CLINICAL STUDY PROTOCOL

SCGAM-06

CLINICAL PHASE 3 STUDY TO MONITOR THE SAFETY, TOLERABILITY, AND EFFICACY OF SUBCUTANEOUS HUMAN IMMUNOGLOBULIN (CUTAQUIG®) ADMINISTERED AT MODIFIED DOSING REGIMENS IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES

Investigational Product:	CUTAQUIG®
Indication:	Primary immunodeficiency diseases
Study Design:	Prospective, open-label, non-controlled, three-arm, multicenter, phase 3 study
Sponsor:	Octapharma USA, 121 River St. Hoboken, NJ 07030
Study Number:	SCGAM-06
BB-IND Number:	15617
Development Phase:	Phase 3
Planned Clinical Start:	3rd Quarter 2019
Planned Clinical End:	1st Quarter 2021
Date of Protocol:	28-Aug-2019
Version:	02

STUDY OUTLINE

Name of Sponsor/Company: Octapharma USA, 121 River St. Hoboken, NJ 07030	
Name of Investigational Product: CUTAQUIG	**Protocol Identification Code:** SCGAM-06
Name of Active Ingredient: Human Normal Immunoglobulin	**Date of Final Protocol:** 28-Aug-2019

Title of Study:

Clinical phase 3 study to monitor the safety, tolerability, and efficacy of subcutaneous human immunoglobulin (CUTAQUIG®) administered at modified dosing regimens in patients with primary immunodeficiency diseases

Indication:

Primary immunodeficiency diseases

Number of Study Center(s):

Approximately 15 study sites in the United States of America

Objectives:

Co-Primary Objectives:

The co-primary objectives of this study are to assess CUTAQUIG administered using the following infusion parameters:

- Compare total IgG trough levels from weekly infusions to every other week infusions
- Safety and tolerability when administered at increased infusion volumes at each infusion site
- Safety and tolerability when administered at increased infusion flow rates at each infusion site
- Safety and tolerability when administered on an every other week dosing regimen

Secondary Objectives:

The secondary objectives of this study are to:

- Assess the effect of CUTAQUIG on quality-of-life (QoL) measures
- Obtain further data on the safety and efficacy of CUTAQUIG

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Tertiary Objective:

A tertiary objective of this study is to evaluate patient satisfaction of various study parameters (such as switching to CUTAQUIG from another SCIG product, satisfaction with infusion pump, changes in infusion regimen parameters, general infection/general observations) using a study-specific questionnaire.

Study Design:

The study is a prospective, open-label, non-controlled, 3-arm, multicenter, phase 3 study.

Patients with a history of primary immunodeficiency (PI) disease that are currently on a stable dose of subcutaneously administered immunoglobulin (SCIG) treatment may be enrolled.

Stabilization Period

After completing the Screening Period and being assigned to 1 of 3 cohorts (as described below), patients will enter a 4-week Stabilization Period. During this period, patients will receive their first 4 CUTAQUIG infusions (Stabilization Period Weeks 0, 1, 2, and 3) at the same body-weight dependent dose (mg/kg) and infusion flow rate (mL/hr/site) as their previous SCIG product; however, this flow rate should not exceed maximum infusion rates listed in protocol.

Note: patients entering the study for participation in Cohort 3 must already be established on a weekly infusion schedule for a minimum of 12 weeks prior to the Screening Visit.

Patients entering the study already established on every other week dosing must enter either Cohort 1 or Cohort 2 and will be required to dose weekly beginning at the Stabilization Week 0.

Note: patients entering the study currently active and established on CUTAQUIG in Study SCGAM-03 will have already been stabilized on CUTAQUIG and would go directly into the Treatment Period following the Screening Visit. The Screening Visit of Study SCGAM-06 will occur on the same day as the final dosing visit for Study SCGAM-03. Procedures performed for Study SCGAM-03 that are also required for the Study SCGAM-06 Screening Visit do not need to be repeated at the same visit. Patients that completed the SCGAM-03 study and went on a commercial SCIG

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product prior to screening for SCGAM-06 are required to enter the Stabilization Period.

Treatment Period

After completing the 4-week Stabilization Period, patients will enter the Treatment Period and begin their infusion parameters according to cohort assignment as described below:

Cohort 1 (increased volume at each infusion site – patients will receive CUTAQUIG weekly and increase infusion volumes every 4 weeks): Patients will return to the clinic for the Treatment Period Baseline Visit at which they will receive the same body-weight dependent (mg/kg) dose but the volume will be increased by up to the maximum allowed volume increase per infusion site of 25 mL/site for patients ≥40 kg or 10 mL/site for patients <40 kg. This volume increase per infusion site can be achieved by reducing the total number of injection sites while maintaining similar or lower flow rates as received with their prior treatment. When introducing increased volumes to an infusion site, Investigators must attempt to maintain flow rates similar to or lower than prior infusions. This may require adjusting pump rate, tubing size, needle gauge, etc. Patients will receive this new volume per site for 4 weekly infusions (Treatment Period Baseline and Weeks 1, 2, and 3), and return to the clinic at Week 4 for their next infusion at an increased volume at each infusion site. This cycle will continue, with infusion volumes increasing by up to a maximum allowed volume increase per infusion site of 25 mL/site for patients ≥40 kg or 10 mL/site for patients <40 kg every 4th infusion until reaching a patient's maximum dose (in mL), maximum tolerated volume (maximum volume based on Investigator's decision of patient's tolerance), or 100 mL at 1 injection site – whichever is reached first.

Note: Sites are encouraged to enroll patients into Cohort 1 who are already on a dosing regimen using at least 3 infusion sites to ensure that volume increases remain below the protocol-specified limits. Patients dosing with 1 infusion site cannot enter Cohort 1.

Investigators should be aware that special considerations are required for volume increases in patients with 2 infusion sites receiving a total dose (volume) of more than 50 mL. To ensure that volume increases do not exceed 25 mL/site, the infusions must be split between the 2 syringes, such that each infusion site will receive a different total volume. For example, if a patient is receiving a total dose of 60 mL divided equally between 2 infusion sites (eg, 30 mL/site), the first syringe could be increased to an infusion volume of 50 mL (an increase of 20 mL) and the

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second syringe would have an infusion volume of 10 mL. If this is tolerated, the next infusion volume increase could be 60 mL at 1 infusion site (an increase of 10 mL) and remain below the maximum allowed volume increase of 25 mL/site.

Cohort 2 (increased infusion rate - patients will receive CUTAQUIG weekly and increase infusion rates every 4 weeks): Patients will return to the clinic for the Treatment Period Baseline Visit, at which they will receive the same body-weight dependent (mg/kg) dose of CUTAQUIG but the infusion rate per site will be increased up to a maximum allowed flow rate increase per infusion site of 25 mL/hr/site for patients ≥40 kg or 10 mL/hr/site for patients <40 kg. Patients will receive this new flow rate for 4 weekly infusions (Treatment Period Baseline and Weeks 1, 2, and 3), and return to the clinic at Week 4 for their next infusion at an increased infusion rate. This cycle will continue, with maximum allowed flow rate increases per infusion site of up to 25 mL/hr/site for patients ≥40 kg or up 10 mL/hr/site for patients <40 kg every 4th infusion until reaching either: 1) a maximum flow rate (100 mL/hr/site) or the maximum flow rate achievable by the pump, or 2) the maximum tolerated flow rate (maximum flow rate based on Investigator's decision of patient's tolerance) – whichever is reached first.

Note: Clinical sites are encouraged to enroll patients that are either currently infusing with 24-gauge needle sets or willing to switch to 24-gauge needle sets. Patients using 27-gauge needles will not be able to achieve adequate infusion rates for this cohort as the needle gauge will not allow for this.

Cohort 3 (every other week dosing - patients will receive CUTAQUIG every other week at the equivalent of twice their body-weight dependent [mg/kg] weekly dose): Patients will return to the clinic for the Treatment Period Baseline Visit to receive their first double mg/kg weekly dose and begin an every other week dosing schedule. Infusion volume increases when switching from weekly dosing to every other week dosing must not exceed a maximum allowed volume increase per infusion site of 25 mL/site for patients ≥40 kg or an increase of 10 mL/site for patients <40 kg at the Treatment Period Baseline Visit. If a patient's doubling of their weekly dose requires dosing with a volume of more than the maximum allowed increase in volume per injection site (25 mL/site or 10 mL/site, dependent on patient body weight), then they will be required to increase the number of infusion sites to remain below the maximum body-weight dependent volume increase. If this occurs, after 2 infusions the patient may remove one of the newly introduced injection sites as long as the volume per injection site increase limit is not exceeded. Infusion flow rates will be

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determined by the patient and Investigator, but initially should not exceed the patient's prior infusion rate, nor the maximum infusion rates listed in the protocol. Patients entering Cohort 3 must already be established on weekly dosing for a minimum of 12 weeks prior to Screening.

Note: Patients entering the study already established on an every other week infusion schedule must participate in either Cohort 1 or Cohort 2 if they agree to begin dosing every week beginning at Stabilization Period Week 0.

Study sites will be encouraged to enroll patients into all open cohorts.

The Sponsor will notify study sites when a cohort has filled and is no longer open to recruitment.

Patients who enter and participate in one cohort may not enter another cohort at a later time.

Patients entering the study currently active and established on CUTAQUIG in Study SCGAM-03 will have the Treatment Period Baseline Visit performed on the same day as Termination Visit on Study SCGAM-03. Patients must first complete their termination procedures for SCGAM-03, prior to their first infusion for Study SCGAM-06. Procedures that are performed on the same day as part of Study SCGAM-03 termination that are also required as part of Study SCGAM-06 Baseline, do not need to be repeated. Patients who completed the SCGAM-03 study and went on a commercial SCIG product prior to screening for SCGAM-06 are required to complete the Stabilization Period.

Number of Patients:

Approximately 65 patients are planned for this study.

- At least 15 patients in Cohort 1
- At least 15 patients in Cohort 2
- At least 35 patients in Cohort 3

Patient Selection Criteria:

Inclusion Criteria:

1. Age ≥2 years and ≤75 years.
2. Confirmed diagnosis of primary immunodeficiency (PI) disease as defined by the European Society for Immunodeficiencies and Pan American Group for

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Immunodeficiency and requiring immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia. **Note:** The exact type of PI disease will be recorded.

3. Established on a consistent or stable mg/kg dose of any SCIG treatment for a minimum of 3 months prior to Screening. **Note:** patients entering Cohort 3 must be on weekly SCIG infusions for a minimum of 12 weeks.
4. Availability of the Immunoglobulin G (IgG) trough levels of 2 previous SCIG infusions within 1 year of Screening, with 1 trough level obtained within 3 months prior to enrollment, and maintenance of trough serum IgG levels ≥5.0 g/L in 2 previous infusions. Patients with no prior IgG trough level within 3 months prior to enrollment may use the Screening IgG trough level as their 2nd reading.
5. Voluntarily given, fully informed signed informed consent. For patients under the legal age of consent, voluntarily given, fully-informed, signed informed consent will be provided by patient's parent or legal guardian, and assent will be provided by patient (per age-appropriate Institutional Review Board [IRB] requirements).
6. Females of childbearing potential, who are not nursing and have no plans for pregnancy during the course of the study, must have been using at least 1 acceptable form of birth control for a minimum of 30 days prior to the Screening visit and must agree to use at least 1 acceptable method of contraception for 30 days after the last dose of CUTAQUIG. Acceptable methods include: intrauterine device (IUD), hormonal contraception, male or female condom, spermicide gel, diaphragm, sponge, cervical cap, or abstinence.
7. For female patients of child-bearing potential, a negative result in a urine pregnancy test conducted at the Screening visit.
8. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

Exclusion Criteria:

1. Evidence of active infection within 4 weeks of Screening or during the Screening Period.
2. Current or clinically-significant history of any cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, neurological, immunological (excluding PI), hematologic, and/or psychiatric disorder(s), or a history of any

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other illness that, in the opinion of the Investigator, might confound the results of the study, or pose additional risk to the patient by participation in the study.

3. Known history of adverse reactions to immunoglobulin A (IgA) in other products.
4. Body mass index (BMI) >40 kg/m^2 for patients entering Cohort 2 or Cohort 3. There are no BMI restrictions for Cohort 1.
5. Ongoing history of hypersensitivity or persistent reactions to blood or plasma derived products, or any component of the investigational product (such as Polysorbate 80).
6. Requirement of any routine premedication for IgG administration.
7. History of malignancies of lymphoid cells and immunodeficiency with lymphoma.
8. Severe liver function impairment (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >3 times above upper limit of normal).
9. Known protein-losing enteropathies or clinically significant proteinuria.
10. Presence of renal function impairment or predisposition for acute renal failure (eg, any degree of pre-existing renal insufficiency or routine treatment with known nephritic drugs).
11. Treatment with oral or parenteral steroids for ≥30 days, or when given intermittently or as bolus at daily doses ≥0.15 mg/kg when taken within 30 days of Screening. **Note:** Short or intermittent courses of steroids (ie, a steroid burst) of >0.15 mg/kg/day is allowed for treatment of a short-term condition such as an asthma exacerbation.
12. Treatment with immunosuppressive or immunomodulatory drugs (except Omalizumab).
13. Use of HYQVIA (Immune Globulin Infusion 10% [Human] with Recombinant Human Hyaluronidase) within 3 months prior to first CUTAQUIG infusion.
14. Live viral vaccination (such as measles, rubella, mumps, and varicella) within 2 months prior to first CUTAQUIG infusion.
15. Exposure to blood or any blood product or derivative, other than sub-cutaneous IgG used for regular PI disease treatment, within 3 months before the first CUTAQUIG infusion.
16. Treatment with any investigational medicinal product within 3 months prior to first CUTAQUIG infusion. **Note:** Patients participating in Study SCGAM-03 will be allowed to enter this study without the 3-month waiting period for an Investigational Product. Patients receiving another investigational SCIG

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product within 3 months prior to the first CUTAQUIG infusion may be considered for enrollment after Sponsor approval.

17. Presence of any condition that is likely to interfere with the evaluation of CUTAQUIG or satisfactory conduct of the trial.
18. Known or suspected to abuse alcohol, drugs, psychotropic agents, or other chemicals within the past 12 months prior to first CUTAQUIG infusion.
19. Known active or chronic hepatitis B, hepatitis C, or HIV infection. Past hepatitis B or hepatitis C infection that has been cured is allowed.

Test Product, Dose, and Mode of Administration:

CUTAQUIG, human normal immunoglobulin for subcutaneous (SC) administration.

CUTAQUIG will be administered by SC infusion every week (±2 days, Cohort 1 and Cohort 2), every other week (±2 days, Cohort 3) at the doubled weekly dose. The dosing frequency will be determined by cohort assignment.

Patients will receive the same mg/kg body weight dose as their previous SCIG product prior to study entry.

If, during the study, a patient's body weight changes by >5% from the first infusion of IMP, the dose will be adjusted to keep a constant mg/kg body weight basis. Additional adjustments will be made by the Investigator at study visits if the patient's body weight changes >5% from the previous adjusted weight.

Each patient's CUTAQUIG dose may be individualized, if considered necessary by the Investigator, by titrating upward or downward.

Batch (lot) numbers will be reported in the final report of the study.

Duration of Treatment:

Individual patient participation will be approximately 30 to 32 weeks:

- Screening Period: 1 to 2 weeks*
- Stabilization Period: 4 weeks**
- CUTAQUIG Treatment Period: 24 weeks (6 months)
- Termination Visit: 1 week after last CUTAQUIG infusion for Cohort 1 and Cohort 2; 2-weeks after last CUTAQUIG infusion for Cohort 3

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* Patients entering the study established on weekly SCIG infusions will have a 1-week (±2 days) Screening Period. Patients entering the study established on every other week dosing will have a 2-week (±2 days) Screening Period.

** Patients entering the study currently active and established on CUTAQUIG in Study SCGAM-03 will skip Stabilization Period.

Reference Therapy, Dose, Mode of Administration:

Not applicable.

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary Endpoint Parameters:

The co-primary objectives are to compare total IgG trough levels from weekly infusions to every other week infusions, to assess safety and tolerability of CUTAQUIG being administered according to 3 different infusion parameters, and to assess efficacy parameters when switching from weekly infusions to every other week infusions. These will be assessed using the following safety variables:

- Change in individual total IgG trough levels from weekly infusions to every other week infusions
- Occurrence of treatment-emergent AEs (TEAEs) throughout the entire Stabilization and Treatment Periods starting with the first infusion of investigational medicinal product (IMP)
- Occurrence of TEAEs temporally associated with CUTAQUIG delivered during the Treatment Period
- Occurrence of TEAEs temporally associated with CUTAQUIG delivered during the Stabilization Period
- TEAEs by speed of infusion
- Local infusion-site reactions
- Laboratory parameters (hematology, clinical chemistry, and basic urinalysis)

Secondary Endpoint Parameters:

Secondary objectives will evaluate quality of life, along with additional evaluations of CUTAQUIG safety and efficacy being administered according to 3 different infusion parameters. These will be assessed using the following variables:

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- Quality of Life questionnaires
- Measurement of individual profiles of IgG trough levels over time (all cohorts)
- Monitoring for all infectious disease occurrence, resolution, and antibiotic use
- Occurrence of serious bacterial infections (SBIs)
- Vital signs (blood pressure, pulse, body temperature, respiratory rate)

Tertiary Endpoint Parameters:

The tertiary objective will evaluate patient satisfaction of the study parameters (such as switching to CUTAQUIG from another SCIG product, satisfaction with infusion pump, changes in infusion regimen parameters, general infection/general observations). This will be assessed using the following parameter:

- Subject Questionnaire

Study Procedures:

Investigators will enroll patients into the study only after written informed consent has been obtained (and written assent where appropriate). During the Screening Period, sites must obtain written approval from Octapharma prior to patients entering the Stabilization Period (or Treatment Period, for subjects who are currently active and established on CUTAQUIG in Study SCGAM-03).

The Flow Chart of Assessments includes full details regarding all of the procedures that will be performed at each study visit. Below is a brief summary of the procedures that will be performed during the study.

Screening Period:

The Screening Visit should occur on approximately the same day the patient is scheduled to infuse with their personal SCIG product (or their final infusion of CUTAQUIG in Study SCGAM-03, if appropriate) in order to get an accurate IgG trough level. After written informed consent/assent has been obtained, patients will be evaluated for study eligibility according to the inclusion/exclusion criteria. These evaluations will include demographics, medical history, physical examinations (including body weight and vital signs), current medication use, blood and urine sample collection (for evaluation of clinical safety laboratory parameters, and IgG trough levels as specified in the Flow Chart of Assessments. Following the completion of all Screening procedures, the patient will dose with their personal SCIG

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product (or CUTAQUIG from Study SCGAM-03, if applicable) at their typical dose and infusion rate.

During the Screening Period (and after the infusion with their personal SCIG product or CUTAQUIG from Study SCGAM-03, if applicable), patients must not receive any other IgG product; therefore, it is anticipated that patients will receive their first dose of CUTAQUIG between 5 days and 16 days after the Screening Visit.

Patients may be enrolled into any open cohort, based on Investigator and patient preference: however, patients entering the study already established on every other week dosing must enter either Cohort 1 or Cohort 2. After receiving written approval from the Sponsor, which will include confirmation that the chosen cohort is still open for enrollment, patients who have met all of the inclusion criteria and none of the exclusion criteria will return to the clinic for their first CUTAQUIG infusion in the Stabilization Period.

Patients entering the study currently active and established on CUTAQUIG in Study SCGAM-03 will have their Screening Visit procedures performed on the same day as their last infusion visit on Study SCGAM-03. Patients must first complete their final infusion for Study SCGAM-03 prior to being consented for Study SCGAM-06. Procedures performed on the same day for Study SCGAM-03 that are also required as part of Study SCGAM-06 do not need to be repeated. These patients will proceed directly into the Treatment Period following completion of Screening. All other patients, including patients who completed their participation in Study SCGAM-03 and went on a commercial SCIG product prior to the Screening Visit, will need to complete the Stabilization Period.

Stabilization Period

Study-required assessments will be performed as specified in the Flow Chart of Assessments including safety evaluations before and after each infusion. These assessments will include updating medical history and current medication use, measuring body weight and vital signs, collecting blood and urine samples (for evaluation of clinical safety laboratory parameters and for hepatitis C), and collecting serum retention samples. Patients will receive their infusion of CUTAQUIG and will be monitored for infusion site reactions and AEs. Any concomitant medication use after the start of the infusion will be recorded.

Prior to leaving the study site, patients will be dispensed CUTAQUIG for in-home infusions between site visits, along with detailed infusion instructions. Patients will

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also be provided with a study diary in which they will record details of their home treatment infusions, AEs, and relevant concomitant medication use. Patients entering the study will have experience with SCIG infusions; however, if necessary, they will be provided with additional training on using an infusion pump.

Treatment Visits:

Study-required assessments will be performed as specified in the Flow Chart of Assessments per cohort assignment, including safety evaluations before and after each infusion. At all on-site visits the following assessments will be performed: measurements of body weight and vital signs, collection of blood samples for IgG trough levels, infusion of CUTAQUIG, monitoring for infusion site reactions and AEs, review and dispensing of patient diary, and updating concomitant medication use. For all cohorts at Baseline, Week 12, and Week 24, the following evaluations will also be performed: physical examination and blood and urine sample collection for evaluation of clinical safety laboratory parameters (including urine pregnancy tests). All patients (or parents/guardians, as age-appropriate) will complete a QoL questionnaire prior to IMP infusion at the Baseline Visit. Patients who entered the Treatment Period after participation in Study SCGAM-03 (and therefore skipping the Stabilization Period) will have serum retention and hepatitis C samples collected at the Baseline Visit.

Prior to leaving the study site, patients will be dispensed CUTAQUIG for in-home infusions between site visits, along with detailed infusion instructions. Patients will also be provided with a study diary in which they will record details of their home treatment infusions, adverse events, and relevant concomitant medication use.

Termination Visit:

Patients in Cohort 1 and Cohort 2 will have their Termination Visit 1 week (± 2 days) after last infusion, and patients in Cohort 3 will have their Termination Visit 2 weeks (± 2 days) after the last infusion. All Termination Visit procedures must be performed prior to the patient receiving any other IgG product.

For either regular or early termination, a Termination Visit will include study assessments as indicated in the Flow Chart of Assessments. These assessments will include physical examinations (including body weight and vital signs), collection of blood and urine samples (for clinical safety laboratory parameters, and IgG trough levels), collection of serum retention and hepatitis C samples, collection of AEs and

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concomitant medication use, evaluation for infusion site reactions, and completion of both a QoL questionnaire and the Subject Questionnaire.

Independent Data Monitoring Committee:

An independent Data Monitoring Committee will periodically review relevant data with emphasis on AEs, including SAEs, and thromboembolic events.

Statistical Analysis:

This is an open-label, non-controlled, 3-arm study to primarily monitor safety and tolerability for 3 different dosing regimens and to assess efficacy parameters when switching from weekly to every other week infusions of CUTAQUIG. The co-primary endpoints and most of the secondary endpoints will be assessed by means of descriptive statistics. One of the primary endpoints, namely the efficacy of CUTAQUIG to maintain total IgG trough levels when administered every other week, will be statistically tested, and the number of patients to be enrolled in Cohort 3 was determined accordingly.

The following populations will be considered for the statistical analysis:

- Safety Analysis Set: all patients who received at least part of one infusion of CUTAQUIG.
- Full Analysis Set (FAS): all patients in the Safety Analysis Set who satisfy all major eligibility criteria and for whom any post-baseline data is available (per intention-to-treat principle). This set of eligible patients will be used for measurement of treatment effects.
- Per-Protocol (PP) Set: all patients in the FAS, excluding those with substantial protocol deviations which may have an impact on the analysis of the co-primary endpoints. This is the set of patients who participated in the study as intended and for whom the co-primary endpoints can be evaluated as planned.

Only substantial protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP set. The membership of each patient in the respective analysis populations will be determined before statistical analysis in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager, and the study statistician.

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In the event that a patient is not treated according to the dosing regimen described for their assigned cohort, the original cohort assignment will still be used for Safety and ITT analyses (SAF and FAS populations). These patients will be removed from the PP population due to protocol violations.

Statistical Analysis Plan:

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to start of the statistical analysis.

The safety analysis will comprise descriptive statistics, tabulations and listings of all TEAEs, safety laboratory results, vital signs and physical examination findings. All reported AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

For each TEAE, the time relative to the start of the infusion will be calculated and the TEAE will be classified as temporally associated if the onset is during the infusion or within 72 hours after the end of the infusion.

All reported AEs will be listed and tabulated in full detail, in particular the following key figures will be presented for each cohort and for the study as a whole:

- Total number of TEAEs reported in the Stabilization and Treatment Periods
- Number of TEAEs temporally associated with CUTAQUIG delivered during the Treatment Period
- Number of TEAEs temporally associated with CUTAQUIG delivered during the Stabilization Period
- Infusion rate at the onset of temporally associated TEAEs (frequencies and percentages)
- Narratives will be prepared describing each death, other serious adverse events (SAEs), and other significant AEs that are judged to be of special interest because of clinical importance.

The QoL data will be presented descriptively by visit, along with the change from Baseline Visit.

The Subject Questionnaire data will be presented descriptively.

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All IgG measurements will be listed and summarized descriptively by time point. Individual courses of IgG trough levels will be presented graphically as Trellis plots.

For Cohort 3 the change in trough total IgG levels from baseline weekly infusions to Week 24 (or Early Termination, if appropriate) of every other week infusions will be evaluated by means of a paired t-test.

FLOW CHARTS OF ASSESSMENTS

Table 1: Screening and Stabilization Periods – Flow Chart of Assessments

ASSESSMENTS	Screening Period	Stabilization Period[5]		Treatment Period
STABILIZATION PERIOD WEEK NUMBER	Screening[4]	Week 0	Weeks 1, 2, 3	Baseline
Informed Consent / Assent	X		Patients infuse CUTAQUIG at home. No on-site visits are required.	Patients return to the clinic 4 weeks after Stabilization Period Week 0 visit and will enter the Treatment Period and their assigned cohort.
Inclusion/exclusion criteria	X			
Demographics	X			
Medical history	X	X[3]		
Body weight	X	X		
Physical examination	X			
Vital signs[1]	X	X		
Urine pregnancy test[1, 2]	X			
IgG trough levels	X	X		
Hematology (CBC, WBC differential, hematocrit, hemoglobin) [1]	X	X		
Clinical Chemistry (sodium, potassium, glucose, ALT, AST, LDH, total bilirubin, blood urea nitrogen, creatinine) [1]	X	X		
Urine analysis: pH, glucose, ketones, leukocytes, hemoglobin[1]	X	X		
Serum retention samples[1]		X		
Hepatitis C sample[1]		X		
Receive written Sponsor approval for enrollment including cohort assignment	X			
Infusion using patient's personal, commercially available SCIG product (or CUTAQUIG from Study SCGAM-03, if appropriate)[4]	X			
Infusion of IMP (on site)		X		
Check for local infusion-site reactions		X		
Patient diary hand-out		X		
Prior / Concomitant medication	X	X		
Adverse events[3]		X		

[1] Vital signs will be measured, and all laboratory samples will be collected, before IgG or IMP infusion (if applicable).

[2] For females of child-bearing potential.

[3] Any untoward medical events that occur prior to the first CUTAQUIG infusion in this study (at Stabilization Period Week 0 or Treatment Period Week 0, as appropriate) will be recorded as medical history

[4] Patients entering the study currently active and established on CUTAQUIG in Study SCGAM-03 will have the Screening Visit performed on the same day as their last infusion visit on Study SCGAM-03. Patients must first complete their final infusion for SCGAM-03, prior to being consented for Study SCGAM-06. Procedures that are performed on the same day as part of Study SCGAM-03 that are also required as part of Study SCGAM-06, do not need to be repeated at the same visit.

[5] Patients entering the study currently active and established on CUTAQUIG from Study SCGAM-03 will proceed directly into the Treatment Period after the completion of Screening Period. All other patients, including patients who completed the SCGAM-03 study and went on a commercial SCIG product prior to screening for SCGAM-06 are required to complete the Stabilization Period.

Table 2 Cohort 1 (Increased Volume) – Flow Chart of Assessments

ASSESSMENTS	Treatment Period							Termination[7]
TREATMENT PERIOD VISIT WEEK OR TIMING	BL[1, 2]	4[1]	8[1]	12[1]	16[3]	20[3]	24[1]	One week after last infusion
Body weight	X	X	X	X	X	X	X	
Physical examination	X			X			X	X
Vital signs[4]	X	X	X	X	X	X	X	X
Urine pregnancy test[4, 5]				X			X	X
IgG trough levels[4]	X	X	X	X	X	X	X	X
Hematology (CBC, WBC differential, hematocrit, hemoglobin)[4]	X			X			X	X
Clinical Chemistry (sodium, potassium, glucose, ALT, AST, LDH, total bilirubin, blood urea nitrogen, creatinine)[4]	X			X			X	X
Urine analysis: pH, glucose, ketones, leukocytes, hemoglobin[4]	X			X			X	X
Serum retention samples: SCGAM-03 patients not participating in the Stabilization Period[4]	X							
Serum retention samples: all patients[4]								X
Hepatitis C samples: SCGAM-03 patients not participating in the Stabilization Period[4]	X							
Hepatitis C samples: all patients[4]								X
Infusion of IMP (on site)[6]	X	X	X	X	X	X	X	
Check for local infusion-site reactions	X	X	X	X	X	X	X	X
Patient diary hand out and check	X	X	X	X	X	X	X	X
Quality-of-Life Questionnaire	X							X
Subject Questionnaire								X
Prior/Concomitant medication	Throughout the study							
Adverse events	Throughout the study							

[1] **Required Onsite Visit** for **all** patients.

[2] Patients entering the study currently active and established on CUTAQUIG in Study SCGAM-03 will have the Baseline Visit performed on the same day as Termination Visit on Study SCGAM-03. Procedures that are performed on the same day as part of Study SCGAM-03 Termination Visit that are also required as part of Study SCGAM-06 Baseline do not need to be repeated at the same visit.

[3] **Optional Onsite Visit**. This visit is not required for patients who are infusing at their maximum volume.

[4] Vital signs will be measured, and all laboratory samples will be collected, before IMP infusion (if applicable).

[5] For females of child-bearing potential.

[6] Increase volumes at each infusion site by up to a maximum increase of 25 mL/site for patients ≥40 kg or a maximum increase of 10 mL/site for patients <40 kg every 4 weeks at each site visit. This increase can be achieved by reducing the total number of injection sites while keeping the same or lower flow rate parameters as received with their prior treatment. This cycle will continue until reaching a patient's maximum dose (in mL), maximum tolerated volume (maximum volume based on Investigator's decision of patient's tolerance) or 100 mL at 1 injection site –whichever is reached first. Further instructions are provided in Section 3.3.2 Dosing, Cohort 1.

[7] Termination Visit MUST take place prior to the patient receiving any other IgG product.

Table 3: Cohort 2 (Increased Infusion Rate) – Flow Chart of Assessments

ASSESSMENTS	Treatment Period							Termination[7]
TREATMENT PERIOD VISIT WEEK OR TIMING	BL[1, 2]	4[1]	8[1]	12[1]	16[3]	20[3]	24[1]	One week after last infusion
Body weight	X	X	X	X	X	X	X	
Physical examination	X			X			X	X
Vital signs[4]	X	X	X	X	X	X	X	X
Urine pregnancy test[4, 5]				X			X	X
IgG trough levels[4]	X	X	X	X	X	X	X	X
Hematology (CBC, WBC differential, hematocrit, hemoglobin)[4]	X			X			X	X
Clinical Chemistry (sodium, potassium, glucose, ALT, AST, LDH, total bilirubin, blood urea nitrogen, creatinine)[4]	X			X			X	X
Urine analysis: pH, glucose, ketones, leukocytes, hemoglobin[4]	X			X			X	X
Serum retention samples: SCGAM-03 patients not participating in the Stabilization Period[4]	X							
Serum retention samples: all patients[4]								X
Hepatitis C samples: SCGAM-03 patients not participating in the Stabilization Period[4]	X							
Hepatitis C samples: all patients[4]								X
Infusion of IMP (on site)[6]	X	X	X	X	X	X	X	
Check for local infusion site reactions	X	X	X	X	X	X	X	X
Patient diary handout and check	X	X	X	X	X	X	X	X
Quality-of-Life Questionnaire	X							X
Subject Questionnaire								X
Prior/Concomitant medication	Throughout the study							
Adverse events	Throughout the study							

[1] **Required Onsite Visit** for **all** patients.

[2] Patients entering the study currently active and established on CUTAQUIG in Study SCGAM-03 will have the Baseline Visit performed on the same day as Termination Visit on Study SCGAM-03. Procedures that are performed on the same day as part of Study SCGAM-03 Termination Visit that are also required as part of Study SCGAM-06 Baseline do not need to be repeated at the same visit.

[3] **Optional Onsite Visit**. This visit is not required for patients who are infusing at their maximum rate.

[4] Vital signs will be measured, and all laboratory samples collected, before IMP infusion (if applicable).

[5] For females of child-bearing potential.

[6] Increase flow rates by up to 25 mL/hr/site for patients ≥40 kg or 10 mL/hr/site for patients <40 kg every 4 weeks at each site visit until reaching either 1: a maximum flow rate (100 mL/hr/site) or the maximum rate achievable by the pump, or 2) the maximum tolerated flow rate (based on Investigator's decision of patient's tolerance) – whichever is reached first.

[7] Termination Visit MUST take place prior to the patient receiving any other IgG product.

Table 4: Cohort 3 (Every Other Week Dosing) – Flow Chart of Assessments

ASSESSMENTS		Treatment Period			Termination
TREATMENT PERIOD VISIT WEEK OR TIMING	BL[1, 2]	4[1]	12[1]	24[1]	Two weeks after last infusion[6]
Body weight	X	X	X	X	
Physical examination	X		X	X	X
Vital signs[3]	X	X	X	X	X
Urine pregnancy test[3, 4]			X	X	X
IgG trough levels[3]	X	X	X	X	X
Hematology (CBC, WBC differential, hematocrit, hemoglobin)[3]	X		X	X	X
Clinical Chemistry (sodium, potassium, glucose, ALT, AST, LDH, total bilirubin, blood urea nitrogen, creatinine)[3]	X		X	X	X
Urine analysis: pH, glucose, ketones, leukocytes, hemoglobin[3]	X		X	X	X
Serum retention samples: SCGAM-03 patients not participating in the Stabilization Period[3]	X				
Serum retention samples: all patients[3]					X
Hepatitis C samples: SCGAM-03 patients not participating in the Stabilization Period[3]	X				
Hepatitis C samples: all patients[3]					X
Infusion of IMP (on site)[5]	X	X	X	X	
Check for local infusion-site reactions	X	X	X	X	X
Patient diary hand-out and check	X	X	X	X	X
Quality-of-Life Questionnaire	X				X
Subject Questionnaire					X
Prior/Concomitant medication	Throughout the study				
Adverse events	Throughout the study				

[1] **Required Onsite Visit** for **all** patients.

[2] Patients entering the study currently active and established on CUTAQUIG in Study SCGAM-03 will have the Baseline Visit performed on the same day as Termination Visit on Study SCGAM-03. Procedures that are performed on the same day as part of Study SCGAM-03 Termination Visit that are also required as part of Study SCGAM-06 Baseline do not need to be repeated at the same visit.

[3] Vital signs will be measured, and all laboratory samples collected, before IMP infusion (if applicable).

[4] For females of child-bearing potential.

[5] Patients entering this cohort must already be established on weekly dosing for a minimum of 12 weeks prior to Screening. Patients will receive double the mg/kg weekly dose and begin an every other week dosing schedule. Infusion flow rates will be determined by the patient and Investigator, but initially should not exceed the patient's prior infusion rate. When switching from weekly to every other week dosing, infusion volumes increases per site must not exceed 25 mL for patients ≥40 kg or a maximum increase of 10 mL/site for patients <40 kg at the Treatment Period Baseline Visit. If a patient's doubling of their weekly dose requires dosing with a volume of more than the maximum allowed volume increase per injection site (25 mL/site or 10 mL/site, dependent on patient body weight), they will be required to increase the number of infusion sites to remain below the maximum body-weight dependent volume increase. If this occurs, after 2 infusions the patient may remove 1 of the newly introduced injection sites as long as the volume per injection site increase limit is not exceeded.

[6] Termination Visit MUST take place prior to the patient receiving any other IgG product.

PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

[redacted] 11.09.2019

Signature Date

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Signature of the Principal Coordinating Investigator

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

[redacted]

[redacted]

9/10/19
Date

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
BL	Baseline
BMI	Body mass index
Cmax	Maximum concentration of drug
Cmin	Minimum concentration of drug
CRO	Contract research organization
CSF	Cerebrospinal fluid
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMP	Investigational medicinal product
IRB	Institutional Review Board
IV	Intravenous
IVIG	Intravenously administered immunoglobulin
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NAT	Nucleic acid testing
PI	Primary immunodeficiency
PK	Pharmacokinetic(s)
PP	Per protocol
QoL	Quality of life
SAE	Serious adverse event
SBI	Serious bacterial infection
SC	Subcutaneous
SCIG	Subcutaneously administered immunoglobulin
SF-10	Short Form Health Survey, 10 item
SF-36	Short Form Health Survey, 36 item
TEAE	Treatment-emergent adverse event
TEE	Thromboembolic event
Tmax	Time to maximum plasma concentration
WBC	White blood cell

GLOSSARY OF TERMS

Term	Definition
Treatment Period Baseline	The first visit during the Treatment Period
CUTAQUIG-naïve patients	Patients who did not participate in Study SCGAM-03
Cohort 1 (increased volume)	This cohort will evaluate the safety and tolerability of CUTAQUIG delivered at increased volume per site than delivered with previous SCIG treatments. During the Stabilization Period, patients will receive CUTAQUIG at the same body-weight dependent (mg/kg) dose and infusion flow rate as their previous SCIG product; however, this flow rate should not to exceed maximum infusion rates listed in protocol. During the Treatment Period, patients will return to the clinic at Baseline to receive their first dose of CUTAQUIG with an infusion volume increase of up to the maximum allowed volume increase per infusion site of 25 mL/site for patients ≥40 kg or 10 mL/site for patients <40 kg. Every 4 weeks the infusion volume will be increased again by up to 25 mL/site or 10 mL/site for patients <40 kg until reaching a maximum dose (in mL), or maximum tolerated volume (maximum volume based on Investigator's decision of patient's tolerance), or 100 mL at 1 injection site – whichever is reached first.
Cohort 2 (increased flow rate)	This cohort will evaluate the safety and tolerability of CUTAQUIG delivered at increased flow rates than those delivered with previous SCIG treatments. During the Stabilization Period, patients will receive CUTAQUIG at the same body-weight dependent (mg/kg) dose and infusion flow rate as their previous SCIG product; however, this flow rate should not exceed maximum infusion rates listed in protocol. During the Treatment Period, patients will return to the clinic at Baseline to receive their first dose of CUTAQUIG with an infusion rate increase up to a maximum allowed flow rate increase per infusion site of 25 mL/hr/site for patients ≥40 kg or 10 mL/hr/site for patients <40 kg. Every 4 weeks the infusion flow rates will be increased again by up to 25 mL/hr/site for patients ≥40 kg or 10 mL/hr/site for patients <40 kg until either 1) a maximum flow rate (100 mL/hr/site) or the maximum flow rate achievable by the pump, or 2) the maximum tolerated flow rate (based on Investigator's decision of patient's tolerance) – whichever is reached first.
Cohort 3 (every other week dosing)	This cohort will evaluate the safety and tolerability of CUTAQUIG delivered at the same or equivalent of twice the weekly mg/kg dose administered every other week with previous SCIG treatment. During the Stabilization Period, patients will receive CUTAQUIG at the same body-weight dependent (mg/kg) dose and infusion flow rate as their previous SCIG product; however, this flow rate must not to exceed maximum infusion rates listed in protocol. During the Treatment Period, patients will return to the clinic at Baseline to receive their first double mg/kg weekly dose and begin an every other week dosing schedule. When switching from weekly to every other week dosing, infusion volume increases per site must not exceed a maximum allowed volume increase per infusion site of 25 mL/site for patients ≥40 kg or 10 mL/site for patients <40 kg at the Treatment Period Baseline Visit. If a patient's doubling of their weekly dose requires dosing with a volume of more than the maximum allowed volume increase per injection site (25 mL/site or 10 mL/site, dependent on patient body weight), they will be required to increase the number of infusion sites to remain below the maximum body-weight dependent volume increase. If this occurs, after 2 infusions the patient may remove 1 of the newly introduced injection sites as long as the volume per injection site increase limit is not exceeded.
CUTAQUIG	Immune Globulin Subcutaneous (Human). BLA approval received December 12, 2018 by US FDA.
Enrolled	Patients will be considered enrolled into the study after written informed consent (and assent, if age-appropriate) has been obtained.
Infusion site	An anatomical location of IMP infusion.

Term	Definition
Stabilization Period	Patients will receive CUTAQUIG infusions at the same body-weight dependent (mg/kg) dose and infusion flow rate (ml/hr/site) as their previous SCIG product; however, this flow rate should not exceed maximum infusion rates listed in protocol. Patients entering the study currently active and established on CUTAQUIG in Study SCGAM-03 will have already been stabilized on CUTAQUIG and will proceed directly into the Treatment Period following completion of Screening. All other patients, including patients who completed their participation in Study SCGAM-03 and went on a commercial SCIG product prior to the Screening Visit, will need to complete the Stabilization Period
Treatment Period	Patient will receive CUTAQUIG infusions according their assigned cohort parameters.

1 INTRODUCTION

1.1 Background

The primary therapeutic use of γ-immunoglobulins (Immunoglobulin G or IgG) is to provide antibodies to prevent viral and bacterial diseases (replacement therapy) in patients with primary immunodeficiency (PI) syndromes who have significant defects of antibody formation (humoral immunity).

The PI syndromes are a heterogeneous group of disorders with an intrinsic defect of the tissues, cells, or proteins of the immune system resulting in immune deficiency. Many of these disorders are characterized by hypogammaglobulinaemia with or without defective antibody production. Children and adults with PI disease have an increased risk of recurrent bacterial and viral infections that typically attack the respiratory tract (sinusitis, bronchitis, pneumonia) but can also affect the gastrointestinal tract (gastroenteritis). They can be severe and can lead to substantial morbidity. Responses to antibacterial therapy are often poor. At present, most PI diseases are not curable, but immunoglobulins have shown to decrease the total number of severe infections and the duration of hospitalization.

In the earlier years (around 1950), the IgG preparations were administered intramuscularly. This route of administration causes substantial discomfort and restricts the amount of IgG that can be given to the patients. During the last 20 years, several IgG preparations have been developed for intravenous (IV) and subcutaneous (SC) administration, and their use has further contributed to the successful treatment of patients with PI disorders.

Administration via the SC route offers some advantages over IV infusion from a patient's and a physician's perspective and therefore become an alternative treatment option to the IV treatment. After the introduction of small, portable syringe drivers, this route of administration has gained even more popularity in Europe and the US as a practical, effective and safe treatment, because home therapy can also be recommended with this kind of administration.

There are two major differences in the pharmacokinetic (PK) characteristics of intravenously administered immunoglobulins (IVIG) and subcutaneously administered immunoglobulins (SCIG): delayed absorption and reduced bioavailability.

Following IV administration, the plasma concentration peaks immediately upon termination of the infusion, frequently reaching concentrations more than twice as high as the trough level. After SC administration, the absorption of IgG into the subcutaneous tissue is slower; the IgG must be delivered into the blood stream by the lymphatic system. Thus, with SCIG, the intravascular IgG concentration increases gradually, peaking at 48 to 72 hours. Most other features of SCIG treatment are consequences of these fundamental differences.[1]

Studies of the PK of SCIG have shown a lower bioavailability than IVIG. This decreased bioavailability may involve degradation in the tissues and/or local binding in the intercellular matrix. Because of this expectation, several studies were designed to directly determine the bioavailability of SCIG as compared to IVIG.[2]

On converting from IVIG to SCIG replacement therapy for PI disease, the equivalent monthly dose of IgG is usually determined in one of two ways:

- 1:1 dosing: The single IVIG dose administered every 3 (or 4) weeks is split into 3 (or 4) equal weekly SCIG infusions.
- Dosing based on the area under the curve (AUC). The SCIG dose is calculated from PK data to provide a monthly exposure to IgG equivalent to that with IVIG.

The former is common in Europe, while the latter is a requirement of the US Food and Drug Administration (FDA) for SCIG labelling studies.[3] A recent study demonstrated the dose conversion factor for CUTAQUIG was 1.37.[4] Also, the CUTAQUIG Package Insert recommends a dose conversion factor of 1.4.[5]

No differences have been reported in the half-life of SCIG and IVIG. With modern IgG preparations, half-lives have generally been reported to be about 30 to 35 days. Thus, there is no clinically significant difference in the half-life of IgG between the two administration routes.[1]

However, SCIGs are usually given weekly, compared with IVIG regimens in which a large dose is given every 3rd or 4th week. The use of smaller doses at more frequent intervals results in stable, higher trough IgG serum concentrations which remain constant between consecutive SCIG infusions.[6]

In 3 prior studies comparing IVIG and SCIG in PI patients, the mean peak serum IgG level immediately after IV infusions was 2303 mg/dL.[7-9] In contrast, the mean peak with SCIG was 1410 mg/dL and the time for the peak IgG concentration (Tmax) was 62.6 h (2.6 days).[10]

With weekly SCIG administrations, only about 4.5 days elapse between the Tmax of one dose and the administration of the next dose. Given the half-life of 30 days, this means that the IgG plasma concentration has dropped by only about 10% to 20% before the serum level starts to rise again. In contrast, with IVIG dosing intervals of 3 to 4 weeks (about one half-life), the drop in plasma concentration will be about 40% to 50% by the time the next dose is due. These differences in the dosing intervals used in most SCIG versus IVIG regimens result in more stable serum IgG levels with SCIG.[1,10]

Pooled data from 7 studies in which equivalent monthly SC IgG doses were given weekly versus IVIG every 21 to 28 days showed that trough serum IgG levels were 10% to 20% higher with weekly SC doses than with the same total monthly IVIG dose. After 6 to 12 weekly infusions, near-steady-state IgG levels were achieved with differences between minimum and peak concentrations of only 5% to 10% of the overall mean.[1,10]

Population PK modelling has been used to predict IgG exposure following a range of SCIG dosing regimens including frequent weekly dosing (1 to 7 times per week) and every other week dosing. This broad range of SCIG dosing regimens was simulated to predict steady-state serum IgG exposures. This PK modelling study consisting of 2,500 patients was simulated to compare steady-state IgG concentration time profiles between weekly SCIG administrations with other frequencies, including daily through every other week dosing. The results produced overlapping steady-state concentration-time profile and similar AUC, Cmax, and Cmin values. This simulation

concluded that the same total weekly SCIG dose can be administered at different intervals, frequent or every other week, with minimal impact on serum IgG levels.[11]

No clinical data are available that would allow comparison of the long-term efficacy of SCIG versus IVIG administration on the development of bronchiectasis or other changes on lung scans, nor on deterioration of pulmonary function in patients who have PI. Similarly, no data are available comparing the efficacy of SCIG versus IVIG on the persistence or progression of chronic sinus disease in PI patients with that problem, or on other complications of PI.[12]

Orange et al (2012) reviewed the clinical efficacy of SCIG and identified 13 clinical studies in a total of 482 patients representing more than 27,500 infusions. The rate of serious bacterial infections (SBIs) was the most common primary efficacy endpoint in these studies. Secondary endpoints included overall infections (ie, infections not meeting SBI criteria), missed days at work or school, days in hospital and days on antibiotics. Definitions of overall infections and SBI were not standardized across studies. In 6 studies, SBIs were defined by FDA criteria and included bacterial pneumonia, meningitis, sepsis, osteomyelitis or visceral abscess. In 2 studies, an SBI was defined as an infection requiring hospitalization.[3]

The rate of SBI was reported in 11 studies and varied from 0 to 0.09 events per patient per year. Infections were reported in 11 studies and varied from 2 to 5.18 events per patient per year. These rates are overall at least as low as those reported for IVIG studies.

To provide adequate protection from infection, a serum IgG concentration of >5 g/L following IgG therapy has been recommended. Several retrospective studies and one prospective study, however, have shown that higher serum IgG concentrations resulting from higher doses of IVIG are associated with a decreased incidence of infections.[3]

A previous meta-analysis in 16 individual studies of IVIG focused on the diagnosis of pneumonia, the most comparable endpoint, and demonstrated a statistically significant inverse correlation between higher IgG dose and a lower incidence of pneumonia, with a 27% decrease in incidence of pneumonia for every 100 mg/kg increase in dose.[13]

Despite its well-established safety profile, IVIG often leads to undesired symptoms ranging from mild systemic adverse reactions (including flushing, fever, muscle aches, tiredness, headache, and dizziness) to severe reactions (including chest pain, tachycardia, changes in blood pressure, aseptic meningitis, thrombosis, and renal failure).[4]

The slower rate of rise towards the peak serum IgG level and the truncation of its height are believed to be responsible for the much lower incidence of systemic adverse events (AEs) with SCIG. This is consistent with observations that many AEs of IVIG infusions are rate-related and have been repeatedly confirmed.[12]

On the other hand, local reactions at SC injection sites are common. These reactions are rarely severe and are accepted by most patients. In the meta-analysis by Orange et al the reporting rate varied from 0.028 to 0.697 per infusion demonstrating that the majority of patients tolerate SCIG well.[3]

CUTAQUIG, the investigational medicinal product (IMP) in this study, is an immunoglobulin preparation from human normal plasma and is manufactured by Octapharma. It contains 16.5% (165 mg/mL) protein. The product is formulated for SC infusion by pump or syringe.

A recent study of 61 patients who were previously treated with IVIG received a total of 64 weekly SCIG infusions of CUTAQUIG (equating to 3,497 total infusions of CUTAQUIG); no serious bacterial infections developed among any patients during the study. The rate of other infections per person-year during the primary observation period was 3.43 (upper 95% CI: 4.57).[4]

CUTAQUIG was approved by the US FDA in December 2018 for the treatment of primary humoral immunodeficiency in adults. Further information on the IMP can be found in the Investigator's Brochure and the US FDA-approved Package Insert.[5]

1.2 Rationale for Conducting the Study

The administration of immunoglobulins via the SC route offers several advantages over IV infusion from a patient's and a physician's perspective. Replacement therapy by rapid SC infusion with a pump was introduced during the late 1980s. Several reports have shown that the SC method is feasible, safe, efficient, cost-effective, and highly appreciated by the patients.[4,14-22]

Self-administration at home with small portable pumps or syringes can easily be learned by patients, which is another advantage of SC administered immunoglobulins (SCIG). It may remarkably improve the patient's quality of life and compliance as it reduces the frequency of hospitalizations and the need for in-home health care visitations. Administration of IgG via the SC route provides more stable and well-balanced IgG plasma levels until the end of the treatment interval, in contrast with the peak IgG plasma concentrations attained with IVIG solutions which weaken at the end of dose. When effective IVIG therapy cannot be continued because of the lack of peripheral and central vein access, SCIG might also be an alternative treatment option.

Patients may desire dosing flexibility to accommodate their personal schedules or reduce the number of injection sites; therefore, this study is investigating modified dosing regimens. These modifications include dosing at higher infusion rates to shorten the duration of infusions, dosing every other week (rather than every week) to reduce the overall number of infusions, and increased volume at injection site(s) to reduce the number of injection sites. These modifications may reduce dosing commitments by shortening infusion times or increasing time intervals between infusions or decreasing injection sites, which may correlate to increased drug compliance.

Experience has shown that replacement therapy with immunoglobulins is lifesaving. If replacement is started early, and if appropriate amounts are given with sufficient frequency, the cycle of recurrent infections and progressive lung damage can be arrested. Near to normal serum IgG levels can be easily maintained.

Post-dose peak levels of SCIG are usually reached 3 to 6 days after infusion. It has been shown that after infusion, exogenous IgG is distributed relatively rapidly between plasma and extravascular fluid until approximately half is partitioned in the extravascular space. Therefore, a rapid initial drop in serum IgG is to be expected.

Several factors such as the endogenous production, the actual catabolism rate, the underlying disease or inter-patient variability help to explain the wide range observed for terminal half-lives. PK data are required for each new product to ensure that it will not behave differently from existing preparations, in terms of appropriate dose and timing of the infusions.

The Sponsor is currently conducting clinical studies that are investigating the PK characteristics (SCGAM-01), along with the efficacy and safety, of CUTAQUIG, (SCGAM-01 and SCGAM-03) in order to provide guidance on the dosing when switching patients from IV to SC treatment in patients suffering from PI disease.

This current study (SCGAM-06) is designed to evaluate modified dosing regimens that, by reducing dosing time commitments or injection sites or allowing greater flexibility with dosing, may result in increased patient compliance and treatment satisfaction. To that aim, the principal purposes of this study are to:

- Compare total IgG trough levels from weekly infusions to every other week infusions
- Assess safety and tolerability of CUTAQUIG when administered at increased infusion volumes
- Assess safety and tolerability of CUTAQUIG when administered at increased infusion rates
- Assess safety and tolerability of CUTAQUIG when administered every other week
- Assess the effect of CUTAQUIG on quality-of-life (QoL) measures
- Acquire additional safety and efficacy data on CUTAQUIG
- Assess patient satisfaction with the study parameters using the Subject Questionnaire

The study will be conducted in compliance with the protocol, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), US FDA Code of Federal Regulations, and other local regulatory requirements.

1.3 Benefit-Risk Statement

Patients with PI need life-long treatment with immunoglobulins. Replacement therapy is expected to achieve protective trough levels of 5 g/L to 6 g/L.

Standard measures are taken to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. Despite this, when medicinal products prepared from human blood or plasma are administered the possibility of transmitting infective agents cannot totally be excluded. The virus inactivation methods for CUTAQUIG are described in the Investigator's Brochure.

The safety profile of SCIG is well characterized, and the same type of adverse reactions may be expected from CUTAQUIG. No new or unknown safety problems are expected to emerge for CUTAQUIG which are not already described in the Investigator's Brochure.

It can be reasonably assumed that CUTAQUIG exhibits the same effectiveness as other SCIG approved products.

Results from Study SCGAM-01 were analyzed in Q1 2017 and none of the results or data acquired in that study affect the above benefit–risk assessment.

2 STUDY OBJECTIVES

2.1 Co-Primary Objectives

The co-primary objectives of this study are to assess CUTAQUIG administered using the following infusion parameters:

- Compare total IgG trough levels from weekly infusions to every other week infusions
- Safety and tolerability when administered at increased infusion volumes at each infusion site
- Safety and tolerability when administered at increased infusion flow rates at each infusion site
- Safety and tolerability when administered on an every other week dosing regimen

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Assess the effect of CUTAQUIG on quality-of-life (QoL) measures
- Obtain further data on the safety and efficacy of CUTAQUIG

2.3 Tertiary Objective

A tertiary objective of this study is to evaluate patient satisfaction of study parameters (such as switching to CUTAQUIG from another SCIG product, satisfaction with infusion pump, changes in infusion regimen parameters, general infection/general observations) using a study-specific questionnaire (Subject Questionnaire)

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoints

There is no single primary endpoint in this study. The co-primary objectives are to compare total IgG trough levels from weekly infusions to every other week infusions and to assess safety and tolerability of increased infusion volumes and increased infusion rates at each infusion site and every other week dosing. These will be assessed using the following variables:

- Change in individual total IgG trough levels from weekly infusions to every other week infusions (Cohort 3)
- Occurrence of treatment-emergent AEs (TEAEs) throughout the entire Stabilization and Treatment Periods starting with the first infusion of IMP
- Occurrence of TEAEs temporally associated with CUTAQUIG delivered during the Treatment Period
- Occurrence of TEAEs temporally associated with CUTAQUIG delivered during the Stabilization Period
- TEAEs by speed of infusion
- Local infusion-site reactions
- Laboratory parameters (hematology, clinical chemistry, urinalysis)

3.1.2 Secondary Endpoints

Secondary assessment criteria will evaluate quality of life, along with additional evaluations of CUTAQUIG safety and efficacy being administered according to 3 different infusion parameters. These will be assessed using the following variables:

- QoL assessments using the Short Form Health Survey, 36 item (SF-36) or 10 item (SF-10)
- Occurrence of serious bacterial infections (SBIs)
- Annual rate of all infections of any kind or seriousness
- Time to resolution of infections
- Use of antibiotics (number of days and annual rate)
- Individual profiles of IgG trough levels over time (all cohorts)
- Vital signs (blood pressure, pulse, body temperature, respiratory rate)

3.1.3 Tertiary Endpoint

Tertiary assessment criteria will evaluate the patient's satisfaction with the study parameters (such as switching to CUTAQUIG from another SCIG product, satisfaction with infusion pump, changes in infusion regimen parameters, general infection/general observations), which will be assessed using a study-specific questionnaire (Subject Questionnaire).

3.2 Overall Study Design and Plan

The study is a prospective, open-label, non-controlled, 3-arm, multicenter, phase 3 safety study with observation of patients receiving weekly doses of CUTAQUIG at increasing infusion volumes or flow rates, receiving every other week doses of CUTAQUIG at double the weekly dose, over a period of up to approximately 6 months.

Patients with a history of PI disease that are currently on a stable dose of SCIG treatment will be enrolled into 1 of 3 cohorts as defined below:

Cohort 1 (increased infusion volume): This cohort will include patients who consent to receiving CUTAQUIG at increasing infusion volumes at each site until reaching a maximum dose (in mL), maximum tolerated volume (maximum infusion volume per site based on Investigator's decision of patient's tolerance), or 100 mL at 1 injection site is reached – whichever is reached first.

Cohort 2 (increased infusion rate): This cohort will include patients who consent to receiving CUTAQUIG at increasing flow rates until either 1) a maximum flow rate (100 mL/hr/site) or the maximum flow rate achievable by the pump, or 2) the maximum tolerated flow rate (maximum flow rate based on Investigator's decision of patient's tolerance) – whichever is reached first.

Cohort 3 (every other week dosing): This cohort will include patients who consent to receiving CUTAQUIG every other week at the same or equivalent of twice their weekly body-weight dependent (mg/kg) dose. Infusion flow rates will be determined by the patient and Investigator, but initially should not exceed the patient's prior infusion rate. Patients in this cohort must be currently on a weekly infusion regimen for a minimum of 12 weeks prior to entering the study.

All Cohorts: All study sites will be encouraged to enroll patients into all open cohorts. It is at the Investigator's discretion, with input from the patient, to determine the optimal cohort based on medical history, patient preference, etc. However, patients entering the study already established on every other week dosing will only be permitted to enter Cohort 1 or Cohort 2, and must agree to begin dosing every week beginning at Stabilization Period Week 0. The Sponsor will notify study sites when a cohort has been filled and is no longer open to recruitment. Study-related procedures will begin only after written informed consent (and assent, if age-appropriate) has been obtained from the patient.

After completing the Screening Period during which they will be assigned to 1 of the 3 study cohorts, patients will enter a 4-week Stabilization Period. During the Stabilization Period, patients will receive CUTAQUIG infusions at the same body-weight dependent dose and infusion rate as their previous SCIG product prior to entering the Treatment Period; however, this flow rate should not to exceed maximum infusion rates listed in protocol (Section 5.5.3). Patients will receive 4 CUTAQUIG infusions during the Stabilization Period. Patients entering the study currently active and established on CUTAQUIG in Study SCGAM-03 will have already been stabilized on CUTAQUIG and will go directly into the Treatment Period following the Screening Visit. Patients that completed the SCGAM-03 study and went on a commercial SCIG product prior to entering SCGAM-06 are required to enter the Stabilization Period. During the Treatment Period, patients will receive CUTAQUIG infusions according to their assigned-cohort infusion parameters.

Throughout the study, the following interventions and procedures will be performed at predefined time points (Section 6.1.2 and the Flow Charts of Assessments Table 1 [Screening and Stabilization Periods], Table 2 [Cohort 1], and Table 3 [Cohort 2], Table 4 [Cohort 3]): blood draws for laboratory assessments, body weight measurement, patient diary review, physical examination including vital signs, local infusion-site reaction assessments, urine sampling, urine pregnancy tests, QoL assessments, and the Subject Questionnaire. AEs and any changes in concomitant medications will be recorded throughout the study period.

Patients who enter and participate in one cohort may not enter another cohort at a later time.

An Independent Data Monitoring Committee (IDMC) will periodically review relevant data throughout the study with emphasis on adverse events including serious adverse events and thromboembolic events.

The study will be conducted at study sites in the USA.

3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

The study design is in line with similar study protocols conducted with other SCIG brands.[21,23,24]

3.3.2 Dosing

Stabilization Period: CUTAQUIG will be administered subcutaneously every week (±2 days).

Treatment Period: CUTAQUIG will be administered subcutaneously every week (±2 days) (or every other week [±2 days], if applicable) for Cohort 1 (increased infusion volume) and Cohort 2 (increased infusion rate). For Cohort 3, CUTAQUIG will be administered every other week (±2 days) at double the weekly dose.

Cohort 1 (increased volume at each infusion site – patients will receive CUTAQUIG weekly and increase infusion volumes every 4 weeks): Patients will return to the clinic for the Treatment Period Baseline Visit, at which they will receive the same body-weight dependent (mg/kg) dose but the volume will be increased by up to the maximum allowed volume increase per infusion site of 25 mL/site for patients ≥40 kg or 10 mL/site for patients <40 kg. This volume increase per infusion site can be achieved by reducing the total number of injection sites while keeping the same or lower flow rates as received with their prior treatment. When introducing increased volumes to an infusion site, Investigators must attempt to maintain flow rates similar to or lower than prior infusions. This may require adjusting pump rate, tubing size, needle gauge, etc. Patients will receive this new volume per site for 4 weekly infusions (Treatment Period Baseline and Weeks 1, 2, and 3), and return to the clinic at Week 4 for their next infusion at an increased volume at each infusion site. This cycle will continue, with infusion volumes increasing by up to a maximum allowed volume increase per infusion site of 25 mL/site for patients ≥40 kg or 10 mL/site for patients <40 kg every 4th infusion until reaching a patient's maximum dose (in mL), maximum tolerated volume (maximum volume based on Investigator's decision of patient's tolerance), or 100 mL

at 1 injection site – whichever is reached first. For patients with maximum volume that exceeds 100 mL at 1 injection site, 2 injection sites should be used.

The following change in volume increments should be followed:

- Baseline: Reduce the number of injection sites by 1 (eg, patients using a 4 needle set will reduce to a 3 needle set). Tubing set, needle gauge, and pump rates (if applicable) may be adjusted to minimize flow rate variations. Investigators must ensure minimal flow rate changes at each injection site when increasing volume. Continue with the same infusion parameters at Weeks 1, 2, and 3.
- Week 4: If the volume increase administered at Baseline through Week 3 is tolerated, reduce the number of injections sites again by 1 (eg, patients using a 3 needle set will reduce to a 2 needle set). Tubing set, needle gauge, and pump rates (if applicable) may be adjusted to minimize flow rate variations. Investigators must ensure minimal flow rate changes at each injection site when increasing volume. Continue with the same infusion parameters at Weeks 5, 6, and 7.
- Week 8: If the volume increase administered at Week 4 through Week 7 is tolerated, reduce the number of injection sites again by 1 (eg, patients using a 2 needle set will reduce to a 1 needle set). Tubing set, needle gauge, and pump rates (if applicable) may be adjusted to minimize flow rate variations. Investigators must ensure minimal flow rate changes at each injection site when increasing volume. Continue with the same infusion parameters at Weeks 9, 10, and 11.
- Weeks 12, 16, and 20: If the volume increase administered at Week 8 through Week 11 is tolerated, continue the step-down process until reaching the patient's maximum dose (in mL), maximum tolerated volume (maximum volume based on Investigator's decision of patient's tolerance), or 100 mL at 1 injection site (whichever is reached first) as described above. The same step-down procedure should be repeated as described at Week 16 and Week 20, if needed and based on the Investigator's decision of patient's tolerance.

Investigators should be aware that special considerations are required for volume increases in patients with 2 infusion sites receiving a total dose (volume) of more than 50 mL divided between 2 infusion sites. To ensure that volume increases do not exceed 25 mL/site, the infusions must be split between the 2 syringes, such that each infusion site will receive a different total volume. For example, if a patient is receiving a total dose of 60 mL divided equally between 2 infusion sites (eg, 30 mL/site), the first syringe could be increased to an infusion volume of 50 mL (an increase of 20 mL) and the second syringe would have an infusion volume of 10 mL. If this is tolerated, the next infusion volume increase could be 60 mL at 1 infusion site (an increase of 10 mL) and remain below the maximum allowed volume increase of 25 mL/site.

If adverse drug reactions (ADRs) occur during an infusion, the patient may go back to the previous regimen that was tolerated if deemed necessary by the Investigator and/or patient; this would include reintroducing an injection site. This infusion regimen will continue until the next study visit at which the patient would again attempt to remove an injection site. If ADRs occur again, the patient may again go back to the previous stable regimen if deemed necessary until the next study visit. Following

unsuccessful attempts to increase volume, the Investigator and patient can cease or hold additional attempts and remain in the study; however, every effort to increase injection site volumes should be attempted.

Optional: When modifying the number of injection sites after previous unsuccessful attempts, the Investigator can make adjustments to lower the flow rate. This may include decreasing pump flow rate, revising the tubing, or changing needle gauge.

Note: Sites are encouraged to enroll patients into Cohort 1 who are already on a dosing regimen using at least 3 infusion sites to ensure that volume increases remain below limits listed in Table 6. Patients dosing with 1 infusion site cannot enter Cohort 1.

Cohort 2 (increased infusion rate - patients will receive CUTAQUIG weekly and increase infusion rates every 4 weeks): Patients will return to the clinic for the Treatment Period Baseline Visit, at which they will receive the same body-weight dependent (mg/kg) dose of CUTAQUIG but the infusion rate per site will be increased by up to a maximum allowed flow rate increase per infusion site of 25 mL/hr/site for patients ≥40 kg or 10 mL/hr/site for patients <40 kg. Patients will receive this new flow rate for 4 weekly infusions (Treatment Period Baseline and Weeks 1, 2, and 3), and return to the clinic at Week 4 for their next infusion at an increased infusion rate. This cycle will continue, with maximum allowed flow rate increases per infusion site of up to 25 mL/hr/site for patients ≥40 kg or 10 mL/hr/site for patients <40 kg every 4th infusion until reaching either 1) a maximum flow rate (100 mL/hr/site) or the maximum flow rate achievable by the pump, or 2) the maximum tolerated flow rate (maximum flow rate based on Investigator's decision of patient's tolerance) – whichever is reached first.

The following rate increases should be followed:

- Baseline: Increase infusion rates up to 25 mL/hr/site. This can be accomplished by increasing the tubing set, needle gauge, and adjusting pump rates (if applicable). Continue with the same infusion parameters at Weeks 1, 2, and 3.
- Week 4: If the infusion rate increase administered at Baseline through Week 3 is tolerated, increase infusion rates again by up to 25 mL/hr/site for patients ≥40 kg or 10 mL/hr/site for patients <40 kg. This can be accomplished by increasing the tubing set, increasing needle gauge, or adjusting pump rates (if applicable). Continue with the same infusion parameters at Weeks 5, 6, and 7.
- Week 8: If the infusion rate increase administered at Week 4 through Week 7 was tolerated, increase infusion rates again by up to 25 mL/hr/site for patients ≥40 kg or 10 mL/hr/site for patients <40 kg. This can be accomplished by revising the tubing, increasing needle gauge, or adjusting pump rates (where applicable). Continue with the same infusion parameters at Weeks 9, 10, and 11.
- Weeks 12, 16 and 20: If necessary and if the infusion rate increase administered at Week 8 through Week 11 was tolerated, the patient should continue the rate increase process as described above.

Note: Clinical sites are encouraged to enroll patients that are either currently infusing with 24-gauge needle sets or willing to switch to 24-gauge needle sets. Patients using 27-gauge needles will not be able to achieve adequate infusion rates for this cohort as the needle gauge will not allow for this.

If ADRs occur during an infusion, the patient may go back to the previous regimen that was tolerated if deemed necessary by the Investigator and/or patient; this would include decreasing the infusion flow by decrease tubing size, increasing needle gauge, or adjusting pump rates. This tolerated infusion regimen will continue until the next study visit, at which the patient would attempt to again increase the infusion rate. If ADRs occur again, the patient may again go back to the previous stable regimen if deemed necessary until the next study visit. If multiple attempts to increase rate are unsuccessful, Investigators should continue attempting to increase rates, but by lower amounts than those previously attempted. Investigators should refer to the provided flow rate tubing calculators to identify optimal rate parameters. Following unsuccessful attempts to increase infusion rate, the Investigator and patient can cease or hold additional attempts and the patient may remain in the study; however, every effort to increase infusion rates should be attempted.

Cohort 3 (every other week dosing - patients will receive CUTAQUIG every other week at the equivalent of twice their weekly body-weight dependent [mg/kg] dose): Patients will return to the clinic for the Treatment Period Baseline Visit to receive their first double mg/kg weekly dose and begin an every other week dosing schedule. Infusion volume increases when switching from weekly dosing to every other week dosing must not exceed a maximum allowed volume increase per infusion site of 25 mL/site for patients ≥40 kg or 10 mL/site for patients <40 kg at the Treatment Period Baseline Visit. If a patient's doubling of their weekly dose requires dosing with a volume of more than the maximum allowed increase in volume per injection site (25 mL/site or 10 mL/site, dependent on patient body weight), then they will be required to increase the number of infusion sites to remain below the maximum body-weight dependent volume increase. If this occurs, after 2 infusions the patient may remove one of the newly introduced injection sites as long as the volume per injection site increase limit is not exceeded. Infusion flow rates will be determined by the patient and Investigator, but initially should not exceed the patient's prior infusion rate, nor the maximum infusion rates listed in the protocol. If a patient initially does not tolerate the dosing regimen, the Investigator should decrease the infusion rate to a tolerable rate (revising the tubing, number of injection sites, needle gauge, etc.).

Note: Patients entering must already be established on weekly dosing for a minimum of 12 weeks prior to Screening.

All Cohorts: If, during the study, a patient's body weight changes by >5% from the first infusion of IMP, the dose will be adjusted to keep a constant mg/kg body weight basis. Additional adjustments will be made if the patient's body weight changes >5% from the previous adjusted weight. In addition, individual patient doses may be titrated up or down, per Investigator discretion.

Dosing will take place on site at study visits, and otherwise at the patient's home by self-administration or with assistance (relative, caregiver, etc.). The Termination Visit must occur prior to the patient receiving any other IgG product.

3.3.3 Control Group(s)

Not applicable: all patients will receive active treatment with CUTAQUIG.

3.3.4 Study Parameters

The outcome measures in this study are consistent with previous studies of other IVIG or SCIG products and are also in compliance with the US FDA Guidance for Industry on Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency.[25]

QoL questionnaires (SF-10 Health Survey from parent or guardian of patients <14 years of age and SF-36 Health Survey in patients ≥14 years of age) used in this study are standardized, validated instruments that have been widely used in clinical studies, including studies in the PI disease population.

4 STUDY POPULATION

4.1 Population Base

Approximately 65 male or female patients, between 2 years and 75 years of age, suffering from PI will be eligible for inclusion.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Age ≥2 years and ≤75 years.
2. Confirmed diagnosis of primary immunodeficiency (PI) disease as defined by ESID and PAGID and requiring immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia. **Note:** The exact type of PI disease will be recorded.
3. Established on a consistent or stable mg/kg dose of any SCIG treatment for a minimum of 3 months prior to Screening. **Note:** patients entering Cohort 3 must be on weekly SCIG infusions for a minimum of 12 weeks.
4. Availability of the Immunoglobulin G (IgG) trough levels of 2 previous SCIG infusions within 1 year of Screening, with 1 trough level obtained within 3 months prior to enrollment, and maintenance of trough serum IgG levels ≥5.0 g/L in 2 previous infusions. Patients with no prior IgG trough level within 3 months prior to enrollment may use the Screening IgG trough level as their 2nd reading.
5. Voluntarily given, fully informed, signed informed consent. For patients under the legal age of consent, voluntarily given, fully-informed, signed informed consent will be provided by patient's parent or legal guardian, and assent will be provided by patient (per age-appropriate Institutional Review Board [IRB] requirements)
6. Females of childbearing potential, who are not nursing and have no plans for pregnancy during the course of the study, must have been using at least 1 acceptable form of birth control for a minimum of 30 days prior to the Screening visit and must agree to use at least 1 acceptable method of contraception for 30 days after the last dose of CUTAQUIG. Acceptable methods include: intrauterine device (IUD), hormonal contraception, male or female condom, spermicide gel, diaphragm, sponge, or cervical cap, or abstinence.
7. For female patients of child-bearing potential, a negative result in a urine pregnancy test conducted at the Screening visit.
8. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria are *not* eligible for the study:

1. Evidence of an active infection within 4 weeks of Screening or during the Screening Period.

2. Current or clinically-significant history of any cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, neurological, immunological (excluding PI), hematologic, and/or psychiatric disorder(s), or a history of any other illness that, in the opinion of the Investigator, might confound the results of the study, or pose additional risk to the patient by participation in the study.
3. Known history of adverse reactions to immunoglobulin A (IgA) in other products.
4. Body mass index (BMI) >40 kg/m^2 for patients entering Cohort 2 or Cohort 3. There are no BMI restrictions for Cohort 1.
5. Ongoing history of hypersensitivity or persistent reactions to blood or plasma derived products, or any component of the investigational product (such as Polysorbate 80).
6. Requirement of any routine premedication for IgG administration.
7. History of malignancies of lymphoid cells and immunodeficiency with lymphoma.
8. Severe liver function impairment (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >3 times above upper limit of normal).
9. Known protein-losing enteropathies or clinically significant proteinuria.
10. Presence of renal function impairment or predisposition for acute renal failure (eg, any degree of pre-existing renal insufficiency or routine treatment with known nephritic drugs).
11. Treatment with oral or parenteral steroids for ≥30 days, or when given intermittently or as bolus at daily doses ≥0.15 mg/kg when taken within 30 days of Screening. **Note:** Short or intermittent courses of steroids (ie, a steroid burst) of >0.15 mg/kg/day is allowed for treatment of a short-term condition such as an asthma exacerbation.
12. Treatment with immunosuppressive or immunomodulatory drugs (except Omalizumab).
13. Use of HYQVIA (Immune Globulin Infusion 10% [Human] with Recombinant Human Hyaluronidase) within 3 months prior to first CUTAQUIG infusion.
14. Live viral vaccination (such as measles, rubella, mumps, and varicella) within 2 months prior to first CUTAQUIG infusion.
15. Exposure to blood or any blood product or derivative, other than sub-cutaneous IgG used for regular PI disease treatment, within 3 months before the first CUTAQUIG infusion.
16. Treatment with any investigational medicinal product within 3 months prior to first CUTAQUIG infusion. **Note:** Patients participating in Study SCGAM-03 will be allowed to enter this study without the 3-month waiting period for an Investigational Product. Patients receiving another investigational SCIG product within 3 months prior to the first CUTAQUIG infusion may be considered for enrollment after Sponsor approval.
17. Presence of any condition that is likely to interfere with the evaluation of CUTAQUIG or satisfactory conduct of the trial.
18. Known or suspected to abuse alcohol, drugs, psychotropic agents, or other chemicals within the past 12 months prior to first CUTAQUIG infusion.

19. Known active or chronic hepatitis B, hepatitis C or HIV infection. Past hepatitis B or hepatitis C infection that has been cured is allowed.

4.2 Prior and Concomitant Therapy

Details on any relevant medications taken within 8 weeks prior to enrollment must be recorded in the electronic Case Report Form (eCRF). The following medications that are considered relevant for the previous 8 weeks include:

- Antibiotics
- Corticosteroids,
- Premedication (if used)
- Immunosuppressive or immunomodulatory drugs
- blood or any blood product or derivative
- IVIG, SCIG, or other IgG preparations

All new and ongoing concomitant medications taken during the Screening Period and throughout the study will be captured in the eCRF.

4.2.1 Permitted Concomitant Therapy

Local anesthetics (EMLA® or lidocaine cream, plaster, or other similar products) to reduce pain associated with needle insertion are allowed. The use of such medication(s) must be recorded.

Routine premedication to alleviate potential tolerability problems is not allowed during the study. However, patients who experience 2 consecutive TEAEs during the study (that are likely to be prevented by premedication) are permitted to receive antipyretics, antihistamines, or antiemetic drugs. Non-steroidal anti-inflammatory drugs should be avoided.

4.2.2 Forbidden Concomitant Therapy

Treatment with any IMP (other than IgG products [including CUTAQUIG] administered during Study SCGAM-03) within 3 months before first infusion of CUTAQUIG, or during the study, is forbidden. Patients receiving another investigational SCIG product within 3 months prior to the first CUTAQUIG infusion may be considered for enrollment after Sponsor approval.

Administration of any blood- or plasma-derived product is forbidden during the study and should only be given for emergency reasons. Patients will be withdrawn from the study if IgG preparations other than CUTAQUIG are administered during the study.

Premedication for study CUTAQUIG infusions shall not be given, with the exception of permitted therapy as stated above (for patients with 2 consecutive TEAEs). Corticosteroids shall not be given as a premedication to alleviate potential tolerability problems.

Treatment with oral or parenteral steroids for ≥30 days (long term daily >0.15 mg of prednisone equivalent/kg/day). Exception: Requirement for short or intermittent courses (ie, a steroid burst) of >0.15 mg/kg/day is allowed for treatment of a short-term condition such as an asthma exacerbation.

Immunosuppressive and immunomodulatory drugs are forbidden, with the exception of Omalizumab.

CUTAQUIG must not be mixed with other medicinal products.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw patients in case of AEs, poor compliance, or other reasons. Because an excessive rate of withdrawals can render the study noninterpretable, any unnecessary withdrawal of patients should be avoided.

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome.

Reasons for premature patient withdrawal may include the following:

- Patient decision: Should a patient decide to withdraw from the study, the Investigator will make a reasonable effort to complete and report all information available at time of withdrawal. The Investigator will document the reason(s) for the patient's discontinuation.
- Withdrawal for safety reason: If the reason a patient is removed from the study is an AE or an abnormal laboratory test result, this specific event or test will also be recorded; the Investigator will make a reasonable effort to clearly document the outcome.
- Administration of other immunoglobulin preparation: If for any reason a patient's therapy is changed to another IVIG or SCIG preparation within this study, the patient will be withdrawn from the study.
- Pregnancy: Pregnant patients may not be included in this study. A pregnancy test is mandatory for all females of child bearing potential at the Screening Visit, at the Treatment Period Weeks 12, 24 and at the Termination Visit. All female patients of childbearing potential are responsible for using effective contraception during their study participation. If a pregnancy occurs, treatment with CUTAQUIG must be stopped immediately and Octapharma's Central Drug Safety Unit must be informed.

If a patient is withdrawn, the Investigator will schedule an (Early) Termination Visit. At this visit, all investigations including laboratory tests should be performed to allow the patient to be included in both safety and efficacy evaluations. This Termination Visit is identical to the follow-up visit of the last CUTAQUIG administration.

4.3.2 Patient Replacement Policy

Patients withdrawn from the study for any reason will not be replaced.

4.4 Assignment of Patients to Treatment Groups

This is an open-label non-randomized study. Patients will be enrolled into Cohort 1, 2, or 3 according to Investigator and patient preference. However, patients entering the study already established on an every other week infusion schedule of another SCIG product may only participate in Cohort 1 or Cohort 2.

All study sites will be permitted to enroll patients in open cohorts. The Sponsor will notify study sites when a cohort has filled and is no longer open to recruitment.

Patients will not be allowed to switch cohorts during the study.

Patients who enter and participate in one cohort may not enter another cohort at a later time.

4.5 Relevant Protocol Deviations

In case of any major protocol deviation, the Investigator and Octapharma will decide on the further participation of the patient in this study after having discussed all relevant aspects.

A list of all included patients with all deviations from the intended study procedures and other criteria that may affect the validity of patient data for statistical analysis will be prepared after the clinical phase of the study is completed. The list will be discussed by a panel consisting of the clinical study manager, a medical expert of the Sponsor, the data manager and the study statistician. This panel will decide upon the inclusion of each patient in the analysis populations prior to database lock.

4.6 Subsequent Therapy

After a patient completes the study, or if a patient decides to withdraw from the study or is withdrawn by the Investigator, he/she may be switched back to the treatment that he/she received before participation in the study or to another commercially available IVIG or SCIG product, per treating physician discretion.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterization of Investigational Product(s)

Name of Medicinal Product: CUTAQUIG

Active ingredient of CUTAQUIG: Human normal immunoglobulin

Table 5: Biochemical Characteristics of CUTAQUIG

Name of Ingredient	Amount
Total protein (of which ≥96% is human IgG)	150 – 180 mg per mL
Maltose	70 – 90 mg per mL
Octoxynol	≤5 µg per mL
TNBP	≤1 µg per mL
IgA	≤0.6 mg per mL
Polysorbate 80	10 – 60 µg per mL
pH	5.0 – 5.8
Osmolality	310 – 380 mosmol/kg
Polymers + Aggregates	≤5% of the total chromatogram area
Monomers + Dimers	≥90% of the total chromatogram area
Fragments	≤5% of the total chromatogram area
Sodium	≤30 mmol/L

Each batch (lot) of CUTAQUIG is prepared from at least 3,500 donations of human fresh frozen plasma. Effective viral reduction is obtained via a combination of 3 validated manufacturing steps: cold-ethanol fractionation, solvent/detergent treatment with TNBP and Octoxynol, and pH 4 treatment. The manufacture of CUTAQUIG is based on the Octagam manufacturing process including an additional adsorption step onto commercially available and widely used chromatography column for the removal of coagulation factor XI. The process is identical up to the step of diafiltration. After this step the product solution is concentrated to a target concentration of 200 g/L. Polysorbate 80 and maltose are added during final formulation to final concentrations of 10 µg/mL to 60 µg/mL and 70 mg/mL to 90 mg/mL, respectively.

5.2 Packaging and Labelling

CUTAQUIG is delivered in 12 mL or 48 mL single-use glass vials. Each CUTAQUIG vial will be labeled in accordance with national regulations. Sample labels will be provided and filed with the Investigational Product File at each investigator site and in the Sponsor TMF.

5.3 Conditions for Storage and Use

CUTAQUIG must be stored and transported light-protected at 36°F to 46°F (2°C to 8°C).

CUTAQUIG must not be frozen.

CUTAQUIG vials must not be shaken.

CUTAQUIG must not be used after its expiration date.

CUTAQUIG must not be mixed with other medicinal products.

Authorized personnel at the individual study centers will ensure that the IMP is stored in appropriate conditions in a secure refrigerator with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

CUTAQUIG will be administered by subcutaneous infusion either every week (±2 days) or every other week (±2 days) at double the weekly dose. The dosing frequency will be determined by the cohort assignment (Section 3.3.2).

A minimum interval of 4 days must be observed between 2 single subcutaneous infusions.

Patients will receive the same mg/kg body weight dose as their previous SCIG product prior to study entry that will be calculated at Screening. The dose (mg/kg) will be calculated by taking a patient's total dose in milligrams (mg) of their prior SCIG and dividing by the patient's weight (kg) at the Screening Visit. This will provide the milligrams of CUTAQUIG required. Study site personnel will use dose calculation worksheets provided by the Sponsor to determine each patient's required quantity (mg) of CUTAQUIG.

If, during the study, body weight changes by >5% from the first infusion of IMP, the dose will be adjusted to keep a constant mg/kg body weight basis. Additional adjustments will be made by the Investigator at study visits if the patient's body weight changes >5% from the previous adjusted weight. In addition, individual patient doses may be titrated up or down, per Investigator discretion.

CUTAQUIG infusions will be administered at the clinic and will be self-administered at home in between scheduled site visits.

Each study visit may deviate from the planned date; however, the deviations must not cumulate. Study visit weeks and time windows are presented in Table 7.

An individual patient's CUTAQUIG dose may be adjusted, if considered necessary by the Investigator, by titrating upward or downward; this dose adjustment should be based on the difference between the patient's measured serum total IgG trough levels while on CUTAQUIG and each patient's target serum total IgG trough level.

5.5 Preparation and Method of Administration

CUTAQUIG vials must be allowed to warm to room or body temperature before infusion.

After CUTAQUIG vials have been brought to room or body temperature, they should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. DO NOT USE IF TURBID and/or DISCOLORATION IS OBSERVED. Solutions that are cloudy or vials that have a deposit must not be used and must be returned to the clinical site by the patient.

CUTAQUIG will be delivered by subcutaneous infusion using syringe drivers in order to deliver the protocol-specified infusion rate.

The correct amount of IgG will be transferred from the 12 mL or 48 mL vials into syringes that are suitable for use with the selected syringe driver.

Used, partially used vials from home infusions must be returned to the study site; all used and partially used vials must be discarded according to local policies and procedures.

Any vials returned to the site by the patient, due to deficiency in vial use or complaint regarding the drug or vials, must be retained by the study site and must not be destroyed. The study site must notify Octapharma and retain the vials on-site until arrangements are made for them to be returned to Octapharma.

Aseptic techniques must be used throughout the infusion procedure.

As appropriate based on cohort assignment, syringe drivers, syringes, and standard infusion materials will be provided by the site for in-home infusions. The patient, his/her relative, and/ or caregiver will be instructed in the use of the following:

- syringe driver
- infusion techniques
- patient diary completion
- measures to be taken in case of severe AEs

At the Stabilization Period Week 0 Visit and the Treatment Period Baseline Visit, patients will perform the infusions at the study site and will be assessed for proper infusion technique. Patients will be re-trained on proper technique, if necessary.

5.5.1 Infusion Sites

No more than 6 infusion sites should be used simultaneously.

Infusion sites should be at least 2 inches (approximately 5 cm) apart.

The anatomical location of infusion sites may be changed with weekly or every other week administration as necessary.

5.5.2 Infusion Volume

The maximum infusion volume is 100 mL per infusion site.

5.5.3 Infusion Flow Rates

- The maximum recommended flow rate is 100 mL/hr/infusion site.
- The maximum infusion rate for all sites combined is 240 mL/hr.
- Infusion volumes and flow rates may only be increased if the previous 2 administrations were tolerated by the patient, and deemed appropriate by the Investigator.
- Infusion volume and flow rate should be increased gradually as tolerated to prevent infusion site reactions. See the parameters listed in Table 6.

Table 6: Infusion Volume and Flow Rate by Patient Weight

	Recommended Increase for Patients <40 kg	Recommended Increase for Patients ≥40 kg
Infusion Volume mL/site per infusion cycle	Approximately ≤10 mL/site	Approximately ≤25 mL/site
Infusion Flow Rate mL/hour/site per infusion cycle	≤10 mL/hour/site	≤25 mL/hour/site

Note: To account for non-precision flow rates of pumps, actual flow rate increases will be dependent on tubing size, number of infusion sites, and needle gauge. Minor deviations in flow rates (<2 mL/site) would not be considered protocol deviations.

Instructions for performing volume increases in Cohort 1 patients who are using 2 infusions sites with a total volume of ≥50 mL are provided in Section 3.3.2.

If AEs occur during an infusion, the flow rate and volume may be reduced if deemed necessary by the Investigator and/or patient to the previous flow rate and volume at which no AE occurred. If appropriate, the infusion may be interrupted until symptoms subside. The infusion may then be resumed at a flow rate or volume tolerated by the patient.

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

Not applicable for this open-label study.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

Any IMP provided to the site will be accounted for. This includes IMP received at the site and IMP dispensed to patients. A Drug Inventory and Dispensing Log will be kept current by the Investigator, detailing the dates and quantities of IMP received and dispensed to each patient and the remaining quantity.

Sponsor or designee will deliver CUTAQUIG to the participating Investigator sites. Each Investigator will keep current drug inventory and dispensing log, detailing the dates, batch (lot) numbers, and quantities of IMP received and dispensed to each patient and the remaining quantity. A packet containing IMP Release, Confirmation of receipt, transport temperature log, and signed packing slip should be made available for the study monitor to review.

The inventory and drug dispensing log will be available to the monitor to verify drug accountability during the study. The study monitor will review all empty and partially used vials of IMP and will cross-check versus the patient source documentation (records), eCRF, and drug dispensing log.

After this check, and after the Sponsor has granted written approval of destruction, empty or partially used vials should be destroyed at the study site following local policies. The destruction must be documented.

For home treatments, a sufficient number of CUTAQUIG vials will be dispensed to each patient. The Investigator or his/her designee will document the date, vial quantities, and batch (lot) number(s) of IMP dispensed to a given patient (using the corresponding patient number). Patients will be instructed to return used or expired

vials to the study site at their on-site visits, and to return all used and unused vials at the (Early) Termination Visit.

Patient-returned IMP (used or unused) must not be re-dispensed and must be destroyed after completion of drug accountability.

5.7.2 Assessment of Treatment Compliance

Patients will receive infusions at the clinic and at home (administered by the patient, his/her relative, or caregiver). Infusion details will be documented together with the batch number(s) in the eCRF.

Throughout the study, patients will be asked to document on a diary the date, batch (lot) numbers, number of vials, speed of infusion, infusion site(s), occurrence of infections, TEAEs and local tissue reactions at infusion sites, missed days from work or school, inpatient hospital stays, and any changes in concomitant therapy between visits. The diary will be reviewed during the patient's infusion visit at the study site.

6 STUDY CONDUCT

6.1 Observations by Visit

Observations by visit are provided in the following tables:

Table 1 Screening and Stabilization Periods – Flow Chart of Assessments

Table 2 Cohort 1 (Increased Flow Volume) – Flow Chart of Assessments

Table 3 Cohort 2 (Increased Infusion Rate) – Flow Chart of Assessments

Table 4 Cohort 3 (Every Other Week Dosing) – Flow Chart of Assessments

Descriptions of the assessments and methods performed at study visits are provided in Section 7.

Descriptions of visit windows are provided in Table 7.

6.1.1 Screening Visit

Study-related procedures will begin only after written informed consent (and assent, if appropriate) has been obtained from the patient and/or their legal guardians.

Note: Patients who participated in Study SCGAM-03 must receive their final infusion of CUTAQUIG for Study SCGAM-03 prior to being consented for Study SCGAM-06.

At the Screening Visit the following activities will be performed:

- Written (signed and dated) informed consent (and assent, if age appropriate)
- Check of inclusion and exclusion criteria
- Record demographic data
- Document medical history
- Record previous drug and non-drug therapies
- General physical examination, including body weight and vital signs
- Draw blood samples for total IgG trough level
- Draw blood samples for safety laboratory parameters
- Collect urine sample including sample for urine pregnancy test (females of childbearing potential, only)
- Infusion by the patient of their personal, commercially available SCIG product at the same body-weight dependent dose (mg/kg) and infusion flow rate (ml/hr/site) as their previous infusions; however, this flow rate should not to exceed maximum infusion rates listed in protocol (Section 5.5.3). Patients who participated in Study SCGAM-03 will have already received a CUTAQUIG infusion on the same day prior to providing written informed consent (and assent, if appropriate) for Study SCGAM-06.
- Receive written approval from the Sponsor, which will include confirmation that the chosen cohort is open for enrollment, prior to entering the patient into the Stabilization Period.

It is anticipated that the patients will receive their first dose of CUTAQUIG 5 days to 16 days after the Screening Visit, depending when their last infusion occurred.

6.1.2 CUTAQUIG Stabilization Period (Stabilization Period Week 0 through Stabilization Period Week 4)

After completing the Screening Period and receiving written Sponsor Acknowledgment of the cohort assignment during the Treatment Period, patients will enter a 4-week Stabilization Period during which they will receive CUTAQUIG infusions at the same body-weight dependent (mg/kg) dose and infusion flow rate (ml/hr/site) as their previous SCIG product; however, this flow rate should not to exceed maximum infusion rates listed in protocol (Section 5.5.3).

Patients entering the study currently active and established on CUTAQUIG in Study SCGAM-03 will have already been stabilized on CUTAQUIG and will skip the Stabilization Period to go directly into the Treatment Period. Patients that completed the SCGAM-03 study and went on a commercial SCIG product prior to entering SCGAM-06 are required to enter the Stabilization Period.

Patients entering the study already established on every other week dosing for either Cohort 1 or Cohort 2 will be required to dose weekly beginning at the Stabilization Week 0.

At Stabilization Period Week 0, the CUTAQUIG administration will be performed on-site. Otherwise, CUTAQUIG will be administered at home (Section 3.3.2).

The following activities will be performed before the on-site CUTAQUIG administration:

- Record body weight
- Collect vital signs
- Draw blood samples for total IgG trough level
- Draw blood samples for safety laboratory parameters
- Draw blood for serum retention samples
- Update medical history

The following activities will be performed during or after CUTAQUIG administration

- CUTAQUIG infusion by the patient at the same body-weight dependent (mg/kg) dose and infusion flow rate (ml/hr/site) as their previous SCIG product; however, this flow rate should not to exceed maximum infusion rates listed in protocol (Section 5.5.3).
- Assess patient infusion technique and, if necessary, re-train on proper administration
- Assess for local infusion-site reactions

The following activities will be performed after CUTAQUIG administration:

- Assess for local infusion-site reactions
- AE assessment and record any changes in concomitant medications use during the study visit
- Dispense patient diary

6.1.3 CUTAQUIG Treatment Visits (Baseline [Week 0] through Week 24)

After completing the 4-week Stabilization Period (or Screening Visit for patients who are currently enrolled in Study SCGAM-03), patients will enter the Treatment Period

and begin their infusion parameters according to their corresponding cohort assignment (Section 3.3.2).

On study visit days, CUTAQUIG administration will be performed on site; otherwise, CUTAQUIG will be administered at home.

During the Treatment Period, the following on-site visits are required as specified below:

Cohort 1	Baseline, Weeks 4, 8, 12, and 24
Cohort 2	Baseline, Weeks 4, 8, 12, and 24
Cohort 3	Baseline, Weeks 4, 12, and 24

For Cohort 1 and Cohort 2, if a patient has reached their maximum achievable volume or flow rate per infusion site at Week 12, they do not need to complete remaining interim (4-week interval) on-site study visits at Week 16 and Week 20.

The following activities will be performed before on-site CUTAQUIG administrations:

- General physical examination (See Table 2 [Cohort 1], Table 3 [Cohort 2], and Table 4 [Cohort 3] for assessment schedules)
- Record body weight (all visits)
- Draw blood samples for total IgG trough level (See Table 9 for collection schedule)
- Draw blood samples for safety laboratory parameters (See Table 9 for collection schedule)
- Draw blood for serum retention samples, for patients who were previously enrolled in SCGAM-03 and did not participate in the Stabilization Period (Baseline Visit, only)
- Collect urine sample including sample for urine pregnancy test (females of childbearing potential, only) (See Table 9 for collection schedule)
- Collect vital signs (all visits)
- Complete QoL questionnaire (Baseline Visit, only)

The following activities will be performed during or after CUTAQUIG administration:

- Collect patient diary. The Investigator will review diary entries and query the patient about any AEs that may have occurred and any changes in concomitant therapies (medication and non-drug therapy). Any updates to concomitant medication use and adverse events will be recorded. Relevant diary data will be transferred to the eCRF. Discrepancies between patient diary entries and eCRF entries must be explained by the Investigator.
- Infusion of CUTAQUIG by the patient, according to cohort assignment (every visit – see Section 3.3.2 for dosing information)
- Assess patient infusion technique and, if necessary, re-train on proper administration

The following activities will be performed after CUTAQUIG administration:

- Assess for local infusion-site reactions (every visit, prior to discharging patient)
- AE assessment and record any changes in concomitant medications use during the study visit (every visit, prior to discharging the patient)

- Dispense patient diary

6.1.4 Termination Visit

The Termination Visit must occur prior the patient receiving another IgG product. This visit will take place 1 week after the last infusion for Cohort 1 and Cohort 2, or 2 weeks after the last infusion for Cohort 3; however, these visits may occur sooner if a patient withdraws early from the study or if the study is ended earlier by one of the events described in Section 6.2.3.

The Termination Visit will include the following assessments:

- General physical examination
- Collect vital signs
- Draw blood samples for safety laboratory parameters
- Draw blood for serum retention samples
- Draw blood samples for total IgG trough level
- Collect urine sample including sample for urine pregnancy test (females of childbearing potential, only)
- Complete QoL questionnaire
- Complete Subject Questionnaire
- Collect and review patient diary as at the earlier visits (Section 6.1.2) and record any AEs and/or changes in concomitant medication use
- Assess for local infusion-site reactions

After the Termination Visit, the clinical study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (eg, ongoing AEs, newly-reported SAEs [Section 7.3.8.1]) require follow-up.

6.1.5 Time Windows Used in this Study, including Tolerances

In this study, the following time windows and tolerances apply:

Table 7: Study Visit Times and Windows Used in this Study

Time point	Time stated	Tolerance
Stabilization Period Week 0: Cohort 1 and Cohort 2	1 week after Screening Visit	± 2 days
Stabilization Period Week 0: Cohort 3	2 weeks after Screening Visit	± 2 days
Treatment Period Baseline Visit	4 weeks after Stabilization Period Week 0	± 3 days
Treatment Period required on-site visits: Cohort 1 and Cohort 2	Weeks 4, 8, 12, and 24	± 1 week
Treatment Period required on-site visits: Cohort 3	Weeks 4, 12, and 24	± 1 week
Treatment Period optional on-site visits: all cohorts	Weeks 16, and 20	± 1 week
Interval between Last Treatment Visit and (Early) Termination Visit: Cohort 1 and Cohort 2	1 week	± 2 days (and prior to another IgG product)

Time point	Time stated	Tolerance
Interval between Last Treatment Visit and (Early) Termination Visit: Cohort 3	2 weeks	± 2 days (and prior to another IgG product)
Blood and urine sampling	Before IMP administrations conducted at the study site	none
CUTAQUIG infusions at patient's home	Every week (every 7 days), or Every other week (every 14 days) at double the weekly dose	±2 days ±2 days

Study visit days and windows/tolerances are not additive, but always refer back to the first visit time point for each study period.

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration for each patient in the study will be approximately 30 to 32 weeks: approximately 1 to 2 weeks in the Screening Period, 4 weeks in the Stabilization Period, 24 weeks in the Treatment Period, and 1 to 2 weeks to Termination Visit.

Patients entering the study established on weekly SCIG infusions will have a 1 week Screening Period. Patients entering the study established on every other week dosing will have a 2 week Screening Period.

Patients entering the study currently active and established on SCGAM-03 CUTIQUIG will skip the 4 week Stabilization Period.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when all patients have completed the Termination Visit.

The estimated study start (enrollment of first patient) is the 3rd quarter 2019. Recruitment duration is expected to be approximately 18 months; therefore, the estimated study completion (last patient last visit) is anticipated in the 1st quarter 2021.

6.2.3 Premature Termination of the Study

Both the responsible Investigators and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, study close-out procedures will be arranged on an individual site basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

Furthermore, the Investigator should promptly inform the IRB and provide a detailed written explanation. Pertinent regulatory authorities and IRBs will be informed in accordance with applicable regulatory requirements.

6.2.3.1 Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk assessment.

- If more than 2 independent thromboembolic events (TEEs) (ie, ischemic stroke, transient ischemic attack, cerebral infarction, cerebrovascular accident, cerebral thrombosis, embolic infarctions, [acute] myocardial infarction, deep vein thrombosis, pulmonary embolism, venous thrombosis excluding thrombophlebitis) are observed fulfilling the following criteria:
  - Assessed as probably or possibly related to CUTAQUIG treatment by Investigator and/or Sponsor
  - Confirmed by the IDMC
- Any other reason rendering the continuation of the study impossible for the Sponsor

6.2.3.2 Early Termination at an Individual Study Site

At any time, the study can be terminated at an individual study site if the site:

- Cannot comply with the requirements of the protocol
- Cannot comply with applicable standards
- Does not meet the required recruitment rate

Should the study be prematurely terminated, all study materials, including IMP, must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

Demographic and baseline information will be recorded during the Screening Visit.

7.1.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics are sex, age, race and ethnic origin, height, weight, calculated BMI, and ABO Rhesus blood type.

7.1.2 Medical History

Medical history (conditions and surgical treatment) will be obtained by patient interview. Records of past diseases and treatments (eg, hospital discharge letters) will be obtained for the study files, if available. Any untoward medical events that occur from the time/date of informed consent signature until the first Study SCGAM-06 specified CUTAQUIG dose will be recorded as medical history.

7.1.3 Prior and Concomitant Medication Use

Prior and concomitant medications and therapies will be obtained by patient interview. See Section 4.2 for details on prior and concomitant medication collections.

7.1.4 Documentation of Previous SCIG Treatment and IgG Trough Levels

Documentation of consistent or stable doses of SCIG treatment will be collected from patients' medical records.

Documentation of IgG trough levels will be collected from pre-study laboratory results obtained prior to enrollment; 2 prior IgG trough levels are required within 1 year of Screening, with 1 trough level obtained within 3 months prior to enrollment. If no prior IgG trough level is available within 3 months prior to Screening, the Screening IgG trough level may be used as the 2nd reading.

7.2 Efficacy Assessments

To study the effectiveness of CUTAQUIG to maintain total IgG trough levels when administered every other week, in the prevention of infections, and changes in patient QoL assessments, the following measurements will be recorded and efficacy parameters assessed, throughout the study:

- Change in IgG trough levels when switched from every week to every other week administration (Cohort 3) (See Section 7.4.1)
- Number of episodes of SBI, per person-year on treatment, along with type and severity of infection, and time to resolution
- Number of episodes of any other infections (including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea etc.), along with type and severity of infection, and time to resolution
- Number of days of use and annual rate of antibiotics (oral, parenteral, oral plus parenteral, prophylactic and therapeutic), along with type and dosage of antibiotic

- QoL assessments (See Section 7.4.2)

For data collection of bacterial infections, in addition to on-site AE assessments, each patient will be provided with an individual diary to be completed by the patient during the home therapy time. The patient's diary will be checked for accuracy of the data by the Investigator and collected at each study visit. The data will be then transferred into the eCRF. A new diary will be handed out to the patient for the following period until the next infusion visit at the site.

For the purpose of this study the following events will be considered as SBIs, to be included in the primary efficacy analysis:

- Bacterial pneumonia
- Bacteremia/sepsis
- Osteomyelitis/septic arthritis
- Visceral abscess
- Bacterial meningitis

The presence of any of these infections should be verified by the specific differentiated diagnostic examinations [25] given in Table 8.

Table 8: Diagnostic Criteria for Serious Bacterial Infection Types

Infection: Bacteremia/sepsis[a] • *Symptoms*: chills, rigors. • *Physical findings*: fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure <90 mm Hg or a reduction of >40 mm Hg from baseline in the absence of other causes of hypotension), altered mental status, petechiae, purpura, oligouria, cutaneous vasodilation/vasoconstriction. • *Laboratory tests:* **positive blood culture**[b], leukocytosis (white blood cell (WBC) count • >12,000/mm^3), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis.
Infection: Bacterial Meningitis • *Symptoms:* headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea/vomiting, rigors, seizures. • *Physical findings*: Kernig's sign, Brudzinski's sign, meningococcal rash, fever of >38°C oral or >39°C rectal. • *Laboratory tests:* **positive cerebrospinal fluid (CSF) Gram stain and/or culture and/or positive CSF bacterial antigen assay**, positive blood culture[c], CSF leukocytosis with neutrophil predominance, decrease in CSF glucose.
Infection: Osteomyelitis/Septic Arthritis • *Symptoms:* pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (local inflammatory symptoms/signs may be lacking in adults).

• *Physical findings:* evidence of soft tissue infection adjacent to the involved bone/joint, drainage from sinus tract from involved bone, fever of >38°C oral or >39°C rectal. • *Laboratory tests:* positive blood culture, positive probe to bone, positive bone aspirate culture, positive bone biopsy culture, positive bone histopathology, positive joint fluid Gram stain and culture. • *Imaging studies:* **positive X-ray, nuclear medicine bone scan, magnetic resonance imaging scan, or computed tomography scan showing bony destruction with radiolucent areas; for chronic osteomyelitis: sequestra, involucra.**
Infection: Bacterial Pneumonia[d] • *Symptoms:* productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgia. • *Physical findings:* rales; pulmonary consolidation as reflected by: dullness on percussion, bronchial breath sounds, egophony; fever >38°C oral or >39°C rectal, or <36°C, hypothermia (temperature <36°C oral or <37°C rectal). • *Laboratory tests:* leukocytosis, differential WBC count of >10% band neutrophils, leukopenia, hypoxemia (PaO2 <60 mm Hg on room air), positive blood culture, Gram stain and culture of deep expectorated sputum e, positive culture with or without positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with bronchoalveolar lavage or protected brush sampling. • *Imaging studies:* **Pulmonary infiltrate with consolidation on chest X-ray** (new in comparison with baseline chest X-ray)
Infection: Visceral Abscess • *Symptoms:* abdominal pain, anorexia, weight loss, cough/pleuritic chest pain (hepatic abscess), rigors (seldom present). • *Physical findings:* intermittent fevers (temperature >38°C oral or >39°C rectal), abdominal tenderness, palpable mass, hepatomegaly, jaundice. • *Laboratory tests:* **positive Gram stain and/or culture from the infected site, with isolation of an appropriate pathogen**, positive blood culture, leukocytosis with accompanying left shift, differential WBC count of >10% immature (band) neutrophils, elevated serum amylase concentration (pancreatic abscess), elevated alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess. • *Imaging studies:* **typical findings on ultrasound, computed tomography scan, magnetic resonance imaging scan, or radionuclide scan**

Notes to Table 8:

Items in bold are considered essential diagnostic features.

a. Two of the following should be present to make the diagnosis of sepsis in adults: temperature >38°C oral/>39°C rectal or <36°C oral or <37°C rectal; heart rate >90 beats/min; respiratory rate >20 breaths/min, or $PaCO^2$ <32 mm Hg; WBC count >12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms. For pediatric patients, the definition of sepsis using age-specific criteria as

recommended by the International Consensus Conference on Pediatric Sepsis should be employed.[26]

b. Indwelling catheter- or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IVIG replacement therapy. For patients without indwelling catheters or vascular access devices, a single blood culture positive for a pathogenic organism will meet the diagnostic criteria for bacteremia. Patients meeting criteria for positive blood culture but without 2 or more of the sepsis criteria listed above will be classified as having bacteremia.

c. A blood culture positive for growth of Streptococcus pneumoniae, Neisseria meningitides, or Haemophilus influenzae, in combination with CSF leukocytosis and/or decrease in CSF glucose, can serve to confirm the diagnosis of acute bacterial meningitis.

d. For the diagnosis of pneumonia in adults, commonly at least 2 of the listed symptoms and/or signs should be present in conjunction with at least one laboratory and one imaging studies diagnostic element. However, for the purposes of counting serious bacterial infection episodes in a clinical trial of IVIG, the finding of a new pulmonary infiltrate with consolidation on chest X-ray is considered sufficient. To establish the diagnosis of bacterial pneumonia for pediatric patients, most of the same diagnostic criteria listed may be used, with the following exceptions: Because pediatric patients may not produce a sputum specimen for culture, blood cultures or serology may be substituted to identify the etiologic bacterial pathogen. In infants age 3 to 24 months, who tend to have a higher baseline temperature, fever is defined as a rectal temperature >38.3°C (101°F). In children >2 years, fever is more commonly defined as a rectal temperature >38°C (100.4°F). In pediatric patients, elevations of WBC counts >15,000/mm^3 are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count <5000/mm^3 may be observed, usually associated with severe infection.

e. It is recommended to obtain a deep expectorated sputum gram stain to demonstrate the presence of microorganisms on examination of 10-20 oil immersion microscopic fields and <10 squamous epithelial cells and >25 polymorphonuclear leukocytes at 10X low power magnification to determine suitability of sputum culture.

7.3 Safety Assessments

The following safety assessments shall be collected:

- Adverse events (AEs) and serious adverse events (SAEs) temporally associated with the administration of IMP (for definitions and reporting requirements, see Section 7.3.1 for AEs and Section 7.3.3 for SAEs)
- Pregnancies (Section 7.3.8.2)

7.3.1 Adverse Events

7.3.1.1 Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

An AE is defined as treatment-emergent (TEAE) if the event began or worsened after the start of first infusion of trial medication. For patients in this study, "treatment-emergent" will refer to events with onset date/time after the start of the first CUTAQUIG infusion at the Stabilization Period Week 0 Visit.

Adverse drug reaction (ADR): An ADR is any noxious and unintended response to an IMP related to any dose. The phrase “response to an IMP” means that a causal relationship between the IMP and an AE carries at least a reasonable possibility (ie, the relationship cannot be ruled out).

Other Significant AEs: Any non-serious AE or marked laboratory abnormality that results in:

- withdrawal of IMP treatment
- and/or dose reduction
- and/or initiation of significant additional concomitant therapy (ie, medications given intravenously)

Withdrawal due to AE/ADR: AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.1.2 Collection

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as “How have you been since the last visit/during the previous study period?” In addition, patient diaries (if applicable) will be checked by the Investigator for any documented event.

Any AE which occurs during the study from the time/date of first dose of CUTAQUIG through the Termination Visit will be noted in detail on the appropriate pages of the eCRF. Any untoward medical events that occur from the time/date of informed consent signature until the first CUTAQUIG dose will be recorded as medical history. If the patient reports several signs or symptoms representing one syndrome or diagnosis, the diagnosis should be recorded in the eCRF. The Investigator will grade the severity of all AEs (mild, moderate or severe), the seriousness (non-serious or serious), and causality, as defined below (Section 7.3.1.3, Section 7.3.3, and Section 7.3.1.4, respectively). The Sponsor is also responsible to assess the expectedness of each ADR (expected or unexpected), as defined below (Section 7.3.1.5).

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed and followed-up until they have returned to normal and/or an adequate explanation is available.

Diseases, signs and symptoms and/or laboratory abnormalities already existing before the first administration of IMP are not considered as AEs when observed at a later stage unless they represent an exacerbation in intensity or frequency (worsening).

The Investigator should always provide detailed information concerning any abnormalities and the nature of, and reasons for, any necessary action(s), as well as any other observations or comments which are useful for the interpretation and understanding of patients’ AEs.

7.3.1.3 Severity

The intensity/severity of AEs will be graded as follows:

- **Mild:** an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities
- **Moderate:** an AE which is sufficiently discomforting to interfere with the patient's routine activities
- **Severe:** an AE which is incapacitating and prevents the pursuit of the patient's routine activities

The severity grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

7.3.1.4 Causality

The relationship of AEs to the administered IMP will be assessed by the Investigator:

- **Probable:** reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.
- **Possible:** reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors
- **Unlikely:** reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- **Not related (unrelated):** events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- **Unclassified:** reports which for one reason or another are not yet assessable, eg, because of outstanding information (can only be a temporary assessment). Sites are encouraged not to use this category unless necessary, as it will be assumed there is a causal relationship and may lead to premature fulfillment of Suspected Unexpected Serious Adverse Reaction (SUSAR) criteria.

7.3.1.5 Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

- **Expected:** an ADR that is listed in the current edition of the Investigator's Brochure or other reference safety information.

- **Unexpected:** an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, or that differs because of greater severity or greater specificity.

7.3.1.6 Outcome of AEs

Outcome of all reported AEs will be documented as follows:

- Recovered, resolved
- Recovering, resolving
- Not recovered, not resolved
- Recovered, resolved with sequelae
- Fatal
- Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end and regardless of whether or not it is considered treatment-related.

7.3.1.7 Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (eg, physical) therapy started
- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient is stable, and all relevant follow-up information will be reported to the Sponsor.

7.3.2 Local Site Reactions

Local infusion-site reactions will be assessed by both patients and investigators.

Patients will grade the overall perception of local reactions in their diaries after each infusion using a 4-point rating scale: 0=none, 1=mild, 2=moderate, 3=severe.

Investigators will evaluate local reactions after infusion at every study visit, using a 4-point rating scale: 0=none, 1=mild, 2=moderate, 3=severe.

The following observations must not be reported as local infusion site reactions as all of these can be expected in all patients:

- Local mass (usually reported as "swelling") caused by the injected CUTAQUIG volume
- Small blood drops at the infusion site caused by the needle sticks
- Short and immediate pain at the infusion site caused by the puncture itself

Any other local infusion site reactions such as redness, pain (other than the pain caused by the puncture itself), pruritus, rash or other skin reactions, bleedings (other than small blood drops caused by the needle stick), local thrombosis, induration or swellings (caused by other grounds than the injected volume) must be reported on the adverse events page in the eCRF.

7.3.3 Serious Adverse Events

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (see below)
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is another important medical event

NOTE: The term ‘life-threatening’ refers to an event in which the patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

Medical judgment should be exercised in deciding whether an AE/ADR is serious in other situations: Important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.3.3.1 SAE Reporting

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported immediately to the Octapharma Project Manager by email and to [redacted].

In addition, within 24 hours after recognition of the event, an Octapharma Serious Adverse Event Report must be completed and submitted to:

Octapharma's Corporate Drug Safety Unit

OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

Oberlaaer Strasse 235, 1100 Vienna, Austria

[redacted]

SAE reporting procedures are outlined in the Site Safety Reporting Manual that will be provided to each site and will be communicated at the site initiation visit.

Waivers from the SAE Reporting Requirement

Waivers from the SAE reporting requirement include surgeries that are elective or were planned before study entry or prolongations of existing hospitalizations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs. In addition, any AE that meets the criteria of an SAE but begins prior to the start of the first infusion will be waived from the SAE reporting requirements.

7.3.4 Laboratory Tests

The following laboratory tests will be performed during the course of the study to investigate the efficacy, safety, and tolerability of CUTAQUIG (Table 9). At each visit, laboratory tests will be performed before CUTAQUIG infusions at the study site.

The following laboratory parameters will be investigated during the study at the time points specified in the FLOW CHARTS OF ASSESSMENTS.

Table 9: Laboratory Tests and Time Points

Test	Timing	Laboratory
Total serum IgG trough levels	Screening Visit; Stabilization Period Week 0; all subsequent Treatment Period Visits, and Termination Visit	Central
Hematology (complete blood count, WBC differential, hematocrit, hemoglobin)	Screening Visit; Stabilization Period Week 0; Treatment Period Baseline, Week 12, and Week 24; and Termination Visit	Local
Clinical chemistry (sodium, potassium, glucose, ALT, AST, LDH, total bilirubin, blood urea nitrogen or blood urea, creatinine)	Screening Visit; Stabilization Period Week 0; Treatment Period Baseline, Week 12, and Week 24; and Termination Visit	Local

Test	Timing	Laboratory
Urinalysis (pH, glucose, ketones, leukocytes, hemoglobin)	Screening Visit; Stabilization Period Week 0; Treatment Period Baseline, Week 12, and Week 24; and Termination Visit	Local
Urine pregnancy test (females of childbearing potential)	Screening Visit; Stabilization Period Week 0; Treatment Period Baseline, Week 12 and Week 24; and Termination Visit	Local
Virology (HCV-Nucleic Acid Testing [NAT])	Stabilization Period Week 0: CUTAQUIG—naïve patients and SCGAM-03 patients if commercial SCIG product used following completion of SCGAM-03. Treatment Period Baseline: patients currently active and established on CUTAQUIG in SCGAM-03 at the Screening Visit Termination Visit: all patients	Central
Serum retention samples	Stabilization Period Week 0: CUTAQUIG—naïve patients and SCGAM-03 patients if commercial SCIG product used following completion of SCGAM-03. Treatment Period Baseline: patients currently active and established on CUTAQUIG in SCGAM-03 at the Screening Visit Termination Visit: all patients	Central

The methods of determination and normal ranges for each parameter will be provided in the clinical study report.

7.3.5 Serum Retention Samples

Serum retention samples will be collected at Stabilization Period Week 0 for CUTAQUIG-naïve patients or SCGAM-03 patients that have gone on a commercial SCIG product, at Treatment Period Baseline for patients who are enrolled in SCGAM-03 and directly entering SCGAM-06, and at the Termination Visit for all patients (Table 9). These samples will be shipped to a central laboratory for retention and possible future testing of Hepatitis A, B, C, and HIV I/II. Instructions for sample handling will be provided in the Study Laboratory Manual.

7.3.6 Vital Signs

Vital signs will be measured at the time points specified in the FLOW CHARTS OF ASSESSMENTS and include blood pressure, body temperature, pulse, and respiratory rate.

7.3.7 Physical Examination including Height and Weight

Physical examinations will be performed according to each study site's routine procedures by study personnel who are qualified to perform such evaluations. These examinations will be as comprehensive as necessary to detect relevant somatic or neurological diseases. If any findings are abnormal, the Investigator will document the start date and whether or not the abnormal finding is still present at the start of treatment.

Both height and weight will be measured at Screening. In addition, weight will be measured at all visits prior to dosing in order to allow for dose calculations.

7.3.8 Other Relevant Safety Information

7.3.8.1 Post-study related safety reports

Any SAE which occurs up to 4 weeks after the Termination Visit should be reported by the Investigator to the Sponsor in case the Investigator becomes aware of it. Proactive monitoring for post-study SAEs is not required.

If a post-study SAE is identified, the Investigator should complete an SAE form and also record the relationship of the SAE to the IMP in the SAE report.

Any death occurring within 4 weeks after Termination Visit should also be reported, regardless of whether or not it is considered treatment-related.

7.3.8.2 Pregnancies

Every effort will be made to avoid a pregnancy during the use of an IMP. Pregnancies occurring during the study (fetal exposure to the IMP) need to be reported.

In case of a pregnancy during the study, the Investigator should complete the Pregnancy Notification Form and email or fax it to the Sponsor's representative (Section 7.3.3.1).

7.3.8.3 Drug overdose, interaction, or medication error

The following safety relevant information should be reported as AE or as an SAE if the reaction fulfils one of the criteria for seriousness (Section 7.3.3).

a) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

b) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, ie, increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

c) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

7.4 Other Assessments

7.4.1 Drug Concentration Measurements (IgG Trough Levels)

Samples for total IgG trough levels measurements will be taken at the Screening Visit, before any infusion given at the study site (Section 7.1.4), and at the (Early) Termination Visit (Table 9).

7.4.2 Quality of Life Assessment

QoL assessments will be made using the SF-10 from a parent or guardian of patients <14 years of age and the SF-36 Health Survey in patients ≥14 years of age. The QoL assessments will take place at the Treatment Period Baseline Visit and at the (Early) Termination Visit.

7.4.3 Subject Questionnaire

The Subject Questionnaire will be completed asking for their opinions related to their participation on the trial. This will be completed by all patients (or with the assistance of a parent/guardian for children, when applicable) at the (Early) Termination Visit.

7.5 Appropriateness of Measurements

Safety will be monitored by standard assessments including monitoring AEs, local infusion site reactions, vital signs, laboratory safety tests, and physical examinations.

Therapeutic efficacy, defined as the prevention of SBI, is a very important clinical aspect of any IgG replacement therapy and best characterizes benefit to the patient.

Determination of the pre-next-dose trough level of IgG is a standard method for determination of the correct dose for the individual patient.

The QoL questionnaires are standardized, validated instruments that have been widely used in clinical studies, including studies with PI patients.

8 DATA HANDLING AND RECORD KEEPING

To ensure that data in the eCRFs are accurate and complete and in accordance with source records, source data verification will be performed in accordance with Octapharma standards. The extent of source data verification will be defined in detail in the monitoring manual.

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study; written down in original records or certified copies of original records; or electronic medical records; allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (eg, case histories or patient files) for each patient enrolled. Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participates in this study.

All data entered in the eCRF must be supported by source data in the patient records, with exceptions listed in Section 8.1.2.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorize site staff (eg, sub-Investigators, research nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log and signed by the Investigator.

The following data must be verifiable from the source records: patient number, sex, weight, date of birth, written informed consent (and assent, if appropriate), medical history, main inclusion and exclusion criteria, local laboratory test results, PID-relevant concomitant therapies (medication and non-drug therapy), any AE occurring in the course of the study, details of infusions (batch number, number of vials used, date, dose, rate, and infusion site(s)), date and reason for early termination (if applicable). As part of the source records, laboratory data will be reviewed by the Investigator, assessed as to their clinical significance, signed, and dated.

8.1.2 Electronic Case Report Forms

For each patient enrolled, an eCRF will be completed within the EDC system and approved by the Investigator or an authorized sub-Investigator.

Study site staff (eg, research nurse) will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRF before receiving access to the live database for data entry.

The site will be provided with approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. The site will be notified once the database is

active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must be listed in the Delegation of Authority Log.

If any errors in the eCRFs are found during the data review process, discrepancies will be generated programmatically within the EDC system and manual queries will be generated by either a monitor or Data Management. The programmed edit checks fire automatically once an eCRF page is saved within the system. The outputs of the programmed checks are referred to as discrepancies. Discrepancies are generated by the input of illogical eCRF data with the purpose to clarify the context or insertion of illogical or missing data with the site or designee.

All discrepancies (programmed and manual) will be submitted to the site personnel or monitor for the site within the EDC system. Once the site responds to a discrepancy, Data Management or the monitor will review the new or changed data to ensure an appropriate response and close the discrepancy within the system.

8.1.3 Changes to Electronic Case Report Form Data

Monitors will perform source data verification (SDV) as defined for the study.

Errors occurring in the EDC system can only be corrected by the Investigator(s) or authorized site personnel. An audit trail documents all changes to the data over the entire study period. If data are changed as a result of a query, a comment must be entered stating the reason for the change before closing the query. In addition, any change to a previously saved eCRF page that has not had a query generated will need to have a reason specified for the data change.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks will be performed, and programs will be run throughout the study until the data are clean (all discrepancies resolved) and the database is ready for lock. Source data verification will be confirmed as complete by the monitor and all eCRFs will be approved by the Investigator before database lock.

8.2 Information to Investigators

An Investigator's Brochure will be provided to the Investigator before the start of the study. This brochure contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The Investigator's Brochure will be updated by the Sponsor at regular intervals and the event that relevant new information concerning the IMP becomes available.

All participating investigators will be informed about relevant study procedures, about the methods for rating relevant study outcomes, and how to enter data into the eCRF in order to reduce discrepancies. At the study initiation visit, the eCRF will be explained to all study site staff entitled to document data in the eCRF.

Investigators will be kept informed of important information related to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

The Principal Investigator is accountable for the conduct of the clinical study at each study site. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be completed and signed by the Principal Investigator. In accordance with this authority log, study site staff (eg, sub-Investigators, study coordinators, nurses) will be authorized to perform specific tasks relating to study conduct.

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by Good Clinical Practice (GCP) guidelines and regulations (eg, copies of the protocol, study approval letters, all original informed consent forms and assent forms (as age appropriate), site copies of all eCRFs, drug dispensing and accountability logs, correspondence pertaining to the study) should be filed accurately and retained by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list which provides the unique link between named source records and eCRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party or move them to another location, the Sponsor must be notified in writing.

8.4 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study or copies of relevant source records; the Investigator must ensure that patient confidentiality is maintained on any source documents provided to the Sponsor. This is particularly important when source data are illegible or when errors in data transcription are encountered.

In the event of particular issues or governmental queries, it may also be necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.5 Independent Data Monitoring Committee

The Sponsor will establish an IDMC.

The IDMC will be composed of recognized experts in the field of immunology who are not actively recruiting patients.

During the study, the IDMC will periodically review relevant data and will give advice on the continuation, modification, or termination of the study (Section 6.2.3). A study-

specific Charter will define in detail the composition, responsibilities, and procedures of the IDMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

Statistical analysis will be delegated under an agreement of transfer of responsibilities to an external CRO. All Octapharma procedures and policies must be met by this CRO. Discrepancies or exceptions will be approved by the Sponsor's Manager of Biometrics.

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

9.1 Determination of Sample Size

Approximately 65 patients who meet eligibility criteria will be enrolled in the study:

- At least 15 patients in Cohort 1
- At least 15 patients in Cohort 2
- At least 35 patients in Cohort 3

The co-primary endpoints will be analyzed descriptively, and no formal sample size calculation was done for the overall number of patients enrolled.

For Cohort 3 we plan for a confirmative analysis to evaluate whether the total IgG trough levels are maintained by an every other week dosing regimen; the following pair of hypotheses will be tested:

$$H_a: T_{eow} > T_w - 1 \quad \text{vs.} \quad H_0: T_{eow} \leq T_w - 1$$

where T_{eow} is the mean total IgG trough on steady-state dosing every other week, T_w is the same for weekly dosing, and a maximum decrease of 1 g/L for the mean total IgG trough level is considered acceptable.

T_w will be determined after completion of the Stabilization Period, T_{eow} at the final study visit.

This one-sided hypothesis will be tested by a paired t-test at the alpha=2.5% level of significance. Assuming 3.0 for the standard deviation common to both members of a pair, and 0.8 as the correlation between members of a pair, this results in a required minimum of 31 evaluable patients to achieve a power of 80%.

9.2 Statistical Analysis

All data collected will be listed and presented descriptively in full detail, by cohort as well as in total, to facilitate comparison between the different dosing regimens.

As detailed in Section 9.1, the change in total IgG trough levels when switching from weekly to bi-weekly infusions will be tested in Cohort 3 by means of a one-sided, paired t-test at the α=0.025 level of significance.

Descriptive summaries will be presented for each of the primary and secondary variables according to their individual data types. The results of this study will be presented at the descriptive level only; any additional p-value or confidence interval presented is to be understood in the exploratory sense.

9.2.1 Populations for Analysis

The following populations will be considered for the statistical analysis:

- Safety Analysis Set: all patients who received at least part of one infusion of CUTAQUIG.
- Full Analysis Set (FAS): all patients in the Safety Analysis Set who satisfy all major eligibility criteria and for whom any post-baseline data is available (per intention-to-treat principle). This set of eligible patients will be used for measurement of treatment effects.
- Per-Protocol (PP) Set: all patients in the FAS, excluding those with substantial protocol deviations which may have an impact on the analysis of the co-primary endpoint. This is the set of patients who participated in the study as intended and for whom the co-primary endpoint can be evaluated as planned.

Only substantial protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP set; protocol deviations to be considered will include (but will not be limited to):

- Violations of the study entry criteria
- Administration of any other blood or plasma-derived product or of any other immunoglobulin preparations during Study SCGAM-06
- Any prohibited concomitant medication (including long term daily corticosteroid use of >0.15 mg of prednisone or equivalent/kg/day [with the exception of short or intermittent courses as described in Section 4.2.2], immunosuppressive and immunomodulatory drugs)
- Failure to attend two scheduled consecutive visits OR three or more scheduled visits during the study for reasons other than clinical reasons

Efficacy endpoints will be analyzed using the FAS. Safety endpoints will be analyzed using the Safety Analysis Set. Selected analyses will be repeated for the PP population as detailed in the SAP and its appendices.

In the event that a patient is not treated according to the dosing regimen described for his assigned cohort, the original cohort assignment will still be used for safety and the ITT analyses (SAF and FAS populations). These patients will be removed from the PP population due to protocol violations.

The membership of each patient in the respective analysis populations will be determined before the statistical analysis in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager and the study statistician.

9.2.2 Efficacy Analysis Plan

The rate of SBI per person-year (bacterial pneumonia, bacteremia/sepsis, osteomyelitis/septic arthritis, visceral abscess, bacterial meningitis) during the CUTAQUIG treatment period will be presented as point estimates of the rate along with a 99% CI. Calculation of this confidence interval will account for intra-patient correlation in incidents following a compound Poisson process model. Furthermore, all observed SBIs will be listed individually and in full detail.

The duration of infection will be summarized by standard descriptive statistics by type of infection and by severity. The individual characteristics of each infection, including the time to resolution will be listed.

The use of antibiotics will be reported as a detailed list of all such medications, and the number of patients treated with antibiotics, the number of treatment episodes and the number of treatment days will be tabulated.

The US FDA Guidance for Industry on Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency suggests that, based on historical data, a statistical demonstration of a serious bacterial infection rate per person-year less than 1.0 is adequate to provide substantial evidence of efficacy.[25] Therefore, this background information will be used for a descriptive evaluation of the serious bacterial infection rate in this study as described above. Exploratory statistical testing may be performed if considered appropriate.

The QoL data will be presented descriptively by visit, along with the change from Baseline, defined as the Treatment Period Baseline Visit.

For Cohort 3, the change in total IgG trough levels when switching from weekly to every other week infusions will be tested confirmatory by means of a one-sided, paired t-test at the α=0.025 level of significance. The following pair of hypotheses will be tested:

$$H_a: T_{eow} > T_w - 1 \quad \text{vs.} \quad H_0: T_{eow} \leq T_w - 1$$

where T_{eow} is the mean total IgG trough on steady-state dosing every other week, T_w is the same for weekly dosing, and a maximum decrease of 1 g/L for the mean total IgG trough level is considered acceptable.

T_w will be determined after completion of the Stabilization Period, T_{eow} at the final study visit.

9.2.3 Safety Analysis Plan

The safety analysis will comprise descriptive statistics, tabulations, and listings of all TEAEs, safety laboratory results, vital signs, and physical examination findings.

9.2.3.1 Adverse Events

All reported AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

An AE is defined as treatment-emergent if first onset or worsening is after start of the first infusion of CUTAQUIG. Only TEAEs are accounted for in the analysis.

Any untoward medical events that occur between informed consent and the start of the first infusion of CUTAQUIG will be considered pre-treatment AEs. These events will not be entered into the safety database as they are not TEAE.

For each TEAE, the time relative to the start of the infusion will be calculated and the TEAE will be classified as temporally associated if the onset time is during the infusion or within 72 hours after the end of the infusion.

All reported AEs will be listed and tabulated in full detail, in particular the following data will be presented:

- Total number of TEAEs reported
- Number of TEAEs
- Infusion rate at the onset of TEAEs
- Narratives will be prepared describing each death, other SAEs, and other significant AEs that are judged to be of special interest because of clinical importance

9.2.4 Handling of Missing Data

In general, missing data will not be imputed: calculations pertaining to person-year computations will be based on observed values only. Only in case of missing body weight will the last available weight measurement be used for calculating the dose per kg body weight (last observation carried forward [LOCF]).

9.3 Randomization, Stratification, and Code Release

There is no randomization or stratification in this study. Assignments to the 3 study cohorts will be based on patient eligibility and Investigator and patient preference.

9.4 Interim Analysis

No interim analysis is planned.

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Before submission of the study protocol to the IRB and Competent Authority, the study will be registered in ClinicalTrials.gov. The study protocol and any subsequent substantial amendment(s), as well as a sample of the information sheet, informed consent form, assent form, any other materials provided to the patients, and further requested information will be submitted to the IRB and the Competent Authority. The study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

The study will be conducted under a US Investigational New Drug (IND) application, and therefore must meet the applicable US FDA requirements including Statement of Investigator Form 1572 and financial disclosure statement.

The regulatory application or submission for regulatory approval will be made by the Sponsor as required by national law. Study approval must be available before any patient is exposed to a study-related procedure.

The Competent Authorities and the IRBs will be notified of the end of the clinical study in accordance with local regulations.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, assent form, and further requested information will be submitted to the appropriate IRB and the competent Authority. The study approval letter must be available before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the Investigator and any third party (eg, CRO) involved in obtaining approval, must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The Investigator will obtain freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name, date, and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

For patients not qualified to give legal consent, written consent must be obtained from the legal parent/guardian. If children are old enough to understand the risks and benefits of the study, they should also be informed and provide their written consent using an assent form.

The Investigator will explain to each single patient that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any

consequences for their further care and without the need to justify their withdrawal. The Investigator will date and sign the informed consent form of each patient enrolled.

Each patient (and legal guardian, as age appropriate) will give written consent that his/her source records may be reviewed by study monitors, quality assurance auditors, and/or health authority inspectors, in accordance with applicable regulations. These persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Coordinating Investigator in multicenter studies) and the Sponsor before its implementation. Any such amendments will be submitted to the IRB and/or Competent Authority responsible as required by applicable regulations. IRB approval will at a minimum be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patient Data

The Investigator will ensure that patient confidentiality is preserved. In eCRFs or any other documents submitted to the Sponsor, patients will not be identified by name or initials but by a unique patient identifier. Documents not intended for submission to the Sponsor, including but not limited to the confidential patient identification code list, original consent and assent forms, and source records, will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness, and accuracy of all eCRF entries compared to source data. The Investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will be based on enrollment status and study progress, as outlined in the Study Monitoring Plan.

The monitor must be given direct access to source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IRB/Regulatory Authority inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

The Sponsor will prepare a clinical study report (in accordance with relevant guidelines and Octapharma Standard Operating Procedures) timely after the completion of the study. The Coordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings. If the Investigator wants to publish or present study results, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor before submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multicenter studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

To cover any damage or injury occurring to a patient in association with the investigational medicinal product or the participation in the study, the Sponsor will contract insurance in accordance with local regulations.

All participating investigators are responsible for dispensing the IMP in adherence to this protocol, and for its secure storage and safe handling throughout the study.

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15 APPENDICES

Not applicable.