This clinical study synopsis is provided for informational purposes only. It may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained across the entire product development.
1. SYNOPSIS

**Name of Sponsor/Company:**
Baxter Healthcare Corporation

**Name of Investigational Product (IP):**
GAMMAGARD LIQUID/KIOVIG

**Name(s) of Active Ingredient(s):**
Immune Globulin Intravenous (Human), 10%
Recombinant Human Hyaluronidase (rHuPH20)

**Title of Study:**
Efficacy, tolerability and pharmacokinetic comparison of immune globulin intravenous (human), 10% (GAMMAGARD LIQUID/KIOVIG) administered intravenously or subcutaneously following administration of recombinant human hyaluronidase (rHuPH20) in subjects with primary immunodeficiency diseases (PIDD)

**Investigators and study sites:**

<table>
<thead>
<tr>
<th>Site#</th>
<th>Investigator</th>
<th>Site</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MD, PhD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MD, PhD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>MD MPH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>MD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BAXTER Confidential – Restricted: Do NOT distribute without prior approval
<table>
<thead>
<tr>
<th>Site#</th>
<th>Investigator</th>
<th>Site</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Publications:**


McCoy B, Schiff RI, Wasserman RL, Melamed I, Stein M, Engl W, Leibl H, Gelmont D. Pharmacokinetics of 10% immunoglobulin administered intravenously or subcutaneously alone or following recombinant human hyaluronidase in subjects with PID. Poster. XIVth Meeting of the European Society for Immunodeficiencies; October 6-9, 2010; Istanbul, Turkey.²


Schiff RI, Wasserman RL, Melamed I, Stein M, McCoy B, Leibl H, Engl W. Tolerability of immunoglobulin subcutaneous 10% administered SC following administration of recombinant human hyaluronidase in subjects with PID. Poster. XIVth Meeting of the European Society for Immunodeficiencies; October 6-9, 2010; Istanbul, Turkey.⁴

**Study Period:**

- **Initiation:** 18 Dec 2008
- **Completion:** 11 Nov 2010
- **Duration:** Approximately 1 year and 11 months

**Study Phase:** III

**Study Purpose and Objectives:**

The purpose of the study was to develop a subcutaneous (SC) treatment option for subjects with PID that allows an administration of GAMMAGARD LIQUID/KIOVIG at the same frequency as intravenous (IV) administration.

**Primary Objective:**

The primary objective was to evaluate the efficacy of GAMMAGARD LIQUID/KIOVIG administered via the SC route after an administration of rHuPH20 in preventing serious bacterial infections in subjects with PID.
Secondary Objective:
Secondary objectives of the study, in addition to further efficacy assessments, were to evaluate the tolerability of GAMMAGARD LIQUID/KIOVIG and rHuPH20 administered via the SC route.

Study Design: Prospective, open-label, non-controlled, multi-center study.

Number of subjects
Planned: Approximately 80 subjects with PID
Analyzed: 81 Full Analysis Data Set (FADS); 74 in Per-Protocol Analysis Data Set.

Diagnosis and main criteria for inclusion:

Inclusion criteria
1. Subject was 2 years or older at the time of screening
2. Written informed consent was obtained from either the subject or the subject’s legally acceptable representative prior to any study-related procedures and study product administration
3. Subject had been diagnosed with a PID disorder requiring antibody replacement as defined by WHO criteria
4. Subject had completed or was about to complete Baxter Clinical Study Protocol No. 160601 or had been receiving a regular IGIV-treatment at mean intervals of 21 ± 3 days or 28 ± 3 days, or SC at mean intervals of 5 to 16 days, over a period of at least 3 months prior to enrollment at a minimum dose of 300 mg/kg body weight (BW)/4 weeks
5. Subject had a serum trough level of IgG > 4.5 g/L at the last documented determination
6. If female of childbearing potential, subject presented with a negative urine pregnancy test and agreed to employ adequate birth control measures for the duration of the study.
7. Subject was willing and able to comply with the requirements of the protocol.

Exclusion criteria
1. Subject had a known history of or was positive at enrollment or screening for one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2
2. Subject had levels of alanine aminotransferase (ALT) or aspartate amino transferase (AST) > 2.5 times the upper limit of normal for the testing laboratory
3. Subject had persistent severe neutropenia (defined as an absolute neutrophil count [ANC] ≤500/mm$^3$)
   Subject had creatinine clearance (CLcr) values, calculated according to the formula below, which are < 60% of normal for age and gender:
   for males: $CLcr = \left\{ \frac{(140 - \text{age(years)}) \times \text{(BW (kg))}}{72 \times \text{(serum creatinine (mg/dL))}} \right\}$
   for females: $CLcr = \left\{ \frac{(140 - \text{age(years)}) \times (\text{BW (kg)} \times 0.85)}{72 \times \text{(serum creatinine (mg/dL))}} \right\}^5$
4. Subject had been diagnosed with, or had a malignancy (other than adequately treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix) within the last 12 month prior to enrollment; subjects treated with immunosuppressive chemotherapeutic agents during this period are excluded
5. Subject had a history of thrombotic episodes (including deep vein thrombosis, myocardial infarction, cerebrovascular accident, pulmonary embolism) within the last 12 months
6. Subject had abnormal protein loss (protein losing enteropathy, nephrotic syndrome)
7. Subject had anemia that would have precluded phlebotomy for laboratory studies
8. Subject had received any blood or blood product other than an IGIV, SC immunoglobulin, immune serum globulin (ISG) preparation, or albumin within the 6 months prior to enrollment
9. Subject had an ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IGIV, SC immunoglobulin, and/or ISG infusions
10. Subject had immunoglobulin A (IgA) deficiency and known anti IgA antibodies
11. Subject was on preventative (prophylactic) systemic antibacterial antibiotics and cannot stop these antibiotics at the time of enrollment
12. Subject had active infection and started on antibiotic therapy for the treatment of infection within 7 days prior to screening
13. Subject had a bleeding disorder or was on anti-coagulation therapy that results in a platelet count less than 20,000/µL or International Normalized Ratio (INR) >2X control, or who, in the opinion of the investigator, would have been at significant risk of increased bleeding or bruising as a result of SC therapy
14. Subject had total protein >9 g/dL and subjects with myeloma, macroglobulinemia (IgM) and paraproteinemia
15. Subject had a known allergy to hyaluronidase
16. If female, subject was pregnant or lactating at the time of study enrollment
17. Subject had participated in another clinical study and had been exposed to an investigational product (IP) or device within 2 weeks prior to study enrollment (exception: Baxter Study No. 160601) or was scheduled to participate in another non-Baxter clinical study involving an IP or device during the course of this study
18. Severe dermatitis that would have precluded adequate sites for safe product administration

Investigational Product(s) (IP), dose and mode of administration, and batch number:

**IP(s):**

1. GAMMAGARD LIQUID/KIOVIG
   Dosage form: injectable solution

2. rHuPH20
   Dosage form: injectable SC solution

**Dose:**

1. GAMMAGARD LIQUID/KIOVIG

   **Study Epoch 1 (IV administration):**
   Dosage frequency: once every 3 or 4 weeks, for 13 weeks, last dose 1 week prior to start of Epoch 2
   Dose: as during pre-study period (minimum 300 mg/kg BW/4 weeks)

   **Study Epoch 2 (SC administration):**
   Dosage frequency: starting with a ramp-up with treatment intervals of 1 week, then 2 weeks, then 3 weeks, (then 4 weeks if applicable); then once every 3 or 4 weeks (as tolerated and as scheduled during pre-study period)
   Dose: 108% of the IV dose, calculated on the basis of weekly equivalents, with 1 weekly equivalent being the dose calculated for a 4-week period, divided by 4.
2. rHuPH20

Study Epoch 2 (SC administration):
Dosage frequency: same as for GAMMAGARD LIQUID/KIOVIG when administered IV
Dose: 75 U/g GAMMAGARD LIQUID/KIOVIG immediately before (within 10 minutes)
GAMMAGARD LIQUID/KIOVIG administration

Mode of Administration:

1. GAMMAGARD LIQUID/KIOVIG
   IV in Study Epoch 1, SC in Study Epoch 2

2. rHuPH20
   SC (Study Epoch 2)

Batch number(s):

GAMMAGARD LIQUID/KIOVIG:
LE12H249AB  LE12J074AB  LE12J074AM  LE12H235AC  LE12J045AB  LE12J118AD
LE12J155AC  LE12J257AB  LE12J308AD  LE12H091AF  LE12H229AC  LE12J058AC
LE12J129AC  LE12H195AD  LE12G174AC  LE12G011AD  LE12H163AB  LE12H309AC
LE12G011AC  LE12H163AB  LE12G145AC

rHuPH20
911130; 911529; 911131; 911530

Duration of treatment:
Approximately 17 months (planned): 3 months in Epoch 1 and 14 months in Epoch 2.

Reference therapy, mode of administration, and batch number: None.

Criteria for evaluation

Primary Efficacy Endpoint:
The primary endpoint was the validated acute serious bacterial infection rate, defined as the mean number of
validated acute serious bacterial infections per subject per year in the intent-to-treat population.

Acute serious bacterial infections included bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic
arthritis, bacterial pneumonia, and visceral abscess that were caused by a recognized bacterial pathogen.

Secondary Efficacy Endpoint(s):

1. Pharmacokinetics
   a. Bioavailability of IgG after administration of GAMMAGARD LIQUID/KIOVIG given via IV
      or SC with rHuPH20 as measured by area under the IgG concentration versus time curve (AUC<sub>t</sub>)
      for subjects aged 12 years and older
   b. Bioavailability of IgG after administration of GAMMAGARD LIQUID/KIOVIG given IV or
      SC with rHuPH20 as measured by trough levels of IgG for subjects aged 2 to < 12 years
   c. Comparison of bioavailability of IgG after SC administration of GAMMAGARD
      LIQUID/KIOVIG without rHuPH20 (data from clinical study 160601) and after SC
      administration of GAMMAGARD LIQUID/KIOVIG with rHuPH20 (data from this study,
      Study Arm 2) as measured by AUC/trough levels
2. Infections  
a. The annual rate of all infections was to be calculated per subject.
3. IgG trough levels and specific antibody titers  
b. Trough levels of IgG for IV and SC treatment  
c. Specific antibody levels to pathogens (such as *Clostridium tetani* [tetanus] toxoid, *Haemophilus influenzae*, measles virus and hepatitis B virus)  
d. Pharmacokinetics of IgG, anti-*Clostridium tetani* toxoid antibody and at least one antibody to a PID-relevant pathogen such as *Haemophilus influenzae*, for IV and SC treatment (at the end of each study epoch)
4. Days off school/work, on antibiotics, acute physician visits and in hospital  
e. Days off school or work  
f. Days on antibiotics for any reason  
g. Acute (urgent or unscheduled) physician visits  
h. Days in hospital

**Secondary Safety Endpoints:**

1. Proportion of **subjects** for which the infusion rate was reduced and/or the infusion interrupted or stopped for tolerability concerns or for AEs
2. Proportion of **infusions** for which the infusion rate was reduced and/or the infusion interrupted or stopped for tolerability concerns or for AEs
3. Number of all AEs (including and excluding infections) that begin during infusion or within 72 hours of completion of an infusion (“temporally associated”) divided by the number of infusions/subjects
4. Proportion of **subjects** reporting one or more moderate or severe AEs (including and excluding infections) that began during infusion or within 72 hours of completion of an infusion
5. Proportion of **infusions** associated with one or more moderate or severe AEs (including and excluding infections) that began during or within 72 hours of completion of an infusion
6. Percentage of SC doses of GAMMAGARD LIQUID/KIOVIG and rHuPH20 tolerated at 1 infusion site
7. Proportion of IV infusions (GAMMAGARD LIQUID/KIOVIG alone) and SC infusions (GAMMAGARD LIQUID/KIOVIG and rHuPH20) associated with one or more systemic AEs (including and excluding infections), during or within 72 hours of completion of an infusion
8. Proportion of **subjects** receiving IV infusions (GAMMAGARD LIQUID/KIOVIG alone) and SC infusions (GAMMAGARD LIQUID/KIOVIG and rHuPH20) who reported one or more systemic AEs (including and excluding infections), during or within 72 hours of completion of an infusion
9. Proportion of IV **infusions** (GAMMAGARD LIQUID/KIOVIG alone) and SC infusions (GAMMAGARD LIQUID/KIOVIG and rHuPH20) associated with one or more local AEs (including and excluding infections), during or within 72 hours of completion of an infusion
10. Proportion of IV infusions (GAMMAGARD LIQUID/KIOVIG alone) and SC infusions (GAMMAGARD LIQUID/KIOVIG and rHuPH20) associated with one or more local AEs (including and excluding infections), at any time during the study
11. Proportion of subjects receiving IV infusions (GAMMAGARD LIQUID/KIOVIG alone) and SC infusions (GAMMAGARD LIQUID/KIOVIG and rHuPH20) reporting one or more local AEs (including and excluding infections), during or within 72 hours of completion of an infusion
12. Proportion of subjects receiving IV infusions (GAMMAGARD LIQUID/KIOVIG alone) and SC infusions (GAMMAGARD LIQUID/KIOVIG and rHuPH20) reporting one or more local AEs (including and excluding infections), at any time during the study.

13. Number of AEs (including and excluding infections) determined by the investigator to be related to the study drug that occurred at any time during the study (“related”) divided by the number of infusions/subjects.

14. Frequency of dose corrections based on IgG trough levels 4.5 g/L IgG or below, if any, for each study epoch.

15. Number of all AEs categorized by MedDRA preferred terms, seriousness, relatedness to the study drug, and severity.

16. Rate of AEs defined as number of AEs categorized by MedDRA preferred terms, seriousness, relatedness to the study drug, and severity, divided by the number of infusions/subjects.

17. Proportion of IV and SC infusions associated with one or more AEs (including and excluding infections) related to the study drug.

18. Proportion of infusions tolerated with IV administration and with SC administration at the dose used in Study Epoch 2.

19. The total number of all AEs (including and excluding infections) that began during infusion or within 72 hours of completion of an infusion (“temporally associated”) plus the total number of AEs (including and excluding infections) that started more than 72 hours following the completion of an infusion determined by the investigator to be at least possibly related to the study drug (“related”), divided by the total number of infusions.

20. Number and proportion of all subjects who developed neutralizing antibodies to rHuPH20. The coincidence of the presence of antibodies with the occurrence of AEs, if any, were to be assessed.

21. Number and proportion of subjects who experienced a decline in hemoglobin of > 2.0 g/dL since the previous assessment with evidence of hemolysis on laboratory evaluation.

**Exploratory Endpoints:**

Quality of life, treatment satisfaction and preference were to be measured in all the subjects:

- Quality of life was to be measured prior to the first SC infusion of Study Epoch 2 and at the End-of-Study Visit. The SF-36® was to be used in subjects age 14 and older. In subjects age 2 to 13, Quality of life was to be assessed using the PEDS-QL.® A parent or primary caregiver was to complete the PEDS-QL on behalf of the subject if under 8 years old.

- Treatment satisfaction was to be measured prior to the first SC infusion of Study Epoch 2 and at the End-of-Study Visit using the Life Quality Index (LQI). Subjects 14 years and older were to complete the LQI on their own, while subjects under age 14 were to have the LQI completed by a parent or primary caregiver.

- Treatment preference questions were to be administered at the End-of-Study Visit to all the subjects in the study. For subjects under 14 years of age, a parent or primary caregiver was to answer on their behalf.
**Statistical Methods:**

**Sample Size Calculation**
For the primary endpoint the power to reject the null hypothesis of 1 or more validated acute serious bacterial infections per year at the 1% level of statistical significance against the one-sided alternative of 0.7 or fewer validated acute serious bacterial infections per year was estimated as 81% for the planned sample size of approximately 80 subjects.

**Planned Statistical Analysis**
The primary endpoint, validated acute serious bacterial infections per subject per year, was to be analyzed using a Poisson model. A point estimate of the rate and its 99% upper confidence limit was to be provided. The null hypothesis of one or more validated acute serious bacterial infections per subject per year was to be tested against the alternate hypothesis of less than 1 validated acute serious bacterial infection per subject per year at the 1% level of statistical significance.

In subjects of age 12 years or older, pharmacokinetic equivalence of IV GAMMAGARD LIQUID/KIOVIG and SC GAMMAGARD LIQUID/KIOVIG treatment with rHuPH20 was to be assessed by a 90% confidence interval for the ratio of AUC\(_{0-t}\).

Other secondary endpoints and safety variables were to be analyzed descriptively.

**Summary – Conclusions**
A total of 365 GAMMAGARD LIQUID/KIOVIG infusions were administered IV (Epoch 1) and 1359 were administered SC with rHuPH20 (230 in the ramp-up phase and 1129 after the ramp-up in Epoch 2)

**Efficacy Results:**

**Primary Efficacy Endpoint:**
The rate of validated acute serious bacterial infections per year during SC administration of GAMMAGARD LIQUID/KIOVIG with rHuPH20 was 0.025 with an upper limit of the 99% CI of 0.046 in the FADS, and 0.000 with an upper limit of the 99% CI of 0.130 in the 44 subjects who were naïve to SC IgG treatment prior to the study. In all data sets, upper limit of the 99% CI was lower than 1.0 and the primary endpoint was met (H\(_0\): rate of 1/year, p<0.0001).

**Secondary Efficacy Endpoint(s):**
Infections occurred less frequently during SC treatment with rHuPH20 than during IV treatment: the point estimate of the annualized rate of all infections was 2.97 (95% CI: 2.51; 3.47) for SC administration with rHuPH20 and 4.51 (95% CI: 3.50; 5.69) for IV infusions. Similar point estimates were observed in SC-naïve subjects (3.50 [95% CI: 2.79; 4.32] for SC infusions with rHuPH20 and 4.42 [95% CI: 3.31; 6.06] for IV administration). The results of two sensitivity analyses for the rate of infections per year support the robustness of the original analysis with respect to seasonal effects and incomplete observations due to increase infections rate.

GAMMAGARD LIQUID/KIOVIG was administered at a mean weekly equivalent dose of 0.137 g/kg BW in Epoch 1 (IV treatment) and 0.164 g/kg BW in Epoch 2 excluding the ramp-up (SC treatment with rHuPH20) in subjects aged 2-<12 years. In subjects aged ≥12 years, the mean total dose per week was 0.144 g/kg BW and 0.154 g/kg BW, respectively. In SC-naïve subjects, the mean total dose per week was similar to that in the SADS in subjects aged ≥12 years, but was lower in subjects aged 2-<12 years (0.105 g/kg BW in Epoch 1 and 0.117 g/kg BW in Epoch 2 excluding the ramp-up.)
PK equivalence with respect to AUC_{0-\tau} of IgG for SC administration with rHuPH20 at an adapted dose and for IV administration was demonstrated in subjects aged \geq 12 years. The ratio of AUC_{0-\tau} for SC infusions with rHuPH20 and IV infusions was 93.3\% with a 90\% CI of 91.4\% to 95.2\%. The ratio of the AUC_{0-\tau} and 90\% CIs were similar in SC-naïve subjects (93.9\% [90\% CI: 91.1; 96.8]).

Consistent with these findings, bioavailability determined by serum IgG trough levels was comparable for the two treatment modes. The median ratio of serum IgG trough levels for SC infusions with rHuPH20 to IV infusions 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 \geq 12 years. Comparable results were obtained in SC-naïve subjects. The median trough levels during SC treatment in this study were 9.95 g/L (95\% CI: 7.87 to 15.00) in subjects aged 2 to <12 years and 10.70 g/L (95\% CI: 9.46 to 11.80) in subjects aged \geq 12 years.

Bioavailability of GAMMAGARD LIQUID/KIOVIG administered SC with and without rHuPH20 was analyzed by comparing data from the present study with data from Study 160601. The bioavailability of SC GAMMAGARD LIQUID/KIOVIG with respect to AUC per dose/kg was approximately 20\% higher when administered with rHuPH20 (in the present study) than without rHuPH20 (in Study 160601), as shown by the ratio of AUC per dose/kg of 120.4\% (95\% CI: 115; 125.5).

In agreement with the observation of PK equivalence, the median values for AUC/week were comparable when GAMMAGARD LIQUID/KIOVIG was administered SC with rHuPH20 and IV in all efficacy data sets analyzed. The median values for C_{\text{min}}, and CL/apparent CL were also similar for the two treatment types. Median AUC/week was 90.5 g*days/L [95\% CI: 83.8; 98.4] for SC with rHuPH20 compared to 93.9 g*days/L [95\% CI: 89.1; 102.1] for IV administration. The median C_{\text{min}} was 10.4 g/L (95\% CI: 9.4; 11.2) for SC administration with rHuPH20 and 10.1 g/L (95\% CI: 9.5; 10.9) for IV infusions. The median apparent CL during SC administration with rHuPH20 was 1.6 mL/kg/day (95\% CI: 1.4; 1.79), and median CL was 1.4 mL/kg/day (95\% CI: 1.2; 1.4) for IV administration. The median terminal half-life was higher for SC infusions with rHuPH20 (45.3 days [95\% CI: 41.0; 60.2]) than for IV administration (35.7 days [95\% CI: 32.4; 40.4]) in the FADS. In SC-naïve subjects median terminal half-life was 44.6 days for SC infusions with rHuPH20 (95\% CI: 40.3; 49.8) and 36.5 days for IV infusions (95\% CI: 31.5; 43.2). As expected, a difference between SC infusions with rHuPH20 and IV infusions was evident with respect to the median values for C_{\max} and T_{\max} in all efficacy data sets. Median C_{\max} was lower during SC administration with rHuPH20 (15.5 g/L [95\% CI: 14.5; 17.1]) than during IV administration (21.9 g/L [95\% CI: 20.7; 23.9]). The median T_{\max} was higher for SC infusions with rHuPH20 (5.0 days [95\% CI: 3.3; 5.1]) than for IV infusions (0.1 days [95\% CI: 0.1; 0.1]).

Levels of specific antibodies against Clostridium tetani toxoid, Haemophilus influenzae, measles virus, and HBsAg in all subjects showed no substantial difference between SC administration with rHuPH20 and IV infusions. Individual PK parameters of specific antibodies against Clostridium tetani toxoid and Haemophilus influenzae in subjects aged \geq 12 years generally showed trends that were consistent with the PK results for total IgG, and were comparable for SC-naïve subjects and the FADS.

Point estimates of the monthly rate of days off school/work, monthly acute physician visits and days per month on antibiotics were similar for SC administration with rHuPH20 and IV administration.
Quality of life scores as measured by the PEDS-QL questionnaire in subjects aged 2-7 years and 8-13 years were comparable for SC administration with rHuPH20, SC administration without rHuPH20 (data from Study 160601), and for IV infusions. In subjects aged 14 years and over, quality of life as assessed using the SF-36 survey also showed no substantial difference between these three treatment types. In subjects who were naïve to SC IgG prior to Study 160601, the median total scores were higher than in those previously exposed to SC IgG in the 2-7 year and 8-13 year age groups, there was no difference between SC-naïve subjects and previously SC treated subjects aged 14 years and over.

Treatment satisfaction as measured using the Life Quality Index (LQI) showed similar median scores for SC administration with rHuPH20, SC administration without rHuPH20 and IV administration. The results for subjects who were naïve to SC IgG prior to Study 160601 were comparable to the results for all subjects analyzed.

Preference for home treatment over other treatment sites was reported by 61.5% of parents/caregivers of subjects aged 2-13 years and 58.9% of subjects aged 14 years and over. Consistent with these results, 100.0% of parents/caregiver of subjects aged 2-13 years and 78.6% of subjects aged ≥14 years would have chosen continued SC IgG treatment with rHuPH20. The rates of subjects who gave positive ratings for each treatment preference parameter were generally lower among SC-naïve subjects than in subjects who had previously received SC IgG. In the ≥14 year age group, fewer SC-naïve subjects (73.3%) would have chosen to continue SC treatment with rHuPH20 than those who had previously received SC IgG (84.6%), however there was no difference between SC-naïve and previously exposed subjects for this parameter in the 2-13 year age group.

The median number of infusion sites per month for SC administration with rHuPH20 was 1.09, which is slightly lower than the median number of IV infusion sites used in this study (1.34), and considerably lower than the median number of SC infusion sites without rHuPH20 used in Study 160601 (2.14). Of the 1129 infusions administered SC with rHuPH20 in the present study, 282 (25.0%) were administered at home, 231 of which (20.5%) were completed without intervention by a nurse.

Safety Results:
Secondary Safety Endpoint(s)
Safety was analyzed in the 87 subjects exposed to GAMMAGARD LIQUID/KIOVIG SC and rHuPH20. In 94.0% of subjects, the interval used for IV dosing was reached for SC infusions with rHuPH20 during the ramp-up phase of Epoch 2. By the end of Epoch 2, the median dose (g/kg/week) of GAMMAGARD LIQUID/KIOVIG administered SC with rHuPH20 as a percentage of the IV dose was 107.52% in subjects aged 2-<12 years and 108.98% in subjects aged ≥12 years. Infusions in subjects aged 2-<12 year were administered at a median maximum flow rate of 62.5 mL/hr in Epoch 1 (range: 25.0-316.0) and 160.0 mL/hr (range: 80.0-300.0) in Epoch 2 (excluding the ramp-up). The median maximum infusion rates in subjects aged 12 years and over were 246.0 mL/hr in Epoch 1 (range: 60.0-668.0) and 300.0 mL/hr in Epoch 2 (10.0-300.0). Maximum flow rates utilized for SC infusions with rHuPH20 were significantly higher than those used for IV infusions (p<0.0001) as compared by Wilcoxon test stratified by subject (van Elteren’s test) (van Elteren, 1960). Of the 1359 SC infusions with rHuPH20 during the ramp-up and Epoch 2, 90.1% were administered in the abdomen and 8.6% in the thighs. The median duration of individual infusions was similar or lower when GAMMAGARD LIQUID/KIOVIG was administered SC with rHuPH20 than for IV administration. The median duration of infusions in subjects aged 2-<12 years and ≥12 years respectively
was 2.49 hrs and 2.33 hrs for IV infusions, and 1.73 hrs and 2.13 hrs for SC infusions with rHuPH20 (Epoch 2 excluding the ramp-up). The median dose per site of GAMMAGARD LIQUID/KIOVIG administered SC with rHuPH20 in individual subjects ranged from 9.10 g (ie 91.0 mL) to 64.80 g (ie 648.0 mL). All but 3 SC infusions with rHuPH20 during the ramp-up were tolerated according to the pre-defined criteria. The median rate of infusions tolerated at the dose used in Epoch 2 (excluding the ramp-up) was 100% (95% CI: 100; 100) for both IV administration and SC infusions with rHuPH20. The percentage of subjects who had no infusions that required a reduction in flow rate, interruption, or had to be stopped due to tolerability concerns or adverse events was similar between SC infusions with rHuPH20 (84.0%) and IV administration (88.5%).

No SAEs occurred that were considered by the investigator to be possibly or probably related to either or both of the study drugs.

The median rates of temporally associated AEs per infusion were comparable for SC administration with rHuPH20 and for IV administration regardless of whether infections were included as AEs or excluded. The median rates when infections were included were 0.21 (95% CI: 0.13; 0.31) for SC infusions with rHuPH20 and 0.25 (95% CI: 0.20; 0.50) for IV infusions. When infections were excluded, the median rates were 0.17 (95% CI: 0.09; 0.26) and 0.25 (95% CI: 0.20; 0.40), respectively. As expected, the rate infusions temporally associated with systemic AEs was lower for SC administration with rHuPH20 compared to IV administration, whereas the rate of infusions temporally associated with local AEs was higher for SC administration with rHuPH20. If infections were included as AEs, the median rates of infusions temporally associated with systemic AEs for SC infusions with rHuPH20 and IV infusions were 8.3% (95% CI: 7.7; 12.5) and 25.0% (95% CI: 20.0; 25.0), respectively. Similar results were obtained when infections were excluded. The median rates of infusions temporally associated with one or more local AEs were 5.9% (95% CI: 0.0; 8.3) for SC infusions with rHuPH20 and 0.0 (95% CI: 0; 0) for IV infusions.

The trend toward less frequent systemic AEs and more frequent local AEs during SC administration with rHuPH20 compared to IV treatment was also evident in the nature of AEs reported in MedDRA preferred terms. Of the AEs in Epoch 1 that were considered by the investigator to be possibly or probably related to GAMMAGARD LIQUID/KIOVIG, the most common were headache, chills, nausea, fatigue, pyrexia and vomiting. The most common AEs possibly or probably related to both GAMMAGARD LIQUID/KIOVIG and rHuPH20 in Epoch 2 (excluding the ramp-up) were infusion site pain, infusion site erythema, infusion site discomfort, headache, infusion site pruritis, infusion site edema, and infusion site swelling. The rates of mild and moderate instances of headache related to GAMMAGARD LIQUID/KIOVIG and rHuPH20 in Epoch 2 were 0.008 and 0.007 per infusion, respectively. No severe headache was related to SC infusions with rHuPH20. AEs possibly or probably related to rHuPH20 but not GAMMAGARD LIQUID/KIOVIG in Epoch 2 (excluding the ramp-up) included infusion site pain and infusion site pruritis. The majority of AEs were mild; very few severe AEs occurred.

Comparison of data from the present study and from Study 160601 demonstrated no appreciable differences between SC administration with and without rHuPH20 in regard to the median rates of AEs temporally associated or related to either or both study drugs. The median rates (including infections) were 0.18 (95% CI: 0.12; 0.31) for SC administration with rHuPH20 and 0.09 (95% CI: 0.06; 0.15) for SC administration without rHuPH20. When infections were excluded as AEs, the median rates were 0.15 (95% CI: 0.06; 0.31) and 0.07 (95% CI: 0.05; 0.10), respectively.

Assessment of hemolysis and other clinical laboratory parameters, or of immunogenicity with respect to
neutralizing antibodies against rHuPH20, did not raise any safety concerns with respect to SC administration of GAMMAGARD LIQUID/KIOVIG with rHuPH20. No subjects developed neutralizing antibodies against rHuPH20, and no confirmed incidences of hemolysis occurred.

**Conclusion:**

In conclusion, the primary endpoint of this study was met: GAMMAGARD LIQUID/KIOVIG administered SC with rHuPH20 at 108% of the IV dose was effective in preventing bacterial infections in pediatric and adult subjects with PIDD. Analysis of the secondary endpoints demonstrated that GAMMAGARD LIQUID/KIOVIG given SC with rHuPH20 had higher bioavailability as determined by AUC per dose/kg than when infused SC without rHuPH20. Compared to IV infusion, SC administration with rHuPH20 was able to be administered at the same dosing interval and resulted in similar IgG trough levels, while eliciting fewer systemic adverse reactions. Furthermore, SC infusion with rHuPH20 was the subjects’ preferred mode of treatment with GAMMAGARD LIQUID/KIOVIG.

**Date of Report:** 16 May 2011