Summary Basis for Regulatory Action

Date: December 12, 2018

From: Michael Kennedy, PhD, Chair of the Review Committee, OTAT/DPPT/PDB

STN#: BLA 125668/0

Applicant Name: OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

Date of Submission: December 28, 2017

PDUFA Goal Date: December 28, 2018

Proprietary Name/ Established Name: CUTAQUIG/ Immune Globulin Subcutaneous (Human)

Indication: Treatment of primary humoral immunodeficiency

Recommended Action:
The Review Committee recommends approval of this product.

Review Office Signatory Authority: Wilson W. Bryan, MD, Director, Office of Tissues and Advanced Therapies

☐ **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.**

The table below indicates the material reviewed when developing the SBRA:

Document title	**Reviewer name, Document date**
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)*	Nancy Eller, MS, OTAT/DPPT Lu Deng, PhD, OTAT/DPPT Malgorzata Norton, MS, OTAT/DPPT Randa Melhem, PhD, OCBQ/DMPQ Amanda Trayer, OCBQ/DMPQ
Clinical Review(s) • *Clinical (product office)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Leland R. Pierce, MD, OTAT/DCEPT Shaokui We, MD, OBE/DE Erin McDowell, OCBQ/DIS
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Boris Zaslavsky, PhD, OBE/DB
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	Evi Struble, PhD, OTAT/DPPT
Clinical Pharmacology Review(s)	Xiaofei Wang, PhD, OTAT/DCEPT
Labeling Review(s) • *APLB (OCBQ/APLB)*	Stephanie Donahoe, OCBQ/DCM Alpita Popat, OCBQ/DCM
Other Review(s) • *Lot release protocol/testing plan* • *Test method validations*	Varsha Garnepudi, OCBQ/DBSQC Leslyn Aaron, OCBQ/DBSQC Hsiaoling (Charlene) Wang, OCBQ/DBSQC Simleen Kaur M.Sc., OCBQ/DBSQC Jing Lin, OCBQ/DBSQC
Advisory Committee summary	BLA was not presented to Blood Products Advisory Committee (BPAC)

1. Introduction

Cutaquig is a 16.5% subcutaneous immune globulin product which is indicated for the treatment of primary humoral immune deficiency (PI). It is manufactured by a process that is nearly identical to Octapharma's licensed intravenous immune globulin Octagam 5% and 10%. It is only manufactured at Octapharma's licensed Vienna, Austria facility with labeling and packaging at either Vienna or Octapharma's Dessau, Germany facility. The Biologics License Application (BLA) for this product was received on December 28, 2017 and it received a standard 12-month review.

2. Background

Octapharma's Immune Globulin Subcutaneous (Human) (IGSC) product (Cutaquig, formerly termed (b) (4) was developed as a replacement therapy in primary humoral immune deficiency (PI). PI represents a heterogenous group of disorders resulting from largely inherited defects of the immune system. It is estimated that 1-2% of the population worldwide is affected[1]. The major antibody deficiency syndromes of clinical significance include X-linked agammaglobulinemia (XLA), Common Variable Immunodeficiency (CVID), Wiskott-Aldrich Syndrome, Hyper IgM Syndrome, Severe Combined Immunodeficiency (SCID), Chronic Granulomatous Disease (CGD), and IgG subclass deficiency. These disorders are marked by hypogammaglobulinemia, which increases susceptibility to infections. Patients with PI are at increased risk for recurrent, severe bacterial infections, especially respiratory tract infections. Replacement therapy with immunoglobulins, such as Immune Globulin Intravenous (Human) (IGIV) and IGSC, provides antibodies to help prevent viral and bacterial diseases and is a mainstay of treatment. At the time of the BLA submission, Cutaquig has not been marketed in any country.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

Cutaquig is a liquid formulation of 16.5% human IgG, manufactured from U.S. (b) (4) plasma only. The Cutaquig manufacturing process has a shared manufacturing scheme with Octapharma's intravenous immunoglobulins (U.S. licensed Octagam 5% and 10%) using the (b) (4) step where the product is (b) (4) to 16.5% and final formulation occurs. Virus clearance is ensured by the steps of Separation of (b) (4) (b) (4), S/D Treatment and pH 4 Treatment. The final product is (b) (4) with (b) (4) mg/mL of maltose and (b) (4) of Polysorbate 80 with a pH range of 5.0-5.5. Octapharma requested a shelf-life of 2 years at 5 ± 3°C with 6 months at 25 (b) (4) during the shelf-life. If the material is not used during this latter 6 months, it will be discarded. The 24 months of stability data for both long-term conditions at both 5°C (b) (4) were within specifications except for some measles results. The measles results were within specifications at future test points. The levels of aggregates and fragments were well below the requested specification of (b) (4); FDA requested that Octapharma reduce the specification to 3%. Octapharma agreed to this change.

For the U.S. market, Cutaquig will be manufactured at Octapharma Pharmazeutika Produktionsges.m.b.H., Oberlaaer Strasse 235, 1100 Vienna, Austria (OPG, FEI: 3002809097), including visual inspection, labeling and packaging. Visual inspection, labeling and packaging can alternatively be performed at Octapharma GmbH Dessau, Otto-Reuter-Str. 3, 06847 Dessau, Germany, (ODE, FEI: 3008923644).

[1] Modell V, Quinn J, Orange J, et al. Primary immunodeficiencies worldwide: an updated overview from the Jeffrey Modell Centers Global Network. *Immunol Res*. 2016;64:736-753.

The analytical methods and their qualifications and/or validations reviewed for the Immune Globulin Subcutaneous (Human) drug substance and drug product were found to be adequate for their intended use.

Polysorbate 80 (PS80) content in Cutaquig was not measured in the stability studies. Since PS80 has been shown to reduce the level of aggregation in biologics; FDA requested that the applicant include PS80 measurement in stability studies. It was also requested that IgG Content and (b) (4) be included as release and stability tests. IgG Content and Clarity are currently included in testing for the applicant's intravenous immune globulins products. (b) (4) is a (b) (4) test which includes a standard for (b) (4) which will improve the standardization of their visual inspection.

b) CBER Lot Release

The lot release protocol template was submitted to the Center for Biologics Evaluation and Research (CBER) for review and found to be acceptable after revisions. 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 Cutaquig (immune globulin subcutaneous, human) are listed in the table below. The activities and inspectional histories for each facility are noted in the table and further described in the paragraphs that follow:

Manufacturing Facilities for Cutaquig

Name/Address	***FEI Number***	***DUNS Number***	***Inspection / Waiver***	***Justification / Results***
Drug Substance *Drug Product* *Visual Inspection* *Labeling and packaging* *Release Testing* *Batch Release* Octapharma OPG Oberlaaer Strasse 235, A-1100, Vienna, Austria	3002809097	301119178	Waived	Team Biologics January 9 – 17, 2017 VAI
Drug Product *Visual Inspection* *Labeling & Packaging* Octapharma ODE Otto-Reuter-Straße 3, Dessau-Roßlau, 06847 Germany	3008923644	312916852	Waived	Team Biologics February 15 – 18, 2016 VAI

Team Biologics performed a surveillance inspection of Octapharma OPG from January 9 – 17, 2017. All issues that were listed in Form 483 were resolved, and the inspection was classified as voluntary action indicated (VAI).

The Octapharma ODE facility was inspected by Team Biologics from February 15 – 18, 2016. All 483 issues were resolved, and the inspection was classified as VAI.

d) Container Closure System

Cutaquig is a liquid formulation and intended for subcutaneous injection. It is available in six different fill volumes in 4 different vial sizes. A description for the primary packaging (vial, stopper, and cap) is summarized in the following Table:

Primary Packaging Description

Container closure system	**Size/Fill Volume**
Vials: Non-siliconized glass (b) (4) (b) (4) clear/colorless, (b) (4) (b) (4) supplied by (b) (4) (b) (4)	10mL (6mL fill volume)
	20mL (10mL and 12mL fill volumes)
	30mL (20mL and 24mL fill volumes)
	50mL (48mL fill volume)
Stopper: Bromobutyl rubber, (b) (4) (b) (4) supplied by (b) (4)	20 mm light grey ((b) (4)) used for all vial sizes (10mL - 50mL)
Cap: Aluminum flip off supplied by (b) (4)	20mm blue cap – used for all vial sizes

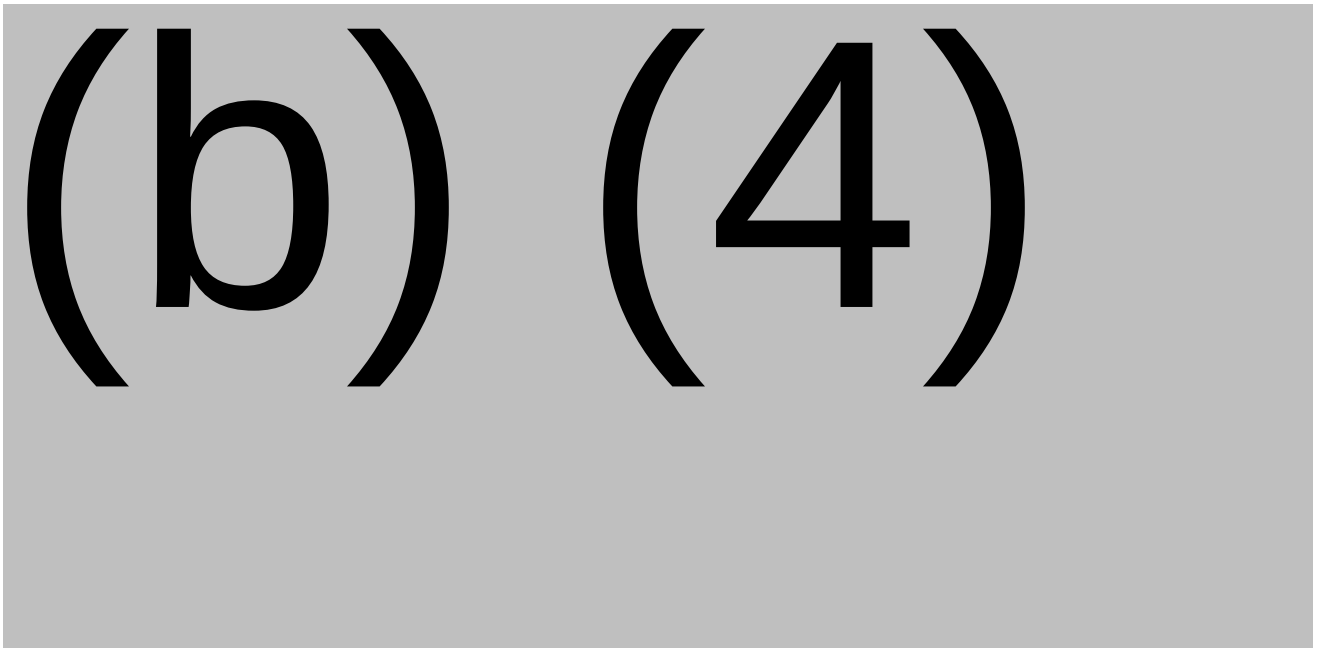
Container closure integrity testing (CCIT) was performed at the OPG Vienna facility by the (b) (4) method; all acceptance criteria were met.

e) 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.

f) Product Comparability

The clinical lots were manufactured at Octapharma's (b) (4) facility. The conformance lots were manufactured in Octapharma's Vienna facility where they will manufacture all future lots of Cutaquig. There are a few differences between the facilities including:



4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Cutaquig is a 16.5% immune globulin preparation intended for subcutaneous administration. Given the existing safety database for IGIV products, the toxicology program was tailored to the new subcutaneous preparation and consisted of two safety pharmacology studies and a local tolerance study. There were no adverse effects attributed to Cutaquig in any of the safety studies, and findings are summarized below:

a) When administered to rabbits intravenously at a dose volume of 2.4 mL/kg, equal to the highest human dose used in the clinical trial, Cutaquig did not display any thrombogenic properties.

b) When administered to dogs at 3 mL/kg, or 1.25 times higher than the highest human dose used in the clinical trial, Cutaquig did not show cardiovascular adverse effects or potential for QT interval prolongation.

c) A single subcutaneous injection of 5 mL Cutaquig in rabbits did not cause any adverse effects systemically or at the injection site.

Cutaquig contains maltose and polysorbate 80 (PS80) as excipients. These substances are present in other approved IGIV products and their presence and quantity in Cutaquig do not raise toxicologic concerns.

There are no toxicologic concerns with the impurity profile of Cutaquig.
Given the lack of toxicity of Cutaquig when administered in animals and its favorable formulation and impurity profiles, there are no pharmacology and toxicology issues that would prevent the approval of this BLA.

5. CLINICAL PHARMACOLOGY

The clinical pharmacology section of this BLA is supported by a prospective, open-label, non-controlled, single-arm, multicenter Phase 3 study that evaluated the

pharmacokinetics (PK), efficacy, tolerability and safety of subcutaneous human immunoglobulin (Cutaquig, also referred to as (b) (4) 16.5%) in subjects with PI.

The PK sub-study comprised a full PK profile after the last administration of the previously used IGIV product before a subject was switched to Cutaquig (PK_{IV}), a full PK profile at the end of the 12-week wash-in/wash-out phase (PK_{SC1}) and a final PK profile after 28 administrations of (b) (4) 16.5% (at steady state) to assess the bioavailability of total IgG with respect to the two administration methods (PK_{SC2}). All study subjects were on regular, steady-state intravenously administered immunoglobulin (IGIV) treatment before entering the study.

The PK sub-study included 19 adult subjects (17 years of age and older), and eighteen adult subjects completed all PK assessments. Compared to IGIV administration, IGSC administration showed notably flat PK profiles at steady-state. Steady-state bioavailability (AUCτ) of total IgG was comparable between IGSC and IGIV (standardized to a 7-day period) of IGIV. The least squares geometric mean of the ratio (SC2:IV) in the adult subjects was 1.02 (90% CI: 0.96 – 1.08, n=18). The actual dose conversion factors from IGIV to IGSC of individual subjects ranged from 1.23 to 1.89 (mean: 1.40).

The PK parameters of total IgG following IGIV and IGSC administration at steady-state in adult subjects are shown in Table 1.

Table 1. Key Pharmacokinetic Parameters for CUTAQUIG and IGIV in Adults

Parameter [Arithmetic Mean (SD)]	**IGIV** (n=18)	**CUTAQUIG** (n=18)
C_{max} [g/L]	19.7 (5.6)	14.0 (4.4)
C_{min} [g/L]	10.5 (2.6)	12.0 (3.5)
T_{max} [h] #	2.9 (2.1 - 69.5)	49.3 (1.8 - 98.3)
AUC_{tau} [g*hr/L]	2182 (692)*	2408 (673)
AUC_{tau} [mg*day/dL]	9091 (2881)*	10031 (2804)
Actual IgG Dose per kg Body Weight and Week (g/kg/week)	0.135 (0.059)	0.188 (0.083)

T_{max} is presented as Median (range)
* standardized to a 7-day period

In addition to weekly administration of Cutaquig, the applicant proposed alternative dosing regimens: frequent (b) (4) . To support the alternative dosing regimens, the applicant submitted a population pharmacokinetic (PopPK) study. However, the PopPK study is inadequate to support frequent dosing regimens due to the lack of evaluation of the absorption phase and likelihood of inappropriate half-life estimation in the modeling and simulation for subcutaneous administration of Cutaquig. Considering the long half-life of IgG, frequent dosing regimens ((b) (4)) may lead to drug accumulation and raise safety concerns. Therefore, the applicant's proposed frequent dosing regimens ((b) (4) (b) (4) are not acceptable.

From a clinical pharmacology standpoint, the PK data contained in the BLA acceptably support approval for weekly subcutaneous administration of Cutaquig for the treatment of PI in adults.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The BLA was reviewed under the traditional regulatory approval pathway.

A Phase 3 study (Protocol SCGAM-01) conducted under IND at 18 sites in the U.S., Eastern Europe, and Canada was the primary basis for evaluation of safety and effectiveness. A non-IND study (SCGAM-04), which was conducted in Russia with 25 subjects with an observation period of up to six months, was considered supportive. A total of 61 subjects with PI was enrolled in Study SCGAM-01: 23 pediatric subjects aged <16 years and 38 adult subjects. This included 4 subjects aged 2 to < 5 years, 11 subjects 5 to < 12 years, and 8 subjects 12 to < 16 years of age. The weekly subcutaneous dose of Cutaquig used in the study was calculated by taking the subject's IGIV dose, dividing by the number of weeks of the IGIV inter-dose interval, and multiplying by 1.50, the dosage correction factor. The dosage correction factor was used in an attempt to match the area under the curve (AUC) of serum IgG concentration under Cutaquig treatment to the AUC under prior IGIV treatment and was used because of the lower bioavailability of IGSC compared to IGIV. However, following review of preliminary pharmacokinetic data, the actual mean dosage correction factor was changed as it was observed to be 1.40, which is the recommended value in the package insert. The study involved a 15-month treatment/observation period (including a 3-month washout/wash-in period and a 12-month primary efficacy period) with the incidence of serious bacterial infections (SBIs) as the primary endpoint. The study was ongoing at the time of the BLA submission and the 4-month safety update. All adult subjects had completed participation, but eight pediatric subjects had not yet completed study participation at the time of the data cutoff date. A total of six subjects (9.8%) terminated the study early (three adolescents [37.5%] and 3 adults [7.9%] had withdrawn consent). The number of subject-years of exposure/observation during the 12-month primary analysis period was 4.2 for adolescents, 9.1 for younger children, and 32.5 subject-years for adults. No SBIs were observed in the trial, and the upper bound of the 99% confidence interval for the incidence of SBIs (0.084) was < 1.0 SBI per subject-year; therefore, the study met the primary efficacy endpoint.

Secondary efficacy endpoints consisted of the following:

- Annual rate of all infections regardless of seriousness
- Non-serious infections (total and by category)
- Time to resolution of infections
- Use of antibiotics (number of days and annual rate)
- Hospitalizations due to infection (number of days and annual rate)
- Episodes of fever

- Days missed from work/school/kindergarten/day care due to infections and their treatment
- QoL assessments using the Child Health Questionnaire-Parent Form (CHQ-PF50) or SF-36 Health Survey

The outcomes of secondary efficacy endpoints were generally within the range observed in Phase 3 IND trials of other U.S.-licensed IGSC products. Results of selected secondary efficacy endpoints are shown in the following table.

Summary of Selected Secondary Efficacy Endpoints (12-month efficacy period, full analysis set)

Number of subjects (efficacy period)	**61**
Total number of subject years	54.77
Infections	
Annual rate of non-SBI infections per subject-year (same as rate of all infections)	3.43 (Upper one-sided 95% confidence limit: 4.57)
Systemic antibiotic use	
Number of subjects (%)	40 (65.6%)
Annual rate (treatment days per subject-year)	39.6 (Upper one-sided 95% confidence limit: 62.7)
Days out of work/school/kindergarten/day care due to infections	
Number of days	134
Annual rate (days per subject-year)	2.6 (Upper one-sided 95% confidence limit: 4.7)
Hospitalization due to infections	1
Number of days	2
Annual rate (days per subject-year)	0.04 (Upper one-sided 95% confidence limit: 0.19)

The biostatistical reviewer confirmed the results of the analyses of the primary efficacy endpoint and the secondary efficacy endpoints presented in the table above, submitted by the applicant.

It is problematic to draw inferences regarding safety and efficacy based on pediatric subgroups due to limited sample size. That said, adolescents had a nominally lower rate of overall infections per subject-year (1.7) than children under 12 years of age (3.2) or adults (3.5 infections per subject-year). Pharmacokinetic (PK) results were available for 18 adults and four pediatric subjects. The number of pediatric subjects who underwent PK testing was insufficient to draw inferences regarding possible PK differences between adults and pediatric age subgroups.

The applicant's request to include flexible dosing (ranging from (b) (4) (b) (4) in the draft package insert was denied. No safety data were submitted to support (b) (4)) dosing, which would require administering (b) (4) the total product volume and dose compared with that used for weekly dosing. Higher infusion site volumes are anticipated to be less well tolerated in terms of local infusion site reactions, such as swelling. The clinical pharmacology reviewer determined that

there were deficiencies in the applicant's population PK study that precluded accepting the proposal for dosing more frequently than weekly.

The applicant's proposal to recommend a dosage adjustment factor of (b) (4) in the draft package insert was not supported by the data from SCGAM-01, because a dosage adjustment factor of 1.40 was used throughout that trial to convert the prior IGIV dose to the Cutaquig dose. The efficacy in terms of achieving the acceptably low rate of SBIs was established using a dosage adjustment factor of 1.40, so this is recommended in the revised draft package insert.

Please see the **Recommendation for Post-Marketing Activities** section of this document for a discussion of the pediatric postmarketing requirement (PMR). No clinical postmarketing commitment studies are recommended.

Bioresearch Monitoring (BIMO) inspections were conducted at four clinical investigator study sites that participated in the conduct of Study SCGAM-01. The inspections did not reveal significant problems that impact the integrity of the data submitted in support of this Biologics License Application (BLA).

b) Pediatrics

The Office of Tissues and Advanced Therapies (OTAT) accepted the Pediatric Review Committee's (PeRC's) recommendation to agree with the applicant's request for a partial pediatric waiver for ages < 2 years, due to impracticality of conducting clinical trials in this very young age group, and a partial pediatric deferral for ages 2 years to < 17 years, due to the product being ready for approval in adults, with the available safety and efficacy data in this age stratum too limited to establish safety and efficacy for pediatric patients ages 2 years to < 17 years.

c) Other Special Populations

No human data are available to indicate the presence or absence of drug-associated risk during pregnancy or lactation. Clinical studies of Cutaquig did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Three study subjects enrolled in the clinical trial were 65 years of age and over.

d) Statistics

The applicant submitted data from a prospective, open-label, non-controlled, single-arm, multicenter Phase 3 study (SCGAM-01). Sixty-one subjects received Cutaquig treatment over a period of 15 months, comprised of a 12-week wash-in/wash-out period followed by a 12-month efficacy phase. Each subject who stayed in the study for the whole period received 64 weekly infusions. The primary efficacy endpoint was the rate of serious bacterial infections (SBIs) per person-year on treatment. No SBIs were observed during the study.

Of the 61 subjects treated, 57 (93.4%) experienced at least one Treatment-Emergent Adverse Event (TEAE), including infections. There were no TEAEs leading to death or withdrawal or other significant AEs. Five serious adverse events (SAEs) were reported in four subjects. None were assessed as related to product.

In summary, there were no statistical analysis issues in this submission. The results of this study appear to support the use of Cutaquig in adults to prevent SBI.

7. SAFETY

The size of the clinical safety database was considered adequate to support the BLA. No postmarketing data for Cutaquig were available. The Phase 3 IND study, Study SCGAM-01, included 61 subjects (38 adults and 23 pediatric subjects age 2 years to < 16 years of age) who were followed for up to 15 months and underwent a total of 54.77 subject-years of observation under the study. Eight pediatric subjects were continuing to participate in the IND study at the time of BLA submission. A non-IND Phase 3 study (SCGAM-04) that was conducted in Russia enrolled 25 subjects who were followed for up to six months. No deaths occurred during either study, and no subjects in either study were described as having discontinued study medication or participation prematurely due to adverse events. A total of six subjects (9.8%) terminated the IND study early (three adolescents [37.5%] and 3 adults [7.9%] withdrew consent).

Five serious AEs (SAEs) were reported in Study SCGAM-01, none of which appeared causally related to Cutaquig infusion per FDA review. No SAEs were reported in Study SCGAM-04. In Study SCGAM-01, the most commonly reported adverse reactions, other than local infusion site reactions, occurring in > 5% of subjects, excluding infections, were: headache, pyrexia, diarrhea, dermatitis, and excoriation. There did not appear to be any category of adverse reaction that was more frequent among adolescents or younger children compared to adults. No thromboembolic events, hemolysis, or cases of anaphylaxis or of aseptic meningitis were reported.

Of 61 subjects in the Safety Analysis set, 57 (94%) reported at least one adverse event (AE), including infections. Excluding infections and infusion site reactions, 49 subjects (80%) experienced 233 AEs. The number of infection AEs was 239. Overall, 75% of subjects reported local infusion site reactions. All local infusion site reactions were deemed causally related to Cutaquig infusion in the FDA review. Twenty-three percent

of infusions (814/3497) were accompanied by local infusion site reactions. Fourteen subjects (23%) experienced moderate intensity local reactions and two subjects (3.3%) experienced severe intensity reactions (bruising at Week 30 and severe allergic reaction at infusion sites bilaterally at Week 5 in one subject). The most common local infusion site reactions were swelling, redness, and pruritus, which were generally mild and resolved without significant clinical sequelae. A total of nine subjects experienced 12 infusion site hematomas. The most commonly reported AEs excluding infusion site reactions were sinusitis (15 subjects; 25%), nasopharyngitis (14 subjects; 23%) and upper respiratory tract infection (13 patients; 21%). Immunogenicity is not routinely assessed in IGIV trials in PI and was not assessed in the submitted studies. The safety profile of Cutaquig appeared qualitatively similar to that of U.S.-licensed IGSC products.

8. ADVISORY COMMITTEE MEETING

This product was not presented to the Blood Products Advisory Committee (BPAC), because it is not a novel molecular entity, and it is manufactured by a previously licensed manufacturing process for Octagam IGIV with a higher final concentration.

9. OTHER RELEVANT REGULATORY ISSUES

No other relevant regulatory issues were encountered during the review of this BLA.

10. LABELING

The proposed propriety name, CUTAQUIG, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on February 16, 2018 and was found to be acceptable. CBER communicated the acceptability of the proprietary name to the applicant on March 27, 2018. The four-letter suffix to the proper name (hipp) was accepted by APLB on October 30, 2018.

APLB found the package insert, patient package insert (PPI), Information for Use (IFU), and package and container labels acceptable from a promotional and comprehension perspective.

The indication was restricted to adults, because the clinical and PK data for pediatric subjects were too limited to establish safety and effectiveness in pediatric patients.

The applicant's request for a flexible dosing recommendation from (b) (4) dosing to dosing(b) (4) was denied, due to deficiencies in the applicant's population PK analyses and no safety data were available with every (b) (4) dosing.

The recommended dosage adjustment factor for switching from IGIV to Cutaquig was changed from (b) (4) to 1.40 to match what was used during Study SCGAM-01.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review committee recommends licensure.

b) Risk/ Benefit Assessment

The benefit/risk of Cutaquig for treatment of PI in adults is favorable from the clinical perspective. The pre-specified threshold (< 1.0 SBI rate per patient year) was met, which satisfies FDA's requirement for substantial evidence of effectiveness for an IGSC product intended to treat PI. Secondary efficacy endpoints in SCGAM-01 were supportive of efficacy, as were the results of a Phase 3 study conducted in Russia, SCGAM-04.

The most common risks of Cutaquig administration identified in the clinical studies were local infusion site reactions -- swelling, redness, and pruritis were common. However, a majority of infusion site reactions were mild and resolved in a timely fashion without sequelae. The most frequent adverse reactions (suspected adverse reactions plus adverse reactions) occurring in the setting of Cutaquig administration were infections. The most frequent adverse reactions, excluding infections, were: diarrhea, headache, pyrexia, asthma, dermatitis, and excoriation. Importantly, there were no deaths, thromboembolic events, or hemolysis, anaphylaxis, or aseptic meningitis events associated with use of Cutaquig.

The benefits of marked reduction in the risk of serious bacterial infections outweigh the observed risks of Cutaquig and the additional risks known to be associated with other products (IGIV and IGSC) in the class.

c) Recommendation for Post-Marketing Activities

The applicant is required to complete the ongoing Phase 3 study, Study SCGAM-01, and submit a final study report analyzing the safety and effectiveness of Cutaquig in pediatric subjects as a Pediatric Research Equity Act (PREA) postmarketing requirement (PMR). This required study and the study timelines are listed below:

1. Deferred pediatric study (protocol SCGAM-01) under PREA for the treatment of primary humoral immunodeficiency in pediatric patients ages two to < 17 years of age. The study will provide pharmacokinetic data for at least two subjects ages two to < 6 years, at least six subjects ages six to < 12 years, and at least four subjects ages 12 to < 17 years of age, as well as safety and efficacy data for at least four subjects ages two to < 6 years, at least 10 subjects ages six to < 12 years, and at least six subjects ages 12 to < 17 years of age. The final report will compare efficacy and safety between pediatric age cohorts and between pediatric and adult subjects included in the study.

   Final Protocol Submission: January 31, 2019

   Study Completion Date: August 31, 2020

   Final Report Submission: December 31, 2020

CMC

It was requested that the applicant include additional release testing, IgG Content and(b) (4) method). These two assays are performed for their Immune Globulin, Intravenous products (Octagam 5% and 10%). Two postmarketing commitments (PMCs) are needed to validate and set final specifications for these methods for the Cutaquig product.

2. Octapharma commits to setting a final (b) (4) specification following a year of release testing for Cutaquig. The final (b) (4) specification and justification will be submitted as a Prior Approval Supplement by January 1, 2020.