days/patient/year; upper 95% CI:128.53). Eleven patients were receiving antibiotics at study entry, giving a point prevalence of 34.4% on IV therapy. Four of these patients continued on antibiotics for the duration of the study. All patients with bronchiectasis at study entry required antibiotic therapy (11/11; 172.92 days/patient/year). Of the patients without diagnosed bronchiectasis, 76.2% required antibiotic therapy (16/21; 96.14 treatment days/patient/year). Analysis of antibiotic use was carried out post-hoc (Figure 4).

3.4.5 Pharmacokinetic parameters

There was minimal variation in IgG concentrations over the seven day measurement period with a mean peak concentration ($C_{\max}$) of 8.87 g/L (range 6.70 – 11.1 g/L) and mean trough concentration ($C_{\min}$) of 8.32 g/L (range 6.0 – 10.6 g/L), indicating steady state concentrations were achieved.

3.4.6 Quality of Life analysis

Changes in HRQoL were assessed in 27 adults who completed the SF-36v2™ and LQI surveys at baseline and post SCIg, and 25 who completed the Treatment Comparison Questionnaire.

SF-36v2™ results showed no significant changes in most domains and summary scores.

Mean physical component scores (44.0; Range: 23.8 – 61.1) were below the population norm at baseline, but improved to values consistent with population norm (46.9; Range:25.3– 67.5) [12] after switch to Evogam. Mental Component Summary scores improved at Visit 6 (51.1; Range: 34.2 – 61.9) compared with baseline (48.7; Range: 27.7 – 62.4) and dropped back to near baseline scores at Visit 12.

The LQI survey (n=27) showed a significant improvement in the scales of Treatment Interference ($p = 0.002$) and Therapy Setting ($p < 0.001$), with a 20% and 29% improvement respectively.

The Treatment Comparison Questionnaire reported a preference for SCIg by 83.3% (n=20/24) at visit 12, whilst three patients preferred IVIg and one patient reported no preference.

Five children completed the CHQ-PF50 questionnaire on at least one occasion with three completing the questionnaires as required at all three visits. Scores for 'Global Health' (n = 3) improved from Visit 0 to Visit 12. Due to the small number, repeated measures analysis to compare with quality of life on previous treatment was not performed.

3.4.7 Safety and tolerability

There were no discontinuations of treatment or study withdrawals due to AEs and no deaths. Overall 33/35 (94.3%) of the Safety Population reported an AE, at a rate of 0.24 per infusion, regardless of relationship to study drug. Headache (50 episodes in 14/35 (40.0%) patients) and nausea (10 episodes in 8/35 (22.9%) patients) were the most frequently reported. One patient had an interruption to infusion due to an episode of vomiting, which was considered unrelated to infusion procedure or study drug, but was able to recommence infusion and completed the study.

Adverse events considered by the investigator to be treatment related were reported by 43.3% of adults (13/30) and 20.0% of children (1/5), with a rate per infusion of 0.059. Headaches were the most frequent, occurring in 23.3% of adult patients at a rate of 0.031 per infusion (34 events in 7 patients) and were of mild to moderate intensity. Three severe treatment related events were reported by two adults; pyrexia and chills in one and sinusitis recorded as

possibly related by the investigator in another. All events in children were of mild to moderate intensity.

Solicited tolerability symptoms at the infusion site were recorded by 97.1% (34/35) of patients after at least one infusion, with a per infusion rate of 0.72 (803/1111). Most were mild to moderate, with a similar pattern in adults and children. Pain/itching/local heat was reported by 83.3% (25/30) of adults and 80.0% (4/5) of children, erythema by 93.3% (28/30) of adults and 80.0% (4/5) of children, and induration by 96.7% (29/30) of adults and all the children. The majority of reports occurred within 8-12 hours of the infusion, and had declined by more than half 72 hours later (Figure 5). Over the study duration, symptoms declined in incidence from 88.6% (31/35) after the first infusion to 65.6% (21/35) at Week 8 and remained stable thereafter.

The severity of infusion site symptoms also decreased over time. More patients reported severe symptoms (14.3%; 5/35) immediately following infusion, the proportion decreasing to 2.9% (1/35) 72 hours later (Figure 6). This decrease was also seen over the duration of the study, from 8.6% reporting severe symptoms after the first infusion to no reports after infusion 25. Five patients (14.2%) recorded six events of infusion site symptoms that were classified as an AE (n=4 infusion site pain, n=1 injection site haematoma, n=1 injection site pruritis), equating to 0.005 events per infusion (6/1111). All were classed as mild or moderate, and resolved without intervention.

There were no findings of concern in the laboratory data. Ten patients had laboratory findings or vital signs outside the reference range on at least one occasion during the study. All of these findings were either considered not clinically significant, or reported as AEs unrelated to study drug. No changes in viral serology were seen.

DISCUSSION

Results of the current study demonstrate the clinical efficacy of Evogam in PID patients utilising a 1:1 dose transition ratio from previous immunoglobulin therapy, with maintenance of therapeutic trough levels, and prevention of infection. There were no SBIs (upper 99% CI of 0.33 per patient year), thus meeting the FDA criteria for strong evidence of efficacy specified as less than 1.0 SBI per patient-year [7].

The protocol for this study was designed to investigate if efficacy could be achieved with dose equivalence using a 1:1 switch from intravenous to subcutaneous therapy, thus preserving a valuable resource and preventing escalation of costs for replacement therapy. This is in accordance with the European regulatory approach which recommends dosing based on trough levels as a surrogate marker for efficacy, and requires trough serum IgG levels achieved with a subcutaneous product to be equivalent to levels achieved with previous IVIg therapy [6].

In contrast, the FDA require that SCIg dosing achieves equivalent area under the curve (AUC), based on the assumption that the same total exposure is required for the same therapeutic effect, regardless of route [7]. This results in dose increases of 37% – 53% when switching to SCIg in order to achieve noninferiority in AUC [13,14]. There remains debate around the evidence for clinical benefit resulting from the increase in dose and trough levels with this dosing strategy, with parallel studies in the US and Europe using the same SCIg product showing almost identical rates of infection despite the dose transition ratio varying from 1:1.37 to 1:1, respectively [13,15].

The findings of this study showed an 8% increase in trough serum Ig concentrations with 100% equivalence dosing ratio. The clinical significance of an increase in trough level of this

magnitude is uncertain, and the study did not address whether targeting higher trough levels with SCIg replacement offers additional clinical benefit. This question has been addressed for IVIg in a number of recent studies; an Italian meta-analysis showing progressive reduction in pneumonia risk with increase in trough level [16], a long term UK cohort study demonstrating the individual variability in the required trough level for infection prevention [17], and an Italian study characterising the independent risk factor of bronchiectasis for pneumonia development [18]. A key learning from these studies is the requirement for individualised dosing and trough levels, to optimise clinical management and outcomes. This is likely to also apply to SCIg therapy, but is yet to be fully evaluated in clinical studies.

This study does show that a dose increase to achieve AUC equivalence is not necessary to maintain therapeutic IgG serum concentrations when converting from IVIg to SCIg. Potential advantages of using the same dose when switching mode of administration include neutral cost impact for SCIg product if the cost per gram is equivalent, reduced risk of dosing error, greater flexibility for patients to switch between routes of administration if required, and optimisation of a valuable resource.

Evogam pharmacokinetic results are consistent with published literature on other SCIg products, with differences in pharmacokinetic profiles between IVIg and SCIg well described [19]. As a result of shorter dosing intervals, slower absorption, and maintenance of closer equilibrium between intra- and extravascular compartments, SCIg provides more stable, physiologic IgG levels in contrast to the large variations in peak and trough levels seen with IVIg. This variation may contribute to the absence of the recognised phenomenon of malaise and myalgia which can occur at the end of the IVIg dosing interval when using SCIg, as well as reduction of infusion-related adverse effects [19].

The secondary endpoints of this study further support the clinical efficacy and safety of Evogam. The annual rates per patient of 2.82 non-serious bacterial infections, 2.97 days off work/ school and 0.56 days of hospitalisation were all consistent with rates published in the literature for other SCIg products [13-15]. The type and incidence of AEs seen in this study were also consistent with reported clinical experience [13-15]. One infection episode of sinusitis was recorded as possibly related, however given the patients longstanding history of recurrent sinus infections, and trough Ig levels remaining higher than baseline, the authors believe this unlikely to be related to the investigational product.

The comparison of antibiotic usage in this study to published literature is difficult due to variations in definitions, scarcity of reporting as a specific endpoint, and variations in clinical practice of prophylactic antibiotic treatment. Published SCIg studies with antibiotic use as a specific endpoint report a wide range of use; 71-92% of patients using antibacterials, with an annualised rate of 48.5–120 days per patient year [13,14]. Variation in clinical practice in prophylactic antibiotic use is also reflected, with 0.5 days/patient/year reported in a US study [14], compared to 49.5 days/patient/year in this study. The post-hoc subgroup analysis of antibiotic use in this study indicates that patients with pre-existing bronchiectasis were more likely to use antibiotics and showed a baseline rate of maintenance antibiotic therapy, with 13% of patients on continuous treatment.

Local tolerability was acceptable, and consistent with the known profile of subcutaneous infusions, which have reported incidence of infusion site symptoms in 78-100% of patients with other SCIg products [13-15]. Whilst the overall reported incidence of site symptoms in our study was high, most were mild to moderate, reduced in intensity over time, and resolved, with no negative impact on compliance and no patient withdrawals.

Tolerance improved over time, as shown by a reduction in local symptoms, consistent with other SCIg studies [13-15]. The exact mechanism for this improvement is unknown, with proposed reasons including subjectivity in a patient's reporting of symptoms as they adjust to therapy or change in local immunoregulatory response over time. Our study protocol mandated rotation of sites as well as maximum volume limits and infusion rates. In clinical practice there is potential for individualisation of administration, with variation in the rate and number of infusions per week, delivery technique, single site versus site rotation, volume per site, and number of sites per treatment. By tailoring the regimen to meet the needs of individual patients, there may be further improvement in local tolerability [20].

Quality of life scores reflecting general health were similar to scores recorded at baseline whilst patients were receiving IVIg. This is not unexpected, as these domains of physical and mental function are unlikely to alter significantly with a change in route if clinical efficacy remains constant. In contrast, Treatment Interference, Therapy Setting, and Treatment Comparison scales did show a preference for subcutaneous dosing, reflecting the higher satisfaction with home based therapy. Nevertheless, IVIg will remain the preferred option for some patients, as indicated by the three patients who preferred IVIg throughout this study, for reasons including less frequent treatment, hospital location, reluctance to self inject, or difficulty in accessing pumps and infusion equipment. Selection of administration route, therefore, requires individualisation for each patient based on both preference and clinical considerations for each modality.

A limitation of the current study is the small number of paediatric patients. However, from the population studied, there were no differences seen with regard to C_{min} , number and type of adverse events, or tolerability of the infusions.

In conclusion, Evogam is efficacious in the prevention of infection and maintenance of therapeutic serum IgG trough levels using a 1:1 dose conversion, with an acceptable safety and tolerability profile. Treatment comparison results showed preference for SCIg by the majority of patients, which, as a therapeutic option for PID patients, may enable improved integration of a chronic therapy into a patient's lifestyle. As a new immunoglobulin preparation specifically developed for subcutaneous use, Evogam provides a valuable treatment alternative for patients and clinicians to consider.

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Table I. Demographics and baseline information for Safety Population

Baseline Characteristics	Adults N = 30	Children N = 5	Total Patients N = 35
Age (years)	43.04	9.94	41.09
Median (range)	(13.4-67.7)	(8.3-10.9)	(8.3-67.7)
Sex, n (%)			
Male	12 (40.0%)	3 (60.0%)	15 (42.9%)
Female	18 (60.0%)	2 (40.0%)	20 (57.1%)
Race, n (%)			
Asian	1 (3.3%)	0	1 (2.9%)
Maori	1 (3.3%)	0	1 (2.9%)
Caucasian	28 (93.3%)	5 (100.0%)	33 (94.3%)
Screening weight (kg)	74.50	37.80	69.55
Median (range)	(38.7-119.1) ^a	(24.4-64.5)	(24.4-119.1)
Type of PID, n (%)			
XLA	1 (3.3%)	1 (20.0%)	2 (5.7%)
CVID	29 (96.7%)	4 (80.0%)	33 (94.3%)
Medical history of bronchiectasis, n (%)	10 (33.3%)	1 (20.0%)	11 (31.4%)
Time since PID diagnosis (years)	6.5	3.0	6.0
Median (range)	(1-30)	(3-7)	(1-30)
Prior treatment with immunoglobulin, n(%)			
IVIg	29 (96.7%)	5 (100%)	34 (97.1%)
SCIg ^b	1 (3.3%)	0	1 (2.9%)

N = Total number of patients in population; n = Number of patients; PID = primary immunodeficiency; XLA = X-linked agammaglobulinemia; CVID = common variable immunodeficiency disorder; ^a Data for 29 adult patients; ^b Normal Immunoglobulin intramuscular formulation given SC bi-weekly

Table II. Comparison of trough serum IgG concentrations for ITT Population

Trough IgG Concentration	ITT Population	
	Least Square Mean	95% CI
Previous IgG Treatment	8.27	7.81 - 8.76
Evogam (Efficacy Period)	8.94	8.46 - 9.44
Comparison ratio	1.081	1.024 - 1.141
Difference (%)	8.1% ^a	2.4 - 14.1%

^ap = 0.0063; CI = confidence interval; IgG = immunoglobulin G.

Note: Previous IgG Treatment refers to three trough concentrations collected at two Screening Visits and at Visit 0. Efficacy Period refers to trough concentrations collected at Visits 7 to 12 (Weeks 13 to 36).

List of figure captions and legends

Figure 1. Study design

IgG = immunoglobulin G; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; ^a Patients who were given SCIg at Visit 0 returned seven days later for Visit 1 and patients who were given IVIg at Visit 0 returned 14 days later for Visit 1.

Figure 2. Patient disposition

Figure 3. Mean trough serum IgG concentrations over time with standard deviation error bars (linear scale) for ITT Population (N = 32)

Figure 4. Reasons for antibiotic use during study

n = Number of patients; Pt = Patient; Yr = Year

^a Calculated from Efficacy Period; ^b Other included treatment for acne and surgical use.

Note: Data on antibiotic use based on listed indication for use, treatment duration, attribution of adverse event to usage and antibiotic history. The total of subgroup days are greater than 100% of total days due to patients taking antibiotics for both treatment and prophylaxis on the same date being counted in both categories.

Figure 5. Infusion site symptoms over time for Safety Population

- ☐ Before infusion
- ☐ 8 to 12 hrs after infusion
- ☐ 24 hrs after infusion
- ☐ 48 hrs after infusion
- ☐ 72 hrs after infusion

**Figure 6. Reported severity of infusion site symptoms over time at each infusion for
Safety Population**

- ☐ Severe
- ☐ Moderate
- ☐ Mild
- ☐ No symptoms

Figure 1

Figure 2

Figure 3.

Figure 4

Figure 5