



**SAN FRANCISCO** **MARCH**  
**2011 ANNUAL MEETING** **18 - 22**  
THE AMERICAN ACADEMY OF ALLERGY, ASTHMA & IMMUNOLOGY

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

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### *Abstract:*

**RATIONALE:** To evaluate the efficacy of a new IGSC 10% preparation in terms of rate of infections and protective specific antibody titers.

**METHODS:** A multi-center, prospective, open label study evaluated efficacy, tolerability and pharmacokinetics of IGSC, 10% given IV or 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/subject (95% CI 3.2-5.1). SC infusions were distributed almost evenly over the seasons. Trough levels of specific antibody to H. Influenza, 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 three specific antibodies.

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



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**Pharmacokinetic Analysis (PK) of Immune Globulin Subcutaneous (Human), 10% (IGSC) Administered Intravenously or Subcutaneously in Subjects with Primary Immunodeficiency Diseases (PIDD)**

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*Abstract:*

**RATIONALE:** To compare total IgG area under the curve (AUC) following IV and SC administration, with the aim to show pharmacokinetics (PK) equivalence of a new 10% IGSC product.

**METHODS:** A multi-center, prospective, open label study evaluated pharmacokinetics, efficacy, and safety of IGSC 10% given IV and

SC to subjects with PIDD. The dose of IGSC was adjusted during the study to obtain  $AUC_{SC}$  that was comparable to the  $AUC_{IV}$ . Bioavailability was evaluated as IgG-AUC for subjects  $\geq 12$  years old and as IgG trough levels for subjects age 2 to < 12 years old.

IgG trough level assessments were used to individualize dosing.

**RESULTS:** A dose adjustment factor of 137% was determined to obtain equivalent  $AUC_{IV}$  and  $AUC_{SC}$ . The target serum IgG trough level on weekly IGSC treatment was 1.28 times (range: 1.13 - 1.43) the last IGIV trough level. Median IgG trough levels at the end of the study were 1250 mg/dL.

**CONCLUSION:** IGSC therapy at a dosing factor of 1.37 resulted in equivalent bioavailability to IV administration. This adjustment factor was similar to that found in a study with a 16% SC product, but was lower than the adjustment factor found in a study with a 20% SC product (1.52). The trough levels achieved were above the suggested protective range.



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## **New Immune Globulin Subcutaneous (Human), 10% (IGSC) Product is Well Tolerated in Subjects with Primary Immunodeficiency Diseases (PID)**

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### *Abstract:*

**RATIONALE:** To evaluate the tolerability of a new IGSC 10% product in PID subjects. **METHODS:** A multi-center, prospective, open-label study evaluated efficacy, tolerability and pharmacokinetics of IGSC, 10% given IV or SC to 49 PID subjects. Tolerability of SC infusions was evaluated by the frequency of adverse events (AEs), rate and volume of SC infusions, and observing the percentage of interrupted, reduced or stopped infusions due to tolerability reasons.

**RESULTS:** 47 evaluable PID subjects received a total of 2,294 SC infusions. 4.9% of infusions were associated with local AEs at the start of SC treatment, decreasing to 1.1% at

the end of study. No serious AEs were considered related to IGSC 10%. 99.8% of the SC infusions were completed without interruption, rate reductions or discontinuation due to tolerability reasons. The median duration of infusions was 1.2h (range 0.6-

3.7h). The median maximum SC infusion rate was 20.0 mL/h/site (range 10.0-30.0 mL/h/site) in subjects 2 to <12 years of age, and

30.0 mL/h/site (range 8.0-40.0 mL/h/site) in subjects  $\geq$  12 years of age. A low overall temporally associated AE rate (8%), and a low rate of local AEs (2.8%) were seen with infusions volumes of up to 30 mL/site and infusions rates of up to 30 mL/h/site. None of the reported local AEs were severe in nature. **CONCLUSIONS:** This study seems to demonstrate that the IGSC 10% product is well

tolerated in PID subjects tested. IGSC 10% infusion times were similar to reports of higher concentration IGSC products, with less reported local AEs rates.



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## Pharmacokinetics (PK) of Human Immunoglobulin 10% Administered Subcutaneously Alone or Following Recombinant Human Hyaluronidase (rHuPH20) in Primary Immunodeficiency Disease (PID) Patients

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### *Abstract:*

**RATIONALE:** Intravenous (IV) and subcutaneous (SC) routes of immunoglobulin (IG) administration have both advantages and disadvantages. One disadvantage of IGSC therapy is decreased bioavailability compared to IGIV. rHuPH20 is a permeation enhancer that increases systemic absorption of SC infused fluids. This is an interim analysis of Phase 3 study that evaluated PK parameters of 10% IGSC, injected with or without rHuPH20, to assess whether rHuPH20 improves IGSC bioavailability in PID patients.

**METHODS:** PK parameters of IGSC were evaluated in a subset of nine patients with PID  $\geq$  12 years of age who received IVIG every 3-4 weeks, weekly IGSC without rHuPH20, and IGSC every 3-4 weeks with rHuPH20 (75 U/g IgG). IGSC doses were adjusted to ensure equivalent systemic IgG exposure to IV administration.

**RESULTS:** The median area under the curve (AUC) was 110 g $\cdot$ days/L for IV, 107 g $\cdot$ days/L for SC treatment without rHuPH20, and 103 g $\cdot$ days/L for SC treatment with rHuPH20. The median IGSC dose required to obtain equivalent bioavailability when administered with rHuPH20 was 107% (95% CI: 104-134%) of the IV dose, compared to 138% (95% CI: 127-146%) for IGSC without rHuPH20. The dose of IgG per 4 weeks was 488 mg/kg for IGIV, 668 mg/kg for IGSC alone, and 538 mg/kg for IGSC with rHuPH20. Median IgG trough levels of IGSC with rHuPH20 at the same 3- or 4-week interval were 1230 mg/dL versus 1290 mg/dL for IV.

**CONCLUSIONS:** rHuPH20 facilitated IGSC administration at the same intervals as IV, resulting in similar bioavailability at a lower dose compared to IGSC alone.



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## **Tolerability of Human Immunoglobulin 10% Administered Subcutaneously Following Administration of Recombinant Human Hyaluronidase (rHuPH20) in Primary Immunodeficiency Disease (PID) Patients**

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### *Abstract:*

**Rationale:** Intravenous (IV) and subcutaneous (SC) routes of immunoglobulin (IG) administration have both advantages and disadvantages. One disadvantage of IGSC therapy is the small volumes that can be administered subcutaneously, requiring multiple infusion sites and frequent administrations. rHuPH20 is a permeation enhancer that increases systemic absorption of SC infused fluids. This Phase 3 study evaluated the tolerability of rHuPH20-enabled 10% IGSC infusions at rates and frequencies equivalent to IGIV administration in PID patients.

**Methods:** PID patients were injected SC with 75 U of rHuPH20/g IgG, followed at the same site by IGSC doses equivalent to their previous IGIV dose and administration schedule. Subsequent IGSC dosing was adjusted based on IgG trough levels. An interim analysis of tolerability data was performed on a subset of 30 subjects.

**Results:** A total of 486 10% IGSC infusions, with or without rHuPH20, were all administered without interruption. Mean infusion volume every 4 weeks was 302 mL (30.2 g). The mean maximum infusion rate for a single site was 227 mL/h, and the mean time to infuse was 2.4hrs. Of the 30 patients analyzed, 29 reached their previous IV dosing interval, with the vast majority using a single site. Local adverse events (AEs) occurred in 16% of infusions. Most treatment-related AEs were mild and localized to the infusion site. The rate of all treatment-related systemic AEs was 8% of the infusions.

**Conclusion:** The subcutaneous administration of 10% IGSC facilitated by rHuPH20 was well tolerated, at infusion intervals and rates comparable to the patient's previous IGIV administration.



An Analysis of Safety and Tolerability Data on 10%, 16%, and 20% Formulations of Subcutaneous Immunoglobulin (IGSC)

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Abstract:

**RATIONALE:** Research regarding the role of IGSC in immune replacement/modulation and preferred concentrations for IGSC formulations is ongoing. We analyzed the safety and tolerability of 2 new 10% products (Gammagard [IGSC10%] and Gamunex<sup>®</sup> [IVIG-C10%]) and 16% and 20% solutions.

**METHODS:** Parameters included dose adjustment IV/SC, total volume per site, infusion site number, infusion time, adverse-event (AE) profiles, and improvements in tolerability over time.

**RESULTS:** The factor used to obtain equivalent AUC levels IVIG to IGSC was 137% for 10% and 16% formulations and 153% for IGSC20%. Maximum volume infused was 30mL/site for IGSC10%, 20mL/site for IVIG-C10%, ≤15mL/site for 16%, and 25mL/site for IGSC20%. The maximum number of simultaneous infusion sites is unlimited for IGSC10%, 6 for IGSC16%, and 4 for IGSC20%. Infusion time ranged from 0.6 to 3.7 hours for IGSC10%, 0.8 to 8.3 for IVIG-C10%, and 1.6 to 2 for IGSC20%. Percent of local AEs was 44.7%, 32%, 92%, and 100% for IGSC10%, IVIG-C10%, 16%, and 20%, respectively. Local AE rates per infusion were 2.8% for IGSC10%, 25% for IVIG-C10%, 49% for 16%, and 59.1% for IGSC20%. Decreased local AE incidence over time was noted for IGSC10%, IVIG-C10%, and IGSC16%, but not for IGSC20%.

**CONCLUSION:** Subcutaneous immunoglobulins are associated with different features and benefits. More infusion sites are possible with IGSC10%, so infusion time can be similar to that of higher concentration products. IGSC10% is associated with the lowest rate of infusion site reactions. Further research needs to be done to evaluate the benefits of higher concentrations on the immunomodulation effect.