

# Efficacy Analysis of Subcutaneous Immune Globulin (SCIG) (Human) 10%, Administered Intravenously or Subcutaneously in Subjects with Primary Immunodeficiency Diseases (PID)

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## Abstract

**RATIONALE:** To evaluate the efficacy of a new subcutaneous immunoglobulin (SCIG) 10% preparation in terms of rate of infections and protective specific antibody titers.

**METHODS:** A multicenter, prospective, open label study evaluated efficacy, tolerability, and pharmacokinetics of SCIG 10%, given intravenously (IV) or subcutaneously (SC) to 49 PID subjects. Efficacy was determined as the number of acute serious bacterial infections (ASBI) per subject year, and the overall incidence of infections and protective specific antibody titers.

**RESULTS:** The rate of ASBI was 0.067 per subject per year, with an upper confidence limit of 0.134, well below the established limit of 1 ASBI per subject per year. There were 3 episodes of acute serious bacterial pneumonia, none of which required hospitalization. The annualized rate of all infections during SC phase of the study was 4.1 infections per subject (95% CI 3.2–5.1). SC infusions were distributed almost evenly over the seasons. Trough levels of specific antibody to *H. influenzae*, hepatitis B surface antigen, and tetanus were in the protective range for all subjects during both IV and SC therapy, with titers substantially higher during the SC phase of the study for all 3 specific antibodies.

**CONCLUSIONS:** Efficacy of SCIG 10% replacement therapy was confirmed by rates of infection that are comparable to that of other SCIG and IVIG products. These data support application for approval of SCIG 10% as a therapy for patients with PID.

## Background

- Adults and children with primary immunodeficiency disease (PID) are prone to recurrent bacterial infections and usually require lifelong immunoglobulin G (IgG) replacement therapy.<sup>1,2</sup>
- Intravenous IgG (IVIG) therapy has remained the standard treatment in the United States since the 1980s.<sup>3</sup>
- Subcutaneous (SC) preparations may be a safe, effective alternative to IVIG for patients who frequently experience certain systemic adverse reactions (AEs)—such as fever, chills, headache—as well as those with poor venous access.<sup>1,2,4-6</sup>
- Due to the administration of smaller doses at shorter intervals, as well as slow absorption from the SC tissue, SCIG therapy is typically associated with fewer systemic reactions and higher serum IgG trough levels than IVIG.<sup>2,4,5,7,8</sup>
- There are 3 SCIG products approved for use in the United States in various concentrations (10%, 16% and 20%).

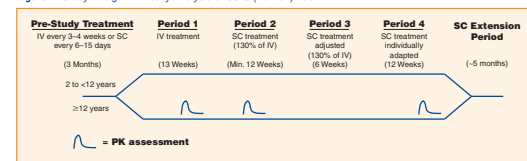
## Objective

To evaluate the efficacy of an established 10% liquid IgG product (GAMMAGARD LIQUID<sup>®</sup>) that was originally developed for IV administration, when administered via the SC route in PID patients

## Methods

- A multicenter, prospective, open-label phase III study evaluated efficacy, tolerability, and pharmacokinetics (PK) of IgG 10% (GAMMAGARD LIQUID<sup>®</sup>) administered IV or SC in subjects with PID (N = 49).
- Study Design: The study had 4 treatment periods and an SC extension period (Figure 1).

Figure 1. Study Design—Efficacy Analysis of SCIG (Human) 10%



Abbreviations: IV = intravenous, SC = subcutaneous

- SCIG Dosing and Administration
  - The dose of SCIG was adjusted during the study to obtain AUC<sub>0-24</sub> that was comparable to the AUC<sub>0-24</sub>.
  - Doses were further individualized (all age groups) if the trough level attained after 4 weekly SC treatments at an adjusted dose was not within 15% of the expected increase.
  - 20 mL/site for subjects weighing <40 kg and 30 mL/site for those ≥40 kg
  - Initial (first and second) SC infusions were started at a rate of 5 mL/hr/infusion site and gradually increased, depending on tolerability.
    - maximum rate of 15 mL/hr/site for subjects weighing <40 kg
    - maximum rate of 20 mL/hr/site for subjects weighing ≥40 kg
  - If the initial rate was tolerated, subsequent infusions were administered at 10 mL/hr/site and the rate of infusion increased every 15 to 20 minutes.
    - maximum rate of 20 mL/hr/site for subjects weighing <40 kg
    - maximum rate of 30 mL/hr/site for subjects weighing ≥40 kg
  - There was no limitation to the number of infusion sites.
- Three efficacy variables were assessed in children and adults:
  - Number of acute serious bacterial infections (ASBI) per subject year (defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis, septic arthritis, bacterial pneumonia, and visceral abscess)<sup>9</sup>
  - Overall incidence of all infections (bacterial, viral, fungal, and protozoal)
  - Specific antibody titers to relevant bacterial and viral antigens
- The infection rate by season was determined to address potential bias due to seasonal variation.

## Results

- A total of 49 subjects were enrolled and treated; 47 received at least 1 infusion of SCIG during the study and were included in the efficacy analysis.
- PK parameters and doses of IVIG and SCIG used are reported elsewhere.<sup>10,11</sup>
- Demographics (Table 1)

Table 1. Study Subject Characteristics

Age and Sex	Age Groups		Total
	2 to <12 yrs	≥ 12 yrs	
Number (range)	14 (9-11)	35 (14-77)	49
Male (n, % subjects)	8 (57.1%)	19 (54.3%)	27 (55.1%)
Female (n, % subjects)	6 (42.9%)	16 (45.7%)	22 (44.9%)
<b>PIDD Diagnoses (n)</b>			
Common variable immunodeficiency (CVID)			27
Hypogammaglobulinemia			15
X-linked agammaglobulinemia (XLA)			3
C3 complement deficiency - IgG deficiency			1
Combined immune deficiency			1
Wijegun chromosomal breakage syndrome			1
Hypogammaglobulinemia secondary to B-cell lymphoma			1
<b>Previous SCIG Experience (n)</b>			
Naïve subjects			38
Experienced subjects			11

- Efficacy (Table 2)
  - During SC treatment, 3 subjects each experienced 1 episode of acute serious bacterial pneumonia (none required hospitalization).
  - The annual rate of ASBI while on SCIG 10% was 0.067 with an upper 99% confidence limit of 0.134 (well below the established limit of 1 ASBI per subject per year).
  - The overall infection rate during SCIG 10% was 4.1 per subject per year.
    - Included bacterial and viral infections
    - Included fungal and protozoal infections (not typically responsive to IVIG therapy)

Table 2. Efficacy Analysis—Summary of Infections and Associated Events During SCIG Treatment

Number of subjects (efficacy phase)	47
<b>Acute Serious Bacterial Infections</b>	
Pneumonia	3
Annual rate of any infection	41 (85% CI 3.2 to 5.1) infections per subject-year
<b>Prophylactic antibiotic use<sup>9</sup></b>	
Total number of subject days	16,236
Number of subjects (%)	12 (25.5%)
Number of days (%)	575 (3.5%)
Annual rate	12.9 (95% CI 6.0 to 23.8) days/subject-year
<b>Therapeutic antibiotic use<sup>9</sup></b>	
Total number of subject days	16,236
Number of subjects (%)	38 (79.6%)
Number of days (%)	1,606 (10.2%)
Annual rate	17.3 (95% CI 14.6 to 20.0) days per subject-year
<b>Days out of work/school/day care or unable to perform normal activities</b>	
Total number of subject days	16,020
Number of subjects (%)	29 (63.2%)
Number of days (%)	176 (1.1%)
Annual rate	4.0 (95% CI 2.5 to 6.1) days per subject-year
<b>Hospitalizations due to infection</b>	
Total number of subject days	16,040
Number of subjects (%)	0 (0%)
Number of days (%)	0 (0%)
Annual rate	0.0 (95% CI 0.0 to 0.1) days per subject-year

<sup>9</sup>Includes systemic antibiomatic, antifungal, and antiviral antimicrobials

<sup>10</sup>Antibiotics were used prophylactically and therapeutically on the same day that day is counted as therapeutic use.

- Infection Rate by Season (Table 3)
  - The majority of IV infusions were administered in winter, while SC infusions were distributed evenly over the seasons.
  - Rate of infections per subject-year during SCIG treatment was winter, 2.3; spring, 2.7; summer, 2.6; and fall, 4.0.

Table 3. Annualized Infection Rates by Season and Study Period

Infusion Period— Infusion Type (Adjustment)	Season								Disregarding Season		
	Winter		Spring		Summer		Fall			Average Rate	
	Days	Rate	Days	Rate	Days	Rate	Days	Rate			
Period 1—IV	2796	4.3	906	3.6	433	5.1	422	3.5	4.1	4557	4.2
Period 2—SC (10% of weekly IV dose)	410	0.9	2734	2.9	737	3.0	334	10.9	4.4	4215	3.4
Period 3—SC (10% of weekly IV dose)	23	0.0	256	2.9	1250	3.2	346	7.4	3.4	1875	3.9
Period 4—SC (adjusted individual dose)	587	4.4	6	0.0	1730	1.9	1469	3.5	2.4	3782	2.9
Extension Period—SC	2656	2.1	1946	2.3	211	3.5	1551	2.4	2.5	6264	2.2
All SC treatment periods	3476	2.3	4942	2.7	3918	2.4	3700	4.0	2.9	16,236	2.9

- Specific Antibody Titers (Table 4)

Table 4. Specific Antibody Titers

Study Visit (Study Part)	Ranges of Medians Over All Visits		
	<i>H. influenzae</i> µg/mL	Tetanus IU/mL	Hepatitis B mIU/mL
Screening	2.79	2.84	239
IV (part 1)			
3-week interval	2.89–3.15	3.21–3.52	251–282
4-week interval	2.03–2.14	2.13–2.36	203–214
SC treatment	2.81–3.29	3.09–3.86	314–385

## Summary & Conclusions

- In this study, the overall infection rate (4.1) is consistent with infection rates previously reported from IV or SC administration of immunoglobulin.<sup>5,12-15</sup>
- Rates of missed school days, use of antibiotics, and hospitalizations were also similar to rates previously reported with other SCIG and IVIG products.<sup>5,6,16</sup>
- The number of serious bacterial infections (0.067) was well below the 1 per year FDA-allowed maximum.<sup>9</sup> Though meeting the FDA definition, none required parenteral antibiotics or hospitalization.
- In contrast to the common assumption that most infections occur during the winter, the incidence of all infections is rather evenly distributed during the year. Future studies should prospectively look at the seasonal incidence of bacterial and viral infections.
- These data support the use of SCIG 10% as a therapy for patients with PID.

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