



Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Biostatistics and Epidemiology  
Division of Epidemiology

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**Cuvitru (immune globulin subcutaneous (human), 20% solution), original BLA 125596  
Pharmacovigilance Plan Review Memorandum**

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Office of Blood Research and Review (OBRR)

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Subject: Pharmacovigilance Plan Review Memorandum

Sponsor: Baxalta US Inc.

Product: Immune Globulin Subcutaneous (Human), 20% solution (IGSC, 20%);  
proposed name: Cuvitru

Submission: Original BLA 125596\0

Proposed indication: Replacement therapy for primary humoral immunodeficiency in adult  
and pediatric patients two years of age or older

Action Due Date: September 13, 2016

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## 1. INTRODUCTION

### 1.1 Product Description

Immune Globulin Subcutaneous (Human), 20% solution (IGSC, 20%) was developed by Baxalta for the proposed indication: replacement therapy for primary humoral immunodeficiency in adult and pediatric patients two years of age or older. Primary immunodeficiency disease (PID) includes congenital X-linked agammaglobulinemia, common variable immune deficiency, Wiskott-Aldrich syndrome and severe combined immunodeficiency. This product will be referred to in this memorandum by its proposed proprietary name – Cuvitru.

Replacement of IgG using human immunoglobulin is standard treatment for PID and has been shown to be effective in preventing serious infections. As per the sponsor, Cuvitru “supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents.” The subcutaneous route of administration offers several advantages over intravenous administration: smaller needle access (particularly important for patients with poor venous access) leads to milder local reaction and less local pain; flexibility in dosing regimen; the option of self-administration at home leads to improved lifestyle/patient autonomy. However, one of the disadvantages of IGSC is that delivery volume per subcutaneous injection site is limited, thus requiring multiple injection sites and weekly therapy. Use of the 20% IGSC formulation in Cuvitru reduces the infusion volume compared to 10% preparations and as per the sponsor, Cuvitru was developed “with the aim of providing a more concentrated product requiring a reduced infusion volume for subcutaneous (SC) administration.”

Cuvitru is derived from (b) (4) human plasma pools. The manufacturing of Cuvitru is based on Baxalta (formerly Baxter) production of licensed immune globulin infusion (10% solution), marketed in the US as Gammagard Liquid (STN 125105) and in Europe as Kiovig. Gammagard Liquid is used for both intravenous and subcutaneous therapy for PID. As per the sponsor, “The IGSC, 20% product is essentially the same as Baxter’s currently licensed GAMMAGARD LIQUID IGI, 10% product (STN BL 125105), with the exception of the (b) (4) and formulation steps.”<sup>1</sup> Formulation of Cuvitru is modified to achieve higher concentration (20% solution), and the proposed indication is only for subcutaneous administration. Similar to Gammagard Liquid, Cuvitru contains glycine as a stabilizer to (b) (4).

Other approved IGSCs include Gamunex, Hizentra, and recently approved HyQvia (approved 2014).

### 1.2 General safety concerns for Ig products

General safety concerns for Ig products<sup>2</sup> include hypersensitivity reactions, hemolysis, thromboembolic events (TEEs), acute renal failure (ARF), aseptic meningitis, and interference with laboratory tests (passively transmitted antibodies). Review of the clinical safety database for Cuvitru will include

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<sup>1</sup> BLA 125596 submission; module 2.2 Introduction, page 1.

<sup>2</sup> Silvergleid et al. Overview of intravenous immune globulin (IVIg) therapy. Accessed on UpToDate 2/15/2016. [http://www.uptodate.com/contents/overview-of-intravenous-immune-globulin-ivig-therapy?topicKey=HEME%2F4431&elapsedTimeMs=6&source=search\\_result&searchTerm=IGIV&selectedTitle=5~150&view=print&displayedView=full](http://www.uptodate.com/contents/overview-of-intravenous-immune-globulin-ivig-therapy?topicKey=HEME%2F4431&elapsedTimeMs=6&source=search_result&searchTerm=IGIV&selectedTitle=5~150&view=print&displayedView=full)

assessment of safety concerns common to the Ig class. A brief timeline on the regulatory history surrounding Ig products is included below.

- 2012: As authorized under Title IX, Section 921 of FDA Amendments Act of 2007, FDA issued a posting for the potential signal for a serious risk of hemolysis with Privigen (IGIV) based on increased number of FAERS reports of hemolysis.<sup>3</sup> FDA further issued a Safety Communication stating that a potential risk of hemolysis has been associated with the administration of human immune globulin.<sup>4</sup>
- 2013: FDA instituted a safety labeling change for the class of Ig products and required manufacturers to add information on thrombosis to the current boxed warning in the labels of all Ig products.<sup>5</sup> The current boxed warning on labels of Ig products also notes the risk of renal dysfunction and acute renal failure.<sup>6</sup>

### 1.3 Regulatory History

- January 2013: Initiation of Phase 2/3 clinical study entitled “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.”
- December 2010: IND Comments regarding comparative PK study with IGIV sufficient for licensure based on similarity with STN 125105 Gammagard Liquid, 10%.
- September 2010: IND filed
- August 2010: Pre-IND Type B meeting to discuss clinical trial design; plan to cross-reference CMC from STN 125105 Gammagard Liquid, 10%.

### 1.4 Objectives and Scope

Office of Biostatistics and Epidemiology, Division of Epidemiology (OBE/DE) has completed its pharmacovigilance review of BLA 125596 seeking initial licensure of Immune Globulin Subcutaneous (Human), 20% solution (IGSC, 20%; proposed trade name Cuvitru). The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance, studies, or other pharmacovigilance activities, should the product be licensed. As part of a comprehensive safety evaluation, the submitted pharmacovigilance plan (PVP) with supporting background clinical trial information from the BLA is hereby reviewed. Currently Cuvitru is not licensed in any country and there are no postlicensure safety data.

## 2. MATERIALS REVIEWED

Materials reviewed in support of this safety assessment are listed below.

- **Manufacturer’s Submissions**

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<sup>3</sup> FDA. Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) between January – March 2012. Available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm307608.htm>

<sup>4</sup> FDA. FDA Safety Communication: Updated information on the risks of thrombosis and hemolysis potentially related to administration of intravenous, subcutaneous and intramuscular human immune globulin products. Available at <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm327934.htm>

<sup>5</sup> FDA. Immune Globulin Products (Human) intravenous, subcutaneous and intramuscular. Detailed View: Safety Labeling Changes Approved By FDA Center for Biologics Evaluation and Research (CBER) – June 2013. Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360566.htm>

<sup>6</sup> FDA. Adverse Event Report for an Immune Globulin: FDA Investigation and Actions. Available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/InternationalActivities/UCM273193.pdf>

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- Module 1.16: Pharmacovigilance Plan (Version 1.0, dated September 1, 2015)
  - Module 2.5: Clinical Overview
  - Module 2.7.4: Summary of Clinical Safety
  - Module 5.3.5.3: Integrated Summary of Safety (ISS)
  - Module 1.14.1.2: Annotated draft label
- Input from BLA review team
  - Published medical literature
  - Literature references (cited as footnotes)

### 3. CLINICAL STUDIES AND CLINICAL SAFETY DATABASE

The clinical data submitted in support of BLA 125596 consist of 3 completed clinical trials: Study 170904, Study 170903 and Supportive Study 160601. Only two studies, 170904 and 170903, were conducted in the indicated PID population (adults and children) using the 20% formulation of IGSC (Cuvitru). Cuvitru was administered at a dose adjusted to achieve the bioavailability of IGIV 10% to provide equivalent IgG exposure. Supportive Study 160601 was conducted using a 10% formulation of IGSC only (i.e. Gammagard Liquid) to evaluate the tolerability and PK of IGIV, 10% given SC in subjects with PID.

Thus the clinical safety database for Cuvitru is based on data from the clinical trials of IGSC 20%:

Study 170903: N = 48

Study 170904: N = 74

Clinical safety database: N = 122

While the clinical trials are briefly described in section 3.1, we defer to the OBRR clinical reviewer for a detailed discussion of study design and efficacy results. The safety data from these clinical trials are discussed in section 3.2.

#### 3.1 Clinical studies: 170903 and 170904

##### 3.1.1 Clinical study 170903 (N = 48)

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

*Study Design:* phase 2/3, prospective, open-label, non-controlled, multi-center study in Europe

*Study Population:* subjects with PID aged 2 years and older

*Study duration:* Approximately 2 years and 9 months

*Duration of treatment:* Approximately 16 months

*Treatment:* IV administration of Gammagard Liquid/Kiovig (IGIV, 10%); SC administration of Subcuvia (IGSC, 16%); SC administration of investigational product IGSC, 20% (Cuvitru)

*Treatment schedule –*

Epoch 1: IGIV, 10% (once every 3 or 4 weeks) or IGSC, 16% (once per week or once every other week) at pre-study dose (0.3-1.0 g/kg BW/4 weeks), for 3 months

Epoch 2: Cuvitru once per week, at the same monthly dose used during Epoch 1, for 12 months

*Primary efficacy outcome:* Annualized rate of validated acute serious bacterial infection per subject (VASBI) such as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess that were caused by a recognized bacterial pathogen.

*Safety outcomes:* occurrence of adverse events (AEs) and potential hemolysis; infusion tolerability; viral safety; clinically significant laboratory values (hematology and clinical chemistry); physical assessments and vital signs. Note that for assessment of AEs, “Recovering/resolving AEs were followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever occurred first.” [Full Clinical Study Report 170903, p. 40]

*Efficacy Study Results:* Two VASBIs occurred in 1 subject during the study: one VASBI occurred during IGSC, 16% treatment and one during Cuvitru treatment. The annualized rate of VASBIs for Cuvitru (point estimate: 0.022; upper limit of 99% CI: 0.049) was statistically significantly lower than the threshold specified as providing substantial evidence of efficacy. This rate compares favorably to the FDA recommended threshold of 1.0 acute serious bacterial infection /year<sup>7</sup>. Per the sponsor, “Analysis of the efficacy results in this study indicates that IGSC, 20% is efficacious for adult and pediatric subjects in the treatment PID, in terms of IgG trough levels, infection rates, and patient-related outcomes.” [Source: CSR Synopsis Study 170903, Annex II of Pharmacovigilance Plan, p.91].

### **3.1.2 Clinical study 170904 (N = 74)**

*Study Title:* 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

*Study Design:* phase 2/3, prospective, open-label, non-controlled, multicenter study in US and Canada

*Study Population:* subjects with PID aged 2 years and older

*Study duration:* approximately 26 months

*Duration of treatment:* Approximately 20 months for subjects enrolled earlier in the study, and 17 months for subjects enrolled after the Adjusted Dose was already available

*Treatment:* IV administration of Gammagard Liquid/Kiovig (IGIV, 10%); SC administration of Subcuvia (IGSC, 16%); SC administration of investigational product: IGSC, 20% (Cuvitru)

#### *Treatment schedule –*

Epoch 1: IGIV, 10% (once every 3 or 4 weeks), at prestudy dose (0.3-1.0 g/kg body weight), for 3 months

Epoch 2: IGSC, 20% once per week, at 145% of the weekly dose used during Epoch 1, for up to 4 months

Epoch 3: IGSC, 20% once per week, at the Adjusted Dose, for 3 months

Epoch 4: IGSC, 20% once per week, at the Individually Adapted Dose, for 10 months

*Primary efficacy outcome:* Annualized rate of validated acute serious bacterial infection per subject (VASBI) such as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess that were caused by a recognized bacterial pathogen.

*Safety outcomes:* occurrence of adverse events (AEs) and potential hemolysis; infusion tolerability; viral safety; clinically significant laboratory values (hematology and clinical chemistry); physical assessments and vital signs. Note that for assessment of AEs, “Recovering/resolving AEs were followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever occurred first.” [Full Clinical Study Report 170904, p. 44]

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<sup>7</sup> FDA Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency (dated June 2008) <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/BLD/ucm078526.pdf>

*Efficacy Study Results:* A single VASBI occurred in 1 subject during Cuvitru treatment. The annualized rate of VASBIs for Cuvitru (point estimate 0.012, upper limit of 99% CI: 0.024) was statistically significantly lower than the threshold specified as providing substantial evidence of efficacy. This rate compares favorably to the FDA recommended threshold of 1.0 acute serious bacterial infection /year<sup>8</sup>. As per sponsor, “Analysis of the efficacy results in this study indicates that IGSC, 20% replacement therapy is efficacious in adult and pediatric subjects for the treatment of PIDD with antibody deficiencies.” [Source: CSR Synopsis Study 170904, Annex II of Pharmacovigilance Plan, p101.].

### 3.2 Clinical Safety Database (N = 122)

#### Study population

The clinical safety database comprises of 122 subjects treated with Cuvitru (IGSC, 20%) in a pooled analysis set (Studies 170903 and 170904). Adults and children ≥2 years with PID were included. The study population is further described in Table 1.

**Table 1: Patient characteristics in study population**  
(pooled data from clinical studies 170903 and 170904)

<b>Total</b>	<b>N = 122</b>
<b>Gender</b>	
Male	68 (56%)
Female	54 (44%)
<b>Age</b>	
Median age	32 years
Age range	2 – 83 years
≥65 years	12 (9.8%)
16 to < 65 years	71 (58.2%)
12 to < 16 years	11 (9.0%)
6 to <12 years	22 (18.0%)
≥2 to < 6 years	6 (4.9%)
<b>Race/Ethnicity</b>	
White	114 (93.4%)
Black	3 (2.5%)
Asian	3 (2.5%)
Multiple races	2 (1.6%)

Reviewer comment: Most subjects in safety dataset are adults < 65 years. Thus there are limited clinical data available on use of Cuvitru in younger children and elderly persons ≥ 65 years.

#### Treatment exposure

122 subjects received 6,856 infusions of Cuvitru over a median of 365 exposure days; range of exposure: 30 – 629 days (Table 2). The median (range) weekly dose of Cuvitru was 0.17 (0.08 – 0.46) g/kg/week.

<sup>8</sup> FDA Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency (dated June 2008) <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm078526.pdf>

The maximum infusion volume per injection site varied between pediatric and adult patients. For subjects with a body weight  $\geq 40$  kg, up to 60 mL was to be administered per infusion site if well tolerated. For subjects with a body weight  $<40$  kg, 20 mL per infusion site was administered for the initial two infusions, but if well tolerated the volume was to be increased to a maximum of 60 mL for subsequent infusions. In Study 170904, the median maximum rate of Cuvitru infusion per site was 60 mL/hr and a median of 2.0 sites/infusion were used per administration. In Study 170903, the median maximum rate of Cuvitru infusion per site was 20 mL/hr and a median of 2.0sites/infusion were used per administration.

**Reviewer comment:** The treatment exposure was generally consistent in the study population. As per the sponsor, “median/mean treatment duration did not vary substantially between age groups.” In study 170904, “the maximum infusion rate and volume per site...varied between pediatric and adult patients” which is expected.

**Table 2: Summary of Exposure to Cuvitru**  
[Source: BLA submission, module 2.7.4, page 9]

(N=122, Total Exposure Days=47247, Total Number of Infusions=6856)

Statistics	Exposure days [days]	Number of Infusions	IGI Dose [g]	IGI Dose/Body Weight/Week [g/kg/week]
Mean	387.3	49.7	12.37	0.1858
SD	100.6	19.59	6.675	0.07789
Min	30	3	2.6	0.076
Q1	358	51	6.4	0.123
Median	365	51	11.3	0.171
Q3	414	56	17.4	0.231
Max	629	88	30	0.462

Source: IGSC, 20% ISS [Table 10](#)

### All Adverse Events (AEs)

10 serious AEs (SAEs) in 8 subjects and 1,389 non-serious AEs in 111 subjects were reported in the clinical safety dataset (N = 122). AEs that occurred in 10% or more subjects (very common) included local reactions, infusion/ injection site erythema and injection/ infusion site pain/ infusion site discomfort. AEs reported in 1% to less than 10 % of subjects (common) included headache, injection/ infusion site pruritus, fatigue, nausea, diarrhea, infusion site swelling, infusion site urticaria, myalgia, dizziness, migraine and somnolence.

**Reviewer comment:** Most AEs were non-serious and transient. AEs associated with local injection site reactions are expected with the subcutaneous route of administration, but were mostly mild and self-limited.

### Treatment-related AEs

A total of 394 non-serious AEs (including or excluding infections) in 48/122 (39%) subjects were assessed by investigators as related to Cuvitru, of which there were 229 local AEs and 165 systemic AEs. The rate per subject of non-serious, treatment-related AEs with Cuvitru was 3.230, which compares favorably with a rate of 3.284 when the Cuvitru data are pooled with data from Gammagard Liquid (supportive study 160601). The rates per subject of non-serious AEs are further classified as local v. systemic AEs:

- related non-serious *local* AEs: 1.877 (mild: 1.820 events/subject; moderate: 0.057 events/subject; none severe)
- related non-serious *systemic* AEs: 1.352 (mild: 0.828 events/subject; moderate: 0.525 events/subject; none severe).

Reviewer comment: All AES (local and systemic) that the investigators assessed as treatment-related were non-serious in nature.

### **Infusional AEs**

99.8% of infusions of Cuvitru were tolerated without an infusion rate reduction, interruption or stop. Total of 6,856 Cuvitru infusions administered during Studies 170903 and 170904 were tolerated according to the pre-defined analysis criteria, i.e., these infusions were administered without a need for a dose reduction due to an AE. During Cuvitru treatment, the rate per infusion of all SAEs was 0.001 and the rate of all non-serious AEs was 0.208 events per infusion. The rate per infusion of non-serious treatment-related AEs was 0.059; with 0.025 *systemic* AEs/infusion and 0.034 *local* AEs/infusion (mild and moderate; none severe). Achieving a maximum volume per site of 60 mL was not associated with an increase in the rate of local or systemic AEs. ADRs associated with 1% to less than 10 % of infusions (common) included local reactions, infusion/ injection site erythema and headache.

Reviewer comment: Infusions were generally well tolerated and most commonly associated with local injection site reactions that are expected with the subcutaneous route of administration.

### **Temporally-associated AEs**

There were 654 non-serious temporally-associated AEs in 81 subjects that began during or within 72 hours after completion of Cuvitru infusion, of which there were 382 *systemic* AEs in 73 subjects, and 272 *local* AEs in 41 subjects.

Reviewer comment: All temporally-associated AEs were non-serious.

### **Serious Adverse Events (SAEs)**

A total of 10 SAEs were reported in 8 subjects receiving Cuvitru. The annualized rate was 0.077 SAEs per subject during Cuvitru treatment.

- Study 170904: 2 subjects treated with Cuvitru reported 2 SAEs
  1. Lung adenocarcinoma (Subject (b) (6)): 68 year-old female with PID, who was a former smoker and had a family history of lung cancer, was diagnosed with lung adenocarcinoma/non-small cell lung cancer. She underwent surgery and began chemotherapy. This AE was categorized as unrelated to treatment.
  2. Pneumonia (Subject (b) (6)): 80 year-old male had a prior history of “specific antibody deficiency with IgG subclass deficiency,” past episodes of pneumonia, bronchiectasis, chronic bronchitis, allergic bronchopulmonary aspergillosis, asthma, and cardiac disease. While on Cuvitru treatment during the clinical study (3 days following last Cuvitru administration), he developed pneumonia with perihilar and lower lobe infiltrates on chest X-Ray. Blood cultures showed no growth. He was treated with Levaquin and recovered. This AE was categorized as unrelated to treatment.
- Study 170903: 6 subjects treated with Cuvitru reported 8 SAEs
  1. Acute myocardial infarction, ventricular fibrillation and brain stem infarction (Subject (b) (6)): 62 year-old male with common variable immunodeficiency and history of hypertension, hyperlipidemia and coronary artery disease (reported as “3-vessel heart disease”) experienced non-ST segment elevation myocardial infarction and underwent minimally invasive cardiac surgery. An external pacemaker was used which led to

ventricular fibrillation on the day after surgery, and he needed to be resuscitated. During cardiac resuscitation, he suffered a cerebrovascular accident (embolic) resulting in left brain stem infarction to the mesencephalon and thalamus. Due to multiple risk factors and prior cardiac disease, AEs were categorized as unrelated to treatment by sponsor.

2. Enteritis (Subject (b) (6)): 46 year-old female subject with history of common variable immunodeficiency, giardiasis and celiac disease, presented with vomiting and diarrhea and was diagnosed with acute viral enteritis. This AE was categorized as unrelated to treatment
3. Bacterial pneumonia (Subject (b) (6)): Acute bacterial pneumonia in a 12 year-old male subject with history of X-linked agammaglobulinemia and past episodes of pneumonia. Four days post-treatment, he presented with productive cough and headache, and washospitalized for pneumonia. Chest X-ray showed pulmonary infiltrates; he had leukocytosis (WBC 16.7). He received treatment with Cefuroxim and clarithromycin. This AE was categorized as unrelated to treatment.
4. Chronic sinusitis (Subject (b) (6)): Acute exacerbation of chronic maxillary sinusitis in a 17 year-old female with a history of common variable immunodeficiency. Six days post-treatment, she experienced an acute exacerbation of sinusitis. On an unreported date, she had endoscopic sinus surgery and recovered without complications. This AE was categorized as unrelated to treatment.
5. Rhinorrhea (Subject (b) (6)): Chronic rhinorrhea and dry cough in 6 year-old male with X-linked agammaglobulinemia. He underwent adenoidectomy and symptoms resolved. This AE was categorized as unrelated to treatment.
6. Nasal septum deviation (Subject (b) (6)): 40 year-old male with history of CD40 ligand deficiency, impaired nasal breathing due to nasal septum curvature and chronic sinusitis was planned to undergo a corrective nasal septum surgery prior to clinical study screening. This AE was categorized as unrelated to treatment.

Reviewer comment: SAE case narratives from the Clinical Study Reports were reviewed in detail. Overall, there were very few SAEs in the clinical safety database, and these SAEs were neither causally related to Cuvitru nor temporally-associated with Cuvitru administration; alternate etiologies were present. Two TEEs (acute myocardial infarction and brain stem infarction) were reported in a single subject in study 170903, with a complicated medical history of cardiac disease and multiple pre-existing risk factors. Though the sponsor assessed these AEs as unrelated to treatment, it is difficult to make a determination on relationship to treatment due to multiple confounders. Thromboembolic event is classified as an important potential risk for Cuvitru and the proposed package insert includes a boxed warning for thrombosis. While we defer to the OBRR clinical review of the efficacy results, it should be noted here that lack of efficacy (i.e. bacterial infections due to underlying PID and treatment failure) is closely associated with AEs, and may represent confounding by indication.

#### **Withdrawals due to AEs**

2 subjects receiving Cuvitru withdrew from clinical trials due to AEs.

- Study 170904: Subject (b) (6) experienced 3 non-serious AEs (diarrhea, dizziness and fatigue) of mild severity on April 8, 2014 while receiving Cuvitru. The subject felt that the fatigue was possibly due to treatment, and chose to discontinue from the study on April 23, 2014.
- Study 170903: Subject (b) (6), aged 16 years, reported 3 non-serious AEs of infusion site pain during and after Cuvitru administration and withdrew from the study.

Reviewer comment: Only 2 subjects on Cuvitru treatment withdrew from the studies due to AEs. None of the subjects who had experienced SAEs withdrew due to AEs.

### Analysis of AEs by Organ System or Syndrome

Regardless of seriousness or relatedness, AEs were classified by MedDRA system organ class and preferred term as follows –

- Non-serious AEs in 10% or more of subjects (i.e. “very common”) – local reactions (N = 261), upper respiratory tract infections (N = 67), headache (N = 160), injection site pain, infusion site discomfort and infusion site pain (N = 70), sinusitis (N = 36), diarrhea (N = 79), cough (N = 27), bronchitis (N =28), acute sinusitis (N = 26), infusion site erythema and injection site erythema (N = 77), nasopharyngitis (N = 23), nausea (N = 24), fatigue (N = 20).
- Non-serious AEs associated with 1% to < 10% of infusions: local reactions (N = 261), headache (N = 160), diarrhea (N = 79), infusion site/injection site erythema (N = 77), injection site pain, infusion site discomfort/pain (N = 70) and upper respiratory tract infection (N = 67).
- Headache was the most frequently reported causally-related and/or temporally-associated non-serious AE, followed by diarrhea, fatigue and nausea. Additional causally-related or temporally-associated PTs with corresponding AE rates are provided in Table 3 (data from study 170904).
- Infusion site erythema was the most frequently reported causally related and/or temporally associated non-serious *local* AE. Other *local* non-serious AEs reported frequently included infusion site swelling, infusion site pain, infusion site pruritus, infusion site discomfort, infusion site urticaria and injection site pain. The rates of AEs from the studies with Cuvitru (studies 170903 and 170904) were similar to the rates of AEs from pooled data including supportive study with Gammagard Liquid (pooled studies 170903, 170904 and 160601).

**Table 3: Causally-related and/or temporally-associated non-serious AEs in Study 170904**

[Source: BLA submission, module 2.7.4, page 24]

Preferred Term	AEs Rate per		
	Subject	Infusion	Year
headache	0.676	0.012	0.6
infusion site pain	0.459	0.008	0.41
infusion site erythema	0.311	0.005	0.27
nausea	0.216	0.004	0.19
sinusitis	0.162	0.003	0.14
upper respiratory tract infection	0.162	0.003	0.14
fatigue	0.122	0.002	0.11
infusion site pruritus	0.108	0.002	0.10
diarrhea	0.068	0.001	0.06
vomiting	0.068	0.001	0.06
bronchitis	0.068	0.001	0.06
acute sinusitis	0.054	<0.001	0.14

Source: [Appendix Table 2.](#) and [Table 3.](#)

Rate per Subject = Total number of AEs divided by the total number of subjects under treatment.

Rate per Infusion = Total number of AEs divided by the total number of infusions under treatment.

Rate per Year= Total number of AEs divided by the total number of subject-years under treatment.

Notes:

- Only preferred terms with  $\geq 5\%$  of subjects experiencing them, under the SC 20% treatment, have been included.

- Temporally Associated Adverse Events are defined as adverse events that begin during the infusion or within 72 hours of completion of the infusion

### **AEs of Special Interest (AESI)**

There were no thrombotic or thromboembolic events reported in study 170904. During study 170903, one event of acute myocardial infarction and one event of brain stem infarction were reported in a single subject with cardiovascular risk factors and preexisting cardiac disease; the investigators stated that neither of these TEEs was treatment-related. Thromboembolic event is an important potential risk for Cuvitru. No cases of renal AEs, aseptic meningitis or anaphylactic reaction were reported. Laboratory values were assessed for potential hemolysis. Six subjects in Study 170904 and 6 subjects in Study 170903 experienced a decrease in hemoglobin of  $\geq 2.0$  g/dL; however no cases were confirmed to be due to a treatment-induced hemolytic reaction. As per Baxalta, "At no time was there a concordance of other laboratory tests (e.g., Coomb's test, haptoglobin, LDL, urinary hemosiderin) confirming a diagnosis of hemolysis."

Reviewer comment: Two TEEs were reported in the same subject study 170903, though both were assessed to be unrelated to treatment, as described previously. Hemolysis is an important potential risk for this product. Other AESIs common to the class of IG products were not observed in Cuvitru trials. However the clinical safety database is limited by small sample size with limited follow-up data.

### **Deaths**

No subject died during clinical studies.

### **Conclusion**

Overall assessment of the clinical safety database does not reveal any clinically significant safety issues that would require additional pharmacovigilance measures in the post-licensure period, should the product be licensed.

## **4. PHARMACOVIGILANCE PLAN (PVP) Version 1.0; dated September 1, 2015**

The Pharmacovigilance Plan includes the sponsor's assessment of identified and potential risks and missing information (Table 4) based on pre-licensure clinical trial data, published literature, known product-class effects, and other relevant sources of safety information. As per Baxalta's proposed Pharmacovigilance Plan (Version 1.0 dated September 1, 2015), routine pharmacovigilance is proposed for the identified and potential risks and missing information for Cuvitru (Table 4). Spontaneous AE reports will be captured in the Baxalta database BASIS (Baxalta Safety Information System). Routine pharmacovigilance activities include adverse event reporting in accordance with 21 CFR 600.80, as well as continuous monitoring of the safety profile including signal detection and evaluation. This process will include 15-day expedited reports for serious, unlabeled (unexpected) AEs, and quarterly periodic safety reports for 3 years (annual thereafter).

**Table 4: Summary of Safety Concerns and Proposed Actions**  
 [Source: BLA submission, module 1.16 PVP, page 46]

<b>Safety Concern</b>	<b>Proposed Pharmacovigilance Activities</b>  <b>(Routine and Additional)</b>
<b>Important identified risks</b>	
Interference with serological tests after infusion on immunoglobulin	Routine Pharmacovigilance
Altered immune response to live attenuated vaccines and implications for laboratory testing: Reduced efficacy of live attenuated vaccines such as measles, mumps, rubella, and varicella	Routine Pharmacovigilance
<b>Important potential risks</b>	
Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency and EgA antibodies	Routine Pharmacovigilance
Hemolysis/hemolytic anemia	Routine Pharmacovigilance
Thromboembolic events	Routine Pharmacovigilance
Transmission of infectious agents	Routine Pharmacovigilance
Severe renal adverse reactions including renal failure	Routine Pharmacovigilance
Aseptic meningitis syndrome	Routine Pharmacovigilance
<b>Missing information</b>	
Lack of information on safety in pregnant and lactating women	Routine Pharmacovigilance
Limited information on safety in neonates or infants <2 years old	Routine Pharmacovigilance
Limited information in patients with organ impairment (e.g., kidney, liver, or cardiac)	Routine Pharmacovigilance
Limited information on safety in elderly patients 65 and older	Routine Pharmacovigilance

## 5. INTEGRATED RISK ASSESSMENT

### 5.1 Safety issues common to the IGIV class: *thromboembolic events; hemolysis; acute renal failure; hypersensitivity reactions; aseptic meningitis, interference with serological tests; reduced efficacy of live attenuated vaccines*

Thromboembolic events (TEE), hemolysis and acute renal failure are common to the IGIV class.<sup>9,10,11</sup> True hypersensitivity reactions associated with IGIV are rare<sup>12</sup>, but can occur in patients with anti-IgA

<sup>9</sup> FDA Safety Communication: Updated information on the risks of thrombosis and hemolysis potentially related to administration of intravenous, subcutaneous and intramuscular human immune globulin products. Available at <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm327934.htm>

<sup>10</sup> FDA. Immune Globulin Products (Human) intravenous, subcutaneous and intramuscular. Detailed View: Safety Labeling Changes Approved By FDA Center for Biologics Evaluation and Research (CBER) – June 2013. Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360566.htm>

<sup>11</sup> FDA. Adverse Event Report for an Immune Globulin: FDA Investigation and Actions. Available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/InternationalActivities/UCM273193.pdf>

<sup>12</sup> Guideline on Core SmPC for Human Normal Immunoglobulin for Intravenous Administration (IGIV) European Medicines Agency EMA/CHMP/BPWP/94038/2010 rev. 3.

antibodies and as per Section 4 of the proposed package insert, Cuvitru is “contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity to human immune globulin treatment.” Aseptic meningitis is a rare complication that has been associated with all commercial preparations of IGIV at an estimated rate ranging from 0-1%<sup>13</sup> of patients. Interference with laboratory tests (false positives) and reduced efficacy of live attenuated vaccines are known phenomena due to passive transfer of antibodies during treatment.

Clinical Data: Two TEEs (acute myocardial infarction and brain stem infarction) were reported in a single subject in study 170903; the case was complicated by confounders (pre-existing conditions and risk factors) and TEEs were assessed as unrelated to treatment. Other AESIs common to the class of IG products were not reported in the clinical safety database.

Actions: Routine PV and class labeling are planned for these important identified and potential risks.

## 5.2 Transmission of infectious agents

Cuvitru is derived from large pools of human plasma. The potential risk of transmission of infectious pathogens is common to products derived from donor plasma. Every individual plasma donation is tested for hepatitis B surface antigen (HBsAg), antibodies to human immunodeficiency virus (HIV) and hepatitis C virus (HCV). In addition, Baxalta has implemented a donation sample mini-pool strategy to test for the presence of HIV-1, (b) (4), HCV, (b) (4) and (b) (4) nucleic acids. The manufacturing process includes three virus reduction steps in the downstream purification: (i.) solvent/detergent (S/D) treatment; (ii.) nanofiltration; and (iii.) incubation at low pH and elevated temperature in the final formulation.

Clinical Data: Infectious transmission was not reported in the clinical studies of Cuvitru.

Actions: Routine PV and class labeling are planned for this important potential risk.

## 5.3 Limitations of small sample size and limited follow-up

Based on the rarity of the clinical indication of PID, the clinical trials were small and the clinical safety database included 122 subjects. Most subjects were adults < 65 years. There are limited clinical data available on use of Cuvitru in children (N = 39) and elderly patients ≥65 years (N = 12). There were a total of 39 pediatric subjects (6 subjects aged 2 to <6 years, 22 subjects aged 6 to <12 years and 11 subjects aged 12 to <16 years) and though the pediatric safety dataset is limited, there were no differences in the safety and efficacy profiles as compared with adult subjects in these small trials; specifically no pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The following patient populations were excluded from clinical trials: pregnant and lactating women, patients with renal, liver, or cardiac impairment.

The main limitation of the safety dataset is the small sample size exposed in clinical trials. This limitation makes the detection of rare adverse events unlikely; and there are no safety data on the use of Cuvitru in under-represented patient populations. Therefore, the sponsor has listed the safety profile of Cuvitru in these select populations as Important Missing Information in the proposed PVP, and proposes routine PV. The proposed package insert, section 8 (Use in Specific Populations) also describes these limitations. The clinical trials have limited follow-up and do not provide long term safety data. Subjects were treated 0.5 years to <2 years in clinical trials. PID is a chronic condition which requires long term/lifelong treatment.

## 5.4 Postlicensure Safety Data

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<sup>13</sup> Orbach O, Katz U, Sherer Y, et al: Intravenous immunoglobulin: adverse effects and safe administration. Clin Rev Allergy Immun. 2005; 29(3): 173-84

Cuvitru is currently not licensed in any country, and there are no post-licensure materials for review.

## **5.5 Conclusion**

Final determination of the benefit/risk profile of Cuvitru is pending the clinical, statistical and product reviews. Safety-related data and the proposed pharmacovigilance plan for Cuvitru have been reviewed. 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.

## **6. OBE RECOMMENDATIONS**

Based on review of the pre-licensure clinical trial safety data and the sponsor's proposed Pharmacovigilance Plan (Version 1.0, dated September 1, 2015) in BLA 125596, should the product be licensed, routine pharmacovigilance is recommended to monitor the risks associated with Cuvitru.