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.
SYNOPSIS

Name of Sponsor/Company: Baxter Healthcare Corporation and Baxter Innovations GmbH

Name of Investigational Product (IP): Immune Globulin Infusion (Human), 10% (IGI, 10%) Recombinant Human Hyaluronidase (rHuPH20)

Name(s) of Active Ingredient(s): Immunoglobulin G (IgG) rHuPH20

CLINICAL CONDITION(S)/INDICATION(S):
- Primary Immunodeficiency Diseases (PID)

PROTOCOL IDENTIFIER: 160902

PROTOCOL TITLE: Long-Term Tolerability and Safety of Immune Globulin Subcutaneous Solution (IGSC) Administered Subcutaneously Following Administration of Recombinant Human Hyaluronidase (rHuPH20) in Subjects with Primary Immunodeficiency Diseases

Short Title: Tolerability and Safety of Immune Globulin Subcutaneous Solution and rHuPH20 in PID.

STUDY PHASE: Phase 3
PUBLICATION (REFERENCE): Based on interim data from Study 160902, a total of 4 abstracts have been published in 2012: i; ii; iii; iv

STUDY PERIOD

Initiation
2010 JUL 28 (first subject in)

Study Completion
2013 AUG 06 (last subject out)

Duration
Approximately 3 years

STUDY OBJECTIVES AND PURPOSE

Study Purpose
The purpose of this study was to assess the long-term safety, tolerability, and practicability of the subcutaneous (SC) treatment with IGI, 10% (= IGSC, 10%) facilitated with rHuPH20 in subjects with PID who had completed Baxter Clinical Study Protocol 160603.

Primary Objective
To evaluate the long-term tolerability and safety of IGSC, 10% after an SC infusion of rHuPH20 in subjects with PID. Following discontinuation of rHuPH20, subjects were observed for potential delayed adverse reactions following exposure to rHuPH20 in Protocols 160603 and 160902 prior to August 2012.

Secondary Objective(s)
- To monitor the long-term efficacy of IGSC, 10% after administration of rHuPH20 in subjects with PID
- To evaluate the effect of varying the dose frequency of IGSC, 10%/rHuPH20 on IgG trough levels
- To assess the practicability of treating PID with IGSC, 10% given after administration of rHuPH20 when treatment occurs in a home treatment environment

Tertiary Objective(s)
NA


### STUDY DESIGN

<table>
<thead>
<tr>
<th>Study Type/Classification/ Discipline</th>
<th>Safety, Tolerability, Efficacy</th>
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<tbody>
<tr>
<td>Control Type</td>
<td>Non-controlled</td>
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<tr>
<td>Study Indication Type</td>
<td>Treatment</td>
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<tr>
<td>Intervention model</td>
<td>Non-randomized</td>
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<tr>
<td>Blinding/Masking</td>
<td>Open-label</td>
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**Study Design**

This was a Phase 3, prospective, open-label, non-controlled, multi-center study to evaluate the long-term safety, tolerability, and practicability of IGSC, 10% treatment facilitated with rHuPH20 in subjects with PID. This study was an extension of Baxter Clinical Study Protocol 160603; therefore, only subjects and study sites of Study 160603 had the opportunity to participate in Study 160902.

**Safety Follow-up:**

Following a discussion with the Food and Drug Administration (FDA) at the end of July, 2012, all subjects still active in the study stopped rHuPH20 drug product treatment. They went into a Safety Follow-up period and were treated with IGI, 10% (GAMMAGARD LIQUID) via either the intravenous route (IGIV) or the subcutaneous route (IGSC) at the discretion of the investigator and the subject.

### Safety and Tolerability Endpoints

1. **Serious adverse events (SAEs):** The annual rate of SAEs related and not related.
2. **Infusions requiring adjustment:** Proportion of infusions for which the infusion rate was reduced and/or the infusion interrupted or stopped for tolerability concerns or for adverse events (AEs).
3. **Moderate or severe AEs:** 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.
4. **Antibodies to rHuPH20:** Number and proportion of all subjects who develop antibodies and neutralizing antibodies to rHuPH20. The coincidence of the presence of antibodies with the occurrence of AEs, if any, was assessed.
5. **Categorization of AEs:** Number of all AEs categorized by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, seriousness, relatedness to the study drug, and severity.
6. **Rates of AEs by subject:** Rates of AEs defined as number of AEs categorized by MedDRA preferred terms, seriousness, and severity, divided by the number of subjects.
7. **Rates of AEs by infusion:** Rates of AEs defined as number of AEs categorized by MedDRA preferred terms, seriousness, and severity, divided by the number of infusions.
8. **Causally related AEs by subject:** Number of AEs (including and excluding infections) determined by the investigator to be related to the study drug that occur at any time during the study (“related”) divided by the number of subjects.
9. **Causally related AEs by infusion:** Number of AEs (including and excluding infections) determined by the investigator to be related to the study drug that occur at any time during the study (“related”) divided by the number of infusions.
10. **Temporally associated AEs by subject**: Number of AEs (including and excluding infections) occurring during or within 72 hours of an infusion divided by the number of subjects.

11. **Temporally associated AEs by infusion**: Number of AEs (including and excluding infections) occurring during or within 72 hours of an infusion divided by the number of infusions.

12. **Local AEs by infusion**: Proportion of infusions associated with one or more local AEs (including and excluding infections), at any time during the study.

**Efficacy Endpoints**

*(Not during the Safety Follow-up period)*

1. Serious bacterial infections: Annual rate of serious bacterial infections calculated per subject.

2. Rate of all infections by subjects: Annual rate of all infections by organ system calculated per subject.

3. Trough levels: Trough levels of IgG maintained during the study period in relation to dose frequency.

**Additional Assessments**

*(Not during the Safety Follow-up period, except #6)*

1. Days of school/work missed, days on antibiotics, number of hospitalizations and days hospitalized, and number of acute physician visits (office and emergency room) due to infection or other illnesses.

2. Subject quality of life assessment, including treatment preference and satisfaction.

3. Number of subjects/caregivers unable to continue with self/home infusion and reason(s) for this failure.

4. Number of subjects who preferred a switch to a 2-week treatment interval and reason(s) for this preference.

5. Time required for subject/caregiver to prepare and administer infusions.

6. Characterization of antibodies to rHuPH20: Plasma from select subjects who had higher titers of binding antibodies to rHuPH20 were evaluated for characteristics such as, but not limited to, isotype, subclass distribution, specificity, affinity, avidity, and epitope mapping.

7. At select study sites subjects were asked to participate in a video taping of the infusion procedure and to answer a brief questionnaire regarding any difficulties in carrying out the pooling or SC administration procedure. These videos were only used internally for the purpose of improving the administration procedure. Subjects were not identified on the video. In addition, still photographs of the infusion sites were used for educational and demonstration purposes. Only the infusion site was photographed and no identifying features were included. Questions were administered by the study site personnel or third-party human function specialist and were documented. A third party company managed the videotaping. Subjects who agreed signed a separate consent form.
<table>
<thead>
<tr>
<th>Investigational Product(s)</th>
<th>1. IGI, 10%</th>
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<tbody>
<tr>
<td><strong>Dose:</strong> Variable, as determined during participation in Baxter Clinical Study 160603.</td>
<td></td>
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<tr>
<td><strong>Dosage form:</strong> injectable SC</td>
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<tr>
<td><strong>Dosage frequency</strong> (prior to entering the Safety Follow-up period): once every 2, 3 or 4 weeks</td>
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<tr>
<td><strong>Mode of Administration:</strong> SC</td>
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<tr>
<td>In the Safety Follow-up period: SC or IV infusion</td>
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<tr>
<td><strong>Batch number(s):</strong> LE12H195AD; LE12H309AC; LE12J074AM; LE12J118AD; LE12J129AC; LE12J155AC; LE12J257AB; LE12J308AC; LE12J308AD; LE12J311AC; LE12J344AC; LE12K006AB; LE12K006AC; LE12K202AC; LE12K205AD; LE12K312AE; LE12K312AJ; LE12L134AD; LE12L178AC; LE12L221AD; LE12L264AD; LE12L318AC; LE12LG60AD; LE12M072AC; LE12M088AB; LE12M088AD; LE12M094AB</td>
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| 2. rHuPH20 |
| **Dose:** 75 U/gram IgG |
| **Dosage form:** injectable SC |
| **Dosage frequency** (prior to entering the Safety Follow-up period): same as for IGI, 10% |
| **Mode of Administration:** SC |
| In the Safety Follow-up period: No rHuPH20 was used. |
| **Batch number(s):** 911529; 911530; 913295; 913296; 916277-A; 916785-A; 918154; 918154-A |

| Placebo/ Control/ Comparator | Not Applicable |

<table>
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<tr>
<th>Duration of treatment:</th>
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<tbody>
<tr>
<td>• Prior to the Safety Follow up</td>
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<tr>
<td>• Variable depending on when subject completed Study 160603</td>
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<tr>
<td>• During the Safety Follow-up</td>
</tr>
<tr>
<td>• For subjects with anti-rHuPH20 antibody titers &lt;160 at the last measurement before the Safety Follow-up period (ie, before discontinuation of rHuPH20), approximately 24 weeks.</td>
</tr>
<tr>
<td>• For subjects with anti-rHuPH20 antibody titers ≥160 at the last measurement before the Safety Follow-up period (ie, before discontinuation of rHuPH20), approximately 48 weeks.</td>
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</table>
SUBJECT SELECTION

<table>
<thead>
<tr>
<th>Planned</th>
<th>A maximum of 80 subjects</th>
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<tr>
<td>Analyzed</td>
<td>Safety Analysis Dataset (SADS; n= 66); IGSC, 10% facilitated by rHuPH20 Treatment Dataset (HTDS; n= 66)</td>
</tr>
</tbody>
</table>

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

**Inclusion Criteria**

- Subject had completed or was about to complete Baxter Clinical Study Protocol 160603. Subjects who had discontinued rHuPH20 and reverted to IV or SC treatment due to an anti-rHuPH20 antibody also could enroll for long term safety monitoring.
- Subject/caretaker had reviewed, signed and dated informed consent.
- Subject was willing and able to comply with the requirements of the protocol.

**Exclusion Criteria**

- Subject had a serious medical condition such that the subject’s safety or medical care would be impacted by participation in Study 160902.
- Subject was scheduled to participate in another non-Baxter clinical study involving an Investigational Product (IP) or investigational device during the course of this study.
- If female of childbearing potential, subject was pregnant or had a negative pregnancy test but did not agree to employ adequate birth control measures for the duration of the study.

STATISTICAL METHODS

Point estimates were provided for safety and tolerability endpoints. Medians and non-parametric 95% confidence intervals for medians were calculated for IgG trough levels over time. Descriptive statistics were used for additional assessments.

SUMMARY – CONCLUSIONS

**Efficacy Results:**

**Primary Efficacy Outcome:**
Two validated acute serious bacterial infections (VASBIs) occurred in 66 subjects under IGSC, 10% treatment with rHuPH20. The annual rate of VASBIs (0.020; upper limit of 99% CI: 0.045) was statistically significantly lower (p<0.0001) than the threshold specified as providing substantial evidence of efficacy (1.0).

**Secondary Efficacy Outcome(s):**

- The point estimate for the annualized rate of all infections was 2.86 (95% CI: 2.36-3.43) during IGSC, 10% with rHuPH20 treatment.
- IgG trough levels maintained under IGSC, 10% with rHuPH20 treatment did not substantially vary with infusion interval changes and were lower with the longest (4-week) infusion interval. Percent change of steady-state trough levels was 105.90% (mean and median) for subjects who switched from a 3-week to a 2-week infusion interval and a mean of 113.23% (median 112.44%) for subjects who switched from a 4-week to a 2-week infusion interval.
• The point estimate for the annualized rate of days off school/ work was less than 8 days per year. The rate of days on antibiotics was less than 65 days per year. The rate of hospitalizations was less than 1 per year and the rate of days hospitalized, less than 1 day per year. The rate of acute physician visits due to infection or other illness was less than 5 visits per year.

The following results were obtained for the analysis of the mode of infusion, quality of life, treatment satisfaction and treatment preference during IGSC, 10% with rHuPH20 treatment:

• The median quality of life score assessed in subjects aged 8-13 years (n=6) by the PEDS-QL questionnaire was 79.89. Quality of life scores assessed by the SF-36 survey for subjects aged 8-13 years (n=2) were: median physical component summary score 50.82, median mental component summary score 53.28. Quality of life scores assessed by the SF-36 survey for subjects aged 14 years and older (n=48) were: median physical component summary score 48.67, and median mental component summary score 50.99.

• Median scores for treatment satisfaction as assessed by the Life Quality Index (LQI) in subjects between 2 and 13 years (n=2) as assessed by a parent were 31.50 for treatment interference, 18.00 for therapy-related problems, 17.50 for therapy settings and 7.00 for cost. For subjects aged 14 years and older (n=53), median scores were 36.00 for treatment interference, 24.00 for therapy-related problems, 20.00 for therapy settings and 12.00 for cost. Scores were in the upper part of the possible range indicating treatment satisfaction and satisfaction with cost.

• Scores for treatment preference showed that 21 subjects liked the ability to self-administer, 14 subjects disliked it, and 12 had no preference. A total of 33 subjects scored that they liked the ease of administration, 5 scored that they disliked it, and 10 had no preference. The majority of subjects (31) stated that they preferred IGSC, 10% with rHuPH20 and would continue on this treatment, 2 preferred regular SC administration, 13 had a preference for IV administration, and 2 had no preference.

• Across all age groups the mean time required for the subject/caregiver to prepare, administer and clean up after IGSC, 10% infusions facilitated by rHuPH20 was 2.47 h (range 0.38 h to 5.30 h).

• Across all age groups, 63.5% of subjects were unable to continue with self/home infusion and required medical assistance. Reasons for discontinuation of self/home-infusion were medical reasons for (14.3%), a family member (15.9%), or other reasons for (58.7%)

• Across all age groups, 18/63 (28.6%) subjects chose to switch to a 2-week interval. The main reason for this preference was travel/vacation/no specific reason for 16/63 (25.4%) subjects; with no specific reason prevailing. Other reasons were better health/fewer infections (9.5%); smaller volume/dose (9.5%) shorter infusion time for (4.8%); increased trough levels (1.6%); fewer AEs for (3.2%).

Safety Results:

Primary Safety Outcome

• The annual rate of all SAEs during IGSC, 10% with rHuPH20 treatment, across all age groups, was 0.1392. During the entire study, no SAEs occurred that were considered by the investigator to be related to either of the study drugs.
Secondary Safety Outcome(s)

- Throughout the study, the proportion of infusions requiring adjustment for tolerability concerns or for AEs was low (0.1% of infusions stopped, 0.6% of infusions interrupted; 1% infusion rate reduced).

- No subjects develop neutralizing antibodies in the entire duration of the follow up including data obtained in Study 160603 starting with first exposure to IGSC, 10% facilitated by rHuPH20 and in Study 160902. Out of the 740 related AEs experienced by 57/66 (86.4%) of subjects, 180 related AEs were reported by 12/13 (92.3%) subjects with anti-rHuPH20 antibody titers ≥ 1:160.

- According to MeDRA preferred term classification, under rHuPH20-facilitated IGSC, 10% treatment, the most common related AEs were infusion site pain, infusion site pruritus, nausea, myalgia, infusion site erythema, headache, fatigue, asthenia, chills, infusion site discomfort, and pain. During the Safety Follow-up period the most frequent related AEs related were headache, fatigue, nausea, infusion site pain, and decreased appetite.

- The rate of all AEs related to IGI, 10%, by subject, was 3.317 during rHuPH20-facilitated IGSC, 10% treatment, and 2.588 during the Safety Follow-up period. During rHuPH20-facilitated IGSC, 10% treatment, the rate of all AEs related to rHuPH20, by subject, was 0.365 and the rate of all AEs related to both IGI, 10% and rHuPH20 by subject, was 1.444.

- The rate of all AEs related to IGI, 10%, by infusion, was 0.131 during rHuPH20-facilitated IGSC, 10% treatment, and 0.221 during the Safety Follow-up period. During rHuPH20-facilitated IGSC, 10% treatment, the rate of all AEs related to rHuPH20, by infusion, was 0.014 and the rate of all AEs related to both IGI, 10% and rHuPH20 by infusion, was 0.057.

- The rate of all causally related AEs by subject was 5.127 during rHuPH20-facilitated IGSC, 10% treatment and 2.588 during the Safety Follow-up period. The rate of all causally-related local AEs, by subject, was 2.603 during rHuPH20-facilitated IGSC, 10% treatment and 0.373 during the Safety Follow-up period. During rHuPH20-facilitated IGSC, 10% treatment, the rate of related systemic AEs, by subject, including or excluding infections, was 2.524. During the Safety Follow-up period, the rate of related systemic AEs, by subject, including and excluding infections was 2.216.

- The rate of all causally related AEs by infusion was 0.202 during rHuPH20-facilitated IGSC, 10% treatment and 0.221 during the Safety Follow-up period. The rate of all causally-related local AEs, by infusion, was 0.103 during rHuPH20-facilitated IGSC, 10% treatment and 0.032 during the Safety Follow-up period. During rHuPH20-facilitated IGSC, 10% treatment, the rate of related systemic AEs by infusion, including or excluding infections was 0.099. During the Safety Follow-up period, the rate of related systemic AEs by infusion, including and excluding infections was 0.189.

- The rate of all temporally-associated AEs, by subject, was 7.095 during rHuPH20-facilitated IGSC, 10% treatment and 2.980 during the Safety Follow-up period. The rate of all temporally-associated local AEs, by subject, was 2.619 during rHuPH20-facilitated IGSC, 10% treatment and 0.392 during the Safety Follow-up period. During rHuPH20-facilitated IGSC, 10% treatment, the rate of temporally-associated systemic AEs by subject, including infections was 4.476 and excluding infections, 4.032. During the Safety Follow-up period, the rate of temporally-associated systemic AEs by subject, including infections was 2.588, and excluding infections, 2.392.
• The rate of all temporally-associated AEs, by infusion, was 0.279 during rHuPH20-facilitated IGSC, 10% treatment and 0.254 during the Safety Follow-up period. The rate of all temporally-associated local AEs, by infusion, was 0.103 during rHuPH20-facilitated IGSC, 10% treatment and 0.033 during the Safety Follow-up period. During rHuPH20-facilitated IGSC, 10% treatment, the rate of temporally-associated systemic AEs by infusion, including infections was 0.176, and excluding infections 0.159. During the Safety Follow-up period, the rate of temporally-associated systemic AEs by infusion, including infections was 0.221, and excluding infections, 0.204.

• Throughout the study, 7.4 % of infusions were associated with one or more local AEs.

• Assessment of hematology parameters, clinical chemistry parameters, urinalysis and specific antibody tests and viral pathogen serology did not raise any safety concerns with respect to the SC administration of IGI, 10% with rHuPH20.

Conclusion:
In conclusion, IGI, 10% administered SC with rHuPH20 was safe in adult and pediatric subjects with PID: no related SAEs occurred during the predecessor Study 160603 or in extension 160902. None of the subjects developed neutralizing antibodies to rHuPH20 during Study 160603 and Study 160902. The number and rate of systemic AEs related to rHuPH20-facilitated IGSC, 10% treatment were low. No increase in the rate of local AEs was observed after long-term rHuPH20-facilitated IGSC, 10% treatment. The annual rate of VASBI was below the threshold specified as providing substantial evidence of efficacy. Efficacy of rHuPH20-facilitated IGSC, 10% treatment was confirmed by a low overall infection rate and the maintenance of protective IgG trough levels.

Date of Report: 2014 FEB 03