

**Clinical Pharmacology BLA Review**  
Division of Clinical Evaluation and Pharmacology/Toxicology  
Office of Tissues and Advanced Therapy

BLA	125668/0
Product	Immune Globulin Subcutaneous (Human), (Cutaquig <sup>®</sup> ), 16.5%
Sponsor	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Indication	Treatment of primary immunodeficiency (PI) in adults
Date Received	December 29, 2017
Reviewer	Xiaofei Wang, Ph.D.  Clinical Pharmacology Reviewer, General Medicine Branch 2 Division of Clinical Evaluation and Pharmacology/Toxicology
RPM	Edward Thompson
Through	Tejashri Purohit-Sheth, M.D., FACAAI, CQIA  Director Division of Clinical Evaluation and Pharmacology/Toxicology

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## 1 EXECUTIVE SUMMARY

OCTAPHARMA seeks approval of its immune globulin subcutaneous (Human), Cutaquig (also referred to as (b) (4) 16.5% in submission), for the treatment of primary immunodeficiency (PI) in adults.

Cutaquig is a newly developed immune globulin (human) solution for subcutaneous administration (IGSC). Cutaquig contains 165 mg protein per mL ( $\geq 96\%$  of human immunoglobulin G (IgG), obtained from the normal immunoglobulin fraction from human plasma.

The clinical pharmacology section of this biologics license application (BLA) is supported by one Phase 3 clinical study (Study SCGAM-01) that evaluated the pharmacokinetics, efficacy, tolerability and safety of subcutaneous human immunoglobulin in subjects with primary immunodeficiency disease (PID).

In Study SCGAM-01, weekly subcutaneous administration of Cutaquig has been demonstrated to be clinically effective with a tolerable safety profile. At steady-state, the bioavailability of weekly subcutaneously infused Cutaquig (IGSC) with a dose conversion factor (DCF) of 1.40 was comparable to that of intravenously (IV) administered human immunoglobulin (IGIV) (area under the concentration versus time curve (AUC) of IGIV was standardized to a 7-day period). Compared to IGIV, weekly administration of IGSC resulted in steady-state pharmacokinetic profiles with little fluctuation in IgG levels.

In addition to weekly administration of Cutaquig, the applicant proposed alternative dosing regimens: frequent ((b) (4) ) and ((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. Per clinical review, ((b) (4) ) dosing of Cutaquig may raise safety and local tolerability concerns due to increased volume for infusion. Therefore, the applicant's proposed alternative dosing regimens are not acceptable.

From the clinical pharmacology standpoint, the BLA is acceptable to support approval for weekly subcutaneous administration of Cutaquig for the treatment of primary immunodeficiency (PI) in adults.

## 2 INTRODUCTION

Cutaquig is a solution for subcutaneous administration containing 165 mg of protein per mL (of which  $\geq 96\%$  is human immunoglobulin G (IgG)). Cutaquig is obtained from the normal immunoglobulin fraction from human plasma. Cutaquig is characterized by the applicant as having an especially low content of polymers and aggregates, (b) (4) titer, low IgA (b) (4) content with a broad spectrum of antibodies against infectious agents. It has a distribution of immunoglobulin G subclasses closely proportional to that of native human plasma.

This application is supported by one Phase 3 clinical study:

- a Phase 3 study (Study SCGAM-01) evaluating the pharmacokinetics, efficacy, tolerability and safety of subcutaneous human immunoglobulin (cutaquig, also referred to as (b) (4), 16.5%) in subjects with primary immunodeficiency diseases (PI).

Study SCGAM-01 was conducted in 61 subjects including 37 adults. The pharmacokinetic (PK) sub-study included 23 subjects, of which 19 were adults. There is insufficient PK data from children, and therefore, the PK review is based on pharmacokinetic data from adult subjects only. In the current submission, the applicant seeks approval of Cutaquig for the treatment of primary immunodeficiency (PI) in adults.

## 3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

- Following IGSC administration (average dose: 0.188 g/kg per week, range: 0.111 to 0.376 g/kg per week), serum IgG concentrations increased gradually, peaking at 48 - 72 hours. The C<sub>max</sub> of serum IgG at steady-state was  $14.0 \pm 4.4$  g/L. Compared to IGIV administration, IGSC administration showed notably flat PK profiles. With SCIG, peak serum IgG levels were lower (14.0 g/L vs 19.7 g/L) than those achieved with IGIV while trough levels were generally higher (12.7 g/L vs. 10.3 g/L). Subcutaneous administration of Cutaquig resulted in relatively stable steady-state IgG levels when the product is dosed on a weekly basis.
- Serum IgG and IgG subclass trough levels were nearly constant during the course of the study, with higher mean levels after subcutaneous treatment compared with those following IGIV.

- At steady-state, the bioavailability of weekly IGSC was equivalent to that of IGIV (AUC of IGIV was standardized to a 7-day period for 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 dose conversion factor (DCF) from IGIV to IGSC in individual subjects ranged from 1.23 to 1.89 (median: 1.36, mean: 1.40). This DCF was used throughout the study and the efficacy of Cutaquig was established with this DCF.
- In addition to the weekly dosing regimen used in the clinical study, SCGAM-01, the applicant proposed alternative IGSC dosing regimens: frequent dosing ((b) (4) ) and ((b) (4) ) for its Cutaquig. To support its proposed alternative dosing regimen, the applicant conducted a population pharmacokinetic (PopPK) study (SCGAM-01 PopPK). However, due to the lack of evaluation of the absorption phase and likelihood of inappropriate estimation of half-life in the modeling and simulation for IGSC, this PopPK model is not acceptable for the frequent dose projection. In addition, considering the long half-life of IgG, more frequent dosing ((b) (4) ) will lead to drug accumulation and there are safety concerns. Therefore, the applicant's proposed frequent dosing regimens ((b) (4) ) are not acceptable.

## 4 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125668 and finds it acceptable pending the following revisions shown below.

### 2. DOSAGE AND ADMINISTRATION

**For subcutaneous administration only. Do not inject into a blood vessel.**

#### 2.2. Dosage

- Cutaquig can be administered at regular **weekly** intervals (b) (4).
- Individualize the dose based on the patient's pharmacokinetic and clinical response. Monitor serum IgG trough levels regularly to guide subsequent dose adjustments and dosing intervals as needed (see *Dose Adjustment*).

#### **Dosage for patients switching to Cutaquig from Immune Globulin Intravenous (Human) treatment (IGIV):**

- Establish the initial weekly dose of Cutaquig by converting the monthly IGIV dose into an equivalent weekly dose and increasing it using a dose adjustment factor.
  - To calculate the initial weekly dose of Cutaquig, divide the monthly IGIV dose in grams by the number of weeks between IGIV infusions and then multiply this value with a Dosage Adjustment Factor of (b) (4).
 
$$\text{Initial weekly dose} = \frac{\text{Previous IGIV dose (in grams)} \times (b) (4)}{\text{Number of weeks between IGIV doses}}$$
  - To convert the dose (in grams) to milliliters (mL), multiply the calculated dose (in grams) by 6
- ~~Provided the total weekly dose is maintained, any dosing interval from daily up to (b) (4) can be used and will result in systemic IgG exposure that is comparable to the previous IGIV treatment.~~
- ~~(b) (4)~~

To guide dose adjustments, see [Table 1](#) under *Dose Adjustment*

#### **Dosage for patients switching to Cutaquig from another Immune Globulin Subcutaneous (Human) Treatment (IGSC):**

- It is recommended to maintain the same weekly dosing (in grams) of Cutaquig than was used for the previous IGSC therapy (in grams).
- (b) (4)
- To convert the dose (in grams) to milliliters (mL), multiply the calculated dose (in grams) by 6.

To guide dose adjustments, see [Table 1](#) under *Dose Adjustment*

Start Cutaquig treatment:

- For weekly (b) (4) administration start Cutaquig treatment one week after the last IGIV/IGSC infusion.
- (b) (4)

## 12. CLINICAL PHARMACOLOGY

### 12.1. Mechanism of Action

CUTAQUIG supplies a broad spectrum of opsonizing and neutralizing Immunoglobulin G (IgG) antibodies against a wide variety of bacterial and viral agents. It has a distribution of immune globulin subclasses closely proportional to that ~~in~~of native human plasma. The mechanism of action in PI has not been fully elucidated, however adequate doses may restore abnormally low immune globulin G levels to the normal range and thus help in preventing infections.

### 12.2. Pharmacodynamics

CUTAQUIG contains mainly IgG with a broad spectrum of antibodies against various infectious agents reflecting the IgG activity found in the donor population. CUTAQUIG which is prepared from pooled material from not less than 1000 donors, has an IgG subclass distribution similar to that of native human plasma. Adequate doses of Immune Globulin Subcutaneous (Human) (IGSC) can restore abnormally low IgG level to the normal range. Standard pharmacodynamic studies were not performed.

### 12.3. Pharmacokinetics

A pharmacokinetic (PK) sub-study of the pivotal Phase III study was conducted in ~~22~~18 adult subjects. ~~Blood samples for PK study were collected at various time points: prior to switching to Cutaquig (IVIG profile: PK<sub>IV</sub>), after the 11<sup>th</sup> infusion of Cutaquig (first SC profile: PK<sub>SC1</sub>) and after the 28th infusion of Cutaquig (second SC profile: PK<sub>SC2</sub>). The objective of the PK sub-study was to compare the AUCs following the IV and SC administration. At steady-state, under SCIG treatment with that of IVIG. Bioavailability was calculated: the geometric mean of the ratio (SC2:IV) was 1.0253, (90% CI: 0.9778, 1.08751), indicating comparable exposure thus~~

confirming bioequivalence between SCIG and IVIG treatment. Dose conversion factor from IGIV to SCIG in individual subject ranged from 1.23 to 1.89 (mean = 1.40)....

Trough levels of serum IgG (total and subclasses) and of specific antibodies were also monitored throughout the study.

PlasmaSerum IgG and IgG subclass trough levels were nearly constant during the course of the study, with higher mean levels after SC treatment compared with those following IVIG. ,with a median value of 8.85 g/L on the last day after PK<sub>IV</sub>, 10.75 g/L at PK<sub>SC1</sub> and 11.50 g/L at PK<sub>SC2</sub>. Mean IgG trough values were 9.80 g/L, 12.08 g/L and 12.18 g/L, respectively. At the end of IVIG period, PK assessments, the minimum individual trough levels ranged from were 5.1 g/L predose and 5.8 g/L to 13.9 g/L. on the last day; Over the entire at the SCIG PK assessments at predose and 7 days post dose the minimum treatment period individual trough level of total IgG was between 7.2 and 7.5 g/L and the maximum trough level ranged between 19.0 and 21.0 g/L. By weekly infusion from week 2 onwards, the minimum trough levels ranged between 6.1 to 24.0 g/L and 8.4 g/L. The mean C<sub>max</sub> was 13.5 g/L and was reached after a median of 2.05 days.

Applicant,

Per your submission on 02/07/2018, revised section 16.1.10.1.2., LKF test method summary, serum levels IgG and IgG subclasses were measured. Please clarify and correct.

Table 6 summarizes the Key PK parameters for Cutaquig.

**Table 6 Key Pharmacokinetic Parameters for Cutaquig in Adults**

Parameter	IVIG (n=22)	Cutaquig (n=18)
C <sub>max</sub> [g/L]	18.9	13.5
C <sub>min</sub> [g/L]	10.3	11.6
T <sub>max</sub> [h]	2.9	48.4
AUC <sub>tau</sub> [g*hr/L]	2096*	2293
AUC <sub>tau</sub> [mg*day/dL]	8735*	9554

\* standardized to a 7-day period

Applicant:

For Table 6, 1) please provide the dose given to subjects following IV and SC administration; 2) please present PK parameters for the cohort of adult subjects 17 years of age and above.

For the study subjects completing the PK analysis the individually calculated ratios for dose conversion from IGIV to IGSC (dose conversion factor = DCF) ranged between 0.454 and 2.565. The mean calculated ratio for DCF was 1.370, and the geometric mean 1.232. Therefore a DCF of (b) (4) can be used to convert the previous IGIV dose into the necessary IGSC dosing.

### Pharmacokinetic Modeling and Simulation


(b) (4) ÷




(b) (4)



Applicant,

Your population PK study (SCGAM-01 PopPK) to support alternative dosing regimen (b) (4)  ) for your IGSC is inadequate due to following deficiencies:

1. There is no absorption phase for subcutaneous administration in your model and simulation.
2. There is a large variability in your Tmax. A mean Tmax value of 6 hours may not be correct for simulation.
3. In your modeling and simulation, you used half-life obtained from IGIV data. However, it should be noted that half-life may be route of administration dependent. Therefore, your proposed half-life obtained from IGIV data for PopPK modeling for IGSC may not be appropriate.
4. Due to the lack of absorption phase and likelihood of inappropriate half-life in your modeling and simulation for your IGSC, your model is not acceptable for the frequent dose projection.
5. Considering the long half-life of IgG, more frequent dosing (b) (4)  ) will lead to drug accumulation and there are safety concerns. Therefore, your proposed dosing frequency is not acceptable.

## **5 RECOMMENDATIONS**

The clinical pharmacology information in this BLA is acceptable, provided that satisfactory agreement is reached between the sponsor and FDA regarding the language in Section 2 and Section 12 of the package insert. Please refer to section 4 for detailed Labeling Recommendations.

## 6 APPENDIX - INDIVIDUAL STUDY

### 6.1 Study #1

Note that in Study SCGAM-01, Cutaquig is referred to as (b) (4) 16.5%.

#### 6.1.1 Study Design

**Study Title:** Clinical Phase 3 study to evaluate the pharmacokinetics, efficacy, tolerability and safety of subcutaneous human immunoglobulin ((b) (4) ) in patients with primary immunodeficiency diseases (Study No. SCGAM-01)

#### Objectives

##### Primary Objectives

- To assess the efficacy of (b) (4) in preventing SBI compared with historical control data.
- To evaluate the PKs of (b) (4) and to compare the area under the curve with that of IGIV.

##### Secondary Objectives

- To evaluate the tolerability and safety of (b) (4) .
- To determine the PK profile of (b) (4) .
- To assess the dosing conversion factor (DCF) when switching patients from IGIV treatment.
- To develop guidance and recommendations to support further adjustments of (b) (4) dosing based on the total IgG trough level.
- To assess the effect of (b) (4) on Quality of Life (QoL) measures.

#### Study Design

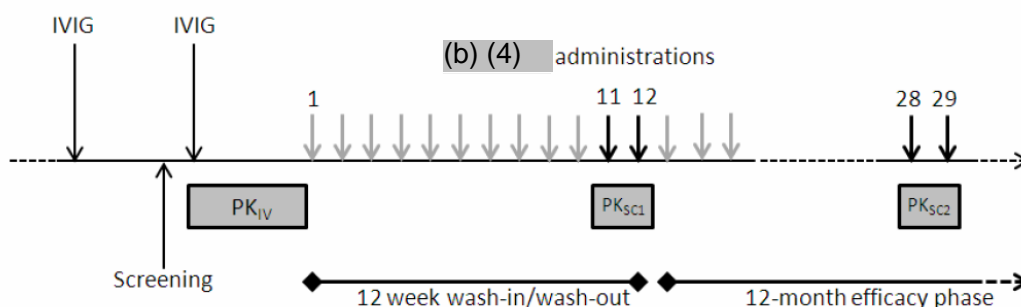
This was a prospective, open-label, non-controlled, single-arm, multicenter Phase 3 study with a 12-week wash-in/wash-out period followed by a 12-month efficacy period. The study also included a PK sub-study in 19 adult subjects. Eighteen (18) adult subjects completed all PK assessments.

All study subjects were on regular, steady-state IGIV treatment before entering the study (dose), with constant dosing of between 200 and 800 mg/kg body weight ( $\pm 20\%$  of the mean dose for the last 6 infusions) and IgG trough levels  $\geq 5.0$  g/L.

As shown in Figure 1, 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 (b) (4) (PK<sub>IV</sub>), a full PK profile at the end of the wash-in/wash-out phase (PK<sub>SC1</sub>) and a final PK profile after 28

administrations of (b) (4) (at steady state) to access the bioavailability of total IgG with respect to the two administration methods (PK<sub>SC2</sub>).

**Figure 1. PK Substudy Schema**



Source: EDR. BLA125668.0. Module 5, section 5.3.3.2. SCGAM-01 Study Report. Figure 1.

The dose of (b) (4) (IGSC) was calculated with an initial dose conversion factor (DCF) of 1.5:

$$\frac{\text{previous IVIG dose (in grams)} \times 1.5}{\text{number of weeks between IVIG doses}}$$

Per the study protocol, a PK interim analysis was planned to be conducted after all PK<sub>SC1</sub> data available to revise the initial DCF of 1.5 to the corrected value according to the AUC<sub>τ</sub> and to obtain a titration scheme to be used by the investigator to achieve the associated target trough levels. However, due to slow recruitment to the PK sub-study, the analysis was finally done at the same time as the analysis for the study report.

Blood samples were collected for PK assessment at the following time points:

First PK evaluation (PK<sub>IV</sub>): pre-dose, and at 15 minutes (± 5 minutes), 60 minutes (± 10 minutes), 24 hours (± 3 hours), 3 days (± 6 hours), 7 days (± 6 hours), 14 days (± 3 days), and 21 days (± 3 days) for subjects on 3-week infusion schedule or 28 days (± 3 days) for subjects on 4-week infusion schedule.

Second and Third PK evaluation (PK<sub>SC1</sub> and PK<sub>SC2</sub>): pre-dose (before start of the (b) (4) SC infusion), 10 minutes before anticipated end of the SC infusion, and at 2 hours (± 30 minutes), 1 day (± 6 hours), 2 days (± 6 hours), 3 days (± 6 hours), 4 days (± 6 hours), and 7 days (± 6 hours).

The PK samples were analyzed for total IgG, IgG subclasses (IgG1, IgG2, IgG3, IgG4), and specific antibodies.

## 6.1.2 Results

### 6.1.2.1 Steady-State Pharmacokinetics of IgG and IgG subclasses following Subcutaneous Administration of Cutaquig (b) (4) 16.5%)

#### 6.1.2.1.1 Pharmacokinetics of IGSC at Steady-State in Adult Subjects

The average IgG dose of IGIV was 0.135 g/kg per week (range: 0.076 to 0.261 g/kg per week). Following IGIV infusion, serum concentrations of IgG peaked at the end of infusion. The peak serum level (C<sub>max</sub>) of IgG was  $20.2 \pm 5.8$  g/L. The clearance and C<sub>min</sub> of IgG were  $1.49 \pm 0.37$  mL/day per kg and  $10.8 \pm 2.8$  g/L. Steady-state serum IgG concentration fluctuation percentage was 71.4%.

The average IgG dose of SCIV was 0.188 g/kg per week (range: 0.111 to 0.376 g/kg per week). Following IGSC administration, serum IgG concentrations increased gradually, peaking at 48 ~ 72 hours. The C<sub>max</sub> of serum IgG of at steady-state was  $14.0 \pm 4.4$  g/L. The apparent clearance was  $2.33 \pm 0.50$  mL/day per kg. The C<sub>min</sub> of IgG was  $12.0 \pm 3.5$  g/L. Steady-state serum IgG concentration fluctuation percentage was 12.3%.

Compared to IGIV administration, IGSC administration showed notably flat PK profiles. With SCIG, peak serum IgG levels were lower (14.0 g/L vs 19.7 g/L) than those achieved with IGIV while trough levels were generally higher (12.7 g/L vs. 10.3 g/L). Subcutaneous administration of (b) (4) 16.5% resulted in relatively stable steady-state serum IgG levels when the product is dosed on a weekly basis.

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

**Table 1. Pharmacokinetic Parameters of IgG at Steady-State in Adult Subjects [Mean (SD), Median (range)]**

	IGIV (N=18)		IGSC2 (N=18)	
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
<b>IgG Dose (g/kg per week)</b>	0.135 (0.059)	0.113 (0.076 – 0.261)	0.188 (0.083)	0.157 (0.111 – 0.376)
<b>C<sub>max</sub> (g/L)</b>	19.7 (5.6)	17.9 (13.7 – 31.5)	14.0 (4.4)	12.5 (8.8 – 23.8)
<b>T<sub>max</sub>* (h)</b>	--	2.86 (2.08 – 69.45)	--	49.31 (1.83 – 98.33)

<b>sAUCτ (h*g/L)**</b>	2181.7 (691.5)	2094.5 (1385.1 – 3596.5)	2407.5 (673.0)	2105.5 (1715.0 – 3762.4)
<b>Cmin (g/L)</b>	10.5 (2.6)	10.6 (6.7 – 14.2)	12.0 (3.5)	11.2 (6.5 – 18.4)
<b>Cavg (g/L)</b>	13.0 (4.1)	12.5 (8.2 – 21.4)	14.3 (4.0)	12.53 (10.2 – 22.4)
<b>Fluctuation (%)</b>	71.4 (17.6)	74.4 (34.5 – 93.8)	12.3 (6.2)	10.5 (4.6 – 24.1)
<b>Clearance# (mL/day per kg)</b>	1.5 (0.4)	1.4 (0.9 – 2.4)	1.9 (0.5)	1.9 (1.2 – 3.1)

\* Tmax values are presented as median, range

\*\* Standardized to a 7-day period

# Apparent clearance for IGSC

Steady-state bioavailability was equivalent between IGSC and IGIV (standardized to a 7-day period). 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).

Steady-state PK parameters of IgG subclasses after weekly administration of (b) (4) 16.5% were listed in Table 2.

**Table 2. Pharmacokinetic Parameters of IgG Subclasses at Steady-State (PK<sub>SC2</sub>) Following Subcutaneous Administration of Cutaquig ((b) (4) 16.5%) in Adult Subjects [Mean (SD), Median (range)]**

	<b>IgG1</b>	<b>IgG2</b>	<b>IgG3</b>	<b>IgG4</b>
<b>Cmax (g/L)</b>	8.7 (2.0)	4.1 (2.0)	0.4 (0.1)	0.2 (0.2)
	8.2 (5.9 – 12.6)	3.5 (2.1 – 10.0)	0.4 (0.2 – 0.6)	0.1 (0.09 – 0.9)
<b>Tmax* (h)</b>	58.68 (1.8 – 98.0)	72.4 (1.8 – 98.0)	58.5 (1.8 – 98.0)	45.2 (0.6 – 98.0)
<b>Cmin (g/L)</b>	7.4 (1.69)	3.4 (1.4)	0.3 (0.1)	0.2 (0.19)
	7.2 (4.9 – 10.5)	3.0 (1.7 – 6.9)	3.0 (0.2 – 0.5)	0.1 (0.07 -0.8)
<b>AUCtau** (h*g/L)</b>	1484.7 (300.2)	748.2 (337.0)	54.9 (20.0)	40.1 (37.5)
	1340.3 (1103.8 – 1957.2)	625.5 (437.7 – 1580.5)	56.1 (27.9 – 92.4)	23.1 (15.4 – 141.9)

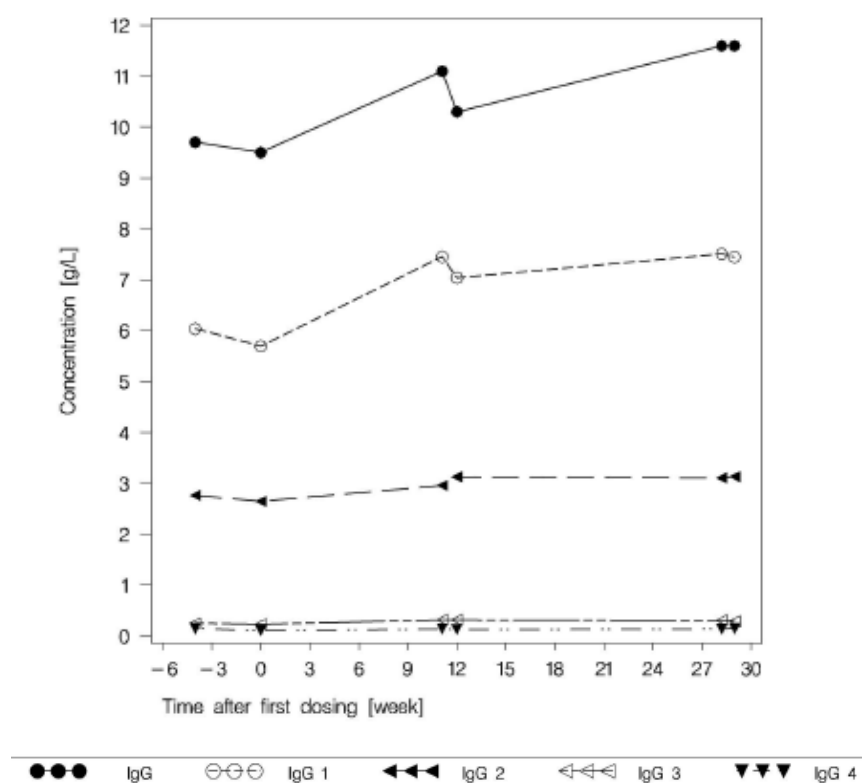
\* Tmax values are presented as median, range

\*\*Standardized to a 7-day period

### 6.1.2.2 Trough Concentrations of IgG and IgG Subclasses

As shown in Figure 2, serum IgG and IgG subclasses trough levels were higher after subcutaneous administration compared to those following IV infusion. The overall trough levels of IgG and IgG subclasses were constant. At the end of the IGIV period, trough levels ranged from 5.8 g/L to 13.9 g/L. Over the entire IGSC treatment period individual trough levels of total IgG ranged between 6.1 g/L to 24.0 g/L. (Table 3).

**Figure 2. Median Trough Concentrations of IgG and IgG subclasses over Time in Adult Subjects**



Source: EDR. BLA125668.0. Module 5, section 5.3.3.2. SCGAM-01 Study Report. Figure 14.4.3.2.2.

**Table 3. Trough Concentrations of IgG and IgG subclasses in Adult Subjects [Mean (SD), Median (range)]**

	Total IgG (g/L)	IgG1 (g/L)	IgG2 (g/L)	IgG3 (g/L)	IgG4 (g/L)
IGIV (N=18)	10.3 (4.1)	6.2 (2.6)	3.3 (1.7)	0.3 (0.1)	0.2 (0.2)

	9.5 (5.8 – 13.9)	5.7 (3.2 – 14.1)	2.7 (1.7 – 8.8)	0.2 (0.09 – 0.48)	0.1 (0.05 – 0.86)
IGSC (N=18)	12.7 (3.8)	7.8 (1.7)	3.7 (1.8)	0.3 (0.1)	0.2 (0.2)
	11.7 (6.1 – 24.0)	7.5 (5.6 – 11.0)	3.2 (1.9 – 9.1)	0.3 (0.2 – 0.6)	0.1 (0.08 – 0.82)

### 6.1.2.3 Dose Conversion Factor for Subcutaneous Administration of Cutaquig (b) (4) 16.5%)

Per the study protocol, a PK interim analysis was planned to be conducted after all PKSC1 data available to revise the initial DCF of 1.5 to the corrected value according to the AUC<sub>τ</sub>, and to obtain a titration scheme to be used by the investigator to achieve the associated target trough levels. However, due to slow recruitment to the PK sub-study, the analysis was finally done at the same time as the analysis for the study report.

In adult subjects with PID, subcutaneously administered (b) (4) 16.5% provided comparable overall exposure of total IgG to that produced by intravenously administered human immunoglobulin (AUC is standardized to a 7-day period). The mean DCF was 1.40 and the median value of DCF was 1.36 (range: 1.23 – 1.89). Per the clinical review, weekly subcutaneously administered (b) (4) 16.5% with a DCF of 1.40 was safe and well-tolerated in adult subjects with PID.

### 6.1.2.4 Dosing Regimens for Subcutaneous Administration of Cutaquig (b) (4) 16.5%)

In addition to the weekly dosing regimen used in the clinical study, SCGAM-01, the applicant proposed alternative IGSC dosing regimens: frequent dosing (b) (4) ) and (b) (4) dosing for Cutaquig. To support its proposed alternative dosing regimen, the applicant performed a population pharmacokinetic (PopPK) study (SCGAM-01 PopPK) entitled “Final Population Pharmacokinetic Report for Octapharma Protocol SCGAM-01”.

The key findings from the applicant’s analysis are summarized below:

#### Population Pharmacokinetic Analysis Methods

The PopPK analysis was designed to model the IgG serum concentrations and all doses administered using actual elapsed times from the start of the first and only IGIV dose to each subsequent SCIG dose. The parameterization of the model was based on clearance (Cl) and volume of distribution (V). The PopPK analysis was conducted using (b) (4).



The PopPK modeling was developed following 3 steps:

1) test different models (compartment number and variance model) of the IgG data to find a tentative model based on Akaike Information Criteria (AIC);

The modeling started with a 1-compartmental model and progressed to add additional compartments depending to how well the simpler model described the data. Additive and multiplicative variance modeling were tested with the structural models. All structural models were searched to optimize the model's fit using both the (b) (4)

search engine and the (b) (4)

engine.

2) examine the tentative model based on convergence, graphical analysis of residual plots, and its ability to provide a statistical description of the parameter estimates; and

3) validate the model: test the robustness of the model using bootstrapping techniques when applied to slightly different datasets.

### Population Pharmacokinetic Analysis Results

The PopPK modeling focused on the IV profiles. This was done because the half-life was too long to meaningfully model the SC profiles over the week-long observation period. Subjects included in the PopPK model had a mean age of 38.32 years (median 40 years, range: 5-71 years). The mean weight at screening was 64.41 kg (median: 64 kg, range: 19 to 98.6 kg). The mean IgG dose was 29.72 g (median 30 g) and ranged from 7.5 to 50 g. The IgG concentrations from the IV profiles ranged from 5.8 g/L to 31.5 g/L.

**Table 4. Summary of the Intravenous IgG Models Examined**

Name	Method	Return Code	LogLik	-2LL	AIC	nParm
1 cmpt Multiplicative AIC=776	FOCE-ELS	1	-383.2423	766.4845	776.4845	5
1 cmpt Multiplicative AIC=779	QRPEM	1	-384.5506	769.1011	779.1011	5
2 cmpt Multiplicative AIC=706	QRPEM	1	-343.9769	687.9537	705.9537	9
2 cmpt Multiplicative AIC=708	FOCE-ELS	1	-344.8164	689.6328	707.6328	9
1 cmpt Additive AIC=796	QRPEM	1	-393.2102	786.4203	796.4203	5
2 cmpt Additive AIC=745	FOCE-ELS	1	-363.4758	726.9516	744.9516	9

Source Data: [Table 7.1-1](#)

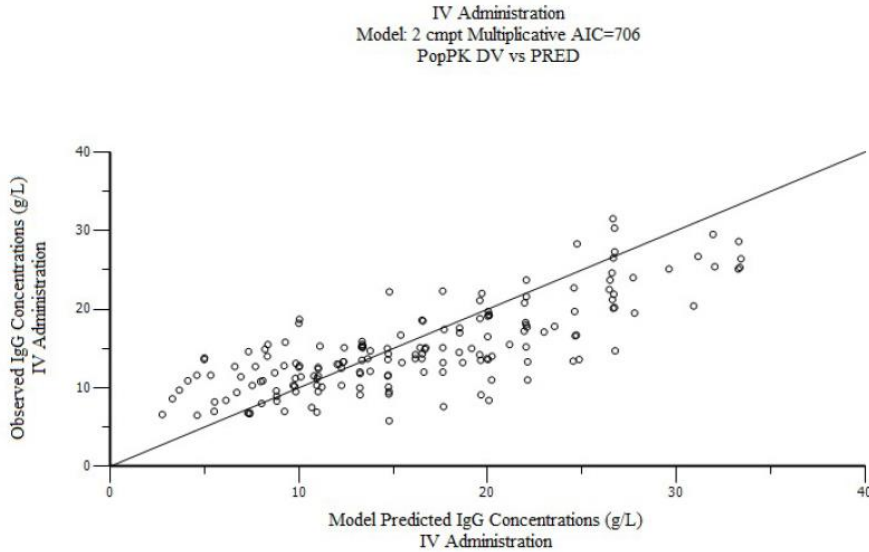
LogLik is the log likelihood. -2(LL) is the negative of twice the log likelihood. AIC is the Akaike Information Criteria.

Source: EDR. BLA125668.0. Module 1, section 1.2. Response to FDA Information Request – Jul. 25, 2018. Table 1.

As depicted in Table 4, the 2-compartmental model with multiplicative variance modeling was selected based on the lowest AIC and graphical evaluation of both the predicted concentrations

and their residuals (Figure 3). The multiplicative 2-compartmental model primary estimates and descriptive statistics are given in Table 5. The estimated elimination half-life from the central compartment of the 2-compartmental model is 1042.8 hours or 43.5 days.

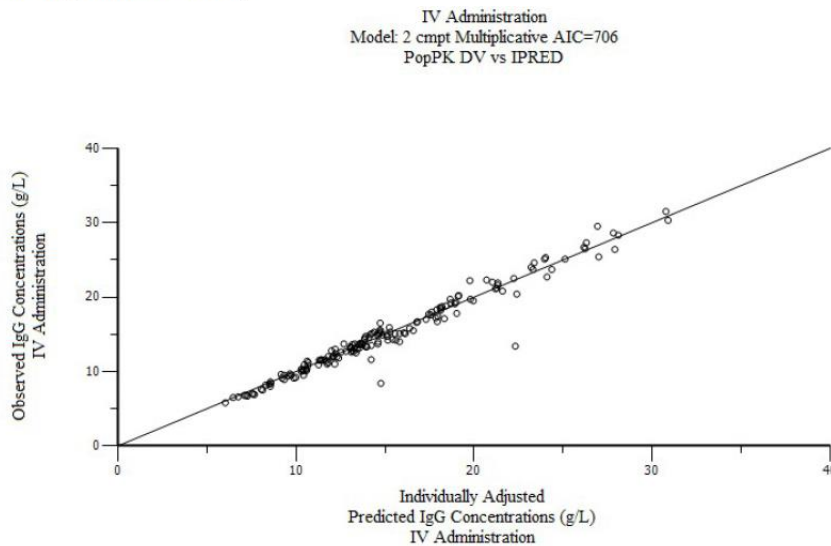
**Figure 3. Predicted versus Observed Goodness-of-Fit Plots**



Source Data: [Figure 7.3-2](#)

Multiplicative 2-Compartmental Model of IgG Concentration IV Data

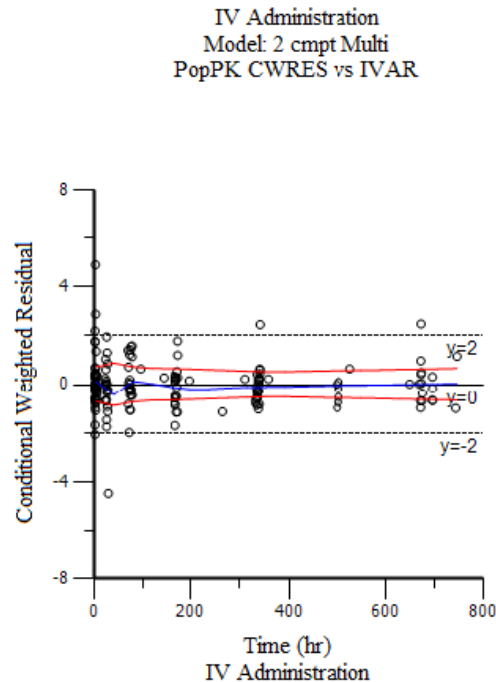
The straight line is a line of unity.



Source Data: [Figure 7.3-3](#)

Multiplicative 2-Compartmental Model of IgG Concentration Data

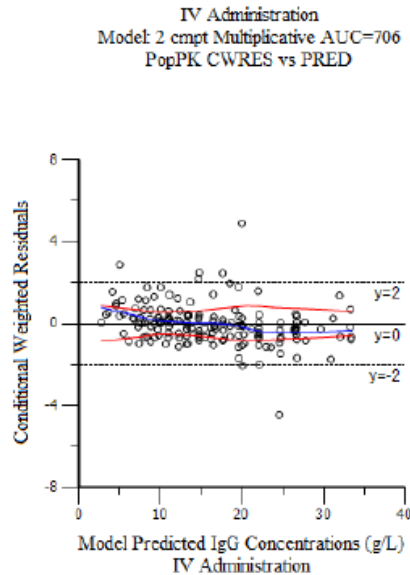
The straight line is a line of unity.



Source Data: [Figure 7.3-4](#)

Multiplicative 2-Compartmental Model of IgG Concentration Data

Blue line represents the Loess curve. The red lines represent the Loess curve generated from the absolute values of the data then reflected around the line of zero residual for reference.



Source Data: [Figure 7.3-4](#)

Multiplicative 2-Compartmental Model of IgG Concentration Data

Blue line represents the Loess curve. The red lines represent the Loess curve generated from the absolute values of the data then reflected around the line of zero residual for reference.

Source: EDR. BLA125668.0. Module 1, section 1.2. Response to FDA Information Request – Jul. 25, 2018.  
Figures 2 -5.

**Table 5. Primary Parameter Estimates from Multiplicative 2-compartmental Model**

Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI
tvV	1.48825	L	0.162237	10.90	1.167816	1.808684
tvV2	0.381957	L	0.125905	32.96	0.133284	0.63063
tvCl	0.000989	L/hr	0.000195	19.76	0.000603	0.001375
tvCl2	0.004874	L/hr	0.001246	25.57	0.002412	0.007336
stdev0	0.075737		0.002415	3.19	0.070967	0.080506

Source Data: [Table 7.1-2](#)

Multiplicative 2-Compartmental Model of IgG Concentration Data

Parameter indicates the model parameter being estimated. The tvV and tvCl are the typical values for the volume of distribution and for clearance of the central compartment, respectively. The tvV2 and tvCl2 are the typical values for the volume of distribution and for clearance of the peripheral compartment, respectively. The stdev0 is the standard deviation of the residual error in the model. The stdev0 is a measure of the overall model error, which is reported as the intrasubject variability. Estimate is the model's estimate for the parameter. Units are the unit of measure applicable to the estimate. Stderr is the standard error estimate. CV% is the coefficient of variation of the estimate expressed as a percentage. The 2.5% CI and the 97.5% CI are the interval for the 95% confidence interval (CI)

Source: EDR. BLA125668.0. Module 1, section 1.2. Response to FDA Information Request – Jul. 25, 2018.

Table 3.

As shown in the Variance-Covariance Matrix Table (Table 6), model parameters for the central compartment parameters had lower levels of variance compared to the peripheral compartment parameters.

**Table 6. Omega Covariance Matrix**

Label	$\eta V$	$\eta Cl$	$\eta V2$	$\eta Cl2$
<b>Omega</b>				
$\eta V$	0.12164			
$\eta Cl$	0	0.420658		
$\eta V2$	0	0	0.459465	
$\eta Cl2$	0	0	0	0.015151
Shrinkage	0.008379	0.194722	0.309568	0.879004

Source Data: [Table 7.1-4](#)

Multiplicative 2-Compartmental Model of IgG Concentration Data

Eta ( $\eta$ ) refers to the between individual variation in the model. Each primary parameter has an eta ( $\eta$ ):  $\eta V$ ,  $\eta Cl$ ,  $\eta V2$ , and  $\eta Cl2$ . The shrinkage provides a measure of model parameterization.

Source: EDR. BLA125668.0. Module 1, section 1.2. Response to FDA Information Request – Jul. 25, 2018.

Table 6.

The bootstrap analysis validated the model's performance across a number of similar datasets. Results of bootstrap analysis (200 replicates of the dataset) showed that the bootstrap mean parameter estimates match well with the model parameter estimates (Table 7).

**Table 7. Comparison of Base and Bootstrap Primary Parameters**

Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	
tvV	1.48825	L	0.162237	10.90	1.167816	1.808684	
tvV2	0.381957	L	0.125905	32.96	0.133284	0.63063	
tvCl	0.000989	L/hr	0.000195	19.76	0.000603	0.001375	
tvCl2	0.004874	L/hr	0.001246	25.57	0.002412	0.007336	
stdev0	0.075737		0.002415	3.19	0.070967	0.080506	
Bootstrap							
Parameter	Mean	Units	Stderr	CV%	2.5%	97.5%	Median
tvV	1.4929189	L	0.1072325	7.18	1.280242	1.6962973	1.4941553
tvV2	0.3964786	L	0.0680143	17.15	0.2925356	0.5526059	0.3875315
tvCl	0.0010117	L/hr	0.0002035	20.12	0.0005481	0.0014203	0.0010197
tvCl2	0.0053333	L/hr	0.001018	19.09	0.0038214	0.0076296	0.0049786
stdev0	0.0721923		0.0163706	22.68	0.0381482	0.1037489	0.0738246

Source Data: [Table 7.1-2](#) and [Table 7.1-5](#)

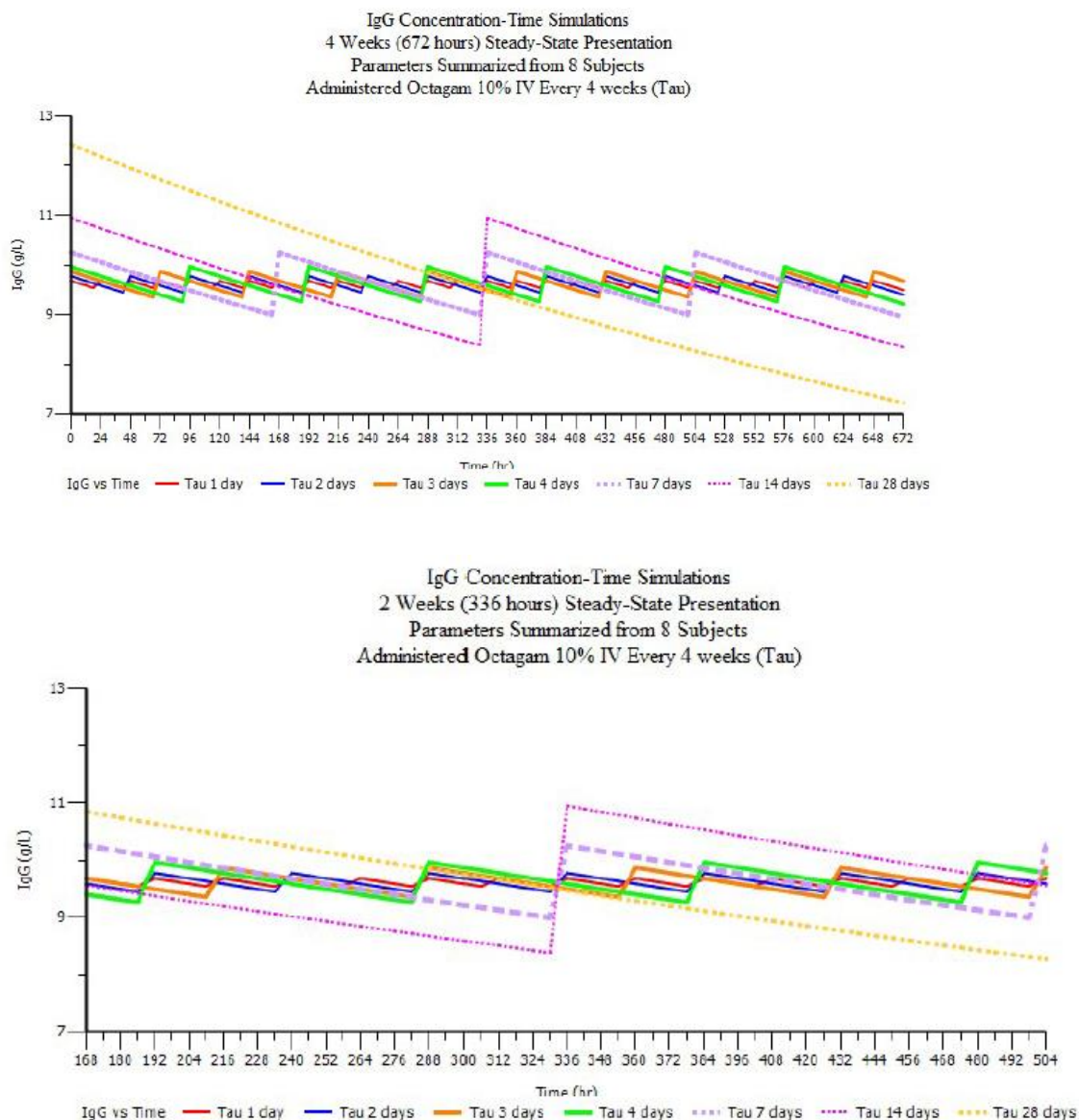
Multiplicative 2-Compartmental Model

Parameter indicates the model parameter being estimated. The tvV and tvCl are the typical values for the volume of distribution and for clearance of the central compartment, respectively. The tvV2 and tvCl2 are the typical values for the volume of distribution and for clearance of the peripheral compartment, respectively. The stdev0 is the standard deviation of the residual error in the model. The stdev0 is a measure of the overall model error, which is reported as the intrasubject variability. Estimate is the model's estimate for the parameter. Units are the unit of measure applicable to the estimate. Stderr is the standard error estimate. CV% is the coefficient of variation of the estimate expressed as a percentage. The 2.5% CI and the 97.5% CI are the interval for the 95% confidence interval (CI)

The results of the covariate analysis indicate that body weight can be added as a covariate for V and provide a meaningful improvement in the model.

### Simulations for Alternative Dosing Regimens

The applicant performed simulations to support alternative dosing regimens for Cutaquig ((b) (4) 16.5%). The simulations were based on the half-life estimates from IV doses since the PopPK modeling of the SC doses produced an inappropriately short half-life for IgG. The IV bolus equation was used. The SC doses were determined using a DCF of 1.39. Data from 8 subjects who received IV Octagam 10% (IGIV formulation) for the 4-week schedule were summarized to simulate the IV Octagam 10% profiles to reduce variance. Simulations are shown in Figure 4.

**Figure 4. Simulations of IgG Concentrations over 4 Weeks at Steady-State****Reviewer's Comments:**

The PopPK study was conducted to support the applicant's proposed alternative dosing regimens for subcutaneously administered Cutaquig (also referred to as (b) (4) 16.5%). The PopPK modeling focused on the IV profiles and a 2-compartmental model with multiplicative variance modeling was selected. The PopPK analysis is inadequate to support the frequent dose projection for Cutaquig due to following deficiencies:

- 1) There was no absorption phase for subcutaneous administration in the model and simulation;

2) There was a large variability in observed Tmax values and the median observed Tmax SC administration was around 48 hours post-infusion. The applicant used a mean Tmax value of 6 hours for its simulation;

3) In the modeling and simulation, the applicant used half-life obtained from IGIV data. However, as half-life may be dependent upon the route of administration, it is difficult to rely on this simulation.

In addition, considering the long half-life of IgG, more frequent dosing (less than weekly dosing interval) will lead to drug accumulation and raise safety concerns. Per the clinical review, bi-weekly dosing of Cutaquig may raise safety and local tolerability concerns due to the increased volume for infusion. Therefore, the applicant's proposed alternative dosing regimens are not acceptable.

**Conclusion**

Based on the PK provided in this submission, weekly subcutaneous administration of Cutaquig is supported for the treatment of primary immunodeficiency (PI) in adults.