Summary Basis for Regulatory Action

Date: September 13, 2016
From: Jennifer L. Reed, Chair of the Review Committee
BLA/ STN#: STN 125596/0
Applicant Name: Baxalta, Inc., Bannockburn, IL USA
Date of Submission: September 14, 2015
PDUFA Goal Date: September 13, 2016
Proprietary Name/ Established Name: Cuvitru™/ Immune Globulin Subcutaneous (Human), 20% Solution
Indication: Treatment of Primary Immune Deficiency Disorders
Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Jay S. Epstein, M.D., _____

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Offices Signatory Authority: Mary A. Malarkey, _____

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Material Reviewed/ Consulted Specific documentation used in developing the SBRA Reviewer Name – Document(s) Date
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1. Introduction

Baxalta, Inc. submitted an original biologics license application (BLA) to seek U.S. licensure for Immune Globulin Subcutaneous (Human), 20% Solution. The intended commercial product is presented in liquid form, in single-use glass vials with product fill sizes of 5mL to 40mL. The proprietary name of the product to be marketed in the U.S. is Cuvitru™. The product is indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older.

Cuvitru is manufactured from large pools of human plasma which are processed to the intermediate (b) (4) at Baxalta's facilities in (b) (4) . Testing of the (b) (4) intermediate occurs at the (b) (4) facility (b) (4) , and at Baxalta's (b) (4) facility in (b) (4) . Further manufacture of the (b) (4) intermediate into final product occurs in Baxalta's facility in (b) (4) . Release and stability testing is carried out at the (b) (4) facilities. All facilities for the manufacture of Cuvitru have been inspected and are FDA licensed.

The manufacturing process for Cuvitru is derived from the manufacturing process of the parent product, Immune Globulin Infusion (Human) 10% Solution (IGI, 10%) licensed in the United States as Gammagard Liquid (BLA STN 125105, licensed April 27, 2005). Upstream manufacturing of Cuvitru is (b) (4) , including Cohn-Oncley cold alcohol fractionation, cation and anion chromatography, solvent-detergent and nanofiltration viral clearance steps, through a downstream (b) (4) step. The (b) (4) and concentrated to 20% during product formulation in 0.25M glycine, prior to low pH hold as a final viral clearance step. Cuvitru is an isotonic solution formulated without preservatives, salts or sugars. The drug product is supplied in 5 mL (1 g), 10 mL (2 g), 20 mL (4 g), and 40 mL (8 g) sizes in (b) (4) glass vials with (b) (4) bromobutyl rubber stoppers. Stability studies demonstrated that the drug product is stable for up to 36 months stored at not more than (NMT) 5°C, and 12 months when stored at NMT 25°C.

2. Background

An original BLA from Baxalta, Inc. was received by CBER on September 14, 2015, requesting U.S. licensure of an Immune Globulin Subcutaneous (IGSC) (Human) 20% Solution product, trade name Cuvitru, and received a standard 10 month BLA review schedule.

The BLA included new data from two prospective, open-label, historic controlled, multicenter clinical trials that were submitted to provide clinical evidence for the safety and effectiveness of Cuvitru. One, Study 170904, was conducted in North America under BB-IND 14505 and the other, Study 170903, was conducted in Europe, not under the IND. Both studies evaluated the efficacy, safety, tolerability, and pharmacokinetics

(PK) of Cuvitru in a combined total of 126 subjects with PI. Also included were data from a third study, Study 160601, a prospective, open-label, historic-controlled, multicenter U.S. study in 49 male and female subjects aged ≥2 years with PI that investigated the tolerability and PK of Gammagard Liquid when administered SC vs. intravenously (IV). Study 160601 was not conducted using the final drug product, i.e. Cuvitru, and therefore the data are supportive but do not provide clinical evidence for Cuvitru's safety and effectiveness.

3. Chemistry, Manufacturing and Controls (CMC)

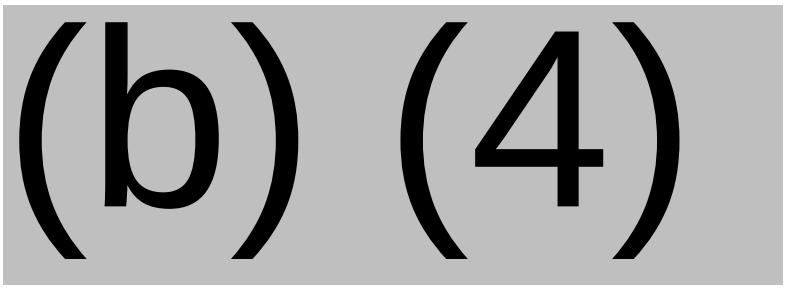
a) Product Quality

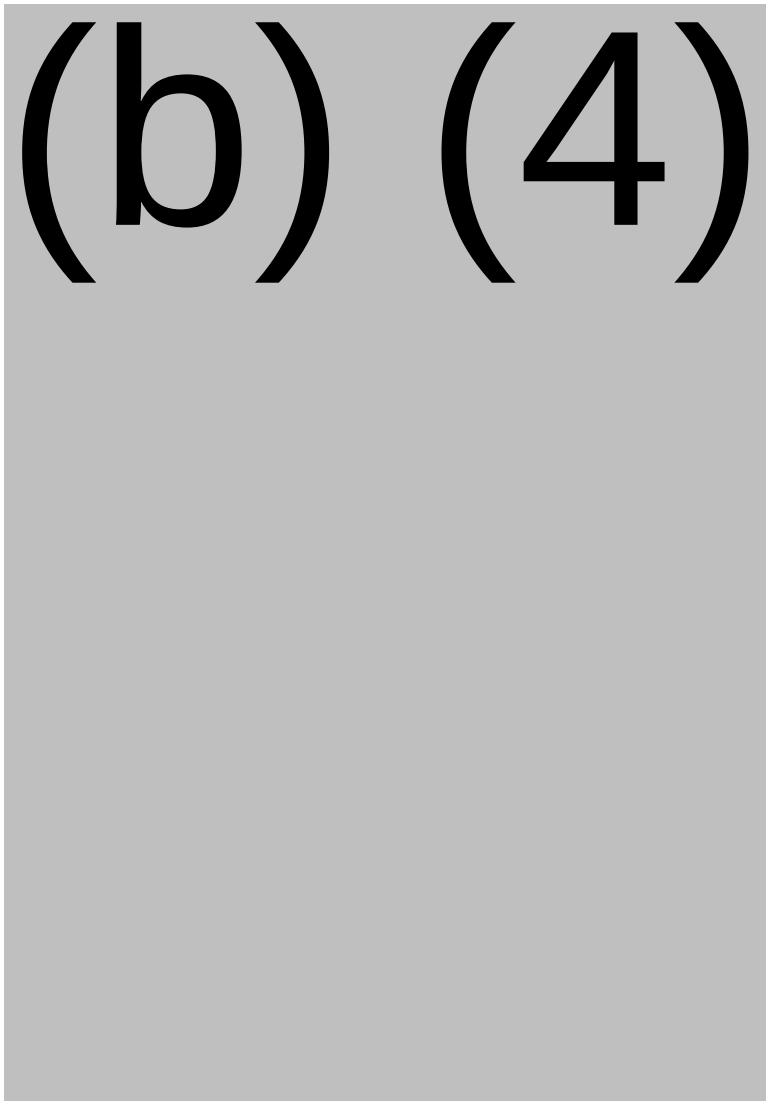
(b) (4) plasma for manufacturing Cuvitru are collected at approximately (b) (4) facilities, located exclusively in the United States. Collection facilities are FDA licensed and inspected. Each plasma donation used for the manufacture of Cuvitru is tested by using FDA-licensed serological assays for hepatitis B surface antigen and antibodies to human immunodeficiency virus (HIV)-1/2 and hepatitis C virus (HCV). Plasma mini-pools (b) (4) are additionally screened using FDA-licensed Nucleic Acid Testing (NAT) for (b) (4), HCV, HIV-1, (b) (4), (b) (4) . All plasma used in Cuvitru manufacture has been found to be nonreactive (negative) in these tests. Only plasma that passed virus screening is used for production. (b) (4)

In the Cuvitru manufacturing process, (b) (4) are used to prepare the critical intermediate (b) (4) at Baxalta's facilities in (b) (4) , and (b) (4) . Further manufacture of the (b) (4) intermediate into final product occurs in Baxalta's facility in (b) (4) . Plasma supplied to these Baxalta facilities is (b) (4), transported, and stored using validated processes. All facilities for the manufacture of Cuvitru have been inspected and licensed. All other raw materials used in the manufacture of Cuvitru are obtained from qualified vendors, quarantined upon receipt, and tested using validated methods. Materials with satisfactory testing results are released to manufacturing by trained QA personnel.

Manufacturing Process

A flow diagram of the Cuvitru manufacturing process is provided below:





Drug Product

Specification
The specifications and validation of analytical methods supporting Cuvitru have been evaluated by review personnel. The final specifications and acceptance limits established for Cuvitru by Baxalta comport with ranges associated with other IGSC products and are acceptable.

The specifications are established based on the results of conformance batches, historical product data from Baxalta's Gammagard product, and the outcome of clinical studies. The testing program includes appropriate measures of product quality attributes, product impurities, and parameters known to affect IGSC safety. All routine methods used as control or release testing of starting materials, process intermediates, drug product, and stability samples, are validated.

Table 1: Lot release testing and specification

1.1. Physico-chemical, biological, and immunological requirements

Test Parameter	Test Method (Reference)	Specification
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Appearance	Visual Inspection ((b) (4), procedure LE-13-A25003)	The liquid preparation is clear and colorless or pale yellow or light-brown
Bacterial Endotoxins	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Glycine	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
IgA	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Octoxynol 9 (or Triton X-100)	(b) (4)	(b) (4)
pH value	(b) (4)	4.6 to 5.1 : (b) (4)
(b) (4)	(b) (4)	(b) (4)
Polysorbate 80 (or Tween 80)	(b) (4)	(b) (4)
Protein Identity	(b) (4)	(b) (4)
Purity	(b) (4)	(b) (4)
Sterility	(b) (4)	Satisfactory
Total Protein	(b) (4)	(b) (4)
Tri-(N-butyl) Phosphate (TNBP)	(b) (4)	(b) (4)

***NIBSC-National Institute for Biological Standards and Control**

1.2 Tests For Information Only

Test Parameter	Test Method
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Osmolality	(b) (4)

Stability of Final Drug Product
The stability-study data provided in the BLA are deemed sufficient to support the proposed storage conditions for final-product Cuvitru of 36 months from date of manufacture for product stored at 2-8°C, and 12 months from date of manufacture for product stored at NMT 25°C.

Table 2: Specifications for stability testing

Atttributes	Product Specification	Methodology
Appearance	The liquid preparation is clear and colorless or pale-yellow or light-brown	Visual Inspection
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
pH	4.6-5.1 (b) (4)	(b) (4)
Purity	(b) (4)	(b) (4)
Bacterial Endotoxins	(b) (4)	(b) (4)
Total Protein	(b) (4)	(b) (4)
Sterility	Satisfactory	(b) (4)

Control of Adventitious Agents
The manufacturing process for Cuvitru contains three dedicated steps which contribute to viral inactivation or removal: 1) Solvent / Detergent (S/D) treatment of (b) (4) ; 2) 35 nm Nanofiltration; and 3) Incubation (b) (4) at low pH and elevated temperature. Cold ethanol fractionation, while not a dedicated virus clearance step, was shown to contribute to virus clearance. These steps in validated studies provided robust viral clearance at the levels listed in the following chart:

Table 3: Log_{10} virus reduction by manufacturing steps

	HIV-1	HAV	(b) (4)	PRV	BVDV	WNV	EMCV	MMV
Virus Property								
Genome	RNA	RNA	(b) (4)	DNA	RNA	RNA	RNA	DNA
Envelope	Yes	No	(b) (4)	Yes	Yes	Yes	No	No
Size (nm)	80-100	27-32	(b) (4)	120-200	50-70	50-70	25-30	18-24
Process Step	**Mean LRF**							
S/D treatment	>4.5	NA	(b) (4)	>4.8	>6.2	4.1	NA	NA
Nanofiltration	>4.5	5.7	(b) (4)	>5.6	>5.1	>6.2	1.4	2.0
Low pH treatment	>5.8	2.4	(b) (4)	>6.5	>5.5	>6.0	>6.3	3.1
EtOH Fractionation	>5.1	3.9	(b) (4)	>4.9	1.3	>6.1	4.2	4.9
Overall Reduction (Log_{10} Units)	**>19.9**	**12.0**	(b) (4)	**>21.8**	**>18.1**	**>22.4**	**>11.9**	**10.3**

HIV-1, human immunodeficiency virus type 1, a model for HIV-1 and HIV-2; HAV, hepatitis A virus; (b) (4) ; PRV, pseudorabies virus, a nonspecific model for large enveloped DNA viruses (e.g., herpes virus); BVDV, bovine viral diarrhea virus, a model for hepatitis C virus; WNV, West Nile virus; EMCV, encephalomyocarditis virus, a model for hepatitis A virus; MMV, minute virus of mice, a model for a small highly resistant non-enveloped DNA virus (e.g., parvovirus); LRF, log_{10} reduction factor; NA, not applicable; ND none detected.

The cold ethanol fractionation step in the upstream manufacturing process of Cuvitru was also investigated for its capacity to decrease the detection by (b) (4)

Conclusion

The CMC reviewers find that sufficient data and information have been provided on the chemistry, manufacturing, and controls to support licensure of Baxalta's Cuvitru.

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. Samples were submitted to CBER in support of the BLA, tested by CBER and found to be acceptable. For routine lot release, the applicant will submit final container samples together with lot release protocols. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Immune Globulin Subcutaneous (Human), 20% Liquid [Cuvitru] are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 4: Manufacturing Facilities Table for Cuvitru

Facility Address	FEI Number	Inspection/ waiver	Results/ Justification
Fractionation of the pooled plasma to (b) (4) Baxalta US Inc. (b) (4)	(b) (4)	Waived	(b) (4) NAI
Fractionation of the pooled plasma (b) (4) (b) (4)	(b) (4)	Waived	(b) (4) VAI
Fractionation of the pooled plasma to (b) (4) (b) (4)	(b) (4)	Waived	(b) (4) VAI
Further manufacture of (b) (4) *into IGSC, 20% Final Product Final Product Testing and Release Final Product Stability Testing* Baxalta (b) (4)	(b) (4)	Waived	(b) (4) VAI

The pre-license inspections for Baxalta, BLA STN 125596 for Cuvitru, have been waived at the manufacturer's facilities in (b) (4) . The waiver was granted based on criteria outlined in Center wide SOPP 8410 "Determining When Pre-Licensing/Pre-Approval Inspections are Necessary." Briefly, it was determined that Baxalta holds an active US license for Gammagard (STN 125105), a product with a nearly identical manufacturing process. The manufacturing sites are currently FDA-licensed facilities, and recent inspections of these facilities revealed no significant GMP violations and no systemic problems.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution

of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Container Closure System

The drug product is filled into 6 mL ((b) (4)), 10 mL ((b) (4)), 20 mL ((b) (4)), and 50 mL ((b) (4)) (b) (4) glass containers with a bromobutyl rubber stopper, (b) (4) and a crimp cap consisting of an aluminum band and a polypropylene flip-off disk to protect the rubber stopper. Baxalta conducted the container closure integrity testing at the (b) (4) facility, employing the (b) (4) test method; all acceptance criteria were met.

4. Nonclinical Pharmacology/Toxicology

The preclinical studies performed with Cuvitru were aimed at assessing the PK properties and local tolerance of this new preparation containing a higher protein concentration compared to the approved product. Additional toxicology studies were performed with Gammagard Liquid 10% and were submitted to provide support for the new, 20% preparation.

In a PK study in dogs, Cuvitru displayed a longer Tmax, lower Cmax and comparable half-life when administered via SC route compared to Gammagard 10% administered IV. It was tolerated at the local administration site in studies performed in rabbits and (b) (4) mini pigs. There were no unexpected toxicities observed with Cuvitru in preclinical studies.

Conclusion

Based on the nonclinical data presented, the safety profile of Cuvitru when used at doses and infusion rates proposed presented no preclinical concerns.

5. Clinical Pharmacology

Study 170903 *"A Clinical Study of Immune Globulin Subcutaneous (Human) (IGSC), 20% for the Evaluation of Efficacy, Safety, and Pharmacokinetics in Subjects with Primary Immunodeficiency Diseases"*

This was a phase 2/3, prospective, open-label, historic controlled, multi-center trial using Cuvitru to evaluate efficacy, safety, tolerability, and PK. The study was planned for approximately 47 subjects with PI, at least 2 years of age at the time of screening, including a minimum of 20 subjects aged 2 to <18 years (at least 6 aged 12 to <18 years of age).

The trial consisted of 2 epochs; Epoch 1 included 12 weeks of treatment with Subcuvia[1] (IGSC, 16%), or 13 weeks of IV treatment with Kiovig[2] (IGIV, 10%). Epoch 2 included 51 weeks of Cuvitru.

Epoch 1

IV treatment: PK assessment was started at IV Infusion 4 (for 3-week treatment interval) or starting at IV Infusion 3 (for 4-week treatment interval). Blood samples were collected till Day 21 or Day 28.

SC treatment: PK assessment was started at SC Infusion 12 (for 1-week treatment interval) or starting at SC Infusion 6 (for 2-week treatment interval). Blood samples were collected till Day 7 or Day 14.

Epoch 2

PK assessment was started at SC Infusion 21 (numbered from the beginning of Epoch 2). Blood samples were collected till Day 7. Blood samples for children <12 years of age were taken at Time 0, and Days 3 and 7 (fewer than subjects >12 years of age). The PK parameters in subjects were estimated by non-compartmental analysis.

Results

Following Kiovig administration (18-<65 years of age), the clearance and C_{min} of IgG were 1 mL/day per kg (range = 0.97-1.05) and 11.7 g/L (10.5-13.0), respectively, for subjects on a 3-week schedule (n = 2). For subjects on a 4-week schedule (n = 9), the clearance and C_{min} of IgG were 1.44 mL/day per kg (range = 1.04-1.89) and 7.0 g/L (range = 5-11.7), respectively. In adolescents (12-<18 years of age; on a 4-week schedule; n = 7), the clearance and C_{min} of Kiovig were comparable with the clearance and C_{min} of Kiovig in subjects ≥18 years of age.

Following Subcuvia administration (18-<65 years of age), the clearance and C_{min} of IgG were 1.62 mL/day per kg (range = 1.4-2.5) and 8.96 g/L (range = 6.9-11.9), respectively, for subjects on a 1-week schedule (n = 9). In the 1 adolescent in this cohort (12-<18 years of age; on a 1-week schedule;), the clearance and C_{min} of Subcuvia were 2.1 mL/day per kg and 10.4 g/L, respectively, but conclusions cannot be drawn because of the small numbers.

Following Cuvitru administration (18-<65 years of age), the clearance and C_{min} of IgG were 1.7 mL/day per kg (range = 1.27-2.85) and 8.05 g/L (range = 5.5-10.4), respectively, for subjects on a 1-week schedule (n =18). In adolescents (12-<18 years of age; on a 1-week schedule; n = 11), the clearance and C_{min} of Cuvitru were 1.9 mL/day per kg (range = 1.1-3.2) and 8.6 g/L (5.4-16.3), respectively. In adolescents (12-<18

[1] Subcuvia (IGSC, 16%; CSL Behring) is licensed by the EMA
[2] Gammagard Liquid is marketed by Baxalta ex-U.S. under the name KIOVIG

years of age; on a 1-week schedule; n = 11), the clearance and C_{min} of Cuvitru were comparable with subjects >18 years of age.

In one child 2-5 years of age (n =1) and in children 6-11 years of age (n =10), the clearance, C_{max}, and C_{min} were comparable with adolescents and adults.

Conclusion

The PK of Subcuvia and Cuvitru are comparable between children (≥6 years of age) and adults. However, the sample size for 2-5 years of age is very small (n =1) which hinders the comparison of PK in this age group with older children and adults. This is the age group in which differences in PK parameters are anticipated from older children, adolescents, and adults.

Study 170904 *"A Clinical Study of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) for the Evaluation of Efficacy, Safety, Tolerability, and Pharmacokinetics in Subjects with Primary Immunodeficiency Diseases"*

This was a phase 2/3, prospective, open-label, historic controlled, multicenter to evaluate efficacy, safety, tolerability, and PK of Cuvitru. The trial consisted of 4 epochs:

- *Epoch 1:* subjects received Gammagard Liquid IV. All subjects aged ≥12 years completed a PK assessment. Dose was 0.3-1.0 g/kg body weight/4 weeks. One week after the last Gammagard Liquid infusion, Epoch 2 began.
- *Epoch 2:* subjects received Cuvitru weekly at a dose adjusted to 145% of the Gammagard Liquid dose. The first 15 subjects aged ≥12 years completed a PK assessment. Based on the PK data from Epoch 1 and Epoch 2, the Cuvitru dose that would, on average, provide equivalent IgG exposure as Gammagard Liquid administration ("Adjusted Dose") was calculated.
- *Epoch 3:* subjects were treated with Cuvitru weekly for 3 months at the "Adjusted Dose." Since this Adjusted Dose represented the average dose-response of only 15 subjects, the possibility that some subjects could be over- or under-dosed, could not be excluded. Thus, for each subject an "Individually Adapted Dose" of Cuvitru was determined by comparing the trough level attained in Epoch 3 to the expected trough level increase calculated from the PK comparison of Epochs 1 and 2.
- *Epoch 4:* subjects were infused with Cuvitru weekly at the "Individually Adapted Dose." Efficacy, safety and tolerability were determined throughout Epochs 2 to 4 (12 months). Of note, treatment in Epoch 3 started as soon as the Adjusted Dose became available. Consequently, later enrolling subjects who completed Epoch 1 after the Adjusted Dose was available, directly went into treatment with the Adjusted Dose (Epoch 3).

Of the 77 treated subjects (51.9% male, 48.1% female), the majority were Caucasian (90.9%) and not of Hispanic or Latino ethnicity (93.5%). The median age of treated

subjects was 36.0 years (range: 3-83 years). The median weight was 68.20 kg (range: 13.20-161.80 kg).

Pharmacokinetic Datasets

The following PK datasets were submitted with the BLA application:

- PK data set for Gammagard Liquid administered every 3 weeks (n= 16), or every 4 weeks (n= 38) (subjects aged 12 years and older).
- PK dataset for Cuvitru at 145% of IV dose (n= 18) (subjects aged 12 years and older).
- PK dataset for Cuvitru at the individualized dose (n= 60) (subjects aged 2 years and older).

Pharmacokinetic Results

Bioavailability

The bioavailability of Cuvitru estimated from the ratio of the geometric means of AUC/week for total IgG during weekly Cuvitru treatment in Epoch 4 (once every week) versus Gammagard Liquid treatment (3 or 4-week interval normalized to weekly equivalent dose) was 1.1 (n = 49).

Subjects aged 12 years and older in Epoch 1 and in Epoch 2

- In subjects who received Gammagard Liquid every 3 weeks, (n=16), the median area under the curve (AUC) for total IgG was 360 g X days/L. The median clearance (CL) was 1.75 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 26 g/L and 13 g/L, respectively.

- In subjects who received Gammagard Liquid every 4 weeks, (n=38), the median area under the curve (AUC) for total IgG was 408 g X days/L. The median clearance (CL) was 1.28 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 25 g/L and 10 g/L, respectively.

- During weekly administration of Cuvitru at 145% of the IGIV, 10% dose (n=18), the median area under the curve (AUC) for total IgG was 108 g X days/L. The median clearance (CL) was 1.94 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 17 g/L and 15 g/L, respectively.

Subjects aged 12 years and older in Epoch 4

- **12 to <16 years:** During weekly administration of Cuvitru at the individualized dose (n=3), the median AUC for total IgG was 116 g X days/L. The median clearance (CL) was 1.80 mL/day per kg. The median

maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 17 g/L and 16 g/L, respectively.

- **16 to <65 years:** During weekly administration of Cuvitru at the individualized dose (n=37), the median AUC for total IgG was 114 g X days/L. The median clearance (CL) was 1.98 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 19 g/L and 14 g/L, respectively.

- **>65 years:** During weekly administration of Cuvitru at the individualized dose (n=7), the median AUC for total IgG was 139 g X days/L. The median clearance (CL) was 1.72 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 24 g/L and 16 g/L, respectively.

Subjects aged 2 to < 12 years in Epoch 4
For subjects in this age range, PK assessments were performed only during Epoch 4, between infusion 17 and infusion 18 of Cuvitru at the individualized dose.

- **2 to <5 years:** There was only one subject in this study. The median AUC for total IgG was 106 g X days/L. The median clearance (CL) was 1.86 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 16 g/L and 15 g/L, respectively.

- **5 to <12 years:** For subjects aged 5 < 12 years receiving weekly infusions of IGSC, 20% at the individualized dose (n=10), the median AUC for total IgG was 110 g X days/L. The median clearance (CL) was 1.85 mL/day per kg. The median maximum concentration (C_{max}) and the median minimum concentration (C_{min}) were 17 g/L and 14 g/L, respectively.

Conclusion

The PK data of Cuvitru are comparable from children to adults. Like the previous study (Study 170903) the sample size for 2-5 years of age is very small (n =1) which hinders the comparison of PK in this age group with older children and adults. This is the age group in which differences in PK parameters are anticipated from older children, adolescents, and adults. Furthermore, the PK of Cuvitru were not different between subjects >65 years and subjects 16-<65 years of age. No gender difference was noted in the PK of IGIV or IGSC.

6. Clinical/ Statistical

a) Clinical Program

The demonstration of Cuvitru's efficacy was based on two (Studies 170904 and 170903) of the three clinical trials that were included in this original BLA submission. The third (Study 160601) was supportive.

Study 170904

Study 170904, conducted under BB-IND 14505, was a phase 2/3, prospective, open-label, historic-controlled, multicenter (United States and Canada) trial designed to evaluate the efficacy, safety, tolerability, and PK of Cuvitru in subjects (N=77) with PI. In this 4-part (i.e., epoch) clinical trial, subjects received Gammagard Liquid IV in Epoch 1 and Cuvitru during Epoch 2 through Epoch 4. Cuvitru dosing was an iterative process that progressed from Epoch 2 (fixed SC dose equivalent to 145% of IV dose) to Epoch 3 ("Adjusted Dose" of Cuvitru every 7 days for 3 months based on PK data from Epoch 1 and Epoch 2) to Epoch 4 ("Individually Adapted Dose" based on a comparison of measured trough levels in Epoch 1 and Epoch 3). The primary endpoint was annualized number of acute serious bacterial infections (SBI)[3].

Study 170903

Study 170903 was a phase 2/3 clinical trial having the same objectives as Study 170904 but conducted in Europe. In Epoch 1, subjects (N=49) received either IV Kiovig (3 or 4-week interval for 13 weeks [N=33]) or SC Subcuvia (every week or every other week for 12 weeks [N=16]). In Epoch 2, subjects received Cuvitru (N=48). When switching to Epoch 2, Epoch 1 subjects in the Kiovig cohort received Cuvitru at the same dose of Kiovig as in Epoch 1 adjusted to a weekly-equivalent dose over a period of 51-weeks. The primary endpoint was annualized number of acute SBI.

Study 160601

Study 160601 was a phase 2/3, prospective, open-label, historic-controlled, multicenter (United States) supportive study in 49 subjects aged ≥2 years with PI. It was designed to determine the tolerability and the PK of SC Gammagard Liquid *versus* IV Gammagard Liquid. A further aim was to evaluate efficacy by measuring the incidence of acute SBI and the total number of infections during SC administration.

Efficacy Results

Table 5 shows that Study 170904 and 170903 both met their primary endpoints and were below the threshold rate of acute SBI ≥1.0 per person-year (each had one acute SBI reported while subjects were receiving Cuvitru), with an annualized acute SBI rate in the Cuvitru treatment cohort of 0.01 and 0.02, respectively. Both values were at the 0.01 level of significance needed to reject the null hypotheses, set forth as providing

[3] Serious bacterial infections (SBI) defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess that were caused by a recognized bacterial pathogen

substantial evidence of efficacy in the FDA Guidance for Industry.[4] Similar values were obtained for pediatric subjects aged <16 years (0.06 for Study 170904 and 0.00 for Study 170903). These results are shown below in Table 5.

Table 5: Analysis of Acute SBI by Study

Study No.	Total No. of Subjects	Epoch	Treatment Cohort	Point Estimate	Upper Limit 99% CI	p-value
170904	77*	2-4	Cuvitru	0.01	0.02	<0.0001
170903	49	2	Cuvitru	0.02	0.05	<0.0001

* In Study 170904, 77 subjects were treated with any investigational product; 74 subjects received Cuvitru. Two subjects were discontinued for non-compliance and one subject experienced an AE that lead to discontinuation during Epoch 1.

As stated above, each trial had one acute SBI reported while subjects were receiving Cuvitru:

- **Study 170904:** an 80 year old White male with a specific antibody deficiency, experienced bilateral pneumonia during treatment with Cuvitru (Epoch 4) that required hospitalization. The pneumonia was reported to be due to a microbial pathogen, and the subject was treated with Levaquin, Solu-Medrol (switched to prednisone after 4 days) and albuterol nebulizer treatments. The event resolved 6 days after onset and the subject was discharged from the hospital.
- **Study 170903:** a pediatric subject aged 12 years with XLA experienced 2 episodes of bacterial pneumonia (moderate severity); the first occurred during Epoch 1 while receiving treatment with Subcuvia, and the second during Epoch 2 while receiving with treatment with Cuvitru. Details of the event while receiving Cuvitru include a 4 day hospitalization, and treatment with Cefuroxin, nasal decongestant spray and saline inhalation. The subject is reported to have recovered from the event 10 days after its onset.

In the supportive Study 160601, a total of 3 subjects (53, 48, and 10 years of age) had acute SBI while on Gammagard Liquid SC treatment. All 3 infections were bacterial pneumonias. This gave an annual rate of acute SBI in the Gammagard Liquid SC treatment cohort of 0.067 (99% upper confidence limit: 0.134).

As shown in Table 6 below, secondary clinical endpoints from all three clinical trials (i.e. Days off school/work, Days on antibiotics, Number of hospitalizations, Days in hospital, and Acute physician/ER visits) were similar for all the products and the data are supportive of the effectiveness of Cuvitru for the proposed indication.

[4] FDA Guidance for Industry: *Safety, Efficacy and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency* – June 2008

Table 6: Annualized Rates for Secondary Endpoints (Infections and Subject-Reported Outcomes) by Study

		Study 170904 Rate per Year		Study 170903 Rate Per Year		Study 160601 Rate Per year	
Parameter	**Product**	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
Number of infections	Cuvitru	2.4	1.9 to 3.0	4.4	3.4 to 5.6	NA	NA
Days off school/work		1.2	0.7 to 1.8	15.6	10.1 to 22.8	NA	NA
Days on antibiotics		57.6	40.7 to 78.6	18.1	13.0 to 24.4	NA	NA
Number of hospitalizations		0.02	0.01 to 0.04	0.2	0.08 to 0.26	NA	NA
Days in Hospital		0.1	0.05 to 0.20	1.7	0.7 to 3.2	NA	NA
Acute physician visits		0.9	0.5 to 1.3	3.8	2.6 to 5.3	NA	NA
Number of infections	Gammagard Liquid IV	3.9	2.8 to 5.2	6.3	4.2 to 9.0	5.1	3.7 to 6.9
Days off school/work		3.2	1.9 to 5.0	10.7	5.3 to 18.8	4.6	2.6 to 7.3
Days on antibiotics		63.2	43.4 to 88.3	19.6	12.6 to 28.8	43.1	25.8 to 66.8
Number of hospitalizations		0.05	0.02 to 0.10	0.1	0.04 to 0.26	-	-
Days in Hospital		0.2	0.1 to 0.4	0.1	0.04 to 0.26	0.7	0.3 to 1.2
Acute physician visits		1.7	1.0 to 27.	5.1	3.0 to 8.1	2.7	1.6 to 4.1
Number of infections	Gammagard Liquid SC	NA	NA	NA	NA	4.1	3.2 to 5.1
Days off school/work		NA	NA	NA	NA	4.0	2.5 to 6.1
Days on antibiotics		NA	NA	NA	NA	50.2	33.4 to 71.9
Number of hospitalizations		NA	NA	NA	NA	-	-
Days in Hospital		NA	NA	NA	NA	0.05	0.02 to 0.09
Acute physician visits		NA	NA	NA	NA	4.7	3.5 to 6.3
Number of infections	Subcuvia	NA	NA	8.9	6.4 to 12.1	NA	NA
Days off school/work		NA	NA	50.4	19.6 to 103.4	NA	NA
Days on antibiotics		NA	NA	54.3	31.4 to 86.3	NA	NA
Number of hospitalizations		NA	NA	0.5	0.2 to 1.3	NA	NA
Days in Hospital		NA	NA	2.4	0.7 to 5.9	NA	NA
Acute physician visits		NA	NA	7.6	3.6 to 13.8	NA	NA

NA=not applicable (not a treatment cohort in the trial); - = not captured per protocol
Point estimate values ≤0.1 carried to two decimal places

b) Pediatrics

Cuvitru was evaluated in 39 pediatric subjects with PI in Studies 170904 and 170903:

- Six subjects were aged 2 to <6 years,
- Twenty-two subjects were aged 6 to <12 years and
- Eleven subjects were aged 12 to <16 years

There were no reported differences in the safety and efficacy profiles in the pediatric subjects as compared with adult subjects.

An agreed initial Pediatric Study Plan was submitted on 17 April 2015 and accepted by FDA on 13 May 2015. A partial waiver of the requirement for pediatric assessments in children aged 0 to <2 years was granted. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. No additional pediatric studies are required because the pediatric study requirement for all relevant pediatric age groups for this application has been fulfilled with the pediatric assessment included in this application.

c) Bioresearch Monitoring

No issues were found during the two Bioresearch Monitoring clinical investigator inspections that were conducted for Study 170904.

7. Safety

A total of 6,675 Cuvitru infusions in 122 subjects were administered in Studies 170904 and 170903.

- **Treatment Emergent Adverse Events (TEAE)**
  Table 5 below shows that most Cuvitru subjects experienced one or more TEAEs, regardless of age. Most events were mild-moderate in intensity and occurred within 72 hours of treatment.

Table 7: Subjects Experiencing TEAEs in Association with Cuvitru Regardless of Causality

Classification	No. of Subjects (%) N=122
Number of subjects experiencing ≥1 TEAE	111 (91.0)
Number of subjects experiencing TEAEs by intensity*	
Mild	64 (52.5)
Moderate	65 (53.3)
Severe	4 (3.2)
Number of subjects experiencing TEAEs by age cohort (years)	
<6 to 16 (N=39)	33 (84.5)
16 to <65 (N=71)	66 (93.0)
≥65 (N=12)	12 (100.0)
Number of subjects experiencing TEAEs within 72 hours	95 (78.0)
<6 to <16 year cohort (N=39)	27 (69.2)

* The same subject could have experienced ≥1 TEAE of different intensities

Table 8 shows that the incidence of local and systemic (other than headache) TEAEs was higher with Cuvitru than with IGIV. Localized reactions would be expected to be higher in an SC preparation in comparison to an IGIV. Systemic incidences of TEAEs may relate to specific features of the product itself, but do not in themselves raise particular safety concerns since they are similar to other IGSC products. Note: some subjects were counted more than once because they experienced one or more local and systemic TEAEs.

Table 8: Incidence ≥5% for Causally Related and/or Temporally Associated TEAEs

TEAEs	Study 170904 (%) N=74		Study 170903 (%) N=48			Study 170904 + Study 170903 (%) N=122
	GAMMAGARD LIQUID (%) N=77	Cuvitru (%) N=74	KIOVIG (%) N=33	SUBCUVIA (%) N=16	Cuvitru (%) N=48	
Local TEAEs	-	**23 (31.1)**	**1 (3.0)**	**1 (6.3)**	**19 (39.6)**	**42 (34.4)**
Infusion site pain	-	14 (18.9)	4 (12.1)	-	6 (12.5)	20 (16.4)
Infusion site erythema	-	8 (10.8)	-	-	9 (18.8)	17 (13.9)
Infusion site pruritus	-	4 (5.4)	-	1 (6.3)	6 (12.5)	10 (8.2)
Systemic TEAEs	**34 (44.2)**	**51 (68.9)**	**26 (78.8)**	**5 (31.3)**	**44 (91.7)**	**95 (77.9)**
Headache	23 (29.9)	12 (16.2)	11 (33.3)	2 (12.5)	15 (31.3)	27 (22.1)
Nausea	6 (7.8)	11 (14.9)	3 (9.1)	1 (6.3)	3 (6.3)	14 (11.5)
Diarrhea	4 (5.2)	8 (10.8)	6 (18.2)	1 (6.3)	12 (25.0)	20 (16.4)
Cough	-	8 (10.8)	3 (9.1)	-	11 (22.9)	19 (15.6)
Fatigue	5 (6.5)	7 (9.5)	-	1 (6.3)	6 (12.5)	13 (10.7)

A hyphen (-) indicates an incidence <5%

- **Serious Adverse Events (SAE)**
  SAEs (N=10) were reported in 8 subjects (6.6%): 2 subjects in Study 170904 and 6 subjects in Study 170903. None of the SAEs (lung adenocarcinoma, myocardial infarction, ventricular fibrillation, nasal septum deviation, brainstem infarction, enteritis) were causally related to Cuvitru. Chronic sinusitis, pneumonia, and rhinorrhea SAEs likely represented treatment failure due to underlying disease of PI. No episodes of thrombosis or hemolysis were reported. There were no deaths reported in the three clinical trials.

8. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this BLA.

10. Labeling

To be consistent with prior package inserts of immunoglobulin products manufactured by Baxalta, tables that excluded infections were used in the final labeling. The proposed proprietary name for the product, CUVITRU, was reviewed by the Advertising and Promotional Labeling Branch (APLB) and recommended to be acceptable on December 18, 2015. The product labeling (i.e., prescribing information and instructions for use) and the product package and container labels were reviewed, commented on, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review team recommends an approval action be taken for this BLA.

b) Risk/ Benefit Assessment

Local and systemic risks associated with administration of Cuvitru were typical of other licensed SC immunoglobulin products. Given the absence of thrombotic, hemolytic or adverse events of special interest in the investigational treatment arm (N=122), the strength and size of the reduction in the incidence of acute SBI indicate a favorable risk-benefit ratio.

c) Recommendation for Postmarketing Risk Management Activities

The available data do not suggest a safety concern that would necessitate either a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint. At this time, routine pharmacovigilance is adequate as per Baxalta's proposed Pharmacovigilance Plan (Version 1.0, dated September 1, 2015).

d) Recommendation for Postmarketing Activities

At this time, routine pharmacovigilance and labeling are adequate to monitor the safety of Cuvitru use in the postmarketing period. Routine pharmacovigilance includes adverse event reporting in accordance with 21 CFR 600.80: 15-day expedited reports for serious unlabeled adverse events and quarterly periodic safety reports for 3 years (annual thereafter).

Post Marketing Commitments

1. Based on one year of manufacturing experience, Baxalta commits to establish specifications for (b) (4) , Osmolality, and (b) (4) for IGSC, 20% final product. The assay validation for these tests, proposed specifications, and testing data will be submitted as a PAS by September 13, 2017.
2. Baxalta will submit as a PAS the recalibrated (b) (4) assay reported as mIU (b) (4) using the (b) (4) international standard, and a proposed lot release specification

based on manufacturing experience, within 12 months of BLA approval (September 13, 2017).