

Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency

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Background: Subcutaneous immunoglobulin (IGSC) replacement therapy for primary immunodeficiency (PI) is equally efficacious to intravenous immunoglobulin (IGIV), induces fewer systemic reactions, and may be self-infused. Limited SC infusion volumes and reduced bioavailability, however, necessitate multiple infusion sites, more frequent treatment, and dose adjustment to achieve pharmacokinetic equivalence. Recombinant human hyaluronidase (rHuPH20) increases SC tissue permeability and facilitates dispersion and absorption, enabling administration of monthly doses in one site.

Objective: This study investigated the efficacy and tolerability of rHuPH20-facilitated IGSC (IGHy) in patients with PI.

Methods: In this open-label, multicenter phase III study, 87 patients with PI aged ≥ 2 years received 10% IGIV for 3 months, then IGHy (n = 83) for approximately 14 to 18 months at 108% of the IGIV dose. IGHy infusions began weekly, increasing to 3- or 4-week intervals.

Results: The majority (94.0%) of IGHy infusions were administered every 3 or 4 weeks, using one site (median, 1.09/month), with a mean volume of 292.2 mL. The bioavailability of IGHy measured by area under the concentration versus time curve was 93.3% of IGIV, which is pharmacokinetically equivalent. Systemic reactions were less frequent with IGHy than with IGIV (8.3% vs 25.0% of infusions). Local reactions to IGHy were generally mild to moderate, with a rate of 0.203 per infusion. The acute serious bacterial infection rate per subject-year for IGHy was low (0.025; upper 99% CI limit, 0.046). Overall infection rates per subject-year were 2.97 for IGHy and 4.51 for IGIV.

Conclusion: IGHy was effective, safe, and pharmacokinetically equivalent to IGIV at the same administration intervals, but it caused fewer systemic reactions. Tolerability was good despite high infusion volumes and rates. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

Key words: Facilitated subcutaneous immunoglobulin, intravenous immunoglobulin, recombinant human hyaluronidase, primary immunodeficiency, efficacy, tolerability, bioavailability

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Persons with antibody deficiency require lifelong IgG replacement therapy, which for >30 years has been most commonly administered by monthly intravenous administration of IgG (IGIV).^{1,2} Intravenous replacement therapy requires IV access, a healthcare professional to administer and monitor the infusion, and can be associated with systemic adverse reactions such as headache, nausea, and vomiting, as well as rare thromboembolic events and hypersensitivity reactions.³ Subcutaneous administration of IgG (IGSC) has become an increasingly common alternative to IGIV. IGSC is equally efficacious to IGIV and causes fewer systemic reactions,^{2,3} providing an important alternative for patients who cannot tolerate IV infusion or who lack reliable venous access.⁴ The SC mode also permits self-infusion in the home, which has been widely reported to improve health-related quality of life.⁵ The primary disadvantage of IGSC is the inherent resistance of the extracellular matrix (ECM), which limits the volume infusible in one site (usually 15-30 mL), and requires multiple infusion sites weekly or every second week, rather than a single monthly IV infusion.⁶⁻¹⁰ Furthermore, in several clinical studies of IGSC, lower bioavailability necessitated an increased dose of 137% to 153% of the IGIV dose to attain equivalent systemic IgG exposure determined by area under the concentration versus time curve (AUC).¹¹⁻¹³

The resistance of the ECM to large-volume SC infusions is partially because of high molecular weight multimers of hyaluronic acid (hyaluronan), the principal glycosaminoglycan of the

Abbreviations used

AUC:	Area under the concentration versus time curve
ECM:	Extracellular matrix
IGHy:	Facilitated subcutaneous administration of Immune Globulin Infusion 10% (Human) with recombinant human hyaluronidase
IGIV:	Immunoglobulin, intravenous
IGSC:	Immunoglobulin, subcutaneous
IV:	Intravenous
PI:	Primary immunodeficiency
rHuPH20:	Recombinant human hyaluronidase
SC:	Subcutaneous

hypodermis. Hyaluronan, a main component of the ECM, causes resistance to bulk fluid flow through the SC tissue. Cleavage of hyaluronan by subcutaneously injected hyaluronidase, a glycosidase enzyme, increases the permeability of SC tissue.¹⁴ Hyaluronan is rapidly resynthesized, and the interstitial permeability is fully restored within 24 to 48 hours.¹⁴ Hyaluronidase preparations of animal origin have been used for >50 years to enhance distribution of SC-delivered drugs to the circulatory compartment, but immunogenicity and low purity precludes their chronic use in humans.¹⁵ Recombinant human hyaluronidase (rHuPH20) is a highly purified, soluble form of the naturally occurring human hyaluronidase enzyme. It has been shown to be safe and effective in enhancing dispersion and absorption of fluids and drugs administered subcutaneously, and received approval by the Food and Drug Administration in the United States.¹⁶⁻¹⁸ Preclinical studies have found that rHuPH20 is short acting, with a half-life of <30 minutes, and is undetectable in plasma after administration at the doses used to facilitate SC infusions.¹⁴

A phase I/II study of facilitated subcutaneous administration of Immune Globulin Infusion 10% (Human) with rHuPH20 (IGHy) in 11 patients with primary immunodeficiency (PI) showed the feasibility of infusing monthly doses of up to 618 mL of IgG 10% solution in a single SC site with bioavailability that approximated that of IGIV.⁷ Subsequently, the present phase III study was conducted to evaluate the safety, efficacy, tolerability, and pharmacokinetic characteristics of IGHy compared with IGIV and to compare the bioavailability of IGHy with IGSC without rHuPH20.

METHODS**Study products**

A 10% preparation of normal human immunoglobulin stabilized with glycine (GAMMAGARD LIQUID in the United States/Canada; elsewhere KIOVIG; Baxter Healthcare Corporation, Westlake Village, Calif) was administered intravenously (hereafter referred to as IGIV) and subcutaneously in combination with rHuPH20 (IGHy). The rHuPH20 (Halozyme Therapeutics, Inc, San Diego, Calif) component of IGHy is a preparation of purified soluble human hyaluronidase produced in Chinese hamster ovary cells formulated at a concentration of 160 U/mL in a buffer solution containing 1% human albumin.

Study population

Patients aged ≥ 2 years with PI involving an antibody formation defect and requiring antibody replacement as defined by the International Union of Immunological Societies^{19,20} were eligible if they had been receiving IgG for ≥ 3 months before enrollment at a dose of ≥ 300 mg/kg of body weight/4 weeks. Subjects and/or their legally authorized representatives provided written informed consent. The study was approved by the appropriate ethics committees.

Study design

This prospective, open-label study in 87 subjects with PI comprised 2 treatment epochs: all subjects received IGIV for 3 months, followed by IGHy for approximately 14 to 18 months. Thirty-one of the 87 subjects had previously received both IGIV and IGSC given conventionally without rHuPH20 during a prior study¹¹ and participated only in the IGHy treatment epoch. Their IV data from the previous study were used in the present study for PK comparison, and the IV and SC data were used for comparison of safety and tolerability to IGHy. The primary end point was the rate of acute serious bacterial infections (SBIs) according to predefined criteria²¹; these did not have to meet the definition of a serious adverse event (AE).

IGHy was administered at the subjects' prestudy dose and frequency of IGIV. rHuPH20, at a dose of 75 U/g IgG, was administered through a 24-gauge SC needle, followed by IgG 10% at 108% of the weekly equivalent IGIV dose, via the same SC needle. The dose of 108% of the IV dose was based on a phase I study that determined the bioavailability of IGHy (according to AUC) to be 92% of the IV dose. To allow adaptation to large SC doses and to facilitate training, treatment began with an initial 1-week dose of IGHy and increased until the prestudy IGIV interval (3 or 4 weeks) was reached. This schedule was then maintained for approximately 1 year. Safety and efficacy were determined during this period when the dose and interval were the same as the IV treatment. Maximum permitted IGHy infusion rates were 160 mL/hour for subjects <40 kg and 300 mL/hour for subjects ≥ 40 kg. There was no maximum volume per site, although subjects who required >600 mL were allowed to use 2 sites. After appropriate training, subjects were allowed to self-administer in a home-based setting, documented by a nurse; any assistance provided by the nurse was recorded.

Analyses of efficacy and safety

Safety, tolerability, infusion rates, durations and volumes, number of infusion sites per month, pharmacokinetics, overall infection rates, SBI rates, number of days absent from school or work, on antibiotics or in hospital, and number of unplanned physician visits were compared between IGIV and IGHy during the 12-month efficacy period. Further, data on efficacy, tolerability, and pharmacokinetics were used from a subgroup of subjects ($n = 31$) who participated in a previous trial that compared IGIV and IGSC.¹¹ Data on all 3 treatment modalities, IGIV, IGSC, and IGHy, were analyzed.

Exploratory analyses

Treatment preference was assessed at the end-of-study visit. Subjects completed the treatment preference questionnaire to assess patient perceptions of the therapy, including convenience, physical appearance, duration, frequency and complexity of administration, and the ability to fit treatment into their schedules.

Statistical analysis

Statistical analyses are described (see this article's Statistical methods section in the Online Repository at www.jacionline.org), and sample size calculations are shown in Table E1 (in the Online Repository at www.jacionline.org).

Role of the funding source

Baxter Healthcare Corporation was responsible for study design and central administration, data management, statistical analysis, interpretation, and medical writing. The decision to publish the study was made collaboratively by all authors.

RESULTS

Eighty-nine (89) patients with PI were enrolled; 87 aged 4 to 78 years received IGIV and 83 received IGHy. The majority presented with common variable immune deficiency ($n = 49$) or hypogammaglobulinemia associated with antibody deficiency

($n = 17$; Table E2). Participants were distributed evenly with respect to sex (see Table E3 in this article's Online Repository at www.jacionline.org). IGIV was administered for a median of 91 days and IGHy for a median of 366 days per subject during the efficacy period. In total, 1129 IGHy infusions were administered after the ramp-up. The mean weekly equivalent IgG dose per kilogram of body weight was 155 mg/kg per week for IGHy with a median ratio to IV of 108.8% (range, 98.6%-138.22%).

Two infections met the SBI criteria during the 1-year efficacy period; both were episodes of bacterial pneumonia treated with oral antibiotics without hospitalization. The rate of SBIs during IGHy treatment was 0.025 (upper 99% CI limit, 0.046) per subject-year. In addition, one episode of staphylococcal pneumonia occurred during the ramp-up phase. The rate of all infections was 2.97 (95% CI, 2.51-3.47) per subject-year for IGHy compared with 4.51 (95% CI, 3.50-5.69) for the IGIV treatment (annualized according to the 3 months of treatment; Table I). Most of the infections were categorized as being related to the upper respiratory tract or viral upper respiratory tract infections. Sinusitis was most frequent with a point estimate of 0.65 infections per patient-year during treatment with IGHy. Bronchitis occurred at a rate of 0.12 infections per patient-year (see Table E4 in this article's Online Repository at www.jacionline.org).

Other parameters related to the impact of illness are also shown in Table I. There were no days in hospital because of infection during the 1-year efficacy period, although one subject with hyper-IgE syndrome was hospitalized with staphylococcal pneumonia during the ramp-up period. Days missed from work or school and acute physician visits per year were comparable for IGIV and IGHy.

For safety and ethical reasons, the pharmacokinetic study was conducted only in subjects aged ≥ 12 years. In the younger subjects (aged 2 to <12 years) trough IgG and specific antibody titers were measured, and the IgG trough levels were used to adjust doses to ensure pharmacokinetic equivalence. When IgG is given at the same frequency intravenously and subcutaneously, any differences in trough levels reflect differences in bioavailability. Serum trough levels were comparable for IGHy and IGIV; the medians were 10.7 g/L for IGHy and 10.4 g/L for IGIV (Table II). Peak serum IgG levels were lower after IGHy than after IGIV. The median time to reach the peak serum IgG level was 5 days, similar to conventional IGSC. Peak to trough variability in IgG serum concentration for IGHy (4.8 vs 11.5 g/L) was much less than for IGIV given at the same 3- or 4-week intervals.

IGHy administered at 108% of the IV dose was pharmacokinetically equivalent to IGIV as measured by AUC: the ratio of geometric mean $AUC_{0-\tau}$ relative to IGIV was 93.3% (2-sided 90% CI, 91.4%-95.2%). Pharmacokinetic equivalence of the treatment modalities was supported by the similar serum IgG trough levels attained in all subjects, including subjects aged 2 to <12 years (Table II). The median ratio of IgG trough levels for IGHy/IGIV was 103.8% (95% CI, 97.5%-115.4%) in subjects aged 2 to <12 years, and 98.5% (95% CI, 94.4%-102.5%) in subjects aged ≥ 12 years. When the AUC, normalized by dose per kilogram, for IGHy is compared with that for IGSC alone in the subgroup who participated in the prior study,¹¹ IGHy improved the bioavailability of IGSC by approximately 20%. The ratio of AUC per dose per kilogram for IGHy/IGSC was 120.4% (90% CI, 115.5%-125.5%).

In the subset of subjects who participated in the previous IGSC study¹¹ the pharmacokinetic profile of IGHy was compared with

TABLE I. Rate of all infections, days absent from school/work, on antibiotics, in hospital, and urgent/unscheduled physician visits in efficacy period

	IGHy		IGIV	
	Point estimate	95% CI	Point estimate	95% CI
Overall rate of infections (per year)	2.97	2.51-3.47	4.51	3.50-5.69
Days off school/work (per year)	0.28	0.20-0.37	0.23	0.15-0.34
Days on antibiotics (per year)	1.69	1.29-2.16	3.15	2.19-4.35
Unscheduled physician visits (per year)	0.40	0.32-0.49	0.33	0.23-0.45
Days in hospital (per year)	0.02	0.01-0.03	0.06	0.03-0.10
Days in hospital due to infection (per year)	0.00	0.00-0.01	0.03	0.01-0.05

TABLE II. Pharmacokinetic parameters for total IgG

	IGHy (n = 60)		IGIV (n = 68)	
	Median	95% CI	Median	95% CI
Summary for subjects aged ≥ 12 y				
AUC/wk ($g \times d/L$)	90.5	83.8-98.4	93.9	89.1-102.1
Terminal half-life (d)	45.3	41.0-60.2	35.7	32.4-40.4
C_{max} (g/L)	15.5	14.5-17.1	21.9	20.7-23.9
T_{max} (d)	5.0	3.3-5.1	0.1	0.1-0.1
IgG trough levels (g/L) in all subjects				
Subjects aged <12 y (n = 11)	9.95	7.87-15.00	9.63	8.29-13.60
Subjects aged ≥ 12 y (n = 70)	10.7	9.46-11.80	10.4	9.63-11.40

T_{max} , Time to reach maximal concentration.

that for IGIV and IGSC. A representative graph is shown for one patient in Fig 1. The higher dose and more frequent interval of IGSC treatment accounts for the higher trough IgG level during IGSC versus IGIV or IGHy.

Serum concentrations of specific antibodies against *Clostridium tetani* toxoid, *Haemophilus influenzae* type b, and hepatitis B surface antigen were similar at the end of treatment with IGHy and IGIV and were well within protective ranges (see Table E5 in this article's Online Repository at www.jacionline.org).

Overall, the majority of adverse reactions to IGHy were mild (265/384) or moderate (114/384); only 5 were severe (for severity grade definitions, see Fig E1 in this article's Online repository at www.jacionline.org). Three severe reactions were local (infusion site pain, infusion site swelling and genital edema resulting from the spread of IGHy in the subcutaneous space), and 2 were systemic (migraine and oral pain). No study drug-related serious AEs occurred. Six subjects withdrew from the study during IGHy treatment because of mild-to-moderate adverse reactions (2 children: headache [1] and local pain [1]; 4 adults: local swelling [2], perceived increase in the incidence of infections [1], and unspecified AEs [1]). The most common AEs after IGHy were local adverse reactions such as discomfort, erythema, and swelling (Tables III and IV). The rate of temporally associated local AEs per infusion, occurring within 72 hours of infusion, was 0.199

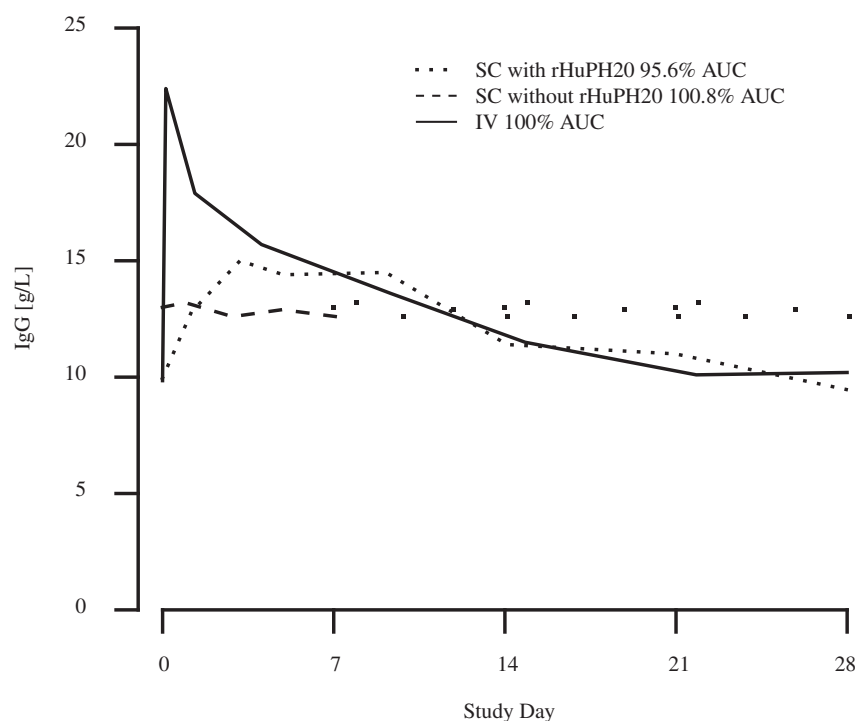


FIG 1. Serum IgG concentration for IGHy compared with IGIV and IGSC. Representative pharmacokinetic curves for one subject comparing a 4-week infusion of IGIV, a weekly infusion of IGSC, 10% at 143% of the IV dose with the same data points extended across the 4-week period to facilitate comparison with the other curves, and a 4-week infusion of IGHy at 104% of the IV dose.

TABLE III. Temporally associated adverse events,* regardless of causality, occurring in >5% of subjects during treatment with IGHy and IGIV in the efficacy period

Adverse event†	IGHy		IGIV	
	Percentage of subjects (N = 81)	Rate of adverse events per infusion‡ (N = 1129)§	Percentage of subjects (n = 87)	Rate of adverse events per infusion (N = 365)§
Local adverse events	51.9	0.199	4.6	0.011
Headache	19.8	0.031	25.3	0.112
Fatigue	8.6	0.012	9.2	0.027
Nausea	7.4	0.010	11.0	0.027
Pyrexia	7.4	0.009	5.7	0.016
Vomiting	7.4	0.008	5.7	0.016
Chills	1.2	0.003	8.0	0.025

*Occurring during or within 72 hours of the infusion.

†Excluding infections.

‡Rate = total number of events divided by total number of infusions.

§N = total number of infusions.

for IGHy, compared with 0.011 for IGIV. The rate of causally related local adverse reactions per IGHy infusion was 0.203, which was comparable with published rates for IGSC despite the larger infusion volume delivered subcutaneously with IGHy. Most of the local adverse reactions were mild or moderate; only 3 of 1129 IGHy infusions were associated with severe local reactions, all of which resolved with no sequelae.

Systemic AEs occurring within 72 hours of infusion were significantly less frequent for IGHy than for IGIV. AEs were reported for 8.3% (95% CI, 6.3%-10.0%) of IGHy infusions compared with 25.0% (95% CI, 16.7%-25.0%) with IGIV. The most frequent systemic AEs were headache, fatigue, nausea, pyrexia, vomiting, and chills (Table III). The rate of headaches,

for example, occurring within 72 hours of infusion for IGHy was less than one-third of the rate for IGIV.

No subjects developed anti-rHuPH20 antibodies capable of neutralizing hyaluronidase activity. Thirteen subjects developed antibodies that bound hyaluronidase as determined by ELISA, but no correlation was observed between the presence of these antibodies and local or systemic AEs. In some subjects the antibody titers declined despite continued exposure to rHuPH20.

Approximately 90% of IGHy infusions were administered in the abdomen and 8.6% in the thighs. IGHy was infused at significantly higher maximum flow rates than IGIV for each patient ($P < .0001$; van Elteren's test²²), resulting in shorter infusion durations (Table V). The median maximum infusion rates

TABLE IV. Most frequent local adverse drug reactions reported in >1% of infusion during efficacy period of IGHy

Infusion site reaction	Rate of reactions per infusion (n = 1129)
Discomfort/pain	0.108
Erythema	0.028
Swelling/edema	0.024
Pruritus	0.017

TABLE V. Duration of infusions

Treatment	Age group	No. of subjects	Duration of infusion (h)		
			Minimum	Median	Maximum
IGIV	Subjects aged 2 to <12 y	14	1.40	2.49	5.03
	Subjects aged ≥12 y	73	0.92	2.33	6.33
	Total	87	0.92	2.33	6.33
IGHy	Subjects aged 2 to <12 y	11	1.15	1.73	3.28
	Subjects aged ≥12 y	70	0.83	2.13	4.68
	Total	81	0.83	2.08	4.68

were 160.0 mL/hour for IGHy and 62.5 mL/hour for IGIV in subjects aged 2 to 12 years, and 300.0 mL/hour and 246.0 mL/hour in subjects aged ≥12 years (Table VI).

Ninety-seven percent of IGHy infusions and 95.9% of IGIV infusions were administered without flow rate reduction, interruption, or cessation. Flow rate was reduced in 1.7%, interrupted in 0.4%, and stopped in 0.2% of IGHy infusions because of AEs or tolerability concerns. IGHy was administered at a mean volume per site of 292.2 mL (Table VII). The median number of infusion sites per month was 1.09 with IGHy, which was the same as during IV administration (see Table E6 in this article's Online Repository at www.jacionline.org). By the end of the transition period from IGIV or IGSC to IGHy (ramp-up phase), 78 of 83 subjects (94.0%) attained the same 3- or 4-week dosing interval used for IGIV before the study; 1 subject decreased to a 3-week interval and 2 to a 2-week interval. The primary reason for interval reduction was discomfort due to swelling.

Sixty-nine subjects completed the treatment preference questionnaire, 83% of whom responded that they would choose to continue receiving IGHy rather than IGIV or IGSC (see Table E7 in this article's Online Repository at www.jacionline.org). Patients who preferred IGHy indicated that they "liked" or "liked very much" the overall convenience (86%), ability to fit treatment into their schedules (83%), and the frequency of administration (77%) of IGHy.

DISCUSSION

The present phase III, open-label, multicenter study was conducted to investigate a novel approach to IgG replacement in patients with PI that would allow self-administration of facilitated SC Immune Globulin Infusion with rHuPH20 using the same volume and frequency as IGIV, in a single site.

The rate of acute SBIs was similar to other IGIV and IGSC products.^{11,23-25} The rate of all infections for IGHy was 2.97 (95%

TABLE VI. Maximum infusion rate

Treatment	Age group	No. of subjects	Maximum infusion rate (mL/h)		
			Minimum	Median	Maximum
IGIV	Subjects aged 2 to <12 y	14	25.0	62.5	316.0
	Subjects aged ≥12 y	73	60.0	246.0	668.0
	Total	87	25.0	200.0	668.0
IGHy	Subjects aged 2 to <12 y	11	80.0	160.0	300.0
	Subjects aged ≥12 y	70	10.0	300.0	300.0
	Total	81	10.0	300.0	300.0

TABLE VII. Volume infused per site

Treatment	Treatment interval category, wk	Mean (mL)	Minimum (mL)	Maximum (mL)
IGIV	3	387.6	125	720
	4	324.0	75	800
	Total	339.2	75	800
IGHy	2	174.6	144	287
	3	276.5	100	646
	4	302.2	6	716
	Total	292.2	6	716

CI, 2.51-3.47) per subject-year during the 12-month efficacy observation period and 4.51 (95% CI, 3.50-5.69) for IGIV during the 3-month treatment period. The study was not designed to assess comparative efficacy because the duration of IGIV and IGHy treatment differed significantly. A *post hoc* analysis indicated no seasonal bias, but selection bias due to the short reporting period cannot be ruled out.

IGHy enabled the administration of large volumes in a single monthly infusion site; the mean volume per site was approximately 10- to 15-fold higher than typical IGSC infusion volumes of 20 to 30 mL per site,^{2,6,26} thus rendering multiple sites and weekly administration unnecessary (Table VII and Table E6). Consequently, the majority of subjects (94.0%) were able to receive IGHy at 3- or 4-week intervals, using a similar number of infusion sites to IGIV treatment (approximately 1), which has not previously been possible with the SC route.^{2,6-8} By comparison, the subgroup of subjects who received IGSC in a previous study (without rHuPH20) required a median of 21.4 sites to administer the monthly IGSC dose.¹¹ Infusion rates were higher for IGHy than for IGIV, leading to shorter infusion times (Table V). This difference may be greater in patients who are intolerant of rapid IV infusions.

Peak IgG plasma levels after treatment with IGHy were comparable with a higher dose of IGSC administered without rHuPH20¹¹ and were lower than after IGIV. With IGHy, the peak-to-trough difference was 4.8 g/L compared with 11.5 g/L for IGIV at 3- or 4-week intervals and 1.5 g/L with weekly IGSC (reported in the previous study).

The median IgG trough level for IGHy was 10.7 g/L. By comparison, in the previous study of IGSC administered weekly at 137% of the IV dose, the median minimum steady-state plasma

concentration of IgG was 12.6 g/L (mean, 12.0 g/L; range, 6.2–17.0 g/L). Thus, although the median IGHy trough is about 1.9 g/L lower than with weekly SC dosing, it is within the range of IGSC despite the lower dose and longer intervals,¹¹ and it is well within the range considered to be sufficient to reduce the incidence of infections such as pneumonia.^{27,28}

Because of the decreased bioavailability of IGSC, a dose adjustment factor of 137% to 153% of the IV dose is required to achieve comparable exposure with IgG as determined by the AUC.^{11,12,24} It has been debated whether such a dose adjustment is clinically necessary. A comparison of 2 clinical studies of a 16% IgG preparation, with and without dose adjustment, did not show a difference in infection rates (4.4 vs 4.3 infections per subject-year).^{9,24,29} However, more recently, in a comparison of a new 20% IGSC product, the rate of infections when the dose was adjusted by 153% was 2.76 per subject-year, with a hospitalization rate of 0.20 day/year,³⁰ whereas in a multinational study with equivalent IV and SC doses the rate of infections per subject-year was 5.18, with 3.48 days/year of hospitalization.³¹ These studies were not designed or powered to determine whether the dose adjustment is clinically useful, but the lack of consistency in the conclusions from these comparisons raises questions about the argument that the dose adjustment has no clinical benefit. In all of these studies the trough IgG levels were within the physiologic range and were close to 9.0 g/L, the level associated in a meta-analysis with decreased occurrence of infections such as pneumonia.²⁷ Thus, small changes in trough levels would be unlikely to result in significant differences in rates of infection.

The most common type of AEs associated with IGHy infusions was local reactions at the infusion site, similar to IGSC, and in contrast to IGIV, where systemic AEs predominate. The rate of temporally related systemic AEs with IGHy was lower than with IGIV and was comparable with other clinical studies of IGSC administration.^{9,12} The lower IGHy systemic AE rate compared with IGIV is consistent with the proposed relation between peak serum IgG levels and systemic AEs.³² Further, local AEs in the present study occurred at a low rate of 0.203 per infusion, despite the high infusion volume per site, were predominantly mild in nature and usually resolved within 1 to 2 days without sequelae. Although 5 of the subjects who received IGHy discontinued the study because of local AEs, predominantly swelling, analysis of treatment preference (Table E7) showed that patients or their parents/caregivers preferred IGHy to alternative modalities, with most reporting that they “liked/liked very much” most aspects of IGHy, including overall convenience, ability to fit treatment into their schedules, and the frequency of administration.

The effects of rHuPH20 are rapidly reversed and similar to endogenous hyaluronidases, because hyaluronan is naturally depolymerized and regenerated with a half-life of 15 to 20 hours.³³ Subcutaneously injected rHuPH20 is not available systemically, so it does not act at distant sites.³⁴ No chronic skin changes were observed during this study, in which median exposure was 12 months with a maximum of approximately 18 months. Additional long-term safety data will be obtained from an ongoing 5-year clinical study.

To date, the strategy to mitigate the low dose and volume of IGSC infusible in each site has been the development of more concentrated IgG preparations. Formulations of 16% and 20% IgG are commercially available in many countries. In addition to the limited amounts that can be administered per site, a reported

disadvantage of these preparations is the increased rates of local adverse reactions compared with 10% IGSC.³⁵ The current study found considerably lower rates of local AEs per infusion than those reported for 16% and 20% preparations.^{9,10,12}

Conclusions

IGHy was safe, effective, and well tolerated in patients with PI. This novel method of delivering IgG brings together the advantages of IGIV and IGSC, the conventional treatments. IGHy provides comparable efficacy while combining the once-monthly, single-site infusion of IGIV with the option of home-based self-administration of IGSC. IGHy accomplishes this with a 20% higher bioavailability than IGSC, good local tolerability, and a lower rate of systemic AEs than with IGIV.

Clinical implications: Immunoglobulin facilitated with rHuPH20 is a novel mode of subcutaneous IgG replacement therapy for primary immunodeficiency that uses regimens similar to IGIV, but induces fewer systemic reactions and is self-infusible.

REFERENCES

- Notarangelo LD. Primary immunodeficiencies. *J Allergy Clin Immunol* 2010; 125(2 suppl 2):S182-94.
- Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin Immunol* 2004;112:1-7.
- Bonilla FA. Intravenous immunoglobulin: adverse reactions and management. *J Allergy Clin Immunol* 2008;122:1238-9.
- Meth MJ, Rosenthal DW, Bonagura VR. Subcutaneous immunoglobulin infusion to treat infants and toddlers with antibody deficiencies. *Ann Allergy Asthma Immunol* 2010;105:187-8.
- Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. *BioDrugs* 2007;21:105-16.
- Moore ML, Quinn JM. Subcutaneous immunoglobulin replacement therapy for primary antibody deficiency: advancements into the 21st century. *Ann Allergy Asthma Immunol* 2008;101:114-21.
- Misbah S, Sturzenegger MH, Borte M, Shapiro RS, Wasserman RL, Berger M, et al. Subcutaneous immunoglobulin: opportunities and outlook. *Clin Exp Immunol* 2009;158(suppl 1):51-9.
- Gustafson R, Gardulf A, Hansen S, Leibl H, Engl W, Linden M, et al. Rapid subcutaneous immunoglobulin administration every second week results in high and stable serum immunoglobulin G levels in patients with primary antibody deficiencies. *Clin Exp Immunol* 2008;152:274-9.
- Gardulf A, Nicolay U, Asensio O, Bernatowska E, Bock A, Carvalho BC, et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies—a prospective multi-national study. *J Clin Immunol* 2006;26:177-85.
- Jolles S, Sleasman JW. Subcutaneous immunoglobulin replacement therapy with Hizentra(R), the first 20% SCIG preparation: a practical approach. *Adv Ther* 2011;28:521-33.
- Wasserman RL, Melamed I, Kobrynski L, Strausbaugh SD, Stein MR, Sharkhawy M, et al. Efficacy, safety, and pharmacokinetics of a 10% liquid immune globulin preparation (GAMMAGARD LIQUID, 10%) administered subcutaneously in subjects with primary immunodeficiency disease. *J Clin Immunol* 2011;31:323-31.
- Wasserman RL, Irani AM, Tracy J, Tsoukas C, Stark D, Levy R, et al. Pharmacokinetics and safety of subcutaneous immune globulin (human), 10% caprylate/chromatography purified in patients with primary immunodeficiency disease. *Clin Exp Immunol* 2010;161:518-26.
- Wasserman RL, Melamed I, Nelson RP Jr, Knutsen AP, Fasano MB, Stein MR, et al. Pharmacokinetics of subcutaneous IgPro20 in patients with primary immunodeficiency. *Clin Pharmacokinet* 2011;50:405-14.
- Frost GI. Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration. *Expert Opin Drug Deliv* 2007;4: 427-40.
- Yocum RC, Kennard D, Heiner LS. Assessment and implication of the allergic sensitivity to a single dose of recombinant human hyaluronidase injection: a double-blind, placebo-controlled clinical trial. *J Infus Nurs* 2007;30:293-9.

16. Harb G, Lebel F, Battikha J, Thackara JW. Safety and pharmacokinetics of subcutaneous ceftriaxone administered with or without recombinant human hyaluronidase (rHuPH20) versus intravenous ceftriaxone administration in adult volunteers. *Curr Med Res Opin* 2010;26:279-88.
17. Allen CH, Etzwiler LS, Miller MK, Maher G, Mace S, Hostetler MA, et al. Recombinant human hyaluronidase-enabled subcutaneous pediatric rehydration. *Pediatrics* 2009;124:e858-67.
18. Thomas JR, Yocum RC, Haller MF, von Gunten CF. Assessing the role of human recombinant hyaluronidase in gravity-driven subcutaneous hydration: the INFUSE-LR study. *J Palliat Med* 2007;10:1312-20.
19. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. *J Allergy Clin Immunol* 2007;20:776-94.
20. Al-Herz W, Bousfiha A, Casanova JL, Chapel H, Conley ME, Cunningham-Rundles C, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. *Front Immunol* 2011;2:54.
21. Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (human) as Replacement Therapy for Primary Humoral Immunodeficiency. Washington, DC: US Department of Health and Human Services, Food and Drug Administration (FDA); 2008.
22. van Elteren PH. On the combination of independent two-sample tests of Wilcoxon. *Bull Inst Int Stat* 1960;37:351-61.
23. Church JA, Leibl H, Stein MR, Melamed IR, Rubinstein A, Schneider LC, et al. Efficacy, safety and tolerability of a new 10% liquid intravenous immune globulin (IGIV 10%) in patients with primary immunodeficiency. *J Clin Immunol* 2006;26:388-95.
24. Ochs HD, Gupta S, Kiessling P, Nicolay U, Berger M. Subcutaneous IgG Study Group. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol* 2006;26:265-73.
25. Berger M, Murphy E, Riley P, Bergman GE. Improved quality of life, immunoglobulin G levels, and infection rates in patients with primary immunodeficiency diseases during self-treatment with subcutaneous immunoglobulin G. *South Med J* 2010;103:856-63.
26. Skoda-Smith S, Torgerson TR, Ochs HD. Subcutaneous immunoglobulin replacement therapy in the treatment of patients with primary immunodeficiency disease. *Ther Clin Risk Manag* 2010;6:1-10.
27. Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies. *Clin Immunol* 2010;137:21-30.
28. Quinti I, Soresina A, Guerra A, Rondelli R, Spadaro G, Agostini C, et al. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. *J Clin Immunol* 2011;31:315-22.
29. Vivaglobin Immune Globulin Subcutaneous (Human) 16% Liquid [package insert]. Marburg, Germany: CSL Behring; 2010.
30. Hagan JB, Fasano MB, Spector S, Wasserman RL, Melamed I, Rojavin MA, et al. Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in patients with primary immunodeficiency. *J Clin Immunol* 2010;30:734-45.
31. Jolles S, Bernatowska E, De Gracia J, Borte M, Cristea V, Peter HH, et al. Efficacy and safety of Hizentra in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. *Clin Immunol* 2011;141:90-102.
32. Gardulf A, Nicolay U, Asensio O, Bernatowska E, Böck A, Costa-Carvalho BT, et al. Children and adults with primary antibody deficiencies gain quality of life by subcutaneous IgG self-infusions at home. *J Allergy Clin Immunol* 2004;114:936-42.
33. Bookbinder LH, Hofer A, Haller MF, Zepeda ML, Keller GA, Lim JE, et al. A recombinant human enzyme for enhanced interstitial transport of therapeutics. *J Control Release* 2006;114:230-41.
34. Wynne C, Harvey V, Schwabe C, Waaka D, McIntyre C, Bittner B. Comparison of subcutaneous and intravenous administration of trastuzumab: a phase I/Ib trial in healthy male volunteers and patients with HER2-positive breast cancer. *J Clin Pharmacol* 2012 [Epub ahead of print].
35. Melamed I, McDonald A, Neff A, Beck A. An analysis of safety and tolerability data on 10%, 16%, and 20% formulations of subcutaneous immunoglobulins (SCIG) [abstract]. *J Allergy Clin Immunol* 2011;127(2 suppl 1):Abstract16.

APPENDIX

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STATISTICAL METHODS

Primary end point

The method of analysis for the primary end point was based on a Poisson model. The null hypothesis of ≥ 1 validated acute serious bacterial infections (VASBIs) per subject per year was tested against the alternate hypothesis of <1 VASBI per subject per year. The acute serious bacterial infection rate, that is, mean number of VASBIs per subject per year, and the corresponding 99% upper confidence limit was calculated with a Poisson model that accounted for the length of the observation periods per subject.

The observation period for each subject started with the day of the first SC infusion after the ramp-up period and ended with the day of the end-of-study visit. Both start and end days were included. Changes in the dosing, if any, or deviations from the infusion intervals had no impact on the observation period. The length of the observation period was expressed in years by dividing the (integer) number of days by the average length of the year in the Gregorian calendar (365.2425 days).

The number of VASBIs was the number of such infections with onset in the observation period.

A generalized linear model that assumed the Poisson distribution for the number of VASBIs with the logarithm as link function was used. The Poisson model included the natural logarithm of the length of the observation period in years as an offset to account for the potentially different lengths of the observation periods per subject. To handle overdispersion, the exponential distribution dispersion parameter was assumed to be given by the deviance divided by the degrees of freedom, and all statistics were adjusted accordingly.

The upper limit of the likelihood ratio-based CI at the 2-sided 98% confidence level provided the 99% upper confidence limit.

The analysis procedure was implemented in SAS (SAS Institute, Cary, NC) with the use of the SAS procedure GENMOD.

To assess the primary outcome for efficacy, the null hypothesis of ≥ 1 VASBIs per subject per year was tested against the 1-sided alternative hypothesis of <1 VASBI per subject per year at the 1% level of statistical significance. This 1-sided hypothesis test used the same Poisson model as for the upper confidence limit. Rejection of the null hypothesis would result in the acceptance of the alternate hypothesis of <1 VASBI per subject per year, resulting in the conclusion that this product provides sufficient protection against acute serious bacterial infections and is therefore efficacious.

The hypothesis test was implemented by inverting the upper confidence limit as described previously, that is, the P value was the value α such that the $1-\alpha$ upper confidence limit is 1 VASBI/year. In this manner, hypothesis test and confidence limit were consistent in the sense that the null hypothesis was only to be rejected if the upper confidence limit was below 1 VASBI/year.

Secondary efficacy end points

Pharmacokinetics. For subjects aged ≥ 12 years, the AUC between adjacent infusions ($AUC_{0-\tau}$) was calculated by the trapezoidal rule. Linear interpolation/extrapolation was used to calculate the AUC for the exact duration of the infusion interval (21 or 28 days).

To assess pharmacokinetic equivalence of IV treatment and SC treatment with rHuPH20 at an adapted dose, the 90% CI for the difference of the mean

logarithms of $AUC_{0-\tau}$ was calculated. The error variance used to calculate this CI was obtained from an ANOVA model. The antilogs of the confidence limits obtained constituted the 90% CI for the ratio of the geometric means (antilog of the means of the logarithms). To establish pharmacokinetic equivalence in terms of $AUC_{0-\tau}$ with a type I error of 5%, the calculated 2-sided 90% CI had to be contained completely in the margins of equivalence defined as 80% to 125%.

Half-life. Terminal in days was calculated as $\log_e(2)/\lambda_z$ where the terminal rate constant (λ_z) was obtained by $\log_e$ -linear fitting with the use of the least squares deviation to the last 4 IgG levels.

Clearance (Cl) was determined by the following formula: $Cl = (\text{dose/kg})/AUC_{0-\tau}$.

Other pharmacokinetic parameters were to include the C_{max} after administration of the study drug, the C_{min} after administration of study drug, and time to reach maximal concentration.

Pharmacokinetic parameters were summarized by medians and nonparametric 95% CIs for medians.

For subjects aged 2 to <12 years, a formal demonstration of pharmacokinetic equivalence was not feasible because of the limited sample size.

Nonetheless, the median and range of the ratios of the geometric mean of 2 IgG trough levels with IV and SC administration was used to assess pharmacokinetic equivalence in subjects aged 2 to <12 years.

All infections. The annual rate of all infections was calculated per subject. Point estimates and 95% CIs for the annual rates were calculated with a Poisson model and the same method that included allowance for overdispersion as described for the primary end points.

IgG trough levels

Trough levels of IgG, for SC treatment and for IV treatment, were summarized by medians and their 95% nonparametric CIs.

Days off school/work, on antibiotics, and in hospital

Monthly rates of days off school/work, on antibiotics, and in hospital (because of infections and for any reason) were calculated per subject. Point estimates and 95% CIs for the monthly rates were calculated with a Poisson model and the same method that included allowance for overdispersion as described for the primary end points. The lengths of the month were defined as average length of the month in the Gregorian calendar.

Acute physician visits

Monthly rates of acute physician visits because of infections were calculated per subject. Point estimates and 95% CIs for the monthly rates were to be calculated with a Poisson model and the same method that included allowance for overdispersion as described for the primary end points.

Specific antibody levels

Levels of specific antibody against *Clostridium tetani* toxoid, *Haemophilus influenzae*, and hepatitis B surface antigen for SC treatment and for IV treatment were summarized by medians and their 95% nonparametric CIs.

Comparison of bioavailability of IgG with and without rHuPH20

The bioavailability of IgG when administered subcutaneously with and without rHuPH20 was assessed in terms of the $AUC_{0-\tau}$ per dose per kilogram.

The ratio of the $AUC_{0-\tau}$ per dose per kilogram for SC administration with and without rHuPH20 and 90% CIs for the ratio was computed with a meta-analysis approach with the weights being inversely proportional to the variance estimates.

Comparison of maximum flow rates

An exploratory analysis that compared the maximum flow rates for IV infusions and SC infusions with rHuPH20 was implemented with the use of

the Wilcoxon test stratified by subject (van Elteren's test).^{E1} The null hypothesis that the distribution of the maximum flow rates for IV infusions and SC infusions with rHuPH20 was the same within each subject was tested against a 2-sided alternative. This analysis was suggested by the apparent difference in median maximum flow rates.

Safety analyses

The sample size selected for the study of approximately 80 was primarily determined by the desire to collect safety data in a sufficient number of subjects (a minimum of approximately 30) who were naive to SC administration, in addition to the subjects rolling over from a previous clinical study^{E2} (about 45).

For the primary end point, the power to reject the null hypothesis of ≥ 1 VASBIs per year at the 1% level of statistical significance against a 1-sided alternative was calculated with the computer program PASS 2008 and is shown in Table E1.

REFERENCE

- E1. van Elteren PH. On the combination of independent two-sample tests of Wilcoxon. *Bull Inst Int Stat* 1960;37:351-61.
- E2. Wasserman RL, Melamed I, Kobrynski L, Strausbaugh SD, Stein MR, Shakhawy M, et al. Efficacy, safety, and pharmacokinetics of a 10% liquid immune globulin preparation (GAMMAGARD LIQUID, 10%) administered subcutaneously in subjects with primary immunodeficiency disease. *J Clin Immunol* 2011;31:323-31.

- Mild
 - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
 - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
 - The AE produces limited impairment of function and may require therapeutic intervention.
 - The AE produces no sequelae.
- Severe
 - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
 - The AE produces sequelae, which require (prolonged) therapeutic intervention.

FIG E1. Definitions of mild, moderate, and severe adverse events.

TABLE E1. Sample size calculation: power to reject the null hypothesis

Sample size (no.)	Rate under H ₁	Rate under H ₀	Power (%)
76	0.7	1.0	79
80	0.7	1.0	81
84	0.7	1.0	83
88	0.7	1.0	85

TABLE E2. PI diagnosis

	No.
CVID	49
Hypogammaglobulinemia	17
XLA	6
IgG subclass deficiency	4
Specific antibody deficiency	4
Hyper IgM syndrome	2
CVID + Hyper IgE syndrome	1
Dysgammaglobulinemia	1
Hyper IgE syndrome	1
SCID	1
SCID + hypogammaglobulinemia	1
Total	87

CVID, Common variable immunodeficiency; *SCID*, severe combined immunodeficiency; *XLA*, X-linked agammaglobulinemia.

TABLE E3. Demographic characteristics

Parameter	Category or statistics	Subjects aged 2 to <12 y (N = 14)	Subjects aged ≥12 y (N = 73)	Total (N = 87)
Sex	Male, no. (%)	8 (57.1)	36 (49.3)	44 (50.6)
	Female, no. (%)	6 (42.9)	37 (50.7)	43 (49.4)
Race	White, no. (%)	14 (100.0)	65 (89.0)	79 (90.8)
	Black or African American, no. (%)	0 (0.0)	2 (2.7)	2 (2.3)
	Asian, no. (%)	0 (0.0)	3 (4.1)	3 (3.4)
	American Indian or Alaska Native, no. (%)	0 (0.0)	1 (1.4)	1 (1.1)
	Multiple	0 (0.0)	2 (2.7)	2 (2.3)
Ethnicity	Hispanic or Latino, no. (%)	1 (7.1)	7 (9.6)	8 (9.2)
	Non-Hispanic or Latino, no. (%)	13 (92.9)	66 (90.4)	79 (90.8)
Age (y)	Median (range)	8.0 (4-11)	44.0 (12-78)	35.0 (4-78)
Height (cm)	Median (range)	130.00 (94-153)	166.00 (108-193)	165.00 (94.0-193.0)
Weight (kg)	Median (range)	27.50 (15.0-59.4)	69.00 (34.5-135.9)	63.80 (15.0-135.9)

TABLE E4. All infections in efficacy period occurring in >5% of subjects

Infection	IGHy			IGIV		
	Subjects with infection(s), no. (%)	No. of infections	Annual rate point estimate (95% CI)	Subjects with infection(s), no. (%)	No. of infections	Annual rate point estimate (95% CI)
Sinusitis	33 (40.74)	53	0.65 (0.47-0.87)	14 (16.09)	19	0.86 (0.55-1.26)
Upper respiratory tract infection	32 (39.51)	44	0.54 (0.39-0.73)	8 (9.20)	9	0.41 (0.25-0.63)
Bronchitis	8 (9.88)	10	0.12 (0.07-0.19)	6 (6.90)	7	0.32 (0.18-0.50)
Urinary tract infection	6 (7.41)	6	0.07 (0.04-0.12)	6 (6.90)	6	0.27 (0.16-0.42)
Gastroenteritis viral	9 (11.11)	12	0.15 (0.09-0.22)			
Viral upper respiratory tract infection	6 (7.41)	9	0.11 (0.06-0.18)			
Viral infection	9 (11.11)	10	0.12 (0.07-0.19)			
Postprocedural infection	7 (8.64)	7	0.09 (0.05-0.13)			
Gastroenteritis	6 (7.41)	6	0.07 (0.04-0.12)			
Cellulitis	5 (6.17)	5	0.06 (0.04-0.10)			
Influenza				5 (5.75)	5	0.23 (0.13-0.36)

TABLE E5. Antibody levels against relevant pathogens

Age group	Pathogen	IGHy			IGIV		
		No.	Median	95% CI	No.	Median	95% CI
2 to <12 y	<i>Haemophilus influenzae</i> (μg/mL)	10	1.97	1.69-4.94	7	2.11	1.59-13.52
	Tetanus toxoid (IU/mL)	10	2.580	0.990-3.810	7	2.230	0.640-4.230
	Hepatitis B (mIU/mL)	10	242.2	125.5-871.9	6	212.9	59.5-291.5
≥12 y	<i>Haemophilus influenzae</i> (μg/mL)	70	2.58	2.30-2.95	24	2.36	2.05-3.05
	Tetanus toxoid (IU/mL)	70	2.525	2.270-2.850	25	2.320	1.810-2.710
	Hepatitis B (mIU/mL)	70	249.2	225.0-289.3	25	222.8	190.3-289.4

TABLE E6. Number of infusion sites per month

Study arm*	Treatment	No.	Minimum	Q1	Median	Q3	Maximum
Study arm 1	IGIV	31	1.1	1.09	1.09	1.10	1.4
	IGSC	31	9.0	17.32	21.43	24.94	43.3
	IGHy	30	1.0	1.08	1.09	1.76	3.5
Study arm 2	IGIV	56	0.4	1.09	1.09	1.16	1.5
	IGHy	51	0.8	1.08	1.09	1.94	4.3

Q, Quartile.

*Study arm 1 included subjects who had also received IGSC without rHuPH20 in a previous study; data from the prior study were used in the present analysis. The remaining subjects were enrolled in Study arm 2.

TABLE E7. Treatment preference

Age group	Assessment	Status	n/N (%)
Subjects aged 2 to 13 y (by parent)	Sites of IgG therapy before trial	At the hospital	2/13 (15.4)
		At the doctor's office	8/13 (61.5)
		At home	1/13 (7.7)
		At the hospital + at home	1/13 (7.7)
		At the hospital + at the doctor's office + at home	1/13 (7.7)
	Preferred site of IgG therapy	At the hospital	1/13 (7.7)
		At the doctor's office	4/13 (30.8)
		At home	8/13 (61.5)
	Frequency of administration	Like very much	5/13 (38.5)
		Like	6/13 (46.2)
		No preference	2/13 (15.4)
	No. of needle sticks per mo	Like very much	5/13 (38.5)
		Like	5/13 (38.5)
		No preference	2/13 (15.4)
	Total time spent for treatment per mo	Dislike	1/13 (7.7)
		Like very much	3/13 (23.1)
		Like	3/13 (23.1)
		No preference	4/13 (30.8)
	Ease of administration	Dislike	3/13 (23.1)
		Like very much	5/13 (38.5)
		Like	6/13 (46.2)
		No preference	2/13 (15.4)
	Potential to self-administer	Like very much	7/13 (53.8)
		Like	2/13 (15.4)
		No preference	1/13 (7.7)
		Dislike	2/13 (15.4)
	Ability to fit treatment into own schedule	Dislike very much	1/13 (7.7)
		Like very much	6/13 (46.2)
		Like	5/13 (38.5)
	Overall convenience	No preference	2/13 (15.4)
		Like very much	6/13 (46.2)
		Like	5/13 (38.5)
	Changes to physical appearance	No preference	1/13 (7.7)
		Dislike	1/13 (7.7)
		Like very much	2/13 (15.4)
	Amount of time administration takes	No preference	11/13 (84.6)
		Like very much	3/13 (23.1)
		Like	3/13 (23.1)
		No preference	3/13 (23.1)
	Complexity of administration process	Dislike	4/13 (30.8)
		Like very much	3/13 (23.1)
		Like	3/13 (23.1)
		No preference	6/13 (46.2)
	Ability to self-administer without medical supervision	Dislike	1/13 (7.7)
		Like very much	6/13 (46.2)
		Like	2/13 (15.4)
		No preference	3/13 (23.1)
	Choose to continue IGHy	Dislike very much	2/13 (15.4)
		Yes	13/13 (100.0)
Subjects aged ≥14 y (by subject)	Sites of IgG therapy before trial	At the hospital	9/56 (16.1)
		At the doctor's office	26/56 (46.4)
		At home	14/56 (25.0)
		At the hospital + at the doctor's office	2/56 (3.6)
		Other ^a	4/56 (7.1)
	Preferred site of IgG therapy	At the doctor's office + at home	1/56 (1.8)
		At the hospital	3/56 (5.4)
		At the doctor's office	13/56 (23.2)
		At home	33/56 (58.9)
		No preference	4/56 (7.1)

(Continued)

TABLE E7. (Continued)

Age group	Assessment	Status	n/N (%)
		Other ^b	3/56 (5.4)
	Frequency of administration	Like very much	19/56 (33.9)
		Like	19/56 (33.9)
		No preference	13/56 (23.2)
		Dislike	4/56 (7.1)
		Dislike very much	1/56 (1.8)
	No. of needle sticks per mo	Like very much	13/55 (23.6)
		Like	19/55 (34.5)
		No preference	18/55 (32.7)
		Dislike	3/55 (5.5)
		Dislike very much	2/55 (3.6)
	Total time spent for treatment per mo	Like very much	12/56 (21.4)
		Like	24/56 (42.9)
		No preference	13/56 (23.2)
		Dislike	6/56 (10.7)
		Dislike very much	1/56 (1.8)
	Ease of administration	Like very much	14/56 (25.0)
		Like	23/56 (41.1)
		No preference	8/56 (14.3)
		Dislike	6/56 (10.7)
		Dislike very much	5/56 (8.9)
	Potential to self-administer	Like very much	19/56 (33.9)
		Like	15/56 (26.8)
		No preference	8/56 (14.3)
		Dislike	8/56 (14.3)
		Dislike very much	6/56 (10.7)
	Ability to fit treatment into own schedule	Like very much	30/56 (53.6)
		Like	14/56 (25.0)
		No preference	6/56 (10.7)
		Dislike	5/56 (8.9)
		Dislike very much	1/56 (1.8)
	Overall convenience	Like very much	25/56 (44.6)
		Like	17/56 (30.4)
		No preference	6/56 (10.7)
		Dislike	7/56 (12.5)
		Dislike very much	1/56 (1.8)
	Changes to physical appearance	Like very much	4/55 (7.3)
		Like	4/55 (7.3)
		No preference	33/55 (60.0)
		Dislike	11/55 (20.0)
		Dislike very much	3/55 (5.5)
	Amount of time administration takes	Like very much	12/56 (21.4)
		Like	15/56 (26.8)
		No preference	19/56 (33.9)
		Dislike	9/56 (16.1)
		Dislike very much	1/56 (1.8)
	Complexity of administration process	Like very much	5/56 (8.9)
		Like	12/56 (21.4)
		No preference	16/56 (28.6)
		Dislike	18/56 (32.1)
		Dislike very much	5/56 (8.9)
	Ability to self-administer without medical supervision	Like very much	18/56 (32.1)
		Like	13/56 (23.2)
		No preference	10/56 (17.9)
		Dislike	8/56 (14.3)
		Dislike very much	7/56 (12.5)
	Choose to continue IGHy	Yes	44/56 (78.6)
		No, IV administration	8/56 (14.3)
		No, regular SC administration	4/56 (7.1)