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| | |
|---|---|
| Application Type | sBLA/Efficacy |
| STN | 125402/818 |
| CBER Received Date | March 8, 2022 |
| PDUFA Goal Date | April 7, 2023 |
| Division / Office | OTP |
| Committee Chair | Sairah Thommi, M.D., MS |
| Clinical Reviewer(s) | Sairah Thommi, M.D., MS |
| Project Manager | Adriane Fisher, M.P.H, M.B.A |
| Priority Review | No |
| Reviewer Name(s) | Boris Zaslavsky, Ph.D., Dr.Sc. |
| Review Completion Date / Stamped Date | |
| Supervisory Concurrence | Tingting Zhou, Ph.D.<br>Team Lead, OBPV/DB/TEB1 |
| | Boguang Zhen, Ph.D.<br>Branch Chief, OBPV/DB/TEB1 |
| | |
| Applicant | Baxalta US Inc |
| Established Name | Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase |
| (Proposed) Trade Name | HYQVIA |
| Dosage Form(s) and Route(s) of Administration | A dual vial unit containing 10% IgG (100 mg/mL) and 160 U/mL Recombinant Human Hyaluronidase for subcutaneous use only |
| Dosing Regimen | Increase the dose and frequency from a 1-week dose to a 3-or 4-week dose Administer HYQVIA at 300 to 600 mg/kg at 3 to 4-week intervals, after initial ramp-up. |
| Indication(s) and Intended Population(s) | Indicated for the treatment of Primary Immunodeficiency (PI) in adults and pediatric patients two years of age and older. |

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## GLOSSARY

| | |
|---|---|
| Ab | antibody |
| AE | adverse event |
| VASBI (ASBI) | (validated) acute serious bacterial Infection |
| BW | body weight |
| CVID | common variable immunodeficiency |
| CI | confidence interval |
| CL | confidence limit |
| Cm | Centimeters |
| CSR | clinical Study Report |
| EOS | end of the study |
| FAS | full analysis set (intent to treat set) |
| iCSR | Interim Clinical Study Report |
| IG | immunoglobulin G |
| IG 10% | Takeda's 10% immunoglobulin preparation for subcutaneous and intravenous replacement therapy |
| IgA | immunoglobulin A |
| IgG | immunoglobulin G |
| IGI | immune globulin infusion |
| IGIV | Immune Globulin Intravenous |
| IGSC | Immune Globulin Subcutaneous |
| IP | investigational product |
| ISE | integrated summary of efficacy |
| IV | intravenous |
| Kg | kilograms |
| PI | primary immunodeficiency |
| PIDD | primary immunodeficiency disease |
| PK | pharmacokinetic |
| PREA | Pediatric Research Equity Act |
| PT | preferred term |
| rHuPH20 | recombinant human hyaluronidase PH20 |
| SAE | serious adverse event |
| sBLA | supplemental Biologics License Application |
| SE | standard error |
| SC | subcutaneous |
| TEAE | treatment-emergent adverse events |
| WHO | World Health Organization |

## 1. Executive Summary

HYQVIA, an immune globulin with Recombinant Human Hyaluronidase (rHuPH20), is currently indicated for the treatment of Primary Immunodeficiency (PI) in adults. HYQVIA can be administered intravenous (IV) or subcutaneous (SC) infusions facilitated by administration of rHuPH20. The applicant submitted the interim results from a pivotal pediatric study 161503 in this supplemental Biologics License Application (sBLA) to expand the current indication to treatment of PI in pediatric subjects. This sBLA is also supported by a pivotal adult and pediatric study 160603 and a long-term follow up study 160902.

Study 161503 was a Phase 3, open-label, prospective, non-controlled, multicenter study. The study consisted of 2 treatment periods (Epoch 1 and Epoch 2) and a 1-year safety follow-up, if needed. A total of 44 pediatric subjects (2-15 years old) were enrolled in the study. One subject reported 2 acute serious bacterial infections (ASBIs) of bacterial pneumonia. The number of ASBIs per subject-year was 0.04, with an upper limit of the 99% confidence interval (CI) of 0.21. The study demonstrated an ASBI rate per person-year that was statistically significantly lower than threshold rate of 1.0 ASBI per subject-year, the threshold specified as providing substantial evidence of efficacy by the FDA Guidance to Industry (2008): Safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency.

Study 160603 was a prospective, open-label, non-controlled, multi-center study. The study consisted of 2 study Epochs. In study Epoch 1, subjects received intravenous (IV) treatment with GAMMAGARD LIQUID/KIOVIG for 13 weeks. In study Epoch 2, subjects received subcutaneous (SC) treatment with GAMMAGARD LIQUID/KIOVIG after administration of rHuPH20 starting with a ramp-up with treatment intervals of 1 week, then 2 weeks, then 3 weeks, (then 4 weeks if applicable) and once every 3 or 4 weeks for 14 months after the ramp-up period. Eighty-seven subjects were enrolled in the study but only 81 subjects were included in the primary efficacy analysis. Of the 81 subjects, 20 were pediatric subjects and 61 were adults. Three validated ASBIs (VASBIs) were reported in the study; all occurred in the pediatric subjects. The number of VASBIs per subject year was 0.099 with an upper 99% CI bound of 0.51.

Study 160902 was a Phase 3, prospective, non-controlled, open-label, multicenter long-term safety study. The study enrolled 66 subjects who had completed Study 160603. Of the 66 subjects, 11 were pediatric subjects and 55 were adults.

Among the 64 pediatric subjects in Study 161503 and in Study 160603, 4 ASBIs of bacterial pneumonia were reported in three subjects. This resulted in a mean rate of 0.06 ASBIs per subject-year with an upper 99% CI bound of 0.18 for pediatric subjects.

No deaths were reported in Study 161503 and Study 160603. Two subjects died in Study 160902. Both subjects were adults.

In Study 161503, a 4-year-old female developed a titer of ≥ 160 for binding antibodies against rHuPH20 and is currently completing additional 2 years of follow up. In Study 160603, 11 subjects had developed anti-rHuPH20 antibody titers ≥1:160. Of the 11 subjects, 2 were pediatric subjects. One of the pediatric subjects continued to experience anti-rHuPH20 antibody titers ≥ 1:160 in Study 160902. A total of 13/66 subjects had anti-rHuPH20 antibody titers ≥1:160 in Study 160902.

I verified the efficacy results that appear in the proposed updated label. Based on the available data, the statistical evidence supports approval of the applicant's labeling update to expand the indication to treatment of PI in pediatric subjects aged ≥ 2 years old.

## 2. Clinical and Regulatory Background

### 2.1 Disease or Health-Related Condition(s) Studied

PI diseases are disorders that result in increased susceptibility to recurrent infections, secondary to the underlying defects in adaptive (humoral and/or cell-mediated immunity) and/or innate immune system. Considered rare diseases until recently, PI diseases may affect up to 1/1200 people worldwide according to current estimates. The number of known PI diseases defects has increased in the last 20 years and the World Health Organization (WHO) currently recognizes more than 220 different disorders that meet the definition of PI diseases.

### 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Therapeutic options for the treatment of infections in PI diseases include standard antibiotic treatment and administration of Immunoglobulin G (IgG) as a replacement therapy. Antibody replacement can be accomplished either intramuscularly, intravenously, or subcutaneously. Therapeutic options for treatment of PI diseases also include transplantation of bone marrow-derived stem cells and gene therapy.

### 2.4 Previous Human Experience with the Product (Including Foreign Experience)

HYQVIA was approved in Europe in 2013 for treatment of PI in adults (ages ≥ 18 years).

## 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Regulatory history with statistical implications is summarized below:

Pre-submission:

1. On September 12, 2014, HYQVIA was approved for the treatment of PI in adults. Under the Pediatric Research Equity Act (PREA), FDA deferred submission of studies in children 2 to < 16 years of age treated by HYQVIA until March 2025.

2. On September 22, 2015, via Written Response, the FDA agreed with the applicant's proposed study design for their proposed Phase 3 pediatric study (Study 161503). The FDA also agreed with their licensure strategy to submit an efficacy supplement with clinical data from an interim safety analysis after 40 pediatric subjects have completed 1 year observation period and to provide results of the ongoing study annually throughout the duration of the study and the final study report as a post-marketing commitment.

3. On March 31, 2017, the original protocol dated July 22, 2016, for the pivotal study on pediatrics 2 to < 16 years of age (Study 161503) was submitted to the FDA (IND 013840 /Serial No. 0100).

4. On June 02, 2017, the FDA informed the applicant that Study 161503 may proceed.

5. On July 27, 2017, the protocol amendment 1 dated July 20, 2017, was submitted to the FDA.

6. On April 18, 2019, the protocol amendment 2 dated March 25, 2019, was submitted to the FDA (IND 013840/Serial No. 0114). Study 161503 is still ongoing. As of the data freeze date for the interim analysis (November 16, 2020), all but one subject had completed efficacy assessments.

7. On August 31, 2021, via Written Response, the FDA did not agree with planned interim analysis of Study 161503 as it was not clear that there would be 1-year safety and efficacy data from at least 40 subjects with at least 6 subjects in each of the age groups 2 to <6, 6 to <12, and 12 to <16 years old.

8. On November 12, 2021, the applicant submitted the study report, protocol and data/analyses for Study 161301, a pregnancy registry under sBLA 125402/805.0 (seq #0593).

Post-submission

9. On April 14, 2022, decision to complete PREA with data from 1 subject pending study completion (subject completed 1-year of data but developed antibodies and is in Epoch 2) was discussed. Given feedback to the applicant (listed above) allowing for efficacy supplement review prior to the completion of the study, decision was made to proceed with filing.

10. On July 05, 2022, the applicant submitted the study report and relevant study information of the Phase 3 European pediatric study 161504, as well as updated reports of Study 161406, completed as part of a post-marketing commitment to evaluate the long-term safety of HYQVIA in 250 subjects including up to 50 subject who developed antibodies.

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

### 3.2 Compliance With Good Clinical Practices And Data Integrity

On March 5, 2012, BIMO reviewer reported issues with one site #11 in Study 160603.

## 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

### 5.1 Review Strategy

In support of the proposed indication, the applicant relies on data for pediatric subjects < 16 years old from Studies 161503, 160603, and 160902.

- Study 161503 is an ongoing Phase 3 study of 44 pediatric subjects: I evaluated the interim analysis result (dated June 4$^{th}$, 2021, data cutoff Nov 16$^{th}$, 2020)
- Study 160603 is a complete Phase 3 study of adult and pediatric subjects: I evaluated the results separated by pediatrics and adults. The review of the complete study report has been reviewed by Chunrong Cheng dated May 17, 2012.
- Study 160902 is a complete long-term safety study for subjects who enrolled in Study 160603: I evaluated the results separated by pediatrics and adults.

In addition, an integrated efficacy analysis utilizing the data from the two pivotal studies 161503 and 160603 is presented in Section 7.

On July 5, 2022, the applicant submitted a Phase 4 post-authorization, prospective, non-controlled European study [660]161504. However, this study is not covered in this review.

### 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

1. Supplement BLA 125402/818.0
    a. 1.14 Labeling
    b. 1.2 Cover Letter
    c. 2.2 Introduction
    d. 2.5 Clinical Overview
    e. 2.7.3 Summary of Clinical Efficacy
    f. 2.7.4 Summary of Clinical Safety
    g. 2.7.6 Synopsis of Individual Studies
    h. 5.2 Tabular Listing of all Clinical Studies
    i. 5.3.5.2 161503 Clinical Study Report
    j. 5.3.5.2 161603 Clinical Study Report
    k. 5.3.5.2 161902 Clinical Study Report
    l. 5.3.5.3 Integrated summary of efficacy
    m. 5.3.5.3 Integrated summary of safety

2. Supplement BLA 125402/818.1
    a. 1.11.4 Multiple Module Information Amendment (Response to FDA Information Request dated 16-Mar-2022)

3. Supplement BLA 125402/818.2
    a. 1.11.3 Response to Efficacy information Request dated 31st-Mar-2022

4. Supplement BLA 125402/818.4
    a. 1.11.3 Response to Efficacy information Request dated 13-Apr-2022

5. Supplement BLA 125402/818.5
    a. 1.11.3 Response to FDA IR dated April 14 2022

6. Supplement BLA 125402/818.7
    a. 1.11.3 Response to Clinical Information Request dated 02-May 2022
    b. 5.3.3.2 Patient PK and Initial Tolerability Study Reports-Analysis datasets for Study 160902
    c. 5.3.5.3 Integrated summary of efficacy-Analysis datasets

7. Supplement BLA 125402/818.8
    a. Cover Letter Response to FDA

8. Supplement BLA 125402/818.14

a. Cover Letter Response to FDA

9. Supplement BLA 125402/818.17
    a. 1.11.3 Clinical Information Amendment

10. Supplement BLA 125402/818/27
    a. 1.11.3 Clinical Information Amendment
    b. 5.3.5.3 Reports of Analyses of Data from More than one study

### 5.3 Table of Studies/Clinical Trials

This review memo focuses on two completed Phase 3 study and a long-term safety study as presented in Table 1.

Table 1. Tabular Listing of All Relevant Clinical Studies on IGI, 10% with rHuPH2

| Study | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Duration of Treatment |
|---|---|---|---|---|---|
| 160603 | To evaluate efficacy, safety, tolerability and PK comparison of IGI, 10% administered IV or SC following administration of rHuPH20 in subjects with PIDD | Phase 3 prospective, open-label, non-randomized, multi-center study | Epoch 1: IGI, 10% at pre-study dose given IV every 3 or 4 weeks<br>Epoch 2: IGSC, 10% at 108% of IV dose given SC every 3 or 4 weeks<br>rHuPH20 was given SC prior to infusions with IGSC, 10% at a dose of 75 U/g IgG | 81 PIDD subjects | IGI, 10%: 91.0 days<br>IGSC, 10% with rHuPH20 after ramp-up: 366.0 days |
| 160902 | To evaluate the long-term tolerability and safety of IGSC, 10% after an SC infusion of rHuPH20 in subjects with PIDD.<br>To monitor the long-term efficacy of IGSC, 10% after administration of rHuPH20 in subjects with PIDD. | Phase 3, prospective, open-label, non-controlled, multi-center study | IGI, 10% injectable SC given once every 2,3, or 4 weeks at dose determined during participation in Study 160603<br>rHuPH20 was given SC prior to infusions with IGI, 10% at a dose of 75 U/g IgG | 66 PIDD subjects | Prior to the Safety Follow-up: variable depending on when subject completed Study 160603<br>During Safety Follow-up: For subjects with anti- rHuPH20 antibody titers <160 at last measurement, 24 weeks.<br>For subjects with anti-rHuPH20 antibody titers ≥160 at last measurement, 48 weeks |
| 161503 | To acquire additional data on efficacy, safety, tolerability, immunogenicity, pharmacokinetic and other parameters of HYQVIA in pediatric subjects with PIDD who received immunoglobulin therapy prior to study enrollment | Phase 3, open-label, prospective, non-controlled, multi-center study | Epoch 1 (Ramp-up): IGI 10% and rHuPH20 SC with a dose or interval ramp-up period of up to six weeks.<br>Epoch 2 (Final Dosing): IGI 10% and rHuPH20 SC once every 3 or 4 weeks<br>Epoch 3 (Safety Follow-up): IGI, 10% IV or SC<br>Subcutaneous and intravenous, if needed | 44 subjects aged 2 to <16 years old | Epoch 1: 6 weeks<br>Epoch 2: 1-3 years<br>Epoch 3: approximately one-year safety follow-up, if needed |

Source: Adapted BLA 125402/818, Module 5.2 Tabular Listing of All Relevant Clinical Studies on IGI, 10% with rHuPH20 Study 161503, Table 5.2, p.1-2.

# 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

## 6.1 Study 161503

The protocol for Study 161503 was titled "Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases." The final version of the protocol was dated March 25, 2019.

### 6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective:

- Assess the efficacy of HYQVIA treatment in pediatric subjects with PI who received prior IV or SC immunoglobulin therapy before enrollment into the study

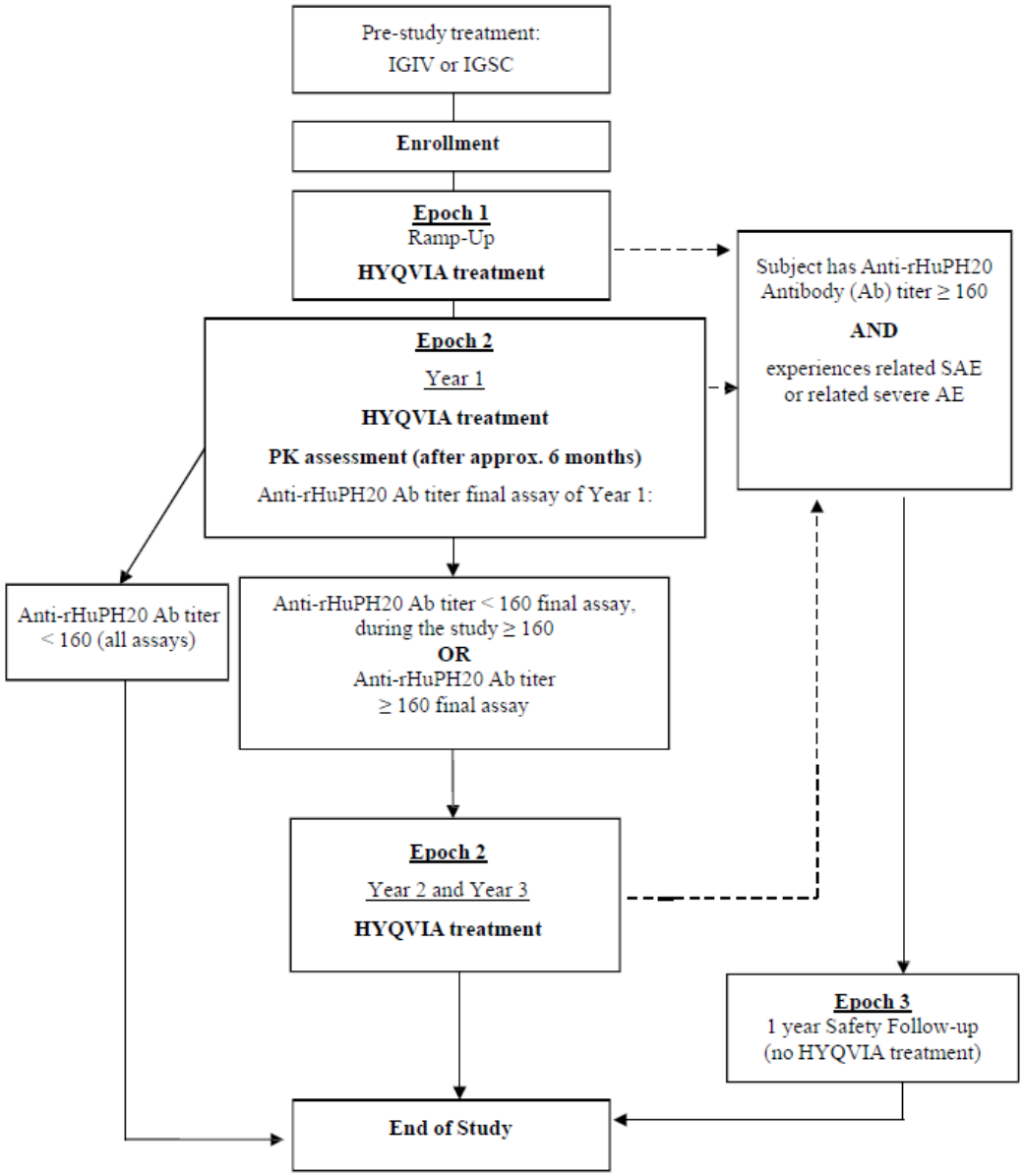
Secondary Objectives:

- Further assess efficacy and safety assessments (e.g., immunogenicity), tolerability, characteristics of product administration, treatment preference and satisfaction, health-related quality of life, and pharmacokinetic (PK) parameters

### 6.1.2 Design Overview

Study 161503 was a Phase 3, open-label, prospective, non-controlled, multicenter study. The study consisted of 2 treatment periods (Epoch 1 and Epoch 2) and a 1-year safety follow-up, if needed. All subjects were tested regularly for binding anti-rHuPH20 antibodies approximately every 3 months throughout the study. Figure 1 provides the overall study design.

Figure 1: The overall study design of Study 161503




Abbreviations: Ab= antibody, AE=adverse event, IGIV=immune globulin intravenous (human), IGSC=Immune globulin subcutaneous (human), PK=pharmacokinetics, rHuPH20= recombinant human hyaluronidase PH20, SAE=serious adverse event.
Source: BLA 125402/818.0: Study 161503 Interim Study Report, complete 2021June 04, Figure 1, p.30.

***Epoch 1***: Subjects were treated with HYQVIA SC with a dose or interval ramp-up period of up to 6 weeks, with all infusions administered at the study site

***Epoch 2:*** Subjects were treated with HYQVIA SC as follows:

- For IV-pretreated subjects – every 3 or 4 weeks depending on the subject's previous IV dosing schedule
- For SC-pretreated subjects – every 3 or 4 weeks at the discretion of the investigator and subject

After 1 year in Epoch 2, the anti-rHuPH20 binding antibody assay results during the year were used to determine the next steps in the study:

- Subjects with anti-rHuPH20 antibody titer < 160 at all time-points during the study completed the study completion visit at the next possible occasion following the 12-month visit
- Subjects with anti-rHuPH20 antibody titer ≥160 during the study and/or at the last measurement continued in Epoch 2 for an additional 2 years of HYQVIA and completed the study completion visit at the next possible occasion following the 36-month visit

***Epoch 3:*** Subjects were treated with GAMMAGARD LIQUID, IGI (human) 10% solution, if needed (no HYQVIA treatment) in this 1-year safety follow-up. Only subjects who had anti-rHuPH20 antibody titer ≥ 160 during either Epoch 1 or Epoch 2 and who experienced either a study drug-related serious adverse event (SAE) or a related severe adverse event (AE) were enrolled.

Subjects in Epoch 1 or in Epoch 2 experienced a study drug-related SAE or related severe SE without anti-rHuPH20 antibody titer ≥ 160, can at the discretion of the investigator: 1) be terminated from the study; 2) enroll directly to Epoch 3; 3) continue in Epoch 1 or 2 with appropriate medical interventions such as decreasing HYQVIA infusion rate and/or premedication.

### 6.1.3 Population

Selected inclusion criteria:

1. Documented diagnosis of a form of primary immunodeficiency involving a defect in antibody formation and requiring gamma-globulin replacement, as defined according to the International Union of Immunological Societies (IUIS) Scientific Committee prior to enrollment. The diagnosis had to be confirmed by the sponsor´s Medical Director prior to first treatment with the investigational product (IP) in the study
2. Between 2 and <16 years of age at the time of screening
3. Been receiving a consistent dose of IgG, administered in compliance with the respective product information for a period of at least 3 months prior to screening. The average minimum pre-study dose over that interval was equivalent to 300 mg/kg body weight (BW)/4 weeks and a maximum dose equivalent to1000 mg/kg BW/4 weeks
4. Serum trough level of IgG >5 g/L at screening
5. Subject/legally authorized representative was willing and able to comply with the requirements of the protocol

Selected exclusion criteria:

1. Had an ongoing history of hypersensitivity or persistent reactions following IV immunoglobulin, SC immunoglobulin, and/or immune serum globulin infusions
2. Had severe immunoglobulin A deficiency (< 7.0 mg/dL) with known anti-immunoglobulin A antibodies and a history of hypersensitivity
3. Had a known allergy to hyaluronidase
4. Had active infection and was receiving antibiotic therapy for the treatment of infection at the time of screening
5. If female, was pregnant or lactating at the time of enrollment

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

***Epoch 1 and Epoch 2:***
*(Investigational) Product*: HYQVIA-immune Globulin Infusion (IGI) 10% (Human) with Recombinant Human Hyaluronidase PH20 (rHuPH20) component)
*Route of administration and schedule*: SC administration every 3 or 4 weeks

- For IV-pretreated subjects – every 3 or 4 weeks depending on the subject's previous IV dosing schedule
- For SC-pretreated subjects – every 3 or 4 weeks at the discretion of the investigator and subject

*Dose*: HYQVIA weekly dose was equivalent to 100% (±5%) of pre-study treatment. The rHuPH20 was administered at a dose ratio of approximately 80 U/g IgG before the infusion of IGI, 10%.

***Epoch 3:***
*Product*: GAMMAGARD LIQUID, immune globulin infusion (human), 10% solution
*Route of administration and schedule*: IV administration every 3 or 4 weeks or SC administration every week
*Dose*:

- For IV administration, the weekly dose is equivalent to 100% (±5%) of the dose in the previous study epoch
- For SC administration, the weekly dose is equivalent to 137% (±5%) of the weekly dose equivalent in the previous study epoch

### 6.1.6 Sites and Centers

A total of 17 sites enrolled subjects into the study

### 6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint:

- Rate of ASBIs, defined as the mean number of ASBIs per subject-year

  ASBIs included bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscesses, diagnosed according to the Diagnostic Criteria for Acute Serious Bacterial Infections, U.S. Food and Drug Administration (FDA) Guidance for

Industry to Support Marketing of Human Immune Globulin Intravenous as Replacement Therapy for Primary Humoral Immunodeficiency (Food and Drug Administration, 2008)

Selected secondary efficacy endpoints:

- Number of all infections

*Health resource utilization:*

- Days not able to go to school or work, or to perform normal daily activities due to infection or other illnesses
- Days on antibiotics
- Number of hospitalizations, indications for the hospitalization (infection or non-infection) and days hospitalized
- Number of acute physician visits (office and emergency room) due to infection or other illnesses

Selected safety endpoints:

- All serious adverse events (SAEs) and adverse events (AEs)
- Number of SAEs and AEs (including and excluding infections) regardless of relationship to the investigational product(s) divided by the number of infusions
- Number/proportion of subjects who develop positive titer ≥160 of binding or neutralizing antibodies to rHuPH20

Criteria for study success:
The study is considered a success if the upper limit of an exact one-sided 99% CI for the ASBI rate is < 1, or alternatively, if the annual validated ASBI rate is less than 1.0 at the 0.01 level of significance. The threshold specified as providing substantial evidence of efficacy by the FDA Guidance to Industry (2008): Safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency.

Since the sponsor planned one interim analysis before the final analysis. To adjust for multiplicity, at the interim analysis, determination of statistical significance was based on the p-value which was benchmarked against the nominal alpha threshold of 0.0089 based on the O'Brien-Fleming boundary obtained via the Lan-DeMets spending function.

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical Hypotheses
Null: ASBI rate is greater than or equal to 1.0 per person-year
Alternative: ASBI rate is less than 1.0 per person-year

Sample Size Estimation

Assuming a true ASBI rate of 0.5 per year, a sample size of 35 would be enough to test the null hypothesis at a one-sided significance level of 0.01 with 83% power. Allowing for 12% dropout rate, approximately 40 subjects were planned. At least 6 subjects were expected in each of the three age groups:

- 2 to < 6 years
- 6 to < 12 years
- 12 to < 16 years

Analysis Populations

- Full analysis set (FAS): all subjects who provided the informed consent and met enrollment eligibility. All efficacy analyses were based on the FAS.
- Per-protocol analysis set (PPS): All subjects in the FAS who had no major protocol deviations. Major protocol deviations would be determined before study clinical database lock for the interim and final analyses. Sensitivity analysis of the primary efficacy endpoint was also conducted on the PPS.
- Safety analysis set: All subjects who received at least one dose of HYQVIA. All safety analyses were based on the safety analysis set.

Statistical Methods

***Primary efficacy endpoint:***

The rate of validated ASBIs and the 99% upper confidence limit for the validated ASBI rate were calculated using a Poisson regression model accounting for the length of the observation period per subject. To handle over-dispersion, the exponential distribution dispersion parameter was assumed to be given by the deviance divided by the degrees of freedom. The number of ASBIs per subject year and the corresponding 99% upper confidence limit were provided. The primary observation period was from start of initial dose of HYQVIA (start of Epoch 1) through end of Epoch 2.

Two sensitivity analyses were performed for the primary efficacy endpoint:

1. Replace FAS with PPS and re-run the primary analysis
2. Exclude Epoch 1 from analysis and re-run the primary analysis. That is, number of infections was counted from start of Epoch 2 through end of Epoch 2

***Secondary efficacy endpoints***

Number of all infections and health resource utilization:
The same methodology as described for the primary efficacy endpoint was used. For each endpoint, the annual rate under HYQVIA treatment and the associated two-sided 95% CI were calculated.

Subgroup analyses

The primary efficacy endpoint was summarized by sex, race and the three age groups

Interim Analysis
The hypothesis was planned to be tested at the interim analysis and at the final analysis. While no early stopping of study was planned, the Lan-DeMets alpha spending function approach was used to preserve the overall type 1 error. O'Brien-Fleming boundary was used to adjust the alpha level at each look. The information fraction at the interim analysis was estimated as the observed subject-years at the interim analysis divided by the expected total subject-years at the final analysis.

- If the test statistic was greater than the pre-specified boundary at the interim analysis, the primary efficacy analysis at the final analysis would be for administrative purpose.
- If the test statistic was less or equal to the pre-specified boundary at the interim analysis, the final analysis would be planned in the statistical inferential manner. The alpha level at the final analysis may be adjusted based on the actual total information at the final analysis.

*Reviewer comment: Only the interim analysis results are reported in this interim CSR (iCSR). The final analysis of the data will be reported in a final CSR.*

*The information fracture was equal to 0.9696. The alpha boundary value at interim analysis was 0.0089. Determination of statistical significance was based on the p-value which was benchmarked against the threshold of 0.0089. The one-sided 99% confidence interval is presented for descriptive purposes only and do not correspond exactly to the p-value which was used for formal assessment of statistical significance.*

Handling of Missing data
No missing data was imputed for the primary efficacy analysis.

### 6.1.10 Study Population and Disposition

#### 6.1.10.1 Populations Enrolled/Analyzed

Table 2 shows the number of subjects in each analysis set. A total of 48 subjects were screened and 44 of them were enrolled in the study. All 44 subjects were included in the FAS, PPS, and safety analysis set.

Table 2: Number of subjects in each analysis set

| | Total (N, %) |
|---|---|
| Number of screened subjects | 48 |
| Number of enrolled subjects | 44 |
| Number of subjects in the FAS | 44 (100.0%) |
| Number of subjects in the PPS | 44 (100.0%) |
| Number of subjects in the safety analysis set | 44 (100.0%) |

Abbreviations: FAS=Full analysis set; PPS=per-protocol analysis set; N=number of subjects; %=percentages are based on the total number of subjects in the full analysis set.
Source: Adapted from sBLA 125402/818.0; Interim Clinical Study Report 161503, Table 14.1.2, p 136.

### 6.1.10.1.1 Demographics

Key demographic characteristics are summarized in Table 3. The median age of subjects at the signing of the informed consent was 9.5 years (range: 3 to 15 years). Twenty-three subjects (52.3%) were in the age category of 6 to <12 years, 12 subjects (27.3%) in the 12 to <16 years category, and 9 subjects (20.5%) in the 2 to <6 years category. A total of 26 subjects (59.1%) were male and 18 subjects (40.9%) were female. Forty subjects (90.9%) were white, and 2 subjects (4.5%) were black or African American. Most subjects were not Hispanic or Latino (39 [88.6%] subjects). The median height was 137.8 centimeters (cm) (range: 86.1 to 170.2 cm) and the median weight was 34.5 kilograms (kg) (range: 11.9 to 92.7 kg).

Table 3. Demographic and Other Baseline Characteristics – (FAS)

| **Subject Characteristics** | **Statistic** | **All Subjects (N=44)** |
|---|---|---|
| Age (Years)[a] | Mean (SD) | 9.0 (3.6) |
| | Median | 9.5 |
| | Min, Max | 3, 15 |
| Age Category (Years) | 2 to <6 years | 9 (20.5) |
| | 6 to <12 years | 23 (52.3) |
| | 12 to <16 years | 12 (27.3) |
| Sex [n (%)] | Male | 26 (59.1) |
| | Female | 18 (40.9) |
| Race [n (%)] | American Indian or Alaska Native | 0 |
| | Asian | 0 |
| | Black or African American | 2 (4.5) |
| | Native Hawaiian or Other Pacific Islanders | 0 |
| | White | 40 (90.9) |
| | Other | 1 (2.3) |
| | Multiple | 1 (2.3) |
| Ethnicity [n (%)] | Hispanic or Latino | 5 (11.4) |
| | Not Hispanic or Latino | 39 (88.6) |
| Height (cm) | Mean (SD) | 133.6 (24.0) |
| | Median | 137.80 |
| | Min, Max | 86.1, 170.2 |
| Weight (kg) | Mean (SD) | 37.8 (19.9) |
| | Median | 34.5 |
| | Min, Max | 11.9, 92.7 |

Abbreviations: SD = standard Deviations; Max = Maximum; Min = Minimum; kg=kilogram; cm=centimeters; n=number of subjects; %=percentages are based on the total number of subjects in the full analysis set.
[a] Age at screening
Source: Adapted BLA 125402/818.0: Study 161503 Interim Study Report, complete 2021 June 04, Table 3, p.64.

**6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population**
All enrolled subjects had at least one medical history. The most frequently reported medical history was infections and infestations (38 subjects [86.4%]).

Common variable immunodeficiency disorder (CVID) was the most commonly diagnosed PIDD in 18/44 subjects (CVID 16 subjects [36.4%]; CVID and "other" 2 subjects [4.5%]), followed by specific antibody deficiency (SAD) in 16/44 subjects (SAD 6 subjects [13.6%], SAD with hypogammaglobulinemia/low IgG 4 subjects [9.1%], SAD with IgG subclass deficiency and "other" 1 subject [2.3%] and specific antibody deficiency and "other" 5 subjects [11.4%]). A summary of PIDD types is displayed in Table 4.

Table 4. PIDD Type - FAS

| **PIDD Type** | **All Subjects (N = 44)** |
|---|---|
| Agammaglobulinemia- X-linked (Bruton's agammaglobulinemia, XLA) [n (%)] | 1 (2.3) |
| Agammaglobulinemia/hypogammaglobulinemia- autosomal recessive [n (%)] | 1 (2.3) |
| Agammaglobulinemia/hypogammaglobulinemia- autosomal recessive; other [n (%)] | 1 (2.3) |
| Common variable immunodeficiency disorder (CVID) [n (%)] | 16 (36.4) |
| Common variable immunodeficiency disorder (CVID); other [n (%)] | 2 (4.5) |
| Severe combined immunodeficiency [n (%)] | 3 (6.8) |
| Specific antibody deficiency [n (%)] | 6 (13.6) |
| Specific antibody deficiency with hypogammaglobulinemia/low IgG [n (%)] | 4 (9.1) |
| Specific antibody deficiency with IgG subclass deficiency; other [n (%)] | 1 (2.3) |
| Specific antibody deficiency; other [n (%)] | 5 (11.4) |
| Other [n (%)] | 4 (9.1) |

Abbreviations: IgG = immunoglobulin G; PIDD=Primary Immunodeficiency Disease; n=number of subjects; %=percentages are based on the total number of subjects in the full analysis set.
The category of "Other" contains two subjects with 'IgG subclass deficiency, low IgA', one subject with 'hypogammaglobulinemia' and one subject with 'hypogammaglobulinemia and IgG subclass deficiency'.
Source: Original BLA 125402/818.0: Study 161503 Interim Study Report complete 2021June04, Table 4, p.66.

### 6.1.10.1.3 Subject Disposition

A total of 48 subjects were screened in the study. Of these, 4 subjects (8.3%) were screen failures, and 44 subjects met eligibility criteria and were enrolled and dosed in the study. At the data-freeze date (16 Nov 2020), of the enrolled subjects, 33 subjects (75%) had completed Epoch 2 of the study. Ten subjects (22.7%) discontinued the study before completing Epoch 2. Of the 10 subjects discontinuing before end of the study (EOS), 2 subjects completed all Epoch 2 mandatory visits/assessments preceding EOS. One subject was ongoing in Epoch 2 at the data-freeze date. Table 5 summarizes the disposition of all subjects.

***Epoch 1:***
One subject discontinued the study during Epoch 1 due to an AE.

***Epoch 2:***
Nine subjects discontinued during Epoch 2. Six subjects discontinued due to withdrawal by subject, the most frequent reason for subject discontinuation. One subject discontinued due to physician's decision and 1 subject withdrew due to a treatment-emergent adverse event (TEAE). One subject was prematurely discontinued from the study due to COVID-19 constraint at the site in conducting final visit. The subject was unable to complete the final visit, prompting the physician to terminate the subject and put the subject on commercial product. This incident of premature discontinuation was reported as “other” reason in the study disposition table.

Table 5. Subject Disposition

| **Disposition** | **All subjects** |
|---|---|
| Enrolled (enrolled set/full analysis set) | 44 |
| Completed study | 33 |
| Discontinued study prematurely | 10 |
| Ongoing in Epoch 2 at time of data cutoff for IA | 1 |
| Completed Epoch 1 | 43 |
| Discontinued during Epoch 1 | 1 |
| Primary reason for premature discontinuation during Epoch 1 | |
| Subject had adverse event(s) | 1 |
| Completed Epoch 2 | 33 |
| Discontinued during Epoch 2 | 9 |
| Primary reason for premature discontinuation during Epoch 2 | |
| Subject had adverse event(s) | 1 |
| Physician Decision | 1 |
| Withdrawal by subject | 6 |
| Other | 1 |

Source: Adapted BLA 125402/818: Study 161503 Interim Study Report, complete 2021June04, Table 2, p.61-62.

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoint(s)

One subject reported 2 ASBIs of bacterial pneumonia. The number of ASBIs per subject-year was 0.04, with an upper limit of the 99% CI of 0.21. The p-value was <0.001, which was lower than the nominal alpha threshold of 0.0089 for the interim analysis. Thus, the number of ASBIs per subject-year was statistically significantly lower than threshold rate of 1.0 ASBI per subject-year. Table 6 summarizes the number of ASBIs per subject year for the FAS.

The results were the same in the PPS as all subjects were in the PPS. The mean rate of ASBIs per subject-year for Epoch 2 excluding Epoch 1 was 0.02 with an upper limit of the 99% CI of 0.23. Both results from the sensitivity analyses were statistically significant at the 1% level adjusted for the interim analysis with p value < 0.001.

Table 6. Acute Serious Bacterial Infections Per subject-year (FAS)

| | **All Subjects (N = 44)** |
|---|---|
| Number of subjects in the analysis | 44 |
| Number of ASBI | 2 |
| Number of subjects with an event [n (%)] | 1 (2.3) |
| Rate of ASBI per subject-year (without adjustment of overdispersion) | |
| Mean Rate (SE) | 0.04 (0.028) |
| 99% Upper CI | 0.21 |
| p-value | <0.001 |

Dispersion parameter is given by the deviance divided by the degrees of freedom, which is equal to 0.347<1, so adjustment for overdispersion is not used.
Abbreviations: SE = Standard error of the Poisson mean, ASBI = acute serious bacterial infection (Infections which meet the protocol defined criteria for acute serious bacterial infection); n=number of subjects; N=total number of subjects; %=percentages are based on the total number of subjects in the full analysis set; CI=confidence interval.
Source: Adapted BLA 125402/818: Study 161503 Interim Study Report complete 2021June 04, Table 5, p.69.

#### 6.1.11.2 Analyses of Secondary Endpoints

***Number of all infections per subject-year***

A total of 160 infections were reported in 34 of 44 subjects (77.3%). The mean rate of all infections per subject-year was 3.20 with an upper limit of the 95% CI of 4.05. The most frequently reported infections (occurring in >10% subjects) by preferred term (PT) included: sinusitis (18 subjects, 40.9%), upper respiratory tract infection and viral upper respiratory tract infection (9 subjects each, 20.5%

each), pharyngitis streptococcal (7 subjects, 15.9%), influenza (6 subjects, 13.6%), otitis media (6 subjects, 13.6%) and acute sinusitis (5 subjects, 11.4%).

***Days missed from school/work due to infection or other illness***
The mean and median number of days missed from school/work was 5.0 and 2.5 days per subject, respectively. The mean number of days missed from school/work per subject year was 4.42 (95% CI: 2.81, 6.94).

***Days on antibiotics***
At the data freeze date for the interim analysis, a total of 113 courses of antibiotics were used by 28 subjects. Among which, 111 courses had ended, and 2 courses were ongoing. A median of 3.0 antibiotic courses were reported per subject. The median days on antibiotics during the treatment period was 34.5 days per subject. The mean days on antibiotics per subject year was 27.67 days. (95% CI: 18.69, 40.96)

***Number of hospitalizations due to infection and days hospitalized***
The mean rate of hospitalizations per subject year due to infection was 0.06 (95% CI: 0.02, 0.19). The mean number of days hospitalized per subject year was 0.22 (95% CI: 0.11, 0.43).

***Number of acute physician visits due to infection***
The mean and median number of acute physician visits per subject due to infection or other illness was 3.6 and 2.5, respectively. The mean rate of acute physician visits due to infection or other illness per subject year was 3.16 (95% CI: 2.39, 4.18).

### 6.1.11.3 Subpopulation Analyses

A total of 2 ASBIs were reported by 1 female subject (5.6%) and no ASBIs were reported in male subjects. One subject (4.3%) from the 6 to <12 years age group reported 2 ASBIs (bacterial pneumonia). No ASBIs were reported in the other two age groups. As most subjects were White, subgroup analyses by race were not informative.

### 6.1.11.4 Dropouts and/or Discontinuations

Among the 44 subjects enrolled and dosed in the study, 11 subjects did not complete the study. Among these 11 subjects, 5 subjects were followed for about 1 year or longer, 3 subjects for over half of a year, 2 subjects for 2-3 months and one subject for less than a month. None of these subjects had any ASBIs during the study. There was no reason to believe that these subjects would have abnormally high ASBIs rates after discontinuation and the conclusion would change. The results appeared to be reasonable.

### 6.1.12 Safety Analyses

#### 6.1.12.3 Deaths

No deaths were reported during the study.

#### 6.1.12.4 Nonfatal Serious Adverse Events

A total of 4 serious treatment emergent adverse events (TEAEs) (including infections) were reported in 4 subjects (9.1%):

- Infections and infestations (3 events in 3 [6.8%] subjects): 1 event each of adenovirus infection, *Clostridium difficile* colitis, and bacterial pneumonia
- Respiratory, thoracic, and mediastinal disorders (1 event in 1 [2.3%] subject): 1 event of tonsillar hypertrophy.

No safety concerns were raised by the 4 TEAEs that occurred during the study as of the cutoff date for the interim analysis, as none were considered by the investigators to be related to the study drug. However, 2 subjects were discontinued from the study due to TEAEs.

#### 6.1.12.5 Adverse Events of Special Interest (AESI)

One subject (2.3%), a 4-year-old female with specific antibody deficiency (Subject (b) (6) , developed a titer of ≥ 160 for binding antibodies against rHuPH20 at Epoch 2 Month 6. A similar result was observed at Month 9, Month 12, and Month 15 of Epoch 2. Anti-rHuPh20 binding antibody titers were 640, 1280, 2560, and 2560 at the Month 6, Month 9, Month 12, and Month 15 visits, respectively. The subject is completing additional 2 years of study treatment and assessments in Epoch 2, as per protocol, including ongoing assessments of antibodies against rHuPH20 – no safety concerns have been identified.

### 6.2 Trial #2 (Study 160603)

Study 160603 (GAMMAGARD LIQUID / KIOVIG and rHuPH20)
The protocol for Study 160603 was titled “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.” The final version of protocol was dated December 16, 2009.

This section focuses on the results from the pediatric subjects enrolled in the study. For other results, see statistical review of BLA 125402/0 by Chunrong Cheng, May 17, 2012.

#### 6.2.1 Objectives (Primary, Secondary, etc)

Primary Objective: to evaluate the efficacy of GAMMARGARD LIQUID/KIOVIG administered via the SC route after an administration of rHupH20 in preventing serious infections in subjects with PIDD.

Secondary Objective: to further assess efficacy and evaluate the tolerability of GAMMAGARD LIQUID/KIOVIG and rHuPH20 administered via the SC route.

### 6.2.2 Design Overview

Study 160603 was a prospective, open-label, non-controlled, multi-center study 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 PIDD. The study consisted of 2 study epochs:

- Study Epoch 1: once every 3 or 4 weeks, for 13 weeks, IV treatment with GAMMAGARD LIQUID/KIOVIG
- Study Epoch 2: 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 for 14 months, SC treatment with GAMMAGARD LIQUID/KIOVIG after administration of rHuPH20

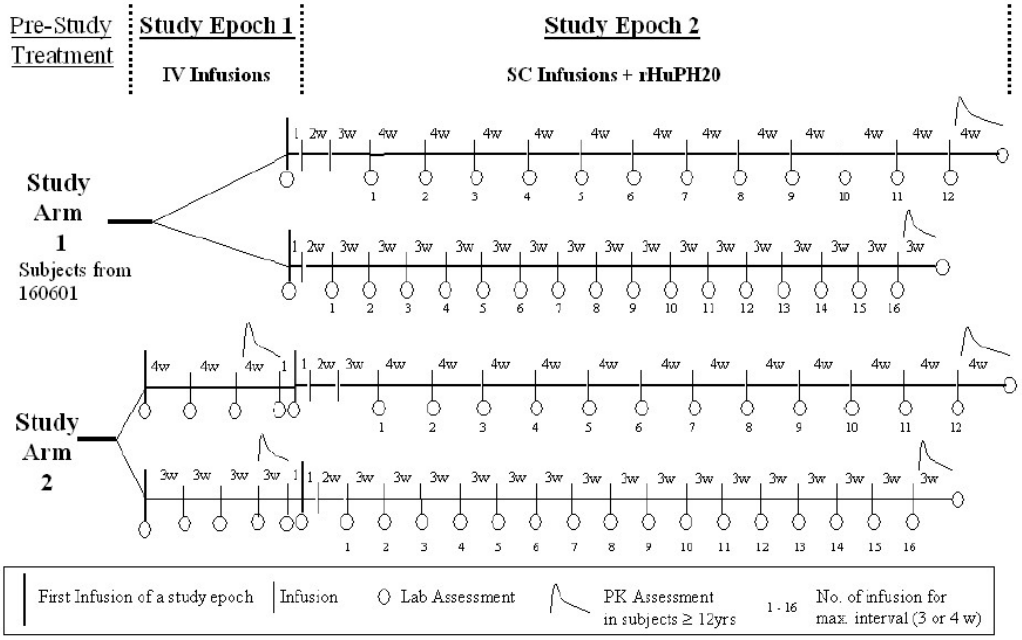
Subjects were enrolled into one of 2 study arms:

- Study Arm 1: Subjects only completed Study Epoch 2
- Study Arm 2: comprised all other subjects. These subjects completed Study Epoch 1 and Study Epoch 2

*Reviewer comment: The purpose of Study Epoch 1 was to perform a pharmacokinetic assessment of IV treatment with GAMMAGARD LIQUID/KIOVIG for comparison of the bioavailability of IV and SC treatment. Subjects who previously participated in Study 160601 had pharmacokinetic data for the IV treatment collected so they proceeded directly into Study Epoch 2 after enrollment in Study 160603.*

The study design overview is summarized in Figure 2.

Figure 2: An overview of the study design for Study 160603




Source: Original BLA 125402/818.0: Study 160603 Statistical Analysis Plan, Version 3.2, Section 3 Figure, p.6.

### 6.2.3 Population

Selected Inclusion Criteria:

- Subject is 2 years or older at the time of screening
- Subject has been diagnosed with a PID disorder requiring antibody replacement as defined by WHO criteria
- Subject has completed or is about to complete Baxter Clinical Study Protocol No. 160601 or has 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 BW/4 weeks
- Subject has a serum trough level of IgG > 4.5 g/L at the last documented determination
- If female of childbearing potential, subject presents with a negative urine pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
- Subject is willing and able to comply with the requirements of the protocol.

*Reviewer comment: Study 160603 enrolled both adult and pediatric subjects with PIDD. However, here I separated the results by adults (aged ≥ 16 years) and pediatrics (aged between 2 and 15 years).*

### 6.2.4 Study Treatments or Agents Mandated by the Protocol

***Epoch 1:***
*IP:* GAMMAGARD LIQUID/KIOVIG
*Route of administration and schedule*:

- Administered via IV route every 3 or 4 weeks with a dose the same as during pre-study period (minimum 300 mg/kg BW/4 weeks).

***Epoch 2:***
*IP:* GAMMAGARD LIQUID/KIOVIG and rHuPH20
*Route of administration and schedule:*

- GAMMAGARD LIQUID/KIOVIG: administered via SC route, starting with a ramp up: treatment interval 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 the pre-study period); with a dose of 108% of the IV dose utilized during Study Epoch 1
- rHuPH20: administered via SC route at a minimum dose of 75 U/gram GAMMAGARD LIQUID/KIOVIG

### 6.2.6 Sites and Centers

The study included a total of 15 sites (14 sites in the US and 1 site in Canada). The pediatric subjects were enrolled in 10 sites and the adult subjects in 12 sites.

### 6.2.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint and secondary efficacy endpoints: the same as Study 161503.

Criteria for study success: the same as Study 161503.

### 6.2.9 Statistical Considerations & Statistical Analysis Plan

Statistical Hypotheses
The same as Study 161503

Sample Size Estimation
Assuming a true ASBI rate of 0.7 per year, a sample size of 88 would be enough to test the null hypothesis at a one-sided significance level of 0.01 with 85% power.

Analysis Populations

- Full analysis set (FAS), the intent-to-treat population, includes all subjects who had been exposed to either or both study drugs and who provided data for the primary endpoint for any period of time.
- Per-protocol set (PPS): A subset of the full analysis set including only subjects who completed at least 6 months of SC treatment after the ramp-up.

- The safety population includes all subjects who received at least one infusion of the either or both study drugs during Epoch 1 and Epoch 2.

*Reviewer comment: Here the intent-to-treat population was defined as all subjects who had been exposed to either or both study drugs and who provided data for the primary endpoint for any period of time. This may introduce selection bias as the definition may exclude subjects who were exposed but did not have data for the primary endpoint.*

Statistical Methods

***Primary efficacy endpoint:***

The same as Study 161503. However, the observation period for each subject started with the day of the first SC infusion at the final infusion interval (i.e., after the ramp-up) and ended with the day of the End of Study visit. The length of the observation period was expressed in years by dividing the number of days in the observation period by the average length of the year, i.e., 365.2425 days.

Sensitivity analyses:

1. Replace FAS with PPS and re-run the analysis
2. Use multiple imputations for the infection rate in unobserved time periods as follows
    a. Subjects who terminate the study for the increased frequency/severity of infections, use twice the highest infection rate observed in subjects who completed more than 2 months in the same season
    b. Subjects who did not leave the study for increased frequency/severity of infections, use the subject's rate in the season. If more than 2 months were observed, use the rate observed in subjects who completed 2 months or more in the same season
3. Analyze a full year in the subset of subjects who completed a full year. Specifically, the first 365 days following the first SC administration were selected.

***Secondary efficacy endpoints***

*Number of all infections and health resource utilization:*

Point estimates and 95% CIs for the annual rates were calculated using the same methodology as the primary efficacy endpoint. The same sensitivity analyses as the primary efficacy endpoint were planned.

Subgroup analyses

In this review memo, the results are separated by adults and pediatrics.

Interim Analysis

An interim analysis was planned of data from subjects in Study Arm 1 who have completed Epoch 2 by the end of May 2010. However, no adjustment for Type 1

error rate inflation was planned. It was expected that this analysis would include most of the subjects in this study arm. This review memo reviews the completed study report.

Handling of Missing data
No missing data was imputed for the primary efficacy analysis.

### 6.2.10 Study Population and Disposition

#### 6.2.10.1 Populations Enrolled/Analyzed

Eighty-nine subjects were screened, and 87 subjects entered the study. Two adult subjects failed the screening so were not treated. Eighty-one subjects were included in the FAS, with 20 pediatric subjects and 61 adults.

Table 7: Number of subjects in each analysis set

| | Pediatrics (≤15 years old) | Adults (≥16 years old) | Total |
|---|---|---|---|
| Number of enrolled subjects | 24 | 63 | 87 |
| Number of subjects in the FAS | 20 | 61 | 81 |
| Number of subjects in the PPS | 18 | 56 | 74 |
| Number of subjects in the safety analysis set | 24 | 63 | 87 |

Abbreviations: FAS=full analysis set; PPS=per-protocol set.

6.2.10.1.1 Demographics
Key demographic characteristics are summarized in Table 8. Among the pediatric subjects, the median age of subjects at the signing of the informed consent was 11 years (range: 2 to 15 years). Eleven subjects (52.3%) were in the age category of 6 to <12 years, 10 subjects (27.3%) in the 12 to <16 years category, and 3 subjects (20.5%) in the 2 to <6 years category. A total of 15 subjects (59.1%) were male and 9 subjects (40.9%) were female. Twenty-three subjects (90.9%) were white, and one subject (4.5%) was black or African American. Most subjects were not Hispanic or Latino (21 [88.6%] subjects). The median height was 145 cm (range: 94 to 175 cm) and the median weight was 40.7 kg (range: 15 to 83.7 kg).

Table 8. Demographic Characteristics. Study 160603: Safety Analysis Set.

| **Subject Characteristics** | **Statistic** | **Pediatrics (N=24)** | **Adults (N=63)** |
|---|---|---|---|
| Age (Years) | Mean (SD) | 10.38 (3.56) | 45.79 (17.03) |
| | Median | 11.00 | 48 |
| | Min, Max | (2.00,15.00) | (16, 78) |
| Age Category (Years) | 2 to <6 years | 3 (12.5) | 0 |
| | 6 to <12 years | 11 (45.8) | 0 |
| | 12 to <16 years | 10 (41.7) | 0 |
| Sex [n (%)] | Male | 15 (62.5) | 29 (46.0) |
| | Female | 9 (37.5) | 34 (54.0) |
| Race [n (%)] | American Indian or Alaska Native | 0 | 1 (1.59) |
| | Asian | 0 | 3 (4.76) |
| | Black or African American | 1 (4.2) | 1 (1.59) |
| | Native Hawaiian or Other Pacific Islanders | 0 | 0 |
| | White | 23 (95.8) | 56 (88.89) |
| | Other | 0 | 0 |
| | Multiple | 0 | 2 (3.17) |
| Ethnicity [n (%)] | Hispanic or Latino | 3 (12.5) | 5 (7.94) |
| | Not Hispanic or Latino | 21 (87.5) | 58 (92.06) |
| Height (cm) | Mean (SD) | 139.73 (20.62) | 166.87 (13.60) |
| | Median | 145 | 167 |
| | Min, Max | (94, 175) | 108, 193 |
| Weight (kg) | Mean (SD) | 41.58 (18.57) | 74.57 (20.27) |
| | Median | 40.70 | 70.70 |
| | Min, Max | 15, 83.7 | (44.50, 135.90) |

Abbreviations: N=total number of subjects; cm=centimeters; kg=kilogram; n=number of subjects; SD=standard deviation; %=percentages are based on the total number of subjects in the full analysis set.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
See statistical review of BLA 125402/0 by Chunrong Cheng, May 17, 2012

6.2.10.1.3 Subject Disposition
Overall, 16 subjects withdrew or were discontinued from the study and 3 subjects (adults) reduced their participation to safety follow-up study. Of the 16 subjects, 6 subjects were pediatric subjects. Four pediatric subjects requested withdrawal and 2 pediatric subjects were discontinued from the study due to adverse events.

For more details, see statistical review of BLA 125402/0 by Chunrong Cheng, May 17, 2012.

### 6.2.11 Efficacy Analyses

#### 6.2.11.1 Analyses of Primary Endpoint(s)

Three validated ASBIs were reported in the study; all occurred in the pediatric subjects. Two validated ASBIs (Subject (b) (6) of age 11 and Subject (b) (6) of age 6) were reported during the primary observation period. One validated ASBIs (Subject (b) (6) of age 14) occurred during the ramp-up period. No validated ASBIs was reported in the adult subjects. The number of VASBIs per subject year was 0.099 with an upper 99% CI bound of 0.51. The study success criterion was met for the pediatric subjects. Similar conclusion was observed in the PP analysis set. The primary efficacy result is summarized in Table 9 below.

Table 9. Validated Acute Serious Bacterial Infections in the FAS during the primary observation period.

| | Pediatrics ≥ 2 to < 16 years (N=20) | Adults ≥16 years (N=61) | Total (N=81) |
|---|---|---|---|
| Total number of ASBIs | 2 | 0 | 2 |
| Number of subjects with an event [n (%)] | 2 (10%) | 0 | 2 (2.47%) |
| Number of ASBIs per subject year (SE) | 0.099 (0.0699) | 0 | 0.025 (0.0172) |
| 99% Upper CI | 0.51[a] | 0.075[b] | 0.13[c] |

Abbreviations: ASBIs=acute serious bacterial infections; n=number of subjects; %=percentages are based on the total number of subjects; SE=standard error; CI=confidence interval
[a] Dispersion parameter, given by the deviance divided by the degrees of freedom, was equal to 0.4673<1, so adjustment for overdispersion was not needed.

[b] The upper limit of rate of SBI was calculated as $\chi^2_{2(Y+1),\,(1-\alpha/2)}$ / (2* total exposure duration), where Y is the observed number of ASBIs and $\chi^2_{2(Y+1),\,(1-\alpha/2)}$ is the chi-square quantile for upper tail probability on $_{2(Y+1)}$ degrees of freedom
[c] Dispersion parameter, given by the deviance divided by the degrees of freedom, was equal to 0.1807<1, so adjustment for overdispersion was not needed.

*Reviewer's comment: The study report and the label included the results obtained with adjustment for overdispersion. The reported upper bound was 0.029 for the combined analysis and 0.30 for the pediatric subjects if adjustment for overdispersion was made. Here, to be consistent with the methods used in Study 161503, I report the results without adjustment for overdispersion since the dispersion parameter was less than 1.*

### 6.2.11.2 Analyses of Secondary Endpoints

***Number of all infections per subject-year***

A total of 53 infections were reported in 17 of the 20 pediatric subjects (85.0%). The mean rate of all infections per subject-year was 2.62 with an upper limit of the 95% CI of 3.83. A total of 189 infections were reported in 54 of the 61 adult subjects (88.5%). The mean rate of all infections per subject year was 3.08 with an upper limit of the 95% CI of 3.68.

Table 10. All Infections (FAS)

| | Pediatrics ≥ 2 to < 16 years (N=20) | Adults Age ≥16 (N=61) | Total (N=81) |
|---|---|---|---|
| Total number of infections | 53 | 189 | 242 |
| Number of subjects with an event [n (%)] | 17 (85.0%) | 54 (88.5%) | 71 (87.65) |
| Number of all infections per subject year (SE) | 2.62 (0.51) | 3.08 (0.28) | 2.97 (0.25) |
| 95% two-sided CIs | (1.79, 3.83) | (2.58, 3.68) | (2.52, 3.49) |

Abbreviations: N=total number of subjects; n=number of subjects; %=percentages are based on the total number of subjects; SE=standard error; CI=confidence interval

***Days missed from school/work due to infection or other illness***

The mean number of days missed from school/work per subject year was 6.13 (95% CI: 3.73, 10.06) for the pediatric subjects and 2.38 (95% CI: 1.60, 3.54) for the adult subjects.

***Days on antibiotics***

The mean days on antibiotics per subject year was 14.78 days (95% CI: 9.30, 23.48) for the pediatric subjects and 22.07 (95% CI: 16.29, 29.91) for the adult subjects.

***Days hospitalized due to infection***
The mean number of days hospitalized per subject year was 0.099 (95% CI: 0.025, 0.40) for the pediatric subjects, and 0.016 (95% CI: 0.0023, 0.12) for the adult subjects.

***Number of acute physician visits***
The mean rate of acute physician visits due to infection or other illness per subject year was 2.92 (95% CI: 2.16, 3.94) for the pediatric subjects, and 5.40 (95% CI: 4.21, 6.93) for the adult subjects.

Table 11: Healthcare utilization (FAS)

| Parameters/ Age | Pediatrics ≥ 2 to <16 years (N=20) | Adults ≥ 16 to ≤ 75 years (N=61) | Total (N=81) |
|---|---|---|---|
| | Annual rate per subject year (SE) [two-sided 95% CI] | Annual rate per subject year (SE) [two-sided 95% CI] | Annual rate per subject year (SE) [two-sided 95% CI] |
| Number of days off school/work | 6.13 (1.55) [3.73, 10.06] | 2.38 (0.48) [1.60, 3.54] | 3.31 (0.54) [2.41, 4.55] |
| Days on antibiotics | 14.78 (3.49) [9.30, 23.48] | 22.07 (3.42) [16.29, 29.91] | 20.26 (2.68) [15.63, 26.26] |
| Days in hospital due to infection | 0.099 (0.0699) [0.025, 0.40] | 0.016 (0.016) [0.0023, 0.12] | 0.037 (0.021) [0.012, 0.11] |
| Number of acute physician visits due to infections | 2.92 (0.45) [2.16, 3.94] | 5.40 (0.69) [4.21, 6.93] | 4.78 (0.52) [3.86, 5.92] |

Abbreviations: N=total number of subjects; %=percentages are based on the total number of subjects; SE=standard error; CI=confidence interval

### 6.2.11.3 Subpopulation Analyses

Subgroup analyses of infection rates by pediatrics and adults are shown in the tables 9-10. The results appeared to be similar between adults and pediatric subjects.

Additional subgroup analyses by sex, race, or the three age categories among pediatric subjects might not be informative due to the small samples in those subgroups.

### 6.2.11.4 Dropouts and/or Discontinuations

No missing data were imputed for the subjects who did not complete the study. However, sensitivity analyses for the primary efficacy endpoint as prespecified in the SAP were conducted to assess the robustness of the conclusion. For more details, see statistical review of BLA 125402/0 by Chunrong Cheng, May 17, 2012.

### 6.2.12 Safety Analyses

### 6.2.12.3 Deaths

No deaths occurred in this study.

### 6.2.12.4 Nonfatal Serious Adverse Events

A total of 18 SAEs were reported, none of which were considered by the investigators to be possibly or probably related to the study drug(s). During Epoch 1, 4 SAEs occurred in 3 adult subjects. During Epoch 2 excluding the ramp-up, 11 SAEs occurred in 6 adult subjects and 2 pediatric subjects (2 in Subject (b) (6) aged 14 years and one in Subject (b) (6) aged 15 years). During the Epoch 2 ramp-up, 3 SAEs occurred in 2 adult subjects and 1 pediatric subject (Subject (b) (6) aged 14 years).

### 6.2.12.5 Adverse Events of Special Interest (AESI)

Eleven subjects had developed anti-rHuPH20 antibody titers ≥1:160 (Subjects (b) (6) . Of the 11 subjects, 2 were pediatric subjects (Subject (b) (6) of 14 years old, and Subject (b) (6) of 13 years old).

## 6.3 Trial #3 (Study 160902)

The protocol was titled “Long-Term Tolerability and Safety of Immune Globulin Subcutaneous (IGSC) Solution Administered Subcutaneously Following Administration of Recombinant Human Hyaluronidase (rHuPH20) in Subjects with Primary Immunodeficiency Diseases.” The final version (Version 5) was dated May 24, 2012.

### 6.3.1 Objectives (Primary, Secondary, etc)

Primary Objective

- to evaluate the long-term tolerability and safety of IGI, 10% given SC after an SC administration of rHuPH20 in subjects with PIDD.

Secondary Objective:

- To monitor the long-term efficacy of IGI, 10% given SC after an administration rHuPH20 in subjects with PIDD.
- To evaluate the effect of varying the dose frequency of IGI, 10% /rHuPH20 on IgG trough levels.

- To assess the practicability of treating PIDD with IGI, 10% given SC after an administration of rHuPH20 when treatment occurs in a home treatment environment.

### 6.3.2 Design Overview

Study 160902 was a Phase 3, prospective, non-controlled, open-label, multicenter study to assess the long-term safety, tolerability, and practicability of the SC treatment with IGI, 10% facilitated with rHuPH20 in 66 subjects with PIDD who had completed Study 160603. This study was an extension of Study 160603; therefore, subjects and study sites of Study 160603 were eligible to participate in Study 160902.

### 6.3.3 Population

The main criteria for inclusion were completion or about to complete Study160603.

### 6.3.4 Study Treatments or Agents Mandated by the Protocol

Prior to the Safety Follow-up Period:
Subjects were administered SC infusions of IGI, 10% (Preceded by SC rHuPH20) at the same doses as at the last infusion in Epoch 2 of Study 160603. To evaluate the effect of varying the dose frequency of IGSC, 10% /rHuPH20 on IgG trough levels, subjects were requested to change their drug administration interval from a 4- or 3-week interval to a 2-week interval (receiving a 2-week dose), provided both the subject and the investigator agreed that the change was appropriate. This new treatment interval started after 3 infusions on the 4- or 3-week interval and was maintained for a minimum of 4 months.

During the Safety Follow-up Period:
No rHuPH20 drug product was used, but IGI, 10% was administered either SC (without rHuPH20) or IV

### 6.3.6 Sites and Centers

The study sites were the same as those in Study 160603.

### 6.3.8 Endpoints and Criteria for Study Success

Selected primary safety endpoints:

- SAEs: annual rate of SAEs, related and not related
- Antibodies to rHuPH20: number and proportion of all subjects who developed antibodies and neutralizing antibodies to rHuPH20

Selected secondary efficacy endpoints:

- SBI rate: annual rate of SBI calculated per subject
- Rate of all infections: annual rate of all infections by organ system calculated per subject

### 6.3.9 Statistical Considerations & Statistical Analysis Plan

Statistical Considerations of Study 160603 and 160902 are identical.

### 6.3.10 Study Population and Disposition

#### 6.3.10.1 Populations Enrolled/Analyzed

All 66 enrolled subjects were included.

6.3.10.1.1 Demographics

Sixty-six subjects were enrolled in the study. Of the 66 subjects, 11 were pediatric subjects and 55 were adults. Subjects enrolled in this study were almost evenly distributed by sex (51.5% males and 48.5% females). Of the 66 enrolled subjects, 59 (89.4%) were White, 3 (4.5%) were Asian and 2 (3.0%) were Black or African American. Most subjects (92.4%) were not of Hispanic or Latino ethnicity. The median age was 43.0 years (range: 9-80 years). Among the 11 pediatric subjects, 4 were between 2 and <12 years old and 7 were between 12 and <16 years old.

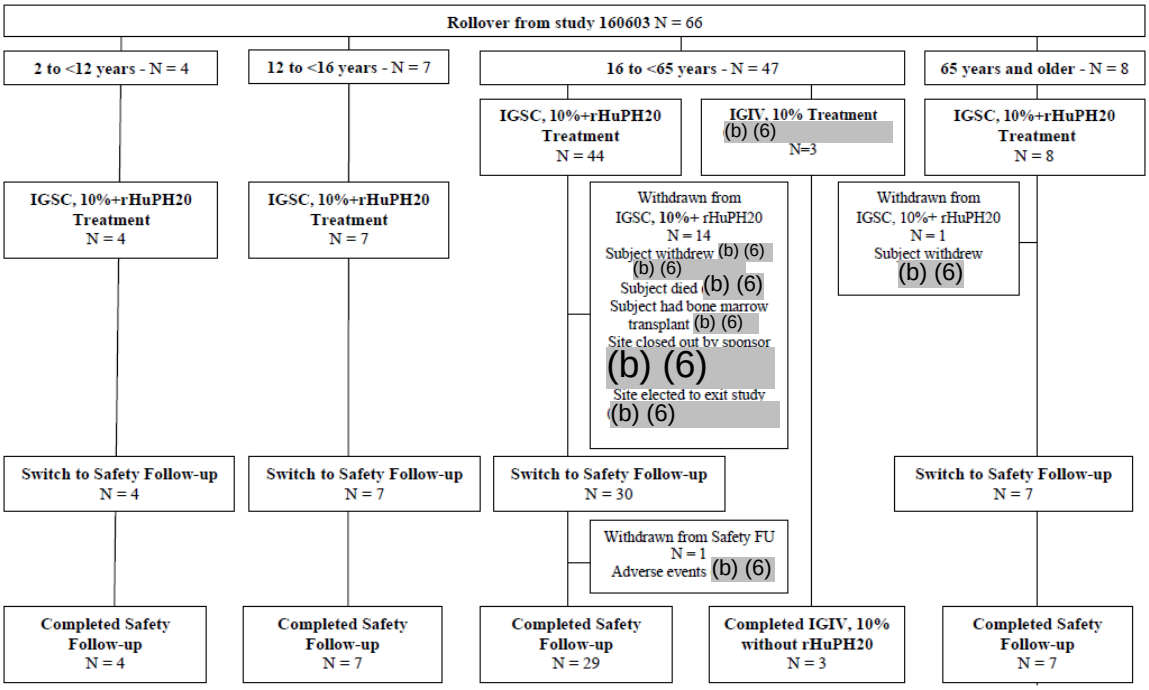
6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Common variable immunodeficiency was the most commonly diagnosed PID (39/66 subjects), followed by Humoral immune deficiency (6/66 subjects) and hypogammaglobulinemia (6/66 subjects).

6.3.10.1.3 Subject Disposition

Sixty-three subjects were treated with IGSC, 10% with rHuPH20; 3 subjects received IGIV, 10%. Of the 63 subjects under IGSC, 10% with rHuPH20 treatment, 15 withdrew or were discontinued from the study. All 11 pediatric subjects completed the study. Figure 3 provides a detailed overview of subject disposition by age group.

Figure 3: Disposition of subjects.




Source: BLA 125402/818. Module 5.3.3.2 Patient PK and initial Tolerability and safety of Immune Globulin Study Report, Figure 1, Page 40 of 864.

### 6.3.11 Efficacy Analyses

#### 6.3.11.1 Analyses of Primary Endpoint(s)

No primary efficacy analyses were performed as the primary objective of this study was to assess the long-term tolerability and safety of IGI, 10% given SC after an SC administration of rHuPH20 in subjects with PIDD

#### 6.3.11.2 Analyses of Secondary Endpoints

VASBI

Two VASBIs were reported during the observation period which began with the day of the first SC infusion until subjects were switched to the Safety Follow-up period or left the study. Subject (b) (6) of 66 years of age experienced 1 VASBI of pseudomonas aeruginosa pneumonia. The other VASBI was bacterial pneumonia reported for Subject (b) (6) of 16 years of age. No pediatric subjects experienced VASBIs.

#### 6.3.11.3 Subpopulation Analyses

There were only 11 pediatric subjects in the study. Subgroup analyses by sex, race and age categories were not informative.

#### 6.3.11.4 Dropouts and/or Discontinuations

Statistical techniques were not used to handle dropouts and discontinuation.

### 6.3.12 Safety Analyses

#### 6.3.12.3 Deaths

Two subjects died. One subject (Subject (b) (6)) died from toxicity to various agents on study day 135. The other subject (Subject (b) (6)) had cardiac arrest approximately 4 weeks from completion of the study. Both subjects were adults.

#### 6.3.12.4 Nonfatal Serious Adverse Events

In total, 11 subjects experienced SAEs during the study (Subjects (b) (6), (b) (6) One subject experienced an SAE after study completion (Subject (b) (6) . Of these subjects, 1 was a pediatric subject (Subject (b) (6) of age 15 years).

#### 6.3.12.5 Adverse Events of Special Interest (AESI)

A total of 13/66 HTDS subjects developed anti-rHuPH20 antibody titers ≥1:160 in Study 160603 or in Study 160902. In 6 of these 11 subjects who had developed anti-rHuPH20 antibody titers ≥ 1:160 in Study 160603 (Subjects (b) (6) , antibody titers ≥ 1:160 persisted in Study (b) (6). Subject (b) (6) was a pediatric subject of age 15 at enrollment of Study (b) (6)

### INTEGRATED OVERVIEW OF EFFICACY

The efficacy of subcutaneous (SC) infusion of human normal immunoglobulin (Immune Globulin, 10% or IG 10%) facilitated by prior administration of Recombinant Human Hyaluronidase (rHuPH20), the combination called HYQVIA, in pediatric subjects aged 2 to <16 years with primary immunodeficiency disease (PIDD) was assessed in an integrated analysis of efficacy. This integrated analysis includes the pediatric subject population of Study 160603 (a phase 3 pivotal study of efficacy, tolerability and pharmacokinetic (PK) comparison of IG 10% administered intravenously [IV] or SC with rHuPH20) and pediatric Study 161503 (a phase 3 study of IG 10% and rHuPH20 investigating efficacy, safety, tolerability, immunogenicity, PK and other parameters in pediatric subjects).

The primary endpoint of the integrated efficacy analysis of Study 160603 and Study 161503 is the rate of acute serious bacterial infections (ASBIs), defined as the mean number of ASBIs per subject-year in the intent-to-treat population (i.e., Full Analysis Set [FAS]). Secondary endpoints are the rate of all infections, healthcare resource utilization, and immunoglobulin G (IgG) trough levels.

## 7.1 Indication #1

### 7.1.1 Methods of Integration

The data from the pediatric study 161503 and from the pediatric subjects in Study 160603 were used as the basis of the claim of efficacy of HYQVIA for treatment of PIDD in pediatrics. The integrated analyses were based on the pooled data from the two studies. The analysis was based on a generalized linear model assuming the Poisson distribution for each outcome, with the natural logarithm of the length of the observation period in years used as an offset. No meta-analysis methods were not used.

In this integrated summary of efficacy (ISE), the FAS consisted of all subjects between 2 years to < 16 years old at baseline who were exposed to any study drugs and provided data for the primary endpoint for any period of time in either one of the studies. In Study 161503, the observation period was counted from start of initial dose of IG 10% and rHuPH20 through end of Epoch 2. In Study 160603, the observation period started with the day of the first SC infusion at the final infusion interval in Study Epoch 2 and ended with the day of the End of Study visit.

### 7.1.2 Demographics and Baseline Characteristics

The demographic characteristics of the pediatric patients in the 2 clinical studies Study 160603 and Study 161503 are described in Tables x in Section 6.

### 7.1.4 Analysis of Primary Endpoint(s)

Among the 64 pediatric subjects in Study 160603 and in Study 161503, 4 ASBIs of bacterial pneumonia were reported in three subjects (4.7%). This resulted in a mean rate of 0.06 (SE 0.028, upper limit of 99% CI 0.18) ASBIs per subject-year for pediatric subjects.

### 7.1.5 Analysis of Secondary Endpoint(s)

*All infections*
A total of 213 infections were reported in 51 of 64 subjects (79.7%). The mean rate of all infections per subject-year was 3.03 (SE 0.352, [95% CI: 2.42, 3.81]). Infections most frequently reported were sinusitis in 24 subjects (37.5%), upper respiratory tract infection in 15 subjects (23.4%), viral upper respiratory tract infection in 10 subjects (15.6%), influenza and streptococcal pharyngitis in 7 subjects (10.9%) each.

*Healthcare Resource Utilization*
Table 12 summarizes the integrated results of the healthcare resource utilization. The mean number of days missed from school/work per subject year was 4.91

(95% CI: 3.49, 6.92). The mean days on antibiotics per subject year was 23.95 days (95% CI: 17.41, 32.96). The mean number of days hospitalized per subject year was 0.19 (95% CI: 0.10, 0.33). The mean rate of acute physician visits due to infection or other illness per subject year was 3.09 (95% CI: 2.49, 3.83).

Table 12: Healthcare Resource Utilization (Studies 160603, 161503: Full Analysis Set) Age group: 2 to < 16 years

| Parameter | Pediatrics 2-15 years (N=64) | |
|---|---|---|
| | Mean Rate per subject year (SE) | 95% CI |
| Days not able to go to school/work or to perform normal daily activities due to infections or other illnesses | 4.42 (0.97) | (2.88, 6.79) |
| Days on antibiotics | 27.67 (4.91) | (19.54, 39.18) |
| Number of acute physician visits for infections | 3.16 (0.41) | (2.45, 4.07) |
| Days in hospital due to infection | 0.22 (0.0696) | (0.12, 0.41) |

Abbreviations: N=total number of subjects; %=percentages are based on the total number of subjects; SE=standard error; CI=confidence interval

### 7.1.7 Subpopulations

Of the 64 pediatric subjects, 43 subjects were between 2 and < 12 years old, and 21 subjects were between 12 and 15 years old. Subgroup analyses did not provide any notable differences across the age categories. In addition, since there were limited sample sizes in the age categories, these subgroup analyses might not be reliable.

### 7.1.11 Efficacy Conclusions

SC administration of IG 10% with rHuPH20 was effective in preventing bacterial infections in pediatric patients 2 to <16 years of age with PIDD. Overall, for the integrated results of Studies 160603 and 161503 rates were below 1.0 validated ASBIs/subject/year, the threshold specified as providing substantial evidence of efficacy by the relevant regulatory guideline. The mean rate of all infections per subject-year was 3.2 in pediatric subjects aged 2 to <16 years. Days of hospitalization due to infection (0.19 per subject-year), number of acute physician visits due to infections (3.09 per subject-year), days not able to go to school/work or to perform normal daily activities due to infections or other illnesses (4.91 per subject-year), and days on antibiotics (23.95 per subject-year) were low across pediatric subjects 2 to <16 years of age.

# 10. CONCLUSIONS

## 10.1 Statistical Issues and Collective Evidence

I verified the primary efficacy and some secondary efficacy results of the pivotal pediatric study 161503 and the efficacy results separated by pediatrics and adults for Study 160603.

Study 161503 was a Phase 3, open-label, prospective, non-controlled, multicenter study. The study consisted of 2 treatment periods (Epoch 1 and Epoch 2) and a 1-year safety follow-up, if needed. A total of 44 pediatric subjects (2-15 years old) were enrolled in the study. One subject reported 2 ASBIs of bacterial pneumonia. The number of ASBIs per subject-year was 0.04, with an upper limit of the 99% CI of 0.21. The study demonstrated a SBI rate per person-year that was statistically significantly lower than threshold rate of 1.0 ASBI per subject-year, the threshold specified as providing substantial evidence of efficacy by the FDA Guidance to Industry (2008): Safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency.

Similar efficacy results were seen in the pediatric subjects from Study 160603. The study was a prospective, open-label, non-controlled, multi-center study. The study consisted of 2 study epochs. In study Epoch 1, subjects received IV treatment with GAMMAGARD LIQUID/KIOVIG for 13 weeks. In study Epoch 2, subjects received SC treatment with GAMMAGARD LIQUID/KIOVIG after administration of rHuPH20 starting with a ramp-up with treatment intervals of 1 week, then 2 weeks, then 3 weeks, (then 4 weeks if applicable) and once every 3 or 4 weeks for 14 months after the ramp-up period. Eighty-seven subjects were enrolled in the study but only 81 subjects were included in the primary efficacy analysis. Of the 81 subjects, 20 were pediatric subjects and 61 were adults. Three validated ASBIs were reported in the study; all occurred in the pediatric subjects. The number of VASBIs per subject year was 0.099 with an upper 99% CI bound of 0.51.

Among the 64 pediatric subjects in Study 160603 and in Study 161503, 4 ASBIs of bacterial pneumonia were reported in three subjects. This resulted in a mean rate of 0.06 ASBIs per subject-year with an upper 99% CI bound of 0.18 for pediatric subjects. A total of 213 infections were reported in 51 of 64 subjects. The mean rate of all infections per subject-year was 3.03 (SE 0.352, upper limit of 95% CI 3.67). The mean number of days missed from school/work per subject year was 4.91 (95% CI: 3.49, 6.92). The mean days on antibiotics per subject year was 23.95 days (95% CI: 17.41, 32.96). The mean number of days hospitalized per subject year was 0.19 (95% CI: 0.10, 0.33). The mean rate of acute physician visits due to infection or other illness per subject year was 3.09 (95% CI: 2.49, 3.83).

No deaths were reported in Studies 161503 and 160603. Two subjects died in Study 160902. One subject died from toxicity to various agents on study day 135. The other subject had cardiac arrest approximately 4 weeks from completion of the study. Both subjects were adults.

In Study 161503, a 4-year-old female developed a titer of ≥ 160 for binding antibodies against rHuPH20 and is currently completing additional 2 years of follow up. In Study 160603, 11 subjects had developed anti-rHuPH20 antibody titers ≥1:160. Of the 11 subjects, 2 were pediatric subjects. One of the pediatric subjects continued to experience anti-rHuPH20 antibody titers ≥ 1:160 in Study 160902. A total of 13/66 subjects had anti-rHuPH20 antibody titers ≥1:160 in Study 160902.

## 10.2 Conclusions and Recommendations

Based on the efficacy results of the pivotal study 161503 and the combined efficacy results of pediatric subjects from Studies 161503 and 160603, substantial statistical evidence of efficacy supports approval of the proposed indication of treatment of PI in adult and pediatric subjects (2 years of age and older). The studies demonstrated a SBI rate per person-year that was statistically significantly lower than threshold rate of 1.0 ASBI per subject-year. However, there might be some safety concerns regarding use of HYQVIA and development of anti-rHuPH20 antibody titers. So far there are limited data to know whether these safety concerns potentially outweigh the benefit of the product.