Official Title:	**A Multi-Center, Open-Label, Single-Arm Trial to Evaluate Efficacy, Pharmacokinetics, and Safety and Tolerability of IGSC 20% in Subjects With Primary Immunodeficiency**
NCT Number:	NCT02806986
Document Dates:	Protocol Version 2: 22 July 2016

Clinical Study Protocol

Protocol Title:	A Multi-Center, Open-Label, Single-Arm Trial to Evaluate Efficacy, Pharmacokinetics, and Safety and Tolerability of IGSC 20% in Subjects with Primary Immunodeficiency
Investigational Products:	IGSC 20% Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified
Sponsor's Name and Address:	Grifols Therapeutics Inc. 79 TW Alexander Drive Research Triangle Park, NC 27709
Sponsor's Telephone Number:	[redacted], MD [redacted]
Study Number/Protocol Version Number/Date:	GTI1503/Version 2.0/22 Jul 2016 Including GTI1503/Version 1.2/04 Dec 2015, GTI1503/Draft Version 1.1/25 Nov 2015, and GTI1503/Version 1.0/06 Jul 2015
EUDRACT/CTA Number:	2015-003290-15/TBD
Development Phase:	3

The undersigned confirm that they agree to conduct the study under the conditions described in this protocol:

Medical Monitor: [redacted], MD

Signature: [redacted] **Date:** 22 July 2016

Summary of Changes for Amendment 2 Version 2.0

Protocol Version	Date of Approval
Version 2.0 Amendment 2 + Integrated Protocol	22 Jul 2016
Version 1.2 Amendment 1 + Integrated Protocol	04 Dec 2015
Draft Version 1.1 Amendment 1 + Integrated Protocol	25 Nov 2015
1.0 Original	06 Jul 2015

Protocol Amendment 2

The protocol for GTI1503 (Version 1.2, dated 04 Dec 2015) has been amended and reissued as Protocol Amendment 2, Version 2.0, dated 22 Jul 2016.

SUMMARY OF CHANGES FOR AMENDMENT 2 VERSION 2.0

(Note: Administrative changes including minor administrative corrections are not included in this Summary of Changes.)

Sections	Change From: (Version 1.2 dated 04 Dec 2015) (Strikethrough is added to highlight deleted text)	Change To: (Version 2.0, dated 22 Jul 2016) (Underline is added to highlight new text)	Rationale:
Synopsis: Study Objectives Section 2.1.1	The primary efficacy objective of this Phase 3 study is to evaluate whether weekly administered Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) over a one year period will achieve ~~not more~~ than 1 serious bacterial infection (SBI) per subject per year in primary immunodeficiency (PI) subjects.	The primary efficacy objective of this Phase 3 study is to evaluate whether weekly administered Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) over a one year period will achieve <u>less</u> than 1 serious bacterial infection (SBI) per subject per year in primary immunodeficiency (PI) subjects.	Edited for consistency with EMA guideline wording
Synopsis: Target Population	A documented trough IgG level of ≥ 500 mg/dL (within the previous ~~3~~ months) on this regimen is required.	A documented trough IgG level of ≥ 500 mg/dL (within the previous <u>6</u> months) on this regimen is required.	Increased the criterion window to allow for varying institutional standards
Synopsis: Key Assessments and Procedures	An SC infusion diary will be provided to each subject at ~~Screening~~ which may be used to record items including but not limited to: local infusion site reactions, concomitant medications (including antibiotics [prophylactic and therapeutic]), and details of SC drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion).	An SC infusion diary will be provided to each subject at <u>the Baseline visit</u> which may be used to record items including but not limited to: local infusion site reactions, concomitant medications (including antibiotics [prophylactic and therapeutic]), and details of SC drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion).	Revised the visit day when recording of diary data begins
Synopsis Inclusion Criteria Section 3.2.1	5. Documentation (within previous ~~3~~ months) of an IgG trough level of ≥ 500 mg/dL on current IgG replacement therapy regimen. 6. Screening/pre-Baseline trough IgG levels must be ≥ 500 mg/dL. Note: If Screening and/or pre-Baseline trough levels are not above this threshold, the subject will be a Screen Failure, but may be re-screened following dose adjustment of their original IgG replacement therapy regimen and maintaining stable dosing for a period of at least 3 consecutive months prior to	5. Documentation (within previous <u>6</u> months) of an IgG trough level of ≥ 500 mg/dL on current IgG replacement therapy regimen. 6. Screening/pre-Baseline trough IgG levels must be ≥ 500 mg/dL. Note: If Screening and/or pre-Baseline trough levels <u>(not including pSC#2 trough)</u> are not above this threshold, the subject will be a Screen Failure, but may be re-screened following dose adjustment of their original IgG replacement therapy regimen and maintaining stable dosing for a period of at least 3	Increased criterion window to allow for varying institutional standards Clarified that the blood draw occurring at the Baseline visit does not apply to this criterion since results are reported after the first investigational medicinal product (IMP) dose

Sections	Change From: (Version 1.2 dated 04 Dec 2015) (Strikethrough is added to highlight deleted text)	Change To: (Version 2.0, dated 22 Jul 2016) (Underline is added to highlight new text)	Rationale:
	Screening a second time.	consecutive months prior to Screening a second time.	
Synopsis Exclusion Criteria Section 3.2.2	5. The subject has known ~~s~~elective ~~i~~mmunoglobulin A (IgA) ~~d~~eficiency (with or without antibodies to IgA) 19. The subject has participated in another clinical trial within 30 days prior to Screening (observational studies without investigative treatments [non-interventional] are permitted) or has received any investigational blood product within the previous 3 months.	5. The subject has known Selective Immunoglobulin A (IgA) Deficiency (with or without antibodies to IgA). (Note: exclusion is for the specific diagnostic entity. It does not exclude other forms of humoral primary immunodeficiency which have decreased IgA in addition to decreased IgG requiring immune globulin [IgG] replacement). 19. The subject has participated in another clinical trial within 30 days prior to Screening (observational studies without investigative treatments [non-interventional] are permitted) or has received any investigational blood product, with the exception of other IgG products, within the previous 3 months.	Note added to explain the intent of this criterion Revised to exclude other IgG products as it is unnecessary to wait 3 months prior to screening a subject if they have received another investigational IgG product
Section 3.1	• Nonconsecutive C_{trough} samples are acceptable for subjects on SCIG. ~~The 4 week time allotment~~ for the Screening/Previous Regimen Phase ~~is necessary in order~~ to ensure Screening human immunodeficiency virus (HIV) nucleic acid amplification technology (NAT) test results will be available before the Baseline Visit/Week 1 visit.	• Nonconsecutive C_{trough} samples are acceptable for subjects on SCIG. A minimum of 10 days is anticipated for the Screening/Previous Regimen Phase to ensure Screening human immunodeficiency virus (HIV) nucleic acid amplification technology (NAT) test results will be available before the Baseline Visit/Week 1 visit.	Revised to define a minimum time frame based on updated information from the Central Lab results timing
Section 3.2	Subjects who initially fail to meet eligibility criteria may be re-screened once upon consultation with the ~~Sponsor~~.	Subjects who initially fail to meet eligibility criteria may be re-screened once upon consultation with the Medical Monitor.	Clarification that the delegated medical monitor role may be consulted for such cases
Section 3.4.3	The medications listed below are not allowed during the study as premedication to an infusion; however, these medications are allowed during the study for general use (e.g., to treat an AE):	The medications listed below are not allowed during the study as premedication to an SC infusion; however, these medications are allowed during the study for general use (e.g., to treat an AE):	"SC" added as it is intended only to be applicable to the IP Treatment Phase
Section 3.6.2	No previous text	If there are logistical issues requiring schedule adjustment for weekly IGSC 20% administration, SC#1 may be scheduled 6 to 9 days after pIV#2. Schedule adjustment may also be made after SC#3 or later (± 2	Expansion of the visit window was added to accommodate subject

Sections	Change From: (Version 1.2 dated 04 Dec 2015) (Strikethrough is added to highlight deleted text)	Change To: (Version 2.0, dated 22 Jul 2016) (Underline is added to highlight new text)	Rationale:
		days from last infusion) when home infusion is initiated.	scheduling
Section 3.6.2.1 Screening Visit Assessments for all subjects	The duration of this phase is also dependent on the need for the HIV screening results that are required prior to Baseline/Week 1 of Treatment Stage 1, which may take ~~more than 3~~ weeks to report. • AEs (including ~~local~~ infusion ~~site~~ reactions [see Section 4.3.1 for definitions]), prior and concomitant medications assessments (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection) • Record results of most recent chest X-ray within 12 months (A chest X-ray will be necessary if not performed within 12 months of the Screening visit.) ~~• SC infusion diary: An SC/IgG infusion diary will be provided to each subject at Screening which may be used to record items including but not limited to: local infusion site reactions, concomitant medications (including antibiotics [prophylactic and therapeutic]), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). The SC infusion diary may also be used to record days of missed work/school/daily activities due to infections and related treatment. During the Screening/Previous Regimen Phase for subjects entering study on IVIG the infusion diary may be used to record concomitant medications and days of missed work/school/daily activities due to infections and related treatment.~~ ~~• Blood sample for previous regimen "random" IgG level~~	The duration of this phase is also dependent on the need for the HIV screening results that are required prior to Baseline/Week 1 of Treatment Stage 1, which may take up to 2 weeks to report. • AEs (including infusion reactions [see Section 4.3.1 for definitions]), prior and concomitant medications assessments (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection) • Record results of most recent chest X-ray within 12 months (A chest X-ray will be necessary if not performed within 12 months of the Screening visit for adult subjects only as permitted per local requirements.) Note: at least one radiographic view (anterior-posterior [AP] or posterior-anterior [PA] is required)	Revised from 3 weeks to up to 2 weeks based on updated information from the Central Lab results timing Expanded AE reporting criterion to include potential systemic infusion reactions Removed requirement for a Screening x-ray to limit radiation exposure for pediatric subjects and to comply with local requirements for adult subjects Moved initial use of the SC infusion diary from Screening to Baseline visit

Sections	Change From: (Version 1.2 dated 04 Dec 2015) (Strikethrough is added to highlight deleted text)	Change To: (Version 2.0, dated 22 Jul 2016) (Underline is added to highlight new text)	Rationale:
Previous Regimen Phase pIV or pSC Visit #1 or #2	~~if pre-dose trough not coincident with the Screening Visit~~ - Note the IgG trough values drawn during the Previous Regimen Phase constitute the Pre-baseline trough values which will confirm the final eligibility for subjects entering the study (must be ≥ 500 mg/dL). ~~Note: For subjects entering the study on an IVIG regimen where the Screening Visit does not coincide with pIV#1, safety laboratory testing (below italicized items only) should be repeated pre IVIG dose at the visit for pIV#1 because of the longer time duration before Baseline (see Figure 3-1 and Appendix 1):~~ ~~– Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential; ARC~~ ~~– Sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, ALP, glucose, total bilirubin, indirect bilirubin~~ ~~– Serum pregnancy test (potential child bearing females only)~~ ~~– Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)~~ ~~• SC infusion diary: An SC/IgG infusion diary will be provided to each subject at Screening which may be used to record items including but not limited to: local infusion site reactions, concomitant medications (including antibiotics [prophylactic and therapeutic]), and details of IgG drug administration (location and number of sites, date/clock time of start and end of~~	- Note the IgG trough values drawn during the Previous Regimen Phase constitute the Pre-baseline trough values which will confirm the final eligibility for subjects entering the study (must be ≥ 500 mg/dL) <u>with the exception of the pSC #2 trough result which will be reported after the Baseline visit.</u>	Exception added for clarification Removed requirement to repeat Screening safety labs as Screening/Pre-regimen Phase window is limited to 8 weeks and such lab parameters are not anticipated to significantly change in this timeframe for the targeted study population Moved initial use of the SC infusion diary from Screening to Baseline visit

Sections	Change From: (Version 1.2 dated 04 Dec 2015) (Strikethrough is added to highlight deleted text)	Change To: (Version 2.0, dated 22 Jul 2016) (Underline is added to highlight new text)	Rationale:
	~~infusion, dose/volume, duration and rates of infusion). All local infusion site reactions will be recorded in the eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator will be considered as AEs. The SC infusion diary may also be used to record days of missed work/school/daily activities due to infections and related treatment. For subjects entering study on IVIG, the infusion diary may be used to record concomitant medications and days of missed work/school/daily activities due to infections and related treatment.~~ ~~Review of the SC infusion diary entries and infusion details will be undertaken with subjects/caregivers during the Previous Regimen Phase.~~ ~~• Record days lost from work/school/daily activities due to infections and treatment~~ • AEs (including ~~local~~ infusion ~~site~~ reactions [see Section 4.3.1 for definitions]), prior and concomitant medications assessments (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection).	• AEs (including infusion reactions [see Section 4.3.1 for definitions]), prior and concomitant medications assessments (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection).	Expanded AE reporting criterion to include potential systemic infusion reactions
Section 3.6.2.2 Baseline Visit (week 1)	• AEs (including ~~local~~ infusion ~~site~~ reactions [see section 4.3.1 for definitions] and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.]) ~~• Review SC infusion diary and infusion details with subjects/caregivers. All local infusion site reactions will be recorded in the eCRF. The subset of local infusion site reactions where the symptoms/signs lead~~	• AEs (including infusion reactions [see section 4.3.1 for definitions] and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.]) • <u>SC infusion diaries: SC/IgG infusion diaries will be provided to each subject at the Baseline visit which may be used to record items including but not limited to: local infusion site reactions,</u>	Expanded AE reporting criterion to include potential systemic infusion reactions Moved initial use of the SC infusion diary from Screening to Baseline visit

Sections	Change From: (Version 1.2 dated 04 Dec 2015) (Strikethrough is added to highlight deleted text)	Change To: (Version 2.0, dated 22 Jul 2016) (Underline is added to highlight new text)	Rationale:
	~~to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator will be considered as AEs. For subjects entering study on IVIG, the infusion diary may be used to record concomitant medications and days of missed work/school/daily activities due to infections and related treatment.~~	concomitant medications (including antibiotics [prophylactic and therapeutic]), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). All local infusion site reactions will be recorded in the eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator will be considered as AEs. The SC infusion diary may also be used to record days of missed work/school/daily activities due to infections and related treatment.	
Sections 3.6.2.3, 3.6.2.4, 3.6.2.5, 3.6.2.6, 3.6.2.7 Appendix 1	• Record AEs including ~~local~~ infusion ~~site~~ reactions (see section 4.3.1 for definitions) and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])	• Record AEs including infusion reactions (see section 4.3.1 for definitions) and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])	Expanded AE reporting criterion to include potential systemic infusion reactions
Table 3-1	Additional special tests [a] DAT, serum free hemoglobin, haptoglobin Central ~~(central DAT if feasible)~~	Additional special tests [a] DAT, serum free hemoglobin, haptoglobin Central	Revised per Central Lab confirmation
Section 3.7	• Pregnancy	• Pregnancy (Note: Subject must be withdrawn from IP administration and the study prior to dosing with a commercially available IgG product.)	Revised for clarification on timing of withdrawal due to pregnancy
Section 4.4.1	Any SAE (see Section 4.3.6) that occurs after signing the study ICF through the Final Visit (i.e., end of study) must be expeditiously reported whether or not considered attributable to the study drug. Each SAE must be fully recorded in the subject's eCRF ~~or~~ SAE Report Form. SAEs will be reported using the designated SAE Report	Any SAE (see Section 4.3.6) that occurs after signing the study ICF through the Final Visit (i.e., end of study) must be expeditiously reported whether or not considered attributable to the study drug. Each SAE must be fully recorded in the subject's eCRF and SAE Report Form.	Revised for internal consistency

Sections	Change From: (Version 1.2 dated 04 Dec 2015) (Strikethrough is added to highlight deleted text)	Change To: (Version 2.0, dated 22 Jul 2016) (Underline is added to highlight new text)	Rationale:
	Form. When the Investigator becomes aware of an SAE, she/he must submit ~~electronically through the electronic data capture (EDC) system or when the EDC system is not available submit~~ a completed, signed, and dated SAE Report Form (in English) within 24 hours to the Sponsor by email/fax. All SAE Report Forms ~~and Pregnancy Report Forms must be reported to Grifols electronically through the EDC system or when the EDC system is not available, reported to:~~	SAEs will be reported using the designated SAE Report Form. When the Investigator becomes aware of an SAE, she/he must submit a completed, signed and dated SAE Report Form (in English) within 24 hours to the Sponsor by email/fax. The date of this SAE discovery by the site staff should be documented in the source documents (ie, medical records). All SAE Report Forms must be reported by email to:	
Section 4.4.2	In any case, a Pregnancy Report Form must be completed and sent as soon as possible to the Sponsor for any pregnancies that occur from time of consent through the Final Visit (i.e., end of study).	In any case, a Pregnancy Report Form must be completed and sent as soon as possible to the Sponsor for any pregnancies that occur in a female subject or partner of a male subject from time of consent through the Final Visit (i.e., end of study).	Revised for internal consistency
Appendix 1	Deleted row IgG level (random) if predose trough does not coincide with visit Deleted Screening, pIV#1/pSC#1, and pIV#2 assessments for Review SC Diary & infusion details with subject/caregiver f Record results of most recent chest X-ray within 12 months (A chest X-ray will be necessary if not performed within 12 months of the Screening visit.) g Laboratory Assessments (chemistry, hematology, haptoglobin, & urinalysis) will be performed at the Screening and Baseline Visits. ~~*For subjects entering study on a prior IVIG regimen who do not have Screening Visit and pIV#1 coincide (pre dose pIV#1) safety laboratory parameters (hematology, chemistry, urinalysis and serum pregnancy test) will be repeated during the Screening/Previous Regimen Phase.*~~	f Record results of most recent chest X-ray within 12 months (A chest X-ray will be necessary if not performed within 12 months of the Screening visit for adult subjects as permitted per local requirements). g Laboratory Assessments (chemistry, hematology, haptoglobin, & urinalysis) will be performed at the Screening and Baseline Visits.	Removed IgG row to avoid an additional blood draw for certain subjects Moved initial use of the SC infusion diary from Screening to Baseline visit; Removed requirement for a Screening x-ray to limit radiation exposure for pediatric subjects and to comply with local requirements for adult subjects Removed requirement to repeat Screening safety labs

Investigator Signature Page

The undersigned confirms that he/she agrees to conduct the study under the conditions described in this protocol and comply with International Conference on Harmonization Good Clinical Practice (ICH GCP) and all applicable regulatory requirements:

_____ _____

INVESTIGATOR NAME (Please Print) LOCATION

_____ _____

INVESTIGATOR SIGNATURE DATE

Protocol Synopsis

Title of Study: A Multi-Center, Open-Label, Single-Arm Trial to Evaluate Efficacy, Pharmacokinetics, and Safety and Tolerability of IGSC 20% in Subjects with Primary Immunodeficiency
Study Number GTI1503
Phase: 3
Number of Subjects Planned: Approximately 60 subjects
Study Centers Planned: Approximately 40 study centers
Study Objectives: The primary efficacy objective of this Phase 3 study is to evaluate whether weekly administered Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) over a one year period will achieve less than 1 serious bacterial infection (SBI) per subject per year in primary immunodeficiency (PI) subjects. The secondary objective of this study is to determine if IGSC 20% replacement therapy maintains mean trough IgG levels that are comparable to the mean trough IgG levels with the previous IgG replacement regimen. Additional secondary objectives include determination of rate of infection of any kind (serious and non-serious), number of days on antibiotics, number of hospitalizations due to infection, and number of days of work/school/daily activities missed per subject year due to infections and their treatment. The safety objectives are to assess the safety and tolerability of IGSC 20% as an IgG replacement therapy in subjects with PI.
Target Population: Eligible participants for this study include male or female subjects who are 2 to 75 years of age and have a diagnosis of PI requiring IgG replacement treatment and who are currently receiving IgG replacement therapy via intravenous (IV) or subcutaneous (SC) infusion as a stable regimen for at least 3 consecutive months. A documented trough IgG level of $\geq$ 500 mg/dL (within the previous 6 months) on this regimen is required. For subjects receiving intravenous immune globulin (IVIG) at study entry, the dose must be at least 200 mg/kg per infusion administered every 3 or 4 weeks. For subjects receiving subcutaneously delivered immune globulin (SCIG) at study entry, there is no prerequisite minimum dose. Subjects who have never received IVIG or SCIG treatment (treatment naïve)

will not be eligible for entry into the study.

Overall Study Description:

This is a prospective, multi-center, open-label, single-arm, efficacy, pharmacokinetic (PK), safety and tolerability study of the investigational product (IP), IGSC 20% in subjects with PI. Approximately 60 subjects will be enrolled in order to have approximately 20 adult subjects and 20 pediatric subjects treated with subcutaneously administered IGSC 20% who complete the entire study. This study will include 3 study stages: Screening/Previous Regimen Phase, IGSC 20% Treatment Stage 1 (13 IGSC 20% weekly doses), and IGSC 20% Treatment Stage 2 (39 IGSC 20% weekly doses).

A total of 52 doses of IGSC 20% will be administered with a final follow-up visit 1 week after the last dose at Week 53. Subjects/caregivers will be trained on self-administration of IGSC 20% by the clinical site personnel.

Study Phases:

This is a prospective, multi-center, open-label, single-arm, efficacy, PK, safety and tolerability study of IGSC 20% in subjects with PI. Approximately 60 subjects will be enrolled in order to have approximately 20 adult subjects and 20 pediatric subjects treated with subcutaneously administered IGSC 20% who complete the entire study. This study will include 3 study stages: Screening/Previous Regimen Phase, IGSC 20% Treatment Stage 1 (13 IGSC 20% weekly doses), and IGSC 20% Treatment Stage 2 (39 IGSC 20% weekly doses).

Subjects who are receiving IVIG at a dose of at least 200 mg/kg per infusion every 3 or 4 weeks at Screening must be on a stable IgG regimen (dose and dosing interval) for at least 3 consecutive months prior to Screening. Subjects who are receiving SCIG must also be on a stable regimen for at least 3 consecutive months prior to Screening; there is no prerequisite minimum dose for subjects entering study on a SCIG regimen. Subjects who have never received IVIG or SCIG treatment (treatment naïve) will not be eligible for entry into the study.

Previous Regimen Phase:

- Subjects will be infused with their current ongoing (“previous regimen”) IVIG/SCIG regimen (pIV/pSC) in the clinic (mandatory) to obtain 2 trough IgG levels (obtained prior to each pIV/pSC infusion) on each subject’s "previous regimen". For subjects entering study on SCIG, the second IgG trough level may be obtained at Baseline, immediately prior to starting the initial infusion of IGSC 20%.
- The Screening Visit may coincide with the pIV/pSC infusion on the previous regimen (pIV#1/pSC#1). Product for the previous IgG regimen is not provided by Grifols. pIV subjects will be enrolled in IGSC 20% Treatment Stage 1 one week after completion of the last IgG trough sampling in the Previous Regimen Phase and therefore the subject must have 2 minimum concentration (C_{trough}) samples on their pIV **prior** to the Baseline/Week 1 visit. pSC subjects will be enrolled in IGSC 20% Treatment Stage 1 (Baseline) in accordance with the time interval that they are currently receiving SCIG

(i.e., if on a weekly SCIG regimen, Baseline will occur 1 week after completion of the last SCIG infusion and a second IgG trough level will be obtained at Baseline. If the interval between pSC infusions is 2 weeks (or more), then Baseline will occur after that time interval has elapsed, a trough IgG level will be obtained, and the eligible subject may commence IGSC 20% after Baseline assessments are complete).

- Nonconsecutive C_{trough} samples are acceptable for subjects on SCIG. The 4-week time allotment for the Screening/Previous Regimen Phase is necessary in order to ensure Screening human immunodeficiency virus (HIV) nucleic acid amplification technology (NAT) test results will be available before the Baseline Visit/Week 1 visit.

20% IGSC Treatment Stage 1:

- The first dose of the IP, IGSC 20%, will be administered immediately after Baseline assessments are complete (SC#1). Subjects will be infused with IGSC 20% at a 1:1 dose-equivalent regimen (per equation in Section 3.3.2) from their previous regimen at the clinical site (or a minimum IGSC 20% dose of 100 mg/kg/week if the derived 1:1 dose from the previous regimen is lower).
- All subjects will receive 13 IGSC 20% infusions at weekly intervals and study visits at the clinical site will occur at Baseline/SC#1, SC#2, #3, #5, #9, and #13. IgG trough blood levels will be measured at all of these visits (except SC#3) occurring at the clinical site. All other doses of IGSC 20% may be infused at home (once properly trained) or in the clinic.
- The mg/kg dose of IGSC 20% (ratio of mg per kg) will be adjusted at clinic visits if the trough level in subjects is below 500 mg/dL, since this level is considered as insufficient to protect against SBI; the goal is to avoid repeated dose adjustments. The precise dose adjustment (mg/kg) should not be more than a 15% to 20% increase from the dose producing the low IgG trough, per the Investigator's discretion. Any dose adjustments beyond this range will be completed in consultation with the Grifols Medical Monitor. The Treatment Stage 1 dose will continue into IGSC 20% Treatment Stage 2. After the 13th IGSC 20% infusion in IGSC 20% Treatment Stage 1, subjects will enter IGSC 20% Treatment Stage 2 to receive an additional 39 weeks of IGSC 20% therapy.

IGSC 20% Treatment Stage 2:

- In this treatment stage, the IGSC 20% dose (mg/kg) will remain constant with no dose adjustment permitted unless it is absolutely medically necessary to change the dose, and such change requires prior consultation with the Grifols Medical Monitor. Weight will be measured at every in-clinic visit and dosing will be based on the subject's most current weight. For the subsequent at home IGSC 20% infusions between clinic visits, the dose will be the same as the total infusion dose calculated at the previous clinic study visit where weight was measured at the clinical site.
- While all subjects will have an SC#17 clinic visit and associated standard assessments, serial PK sampling will be performed only in a subset of subjects: At SC#17, PK profiles in the first (where possible) 20 adult subjects will be measured by obtaining blood draws

for steady-state PK analyses over a period of 7 days just prior to and post the 17th IGSC 20% infusion through SC#18. These subjects will constitute the PK subset in this study.

- Where possible, the PK subset will comprise the first 20 adult subjects enrolled. Any designated PK subject who undergoes a dose adjustment (mg/kg change in dose) at or after the ninth IGSC 20% infusion (SC#9) which corresponds to at or after Week 9 in Treatment Stage 1 will be permitted to remain in the study, though he/she will not participate in PK profiling; however, an additional PK replacement subject may be recruited.
- Similarly, PK subjects who do not complete the full PK profile may be replaced if deemed necessary.

A total of 52 doses of IGSC 20% will be administered (13 doses of IGSC 20% in Treatment Stage 1 and 39 doses of IGSC 20% in Treatment Stage 2) with a final follow-up visit at Week 53 one week after the last dose at Week 52.

Final Visit (Week 53)/Early Termination Visit

One week post last SC infusion of IGSC 20%, a Final Visit will occur. If a subject discontinues at any point during the study after Baseline, the subject will be requested to return to the Investigator's study site for Final Visit/Early Termination Visit (Appendix 1).

Key Assessments and Procedures:

The primary efficacy variable, SBI, is defined as described in Appendix 3.

IgG trough levels will be measured at least twice during the Screening/Previous Regimen Phase, and Baseline as detailed in Appendix 1 and Figure 3-1, just prior to the second IGSC 20% weekly infusion, at the SC#5 Visit, and then about every 4 weeks.

At SC#17, PK profiles in approximately 20 adult subjects will be measured by obtaining blood draws for steady-state PK analyses over a period of 7 days just prior to and post the 17th IGSC 20% infusion as detailed in Appendix 2. An SC infusion diary will be provided to each subject at the Baseline visit which may be used to record items including but not limited to: local infusion site reactions, concomitant medications (including antibiotics [prophylactic and therapeutic]), and details of SC drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). The SC infusion diary will also be used to record days of missed work/school/daily activities due to infections and related treatment.

Duration of Treatment:

The duration of the IGSC 20% treatment periods of the study is 12 months. A total of 52 doses of IGSC 20% will be administered (13 doses of IGSC 20% in Treatment Stage 1 and 39 doses of IGSC 20% in Treatment Stage 2).

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria:

A subject must meet all the following inclusion criteria to be eligible for participation in this study.

1. Adults and adolescents between the ages of 2 and 75 years (inclusive) at Screening.
2. Documented and confirmed pre-existing diagnosis of PI with features of hypogammaglobulinemia requiring IgG replacement therapy including but not limited to the following: humoral-based immunodeficiency syndromes (e.g., X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (e.g., hyper-immunoglobulin M [IgM] immunodeficiency syndrome). Please also refer to Exclusion Criteria.
3. The subject has not had an SBI within the last 3 months prior to Screening and has no SBIs up to the time of the Baseline Visit.

   Note: If an SBI occurs during the Screening/Previous Regimen Phase and prior to the first dose of Grifols IGSC 20%, the subject will be a Screen Failure).
4. Currently on IgG replacement therapy (stable regimen [dose and dosing interval] via IV or SC infusion) for ≥ 3 consecutive months. Subjects receiving IVIG prior to study must receive a dosage of at least 200 mg/kg per infusion.
5. Documentation (within previous 6 months) of an IgG trough level of ≥ 500 mg/dL on current IgG replacement therapy regimen.
6. Screening/pre-Baseline trough IgG levels must be ≥ 500 mg/dL.

   Note: If Screening and/or pre-Baseline trough levels (not including pSC#2 trough) are not above this threshold, the subject will be a Screen Failure, but may be re-screened following dose adjustment of their original IgG replacement therapy regimen and maintaining stable dosing for a period of at least 3 consecutive months prior to Screening a second time.
7. The medical records for all subjects should be available to document diagnosis, previous infections, and treatment.
8. The subject has signed an informed consent.

   Note: The subject must sign the informed consent form (ICF) if at least 18 years old; for children of younger age, the subject's parent or legal guardian must sign the ICF and if appropriate/applicable, the subject must sign a child assent form approved by the Institutional Review Board or Ethics Committee (IRB/EC) per their requirements (see Section 7.4).

Exclusion Criteria:

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study.

1. Clinical evidence of any significant acute or chronic disease that, in the opinion of the Investigator, may interfere with successful completion of the trial or place the subject at undue medical risk.

2. The subject has had a known serious adverse reaction to immunoglobulin or any severe anaphylactic reaction to blood or any blood-derived product.
3. The subject has a history of blistering skin disease, clinically significant thrombocytopenia, bleeding disorder, diffuse rash, recurrent skin infections, or other disorders where SC therapy would be contraindicated during the study.
4. The subject has isolated IgG subclass deficiency, isolated specific antibody deficiency disorder, or transient hypogammaglobulinemia of infancy.
5. The subject has known Selective Immunoglobulin A (IgA) Deficiency (with or without antibodies to IgA). (Note: exclusion is for the specific diagnostic entity. It does not exclude other forms of humoral primary immunodeficiency which have decreased IgA in addition to decreased IgG requiring immune globulin [IgG] replacement)**.**
6. Females of childbearing potential who are pregnant, have a positive pregnancy test at Screening (serum) or Baseline (urine) (human chorionic gonadotropin [HCG]-based assay), are breastfeeding, or unwilling to practice a highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device [IUD] or intrauterine system [IUS], condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence) throughout the study.

   Note: True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)
7. The subject has significant proteinuria (dipstick proteinuria ≥ 3+, known urinary protein loss > 1 g/24 hours, or nephrotic syndrome), has a history of acute renal failure, has severe renal impairment (blood urea nitrogen [BUN] or creatinine more than 2.5 times the upper limit of normal [ULN]), and/or is on dialysis.
8. The subject has Screening Visit values of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding 2.5 times the ULN for the expected normal range for the testing laboratory.
9. The subject has hemoglobin < 9 g/dL at Screening.
10. The subject has a known previous infection with or clinical signs and symptoms consistent with current hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
11. The subject has a history of or current diagnosis of deep venous thrombosis or thromboembolism (e.g., myocardial infarction, cerebrovascular accident, or transient ischemic attack); history refers to an incident in the year prior to Screening or 2 episodes over lifetime.
12. The subject is currently receiving anti-coagulation therapy which would make SC administration inadvisable (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [e.g., dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], parenteral anticoagulants [e.g., fondaparinux]).
13. The subject currently has a known hyperviscosity syndrome.
14. The subject has an acquired medical condition that is known to cause secondary immune deficiency, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma,

chronic or recurrent neutropenia (absolute neutrophil count less than 1000/µL [1.0 x 10^9/L]), or human immunodeficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS).

15. The subject is HIV positive by nucleic acid amplification technology (NAT) based on a Screening blood sample. The subject may enter the Previous Regimen Phase while the Screening blood sample is being tested, but will be a Screen Failure and will not undergo Baseline assessments if the HIV result is positive.
16. The subject (if < 18 years of age) has non-controlled arterial hypertension at a level of greater than or equal to the 90th percentile blood pressure (either systolic or diastolic) for their age and height (see Appendix 4) or the adult subject has non-controlled arterial hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg).
17. The subject is receiving any of the following medications: (a) immunosuppressants including chemotherapeutic agents, (b) immunomodulators, (c) long-term systemic corticosteroids defined as daily dose > 1 mg of prednisone equivalent/kg/day for > 30 days.

    Note: Intermittent courses of corticosteroids of not more than 10 days would not exclude a subject. Inhaled or topical corticosteroids are allowed.
18. The subject has known substance or prescription drug abuse.
19. The subject has participated in another clinical trial within 30 days prior to Screening (observational studies without investigative treatments [non-interventional] are permitted) or has received any investigational blood product, with the exception of other IgG products, within the previous 3 months.
20. The subject/caregiver is unwilling to comply with any aspect of the protocol, including the home SC infusions, blood sampling, and completion of an SC infusion diary for the duration of the study.
21. Mentally challenged subjects who cannot give independent informed consent.
22. In the opinion of the Investigator, the subject may have compliance problems with the protocol and the procedures of the protocol.

Investigational Product, Dose, and Mode of Administration:

The investigational product is Grifols Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) which is a sterile liquid formulation of immunoglobulin that has been purified from human plasma via a multi-step process.

The IGSC 20% mg/kg/week dose to be utilized during Treatment Stage 1 will be calculated based on the subject's prior (pre-study) pIV or pSC replacement regimen with a 1-to-1 (1:1) correspondence in dosage and a minimum dose of IGSC 20% of 100 mg/kg/week. During Treatment Stage 1, adjustment in the dose of IGSC 20% will be made if IgG C_{trough} is less than 500 mg/dL.

The IV regimen to IGSC 20% dose conversion calculation formula is:

$$\frac{\geq 200 \text{ mg/kg (pIV dose)}}{3 \text{ or } 4 \text{ (previous pIV dosing interval in weeks between infusions)}}$$

The alternative SC regimen to IGSC 20% dose conversion calculation formula is:

$$\frac{\text{pSC dose mg/kg}}{\text{previous pSC dosing interval in weeks between infusions}}$$

For subjects on another SCIG regimen at study entry, if the dose is given weekly, the dose of IGSC 20% will be the same. However, if the pre-study SC regimen is dosed over a longer time interval, that dose will be divided by the number of weeks between doses to provide the IGSC 20% dose per week (see protocol Section 3.3.2). The minimum dose for IGSC 20% for either case of transition is 100 mg/kg/week.

During Treatment Stage 2, the mg/kg body weight dose of IGSC 20% is to be kept constant unless it is absolutely medically necessary to change the dose, and such change requires prior consultation with the Grifols Medical Monitor. Weight will be measured at every in-clinic visit and dosing will be based on the subject's current weight.

This is an open-label study.

Study Variables:

Efficacy and Pharmacokinetic Variables:

Primary Efficacy Variable

- The primary efficacy variable is the number of SBIs.

Secondary Variables

- Trough concentrations of total IgG of previous regimen during the Screening/Previous Regimen Phase and the IGSC 20% Treatment Stages 1 and 2
- Rate of infection of any kind (serious and non-serious) including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, and infectious diarrhea, which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "is this an infection?" (verbatim term delineating nature of infection).
- Number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic, and therapeutic). Use of prophylactic antibiotics will be distinguished from antibiotics for treatment of acute infection
- Number of hospitalizations due to infection
- Number of days of work/school/daily activities missed per subject year due to infections and their treatment

Other Variables

- Trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4) in specific pre-dose blood samples in all subjects
- Antibody levels for *Streptococcus pneumoniae, Hemophilus influenzae*, and *Clostridium tetani* (tetanus)
- PK profile for total IgG (area under the concentration-time curve from 0 to 7 days [$AUC_{0\text{-}7\ days}$], maximum concentration [C_{max}], and time to reach C_{max} [t_{max}]) in adult PI subjects at steady state (after approximately 4 months [16 weeks]) of weekly administration of IGSC 20%
- Trough measles antibody titers (functional assay) are an exploratory variable for informational purposes
- Number of validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, or diagnostic testing for microorganisms (e.g., bacterial, viral, fungal, or protozoal pathogens [for instance, rapid streptococcal antigen test])

Safety Variables:

- Adverse events (AEs), suspected adverse drug reactions (suspected ADRs), serious AEs (SAEs), and discontinuations due to AEs and SAEs

  Note: All local infusion site reactions will be recorded in the eCRF. The subset of local infusion site reactions where-the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator will be considered as AEs.
- Vital signs during clinic visits (temperature [T], respiratory rate [RR], heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]).
- Physical assessments: physical exams will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded.
- Laboratory assessments including chemistry, hematology, and urinalysis

Adverse Event Management

Subjects will be carefully monitored for AEs. This monitoring includes clinical and laboratory tests and physical signs. Adverse events should be assessed in terms of their seriousness, severity, and causal relationship to the IP.

Any AE that occurs at any time between the signature of the ICF and last day of the subject's participation in the clinical trial must be reported and recorded in the AE eCRF.

For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE, the time of onset of the AE and the time of AE change materially in intensity and/or resolve will be captured in the eCRF.

In so far as is possible, all individuals will be followed up until the AE or suspected ADR has resolved. If an AE/suspected ADR/SAE is present when the subject has completed the study,

the course of the event must be followed until the final outcome is known, or the event has been stabilized and no further change is expected and the Investigator decides that no further follow-up is necessary.

Any pregnancy must be followed by the Investigator until delivery or to the end of pregnancy.

Statistical and Analytical Methods:

Determination of Sample Size

Assuming that the true rate of the SBIs is 0.25 per subject per year, 40 subjects treated for one year for IGSC 20% will provide at least 90% power to reject the null hypothesis of an SBI rate greater than or equal to 1.0 per person per year, using a one-sided test at the 0.01 level.

In order to obtain a total of 40 PI subjects including 20 adult and 20 pediatric subjects who complete the study, approximately 60 subjects will be enrolled and treated in the study. This sample size is to allow for a moderate to high early discontinuation rate seen in other similar studies.

Safety Population

The safety population will include all subjects who have received any amount of IGSC 20% and will be used for safety analyses.

Efficacy Evaluable Population

The efficacy evaluable population will include all subjects who have received at least one dose of IGSC 20% and will be used for efficacy analyses.

IgG Population

The IgG population will consist of all subjects who receive any amount of IGSC 20% and have total IgG concentration data to facilitate the comparison of mean trough IgG concentration during the IGSC 20% stage versus the pre-treatment phase.

Pharmacokinetic Population

The PK population will consist of all adult subjects who have received IGSC 20% and have sufficient serial IgG concentration versus time data to facilitate calculation of area under the concentration vs. time curve (AUC) PK parameters.

Primary Efficacy Analyses

The primary efficacy variable of SBIs will be analyzed using the efficacy evaluable population.

The number of SBIs from Week 1 to Week 53 during IGSC 20% treatment period and percentage of subjects with SBIs will be summarized. The SBI rate will be compared to the recommended standard rate of 1 SBI per person per year. The following hypothesis testing is

performed with one-sided test at alpha = 0.01 level:

$$H_0 : \lambda \geq 1 \; SBI \; per \; person \; per \; year$$

versus

$$H_A : \lambda < 1 \; SBI \; per \; person \; per \; year$$

Where λ is the SBI rate during IGSC 20% treatment. Occurrence of SBI is assumed to follow the Poisson distribution. The generalized linear model procedure for Poisson regression with log link will be used to estimate the SBI rate for IGSC 20% and its one-sided 99% upper confidence bound. Person-year will be calculated for each subject and will be used in the generalized linear model as offset variable. No covariates but the intercept term are included in the model. The estimated intercept term and the upper limit of its confidence interval (CI) will be transformed by using the natural exponential function.

Secondary and Other Efficacy Analysis

Secondary and other efficacy variables (except the PK variables [discussed below]) will be summarized descriptively. Annualized rate of all infections, days of missed work/school/daily activities, days on antibiotics, and hospitalizations will be calculated and the 95% CI will be provided.

Pharmacokinetic Analysis

Trough concentrations of total IgG during the Screening/Previous Regimen Phase and the IGSC 20% Treatment Stage will be summarized by week for the efficacy evaluable population. Mean trough for IGSC 20% treatment phase will be calculated as the average of all steady state trough concentrations measured during the IGSC 20% Treatment Stage 2 (i.e., IgG trough levels measured at the following visits: SC#17, #20, #24, #28, #32, #36, #40, #44, #48, #52, and #53). Comparison will be made to the mean of 2 troughs for previous IgG treatment (either IVIG or other SCIG products) obtained from the Screening/Previous Regimen Phase. Mean trough data will be summarized. Mean trough summary and analysis will be based on the IgG population.

For samples collected after SC#14 infusion (start of Treatment Stage 2), total IgG concentrations will be summarized by time point. For subjects in the PK subset with an IgG PK profile, individual and mean/median IgG concentrations versus time curves will be plotted. PK parameters for total IgG including $AUC_{0\text{-}7days}$, C_{max}, and t_{max} will be determined by noncompartmental model using WinNonlin software. All PK parameters will be tabulated and summarized descriptively. The analyses will be based on the PK population.

Summaries will be provided for average trough concentration of IgG subclasses (Screening, Baseline, before the 13th, 24th, 36th IGSC 20% infusion, and Final Visit). Summaries of average trough level concentration of antibody titers *S. pneumoniae, H. influenzae,* and *C. tetani* (tetanus) will also be provided.

Trough measles antibody titers (functional assay) are an exploratory variable for

informational purposes.

Safety Analysis

- The safety analyses are based on the safety population.
- All AEs, suspected ADRs, SAEs, and discontinuations due to AEs and SAEs will be summarized by presenting the number of events and the number and percentage of subjects with events. The summaries will be presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. AE summaries by severity will also be provided. Local infusion site reactions will be similarly summarized.
- Subjects with deaths, SAEs, and AEs leading to premature discontinuation from the study will be listed and presented in a narrative form.
- Adverse events temporally associated with SC administration of study drug will be defined as those occurring during or within 72 hours of completion of an infusion.
- Local infusion site reactions will be tabulated and summarized for the total duration of the study and by IGSC 20% infusion week.
- For all laboratory tests and vital signs, the original value and the change from baseline will be summarized for numeric results and frequency/percentage will be summarized for qualitative results. For laboratory tests with normal ranges, out of normal range values will be flagged and shift tables will be provided.

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GLOSSARY AND ABBREVIATIONS

°C	Degrees Celsius
°F	Degrees Fahrenheit
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARC	Absolute reticulocyte count
AST	Aspartate aminotransferase
AUC	Area under the concentration vs. time curve
$AUC_{0\text{-}7days}$	Area under the concentration-time curve from 0 to 7 days
B19V	Parvovirus B19
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
C_{trough}	Minimum concentration
CI	Confidence interval
CRO	Contract research organization
CSF	Cerebrospinal fluid
CXR	Chest X-ray
DAT	Direct antiglobulin test
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH GCP	International Conference on Harmonization Good Clinical Practice
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGIV-C 10%	Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified (Grifols)
IgM	Immunoglobulin M
IGSC 20%	Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (Grifols)
IM	Intramuscular
IP	Investigational product
IRB/EC	Institutional Review Board/Ethics Committee
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVIG	Intravenous Immune Globulin (generic terminology)
kg	Kilogram
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
NAT	Nucleic acid amplification technology
p	Used as a prefix pIV or pSC to denote prior (pre-study) immune globulin replacement regimen
pH	Potential of hydrogen; acidity/alkalinity measure
PI	Primary immunodeficiency
PK	Pharmacokinetics
RNA	Ribonucleic acid
RR	Respiratory rate
SAE	Serious adverse event
SBI	Serious bacterial infection

SBP	Systolic blood pressure
SC	Subcutaneous
SCIG	Subcutaneously delivered immune globulin or subcutaneous immunoglobulin (generic terminology)
SD	Standard deviation
T	Temperature
t_{max}	Time to reach C_{max}
TEAE	Treatment-emergent adverse event
US	United States
WBC	White blood cell

1 INTRODUCTION

1.1 Primary Immunodeficiency

Primary Immunodeficiency (PI) diseases are a family of congenital disorders of the immune system that lead to an increase in frequency of infections, notably, but not limited to, bacterial infections of the respiratory tract (1). Results from a recent study suggest that in the United States (US) alone 1 in 2,000 children and 1 in 1,200 persons (including adults and children) are diagnosed with PI, yielding a total US PI patient population estimate of approximately 250,000 adults and children (2). Worldwide upper estimates suggest that six million people (638,000 in Europe) may be living with a PI, although orders of magnitude fewer patients have been identified in registries (3). Patients with inherited deficiencies leading to impaired humoral immunity are highly susceptible to a wide range of infections, most commonly bacterial infections. The efficacy of immunoglobulin G (IgG) replacement in the treatment of these disorders has been well established (4,5) since 1952 when the use of serum globulin fraction was reported to reduce the frequency of infections in a patient with agammaglobulinemia. The therapeutic management of PI has been carried out via intramuscular (IM), intravenous (IV), and subcutaneous (SC) injections of various IgG preparations (6,7).

1.2 Immunoglobulin Replacement Therapy

Despite its widespread use, the infusion of IV immune globulin (IVIG) is problematic in some patients, especially those who have poor venous access or develop systemic adverse events (AEs), such as headaches, fever, chills, or myalgias from this route of administration (8,9). In children, difficulty in obtaining venous access can prevent or delay IVIG therapy (7,10,11). Over the last several years subcutaneously delivered immune globulin (SCIG) has been developed for administration in the home setting for treatment of PI and has become accepted in the clinical setting (10,11,12).

The results of several adult PI studies with SCIG products have shown good efficacy of replacement therapy and control of bacterial infections (13,14,15). Additionally, the results of several pediatric studies also showed that SC infusion of IgG in children (ages 1-15 years) at home was feasible and safe and also resulted in maintenance of the IgG levels above 500 mg/dL (12,16,17), a level that is considered as sufficient to protect against serious bacterial infection (SBI) in adults and pediatric PI patients. It is now generally accepted that repeated SC infusions of IgG cause few, if any, adverse systemic reactions, and for some patients, including children, the SC route has become a preferred route of administration (8,18-29).

Advantages of home-based SCIG infusions in adults and children with PI include treatment satisfaction and quality-of-life improvement, specifically, greater independence, better control of the therapy situation, and an overall improvement in daily life afforded by home-based therapy. Moreover, the technique involved is deemed easy to learn by adults and children (6,7,24,30).

1.3 Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%)

The investigational product (IP) is Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%), Grifols company designation GRF6017. Henceforth in this document this product will be referred to as IGSC 20%, which is a sterile liquid formulation containing 20% human immune globulin formulated in 0.16-0.26 M glycine and 10-40 parts per million polysorbate 80 at pH 4.1-4.8.

Grifols IGSC 20% is a 20% solution of purified human immunoglobulin (primarily IgG) made from large pools of human plasma via modifications of the Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified (IGIV-C 10%) manufacturing process. The IGIV-C 10% process is licensed under BLA 125046 in the US (trade name Gamunex®-C which is a 10% IgG product), in Europe (Gamunex®), and in a number of other countries around the world.

In addition to the information provided here, please also refer to the IGSC 20% Investigator's Brochure (IB).

1.4 Study Rationale and Dose Selection

1.4.1 Study Rationale

IVIG infusions produce an immediate rise in the serum IgG levels with marked peak levels which gradually decline as the IgG redistributes, equilibration takes place, and the IgG moves into the extravascular space over the typical 3 to 4 week IV dosing regimen period. The IgG decay occurs with first order kinetics over a period of approximately 3-4 weeks (18,31). Consequently the patient experiences substantial IgG concentration variations rather than a steady IgG level throughout the IV dosing period. Maintenance of higher IgG trough levels may benefit patients receiving IgG via the SC route at more frequent intervals (18).

Recent studies with SCIG regimens have documented higher and more constant IgG trough levels with lower IgG peak levels despite the fact that the SC dosing regimen is typically at a lower dose per infusion (yet equates to an equivalent IVIG total monthly dose), using more frequent dosing. The SCIG regimen results in much less variability in IgG levels, and higher and more consistent trough levels when compared to the IVIG regimens (32). One possible reason for the stable blood concentrations is that the SC infused IgG probably remains in the SC fat layer as a depot with a slow and continuous release into the circulatory system (6) in addition to the increased frequency of dosing. It has been reported that the uptake of the antibodies from SC tissue is high and the antibodies are not locally destroyed (18,33), which results in IgG reaching the circulation intact.

Several SCIG products, ranging in protein IgG concentrations from 10% to 20%, are currently being used to treat PI most commonly by either weekly or biweekly administration. IGIV-C 10%, a 10% immunoglobulin product, is licensed in the US and some other countries (e.g., IGIVnex in Canada) for both IV and SC administration. The advantages of higher

concentration SCIG products (20%) are primarily significantly reduced infusion volume and shorter infusion time thereby significantly increasing ease of administration.

The primary objective of this trial is to assess the overall incidence of SBI per subject per year (as defined in the Food and Drug Administration [FDA] Guidance 2008 and European Medicines Agency [EMA] Guidance 2012 [34,35]) using a dose-equivalent dosing regimen for the IP, IGSC 20%, which is common clinical practice in the US and EMA regions. Thus, the data obtained from this trial will be relevant and directly applicable to treaters with regard to efficacy and safety of IGSC 20% in subjects aged 2 years to 75 years inclusive. The duration of the treatment period of the study is 12 months in order to avoid seasonal bias (34,35). Pharmacokinetic (PK) data will be obtained at steady state from a subset of approximately 20 adult (> 16 years) subjects after approximately 4 months (16 weeks) of IGSC 20% dosing.

1.4.2 Dose Rationale

IGIV-C 10% (10% final IgG concentration) is currently approved for SC administration in PI in various geographies. Study 060001 showed that weekly SC administration in 32 adult PI subjects (including 3 adolescent subjects) resulted in a relatively constant steady-state trough plasma concentration of total IgG (1140 mg/dL). There were no SBIs reported in the 24 week SC treatment period (36). In a recently completed pediatric study (T5004-4001), weekly SC administration of IGIV-C 10% in 11 pediatric subjects (age range 4-15 years) also resulted in relatively constant steady-state trough plasma concentration of total IgG (1330 mg/dL). There was no SBI reported in the 12 weeks of the SC treatment period. These results demonstrated that IGIV-C 10% treatment provided protection against SBIs when administered via the SC route of administration.

A dose-equivalent strategy is being utilized for the IGSC 20% product in order to maintain the overall monthly IgG dose for subjects based on their previous regimen (IVIG or SCIG). It is known that physicians commonly optimize each subject's IgG dose based on IgG trough levels, as well as clinical signs and symptoms of PI, and thus the intent of this study is to maintain each subject's monthly dose of IgG. This dose-equivalent rationale is also based on results from several well-controlled clinical trials where dose-equivalent SCIG regimens were studied in patients with PI (reviewed in 14,19,26,27,32,37,38). All of these studies resulted in IgG trough levels on the SCIG regimen slightly higher than the previous IVIG regimens without any loss of efficacy in preventing SBIs as illustrated in Table 1-1 (14,27,37,39).

Table 1-1 Summary of IgG Trough Levels from 1:1 IV to SC Dosing Regimen Studies

Reference	Product	N	Mean pre-IV trough level (mg/dL)[b]	Time Point for SC IgG trough	Mean SC trough level (mg/dL)[b]	% Change in Trough (SC/IV)	Annualized SBI rate
Gardulf[27] (2006)	16% SCIG (Vivaglobin)	n=15 on prior IVIG age 2-11	780	Weeks 16-43	920	18%	0.04
		n=27 on prior IVIG adults	860		890	3.5%	
Borte[39] (2011)[a]	20% SCIG (Hizentra)	n=11 on prior IVIG age 2-11	647	Primary efficacy IgG trough infusions 12-17	792	22%	0.0
		n=1 on prior IVIG adolescents	not provided		not provided	---	
		n=13 on prior IVIG adults	715		814	14%	
Jolles[14] (2011)[a]	20% SCIG (Hizentra)	n=27 on prior IVIG	678		798	18%	
Desai[37] (2009)	10% SCIG (Gamunex)	n=11 age 5-59	1079	6 months	1160	8%	0.09

Note: For studies by Gardulf et al., Borte et al., and Jolles et al., the data presented are from a subset who received IVIG initially. In the Desai et al. publication, all patients initially received IVIG.

[a] The Borte et al. and Jolles et al. publications represent different presentations of data from the same Phase 3 study of Hizentra; the publication by Jolles et al. 2011 does not summarize the pediatric and adult subjects separately whilst Borte et al. present data by age group with in-text detail regarding the subset entering study on IVIG.

[b] For consistency within this table for cross-study comparison, this table uses units of mg/dL; however publications may have used other units such as g/L.

All of the studies summarized in Table 1-1 resulted in IgG trough levels on an SCIG regimen higher than the previous IVIG regimens, with a range of increase on SCIG regimen from 4% to 22% when compared to previous IV regimen. In addition, there was no loss of efficacy in preventing SBIs (range from 0.0 to 0.09 annualized SBI rate). Accordingly, dose-equivalent dosing (1:1 IV to SC [i.e., with no dose conversion factor]) will be employed in this study with a minimum dose of IGSC 20% set at 100 mg/kg/week.

2 STUDY OBJECTIVES

2.1 Efficacy and Pharmacokinetic Objectives

2.1.1 Primary Efficacy Objective

The primary objective of this Phase 3 study is to evaluate whether weekly administered IGSC 20% over a one year period will achieve less than 1 SBI per subject per year in PI subjects.

2.1.2 Secondary Objectives

- To determine if IGSC 20% replacement therapy maintains mean trough IgG levels that are comparable to the mean trough blood levels with the previous IgG replacement regimen
- To evaluate all infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator
- To evaluate number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic, and therapeutic). Use of prophylactic antibiotics will be distinguished from antibiotics for treatment of acute infection.
- To evaluate number of hospitalizations due to infection
- To evaluate number of days of work/school/daily activities missed per subject year due to infections and related treatment

2.1.3 Other Objectives

- To evaluate trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- To evaluate antibody levels for *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Clostridium tetani* (tetanus)
- To evaluate the PK profile for total IgG (area under the concentration-time curve from 0 to 7 days [$AUC_{0\text{-}7\ days}$], maximum concentration [C_{max}], and time to reach C_{max} [t_{max}]) in adult PI subjects at steady state (after approximately 4 months [16 weeks]) of weekly administration of IGSC 20%
- Trough measles antibody titers (functional assay) are an exploratory variable for informational purposes

- To evaluate validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test).

2.2 Safety Objectives

- To assess the safety and tolerability of IGSC 20% as an IgG replacement therapy in subjects with PI.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Plan

This is a prospective, multi-center, open-label, single-arm, efficacy, PK, safety and tolerability study of IGSC 20% in subjects with PI. Approximately 60 subjects will be enrolled in order to have approximately 20 adult subjects and 20 pediatric subjects treated with subcutaneously administered IGSC 20% who complete the entire study. This study will include 3 study stages: Screening/Previous Regimen Phase, IGSC 20% Treatment Stage 1 (13 IGSC 20% weekly doses), and IGSC 20% Treatment Stage 2 (39 IGSC 20% weekly doses).

Subjects who are receiving IVIG at a dose of at least 200 mg/kg per infusion every 3 or 4 weeks at Screening must be on a stable IgG regimen (dose and dosing interval) for at least 3 consecutive months prior to Screening. Subjects who are receiving SCIG must also be on a stable regimen for at least 3 consecutive months prior to Screening; there is no prerequisite minimum dose for subjects entering study on an SCIG regimen. Subjects who have never received IVIG or SCIG treatment (treatment naïve) will not be eligible for entry into the study.

Previous Regimen Phase:

- Subjects will be infused with their current ongoing ("previous regimen") IVIG/SCIG regimen (pIV/pSC) in the clinic (mandatory) to obtain 2 trough IgG levels (obtained prior to each pIV/pSC infusion) on each subject's "previous regimen". For subjects entering study on SCIG, the second IgG trough level may be obtained at Baseline, immediately prior to starting the initial infusion of IGSC 20%.
- The Screening Visit may coincide with the pIV/pSC infusion on the previous regimen (pIV#1/pSC#1). Product for the previous IgG regimen is not provided by Grifols. pIV subjects will be enrolled in IGSC 20% Treatment Stage 1 one week after completion of the last IgG trough sampling in the Previous Regimen Phase and therefore the subject must have 2 minimum concentration (C_{trough}) samples on their pIV **prior** to the Baseline/Week 1 visit. pSC subjects will be enrolled in IGSC 20% Treatment Stage 1 (Baseline) in accordance with the time interval that they are currently receiving SCIG (i.e., if on a weekly SCIG regimen, Baseline will occur 1 week after completion of the

last SCIG infusion and a second IgG trough level will be obtained at Baseline. If the interval between pSC infusions is 2 weeks (or more), then Baseline will occur after that time interval has elapsed, a trough IgG level will be obtained, and the eligible subject may commence IGSC 20% after Baseline assessments are complete).

- Nonconsecutive C_{trough} samples are acceptable for subjects on SCIG. A minimum of 10 days is anticipated for the Screening/Previous Regimen Phase to ensure Screening human immunodeficiency virus (HIV) nucleic acid amplification technology (NAT) test results will be available before the Baseline Visit/Week 1 visit.

20% IGSC Treatment Stage 1:

- The first dose of the IP, IGSC 20%, will be administered immediately after Baseline assessments are complete (SC#1). Subjects will be infused with IGSC 20% at a 1:1 dose-equivalent regimen (per equation in Section 3.3.2) from their previous regimen at the clinical site (or a minimum IGSC 20% dose of 100 mg/kg/week if the derived 1:1 dose from the previous regimen is lower).
- All subjects will receive 13 IGSC 20% infusions at weekly intervals and study visits at the clinical site will occur at Baseline/SC#1, SC#2, #3, #5, #9, and #13. IgG trough blood levels will be measured at all of these visits (except SC#3) occurring at the clinical site. All other doses of IGSC 20% may be infused at home (once properly trained) or in the clinic.
- The mg/kg dose of IGSC 20% (ratio of mg per kg) will be adjusted at clinic visits if the trough level in subjects is below 500 mg/dL, a level that is considered as insufficient to protect against SBI (40-43); the goal is to avoid repeated dose adjustments. The precise dose adjustment (mg/kg) should not be more than a 15% to 20% increase from the dose producing low IgG trough, per the Investigator's discretion. Any dose adjustments beyond this range will be completed in consultation with the Grifols Medical Monitor. The Treatment Stage 1 dose will continue into IGSC 20% Treatment Stage 2. After the 13th IGSC 20% infusion in IGSC 20% Treatment Stage 1, subjects will enter IGSC 20% Treatment Stage 2 to receive an additional 39 weeks of IGSC 20% therapy.

IGSC 20% Treatment Stage 2:

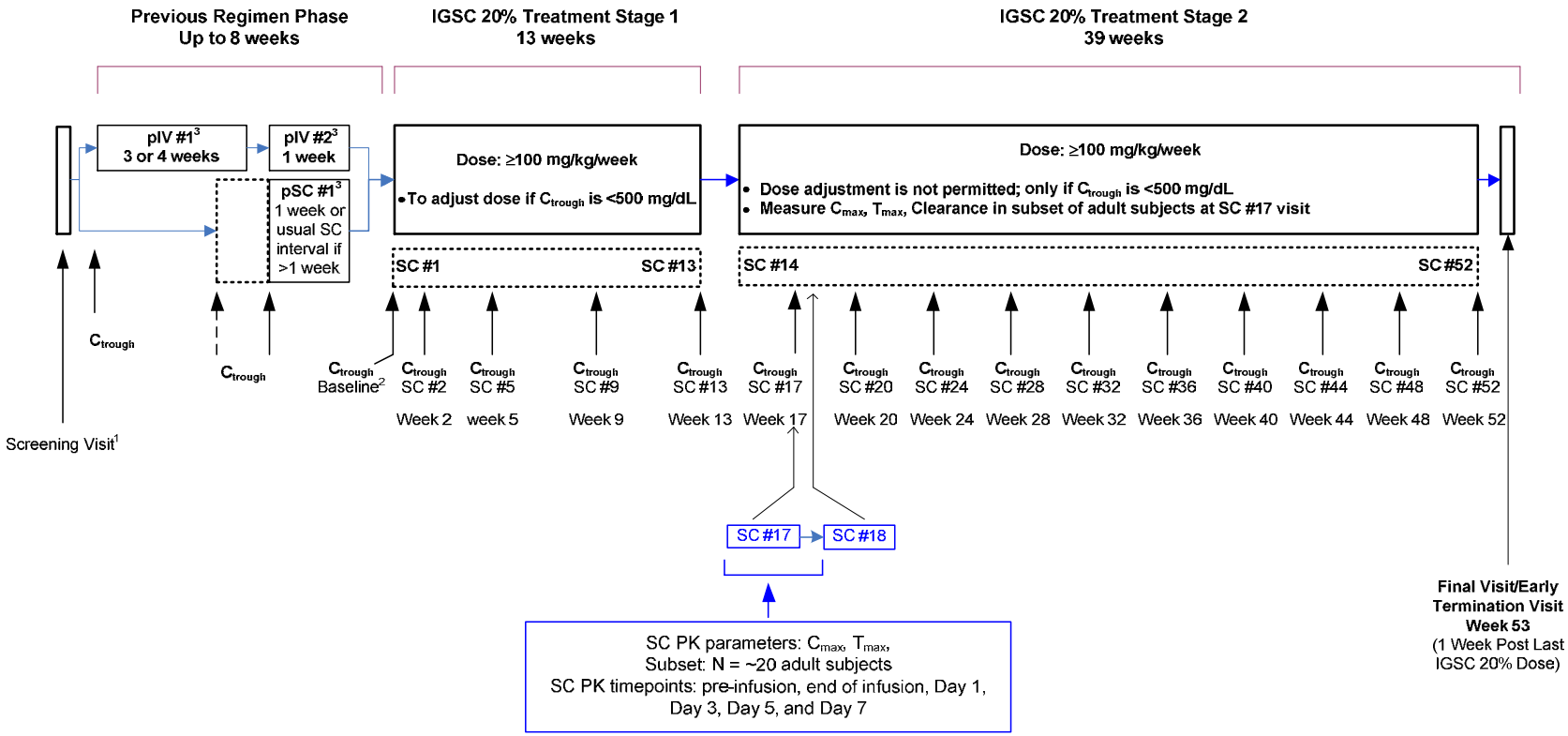
- The IGSC 20% dose (mg/kg) will remain constant with no dose adjustment permitted in this phase, unless it is absolutely medically necessary to change the dose, and such change requires prior consultation with the Grifols Medical Monitor. Weight will be measured at every in-clinic visit and dosing will be based on the subject's most current weight. For the subsequent at home IGSC 20% infusions between clinic visits, the dose will be the same as the total infusion dose calculated at the previous clinic study visit where weight was measured at the clinical site.
- While all subjects will have a SC#17 clinic visit and standard assessments, serial PK sampling will only be performed in a subset of adult subjects: At SC#17, PK profiles in the first (where possible) 20 adult subjects, will be measured by obtaining blood draws

for steady-state PK analyses over a period of 7 days just prior to and post the 17th IGSC 20% infusion through SC#18. These subjects will constitute the PK subset in this study.

- Where possible, the PK subset will comprise the first 20 adult subjects enrolled. Any designated PK subject who undergoes a dose adjustment (mg/kg change in dose) at or after the ninth IGSC 20% infusion (SC#9) which corresponds to at or after Week 9 Treatment Stage 1 will be permitted to continue within the study, though he/she will not participate in PK profiling; however, an additional PK replacement subject may be recruited.
- Similarly, PK subjects who do not complete the full PK profile may be replaced if deemed necessary.

A total of 52 doses of IGSC 20% will be administered (13 doses of IGSC 20% in Treatment Stage 1 and 39 doses of IGSC 20% in Treatment Stage 2) with a final follow-up visit at Week 53 one week after the last dose at Week 52.

The overall study schema and the specific time points for PK sampling for Previous Regimen Phase and IGSC 20% Treatment Stages are outlined in Figure 3-1, and the schedule of study procedures is provided in Appendix 1 with PK details in Appendix 2. Appendix 3 provides definitions for the primary endpoint variable, SBIs.



[1] Screening Visit may coincide with the first IV infusion on previous regimen

[2] C_{trough} at baseline (prior to the first IGSC 20% infusion) is also the second trough level of IgG for the previous SC regimen

[3] pIV or pSC indicates the previous regimen (only in the Previous Regimen Phase)

Note: Clinical visits for all subjects include Screening Visit, Final Visit, and all time points designated by C_{trough} as shown above.

Figure 3-1 Overall Study Schema

3.2 Selection of Study Population

Eligible participants for this study include male or female subjects who are 2 to 75 years of age and have a diagnosis of PI requiring IgG replacement treatment. Subjects who initially fail to meet eligibility criteria may be re-screened once upon consultation with the Medical Monitor. Subjects who fail to meet eligibility criteria upon re-screen are Screen Failures and will not be eligible to participate in the study.

3.2.1 Inclusion Criteria

A subject must meet all the following inclusion criteria to be eligible for participation in this study:

1. Adults and adolescents between the ages of 2 and 75 years (inclusive) at Screening.
2. Documented and confirmed pre-existing diagnosis of PI with features of hypogammaglobulinemia requiring IgG replacement therapy including but not limited to the following: humoral-based immunodeficiency syndromes (e.g., X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (e.g., hyper-immunoglobin [IgM] immunodeficiency syndrome). Please also refer to Exclusion Criteria.
3. The subject has not had an SBI within the last 3 months prior to Screening and has no SBI up to the time of the Baseline Visit.

   Note: if an SBI occurs during the Screening/Previous Regimen Phase and prior to the first dose of Grifols IGSC 20%, the subject will be a Screen Failure

4. Currently on IgG replacement therapy (stable regimen [dose and dosing interval] via IV or SC infusion) for ≥ 3 consecutive months. Subjects receiving IVIG prior to study must receive a dosage of at least 200 mg/kg per infusion.
5. Documentation (within previous 6 months) of an IgG trough level of ≥ 500 mg/dL on current IgG replacement therapy regimen.
6. Screening/pre-Baseline trough IgG levels must be ≥ 500 mg/dL.

   Note: If Screening and/or pre-Baseline trough levels (not including pSC#2 trough) are not above this threshold the subject will be a Screen Failure, but may be re-screened following dose adjustment of their original IgG replacement therapy regimen and maintaining stable dosing for a period of at least 3 consecutive months prior to Screening a second time.

7. The medical records for all subjects should be available to document diagnosis, previous infections and treatment.
8. The subject has signed an informed consent.

   Note: The subject must sign the informed consent form (ICF) if at least 18 years old; for children of younger age the subject's parent or legal guardian must sign the ICF and if appropriate/applicable, the subject must sign a Child Assent form approved by the

Institutional Review Board or Ethics Committee (IRB/EC) per their requirements (see Section 7.4).

3.2.2 Exclusion Criteria

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study.

1. Clinical evidence of any significant acute or chronic disease that, in the opinion of the Investigator, may interfere with successful completion of the trial or place the subject at undue medical risk
2. The subject has had a known serious adverse reaction to immunoglobulin or any severe anaphylactic reaction to blood or any blood-derived product
3. The subject has a history of blistering skin disease, clinically significant thrombocytopenia, bleeding disorder, diffuse rash, recurrent skin infections, or other disorders where SC therapy would be contraindicated during the study
4. The subject has isolated IgG subclass deficiency, isolated specific antibody deficiency disorder, or transient hypogammaglobulinemia of infancy.
5. The subject has known Selective Immunoglobulin A (IgA) Deficiency (with or without antibodies to IgA) (Note: exclusion is for the specific diagnostic entity. It does not exclude other forms of humoral primary immunodeficiency which have decreased IgA in addition to decreased IgG requiring immune globulin [IgG] replacement).
6. Females of childbearing potential who are pregnant, have a positive pregnancy test at Screening (serum) or Baseline (urine) (human chorionic gonadotropin [HCG]-based assay), are breastfeeding, or unwilling to practice a highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device [IUD] or intrauterine system [IUS], condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence) throughout the study

   Note: True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)
7. The subject has significant proteinuria (dipstick proteinuria ≥ 3+, known urinary protein loss > 1 g/24 hours, or nephrotic syndrome), has a history of acute renal failure, has severe renal impairment (blood urea nitrogen [BUN] or creatinine more than 2.5 times the upper limit of normal [ULN]), and/or is on dialysis
8. The subject has Screening Visit values of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding 2.5 times the ULN for the expected normal range for the testing laboratory.
9. The subject has hemoglobin < 9 g/dL at Screening
10. The subject has a known previous infection with or clinical signs and symptoms consistent with current hepatitis B virus (HBV) or hepatitis C virus (HCV) infection

11. The subject has a history of or current diagnosis of deep venous thrombosis or thromboembolism (e.g., myocardial infarction, cerebrovascular accident, or transient ischemic attack); history refers to an incident in the year prior to Screening or 2 episodes over lifetime
12. The subject is currently receiving anti-coagulation therapy which would make SC administration inadvisable (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [e.g., dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], parenteral anticoagulants [e.g., fondaparinux]).
13. The subject currently has a known hyperviscosity syndrome
14. The subject has an acquired medical condition that is known to cause secondary immune deficiency, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, chronic or recurrent neutropenia (absolute neutrophil count less than 1000/µL [1.0 x 10^9/L]), or HIV infection/acquired immune deficiency syndrome (AIDS).
15. The subject is HIV positive by NAT based on a Screening blood sample. The subject may enter the Previous Regimen Phase while the Screening blood sample is being tested, but will be a Screen Failure and will not undergo Baseline assessments if the HIV result is positive.
16. The subject (if < 18 years of age) has non-controlled arterial hypertension at a level of greater than or equal to the 90th percentile blood pressure (either systolic or diastolic) for their age and height (see Appendix 4) or the adult subject has non-controlled arterial hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg)
17. The subject is receiving any of the following medications: (a) immunosuppressants including chemotherapeutic agents, (b) immunomodulators, (c) long-term systemic corticosteroids defined as daily dose > 1 mg of prednisone equivalent/kg/day for > 30 days.

    Note: Intermittent courses of corticosteroids of not more than 10 days would not exclude a subject. Inhaled or topical corticosteroids are allowed.
18. The subject has known substance or prescription drug abuse.
19. The subject has participated in another clinical trial within 30 days prior to Screening (observational studies without investigative treatments [non-interventional] are permitted) or has received any investigational blood product, with the exception of other IgG products, within the previous 3 months
20. The subject/caregiver is unwilling to comply with any aspect of the protocol, including the home SC infusions, blood sampling, and completion of an SC infusion diary for the duration of the study
21. Mentally challenged subjects who cannot give independent informed consent
22. In the opinion of the Investigator the subject may have compliance problems with the protocol and the procedures of the protocol.

3.3 Treatments

3.3.1 Treatments to Be Administered

Grifols Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) is a sterile liquid formulation of immunoglobulin that has been purified from human plasma via a multi-step process. IGSC 20% will be supplied in a 50 mL vial size containing a 20% solution of Immune Globulin, i.e., a concentration of 20 g/100 mL, with a nominal 10 grams Immune Globulin per vial.

3.3.2 Selection of Dose and Interval for Each Subject

Screening/Previous Regimen Phase

Subjects will continue their existing ("previous regimen") IVIG or SCIG regimens (pIV or pSC) during the Screening/Previous Regimen Phase. Product for the Screening/Previous Regimen Phase is not provided by Grifols. Each subject's established IVIG or SCIG replacement regimen will not be changed throughout the Previous Regimen Phase. Subjects receiving IVIG prior to Screening must receive a dosage of at least 200 mg/kg per infusion, and all subjects must fulfill IgG trough level eligibility criteria ≥ 500 mg/dL (for subjects receiving SCIG prior to Screening, no minimum dosage is required).

The Previous Regimen Phase will include measurement of 2 IgG C_{trough} levels on the subject's existing IVIG/SCIG treatment regimen. For subjects receiving IVIG, the 2 IgG C_{trough} levels will be obtained prior to each of the 2 IVIG infusions in this Phase (of up to 8 weeks). For subjects receiving SCIG, the 2 IgG C_{trough} levels obtained prior to each of the 2 SC infusions (one week apart or longer interval based on existing previous regimen) will result in a shorter Screening/Previous Regimen Phase time interval of 4 weeks.

All measured C_{trough} levels of IgG drawn pre-Baseline must be ≥ 500 mg/dL for the subject to qualify for Baseline and receipt of study drug (IGSC 20%). If the C_{trough} levels of IgG are < 500 mg/dL on the subject's existing IVIG or SCIG regimen, the subject will be a Screen Failure. However, the subject may be re-screened once after adjustment in their IgG replacement regimen and maintaining stable dosing for 3 months.

IGSC 20% Treatment Stage 1 and Stage 2

Dosing: The IGSC 20% mg/kg/week dose to be utilized during Treatment Stage 1 will be calculated based on the subject's prior (pre-study) pIV or pSC replacement regimen with a 1 to 1 (1:1) correspondence in dosage and a *minimum dose* of IGSC 20% of 100 mg/kg/week. Treatment Stage 1 will commence 7 days after the last IVIG dose or 7 days after the last SC dose of the subject's previous IgG replacement regimen if on a weekly schedule. If SCIG is given on a biweekly schedule, the dosing interval would be 2 weeks (i.e., the timing of start of Treatment Stage 1 will match the SC dosing interval so that the second SCIG C_{trough} can be obtained immediately prior to dosing with IGSC 20%). During Treatment Stage 1, adjustment in the dose (mg/kg) of IGSC 20% (ratio of mg per kg) will be made at clinic visits

if IgG C_{trough} is less than 500 mg/dL so that adequate immunoglobulin levels are attained. The precise IGSC 20% dose adjustment (mg/kg) should not be more than a 15% to 20% increase (relative to the dose producing low IgG trough), per the Investigator's discretion. Any dose adjustments beyond this range will be completed in consultation with the Grifols Medical Monitor.

The IV regimen to IGSC 20% dose conversion calculation formula is:

$$\frac{\geq 200 \text{ mg/kg (pIV dose)}}{\text{3 or 4 (previous pIV dosing interval in weeks between infusions)}}$$

The alternative SC regimen to IGSC 20% dose conversion calculation formula is:

$$\frac{\text{pSC dose mg/kg}}{\text{previous pSC dosing interval in weeks between infusions}}$$

For subjects on another SCIG regimen at study entry, if the dose is given weekly, the dose of IGSC 20% will be the same. However, if the pre-study SC regimen is dosed over a longer time interval, that dose will be divided by the number of weeks between doses to provide the IGSC 20% dose per week. The minimum dose for IGSC 20% for either case of transition is 100 mg/kg/week.

Weight will be measured at every in-clinic visit and dosing will be based on the subject's most current weight. For the subsequent at home IGSC 20% infusions between clinic visits, the dose will be the same as the total infusion dose calculated at the previous clinic study visit where weight was measured at the clinical site.

During Treatment Stage 2, the mg/kg dose of IGSC 20% (ratio of mg per kg) is to be kept constant unless it is absolutely medically necessary to change the dose, and such change requires prior consultation with the Grifols Medical Monitor.

A total of 52 weekly doses of IGSC 20% will be administered with a final visit at Week 53 one week after the last IGSC 20% infusion at Week 52.

3.3.2.1 Labeling of Investigational Product(s)

Grifols IGSC 20% will be labeled according to the requirements of local law and legislation. Label text will be approved according to agreed Grifols Therapeutics Inc. procedures, and a copy of the labels will be made available to the study site upon request.

3.3.2.2 Storage of Investigational Products

IGSC 20% must be stored in a secure area accessible to study personnel authorized by the Investigator, such as the study staff responsible for the preparation and dispensing of investigative product.

IGSC 20% must be stored at temperatures of 2°C to 8°C (36°F to 46°F) and protected from light. Do not freeze or partially freeze. Investigators, or designees, are responsible for maintaining storage temperature records and for immediately reporting deviations in temperature to the study monitor.

Details for the storage are located in the pharmacy manual provided to each site and instructions will also be provided to participating subjects.

3.3.2.3 Preparation

The volume (i.e., total infusion dose administered) of Grifols IGSC 20% to be prepared for each SC infusion will be individualized for each subject based on dose-equivalence with their previous (pre-study) regimen using body weight based dosing (≥ 100 mg/kg/week).

IGSC 20% must be inspected visually before being administered. The solution must not be used if turbid or if it contains visible particles. Solution that has been frozen should not be used. The Investigator, or designee, is responsible for immediately reporting any issues noted with IGSC 20% to the study monitor.

Reference the pharmacy manual/study manual for detailed instructions for IGSC 20% preparation and administration.

3.3.2.4 Accountability for Investigational Product(s)

IGSC 20% is to be used only for the study in accordance with the directions given in this protocol and pharmacy/study manual. The Investigator, or designee such as the study pharmacist, is responsible for the distribution of the IP in accordance with directions given in the protocol and pharmacy manual.

The Investigator, or designee such as the study pharmacist, is responsible for maintaining accurate records of IGSC 20% for his/her site. IP inventory/dispensing documentation verifying the receipt, dispensing, and destruction or return must be maintained and kept current by the Investigator or designee. The inventory must be made available for inspection by the monitor. IGSC 20% supplies must be accounted for by the monitor and inventory/dispensing logs must be verified by the monitor prior to IGSC 20% return or destruction. Written documentation of all used and unused inventory is required. At the end of the study, a copy of the inventory/dispensing log(s) will be retrieved by the monitor and returned to Grifols Therapeutics Inc.

3.3.3 Rationale for Selection of Doses and Dose Interval for Investigational Products in the Study

The IP, IGSC 20%, is a liquid formulation. The planned dosage regimen for use in PI subjects is to use a dose-equivalent strategy (1:1; i.e., with no dose conversion factor) for Grifols IGSC 20% product to maintain the overall monthly IgG dose for the subjects based on their prior (pre-study) IgG replacement regimen (IVIG or SCIG) administered weekly by SC infusion and evaluated over 12 months.

The minimum dose for the IGSC 20% will be set at 100 mg/kg/week. Data and references illustrating comparability of SC weekly replacement therapy utilizing a 1:1 dose conversion are provided in Section 1.4.2 and Table 1-1 .

The weekly dose of IGSC 20% (mg/kg) will be adjusted in Treatment Stage 1 if the trough IgG blood level in subjects is below 500 mg/dL, which is considered as insufficient to protect against SBI.

Subjects in this study will receive a total of 52 weekly SC infusions of IGSC 20%.

3.3.4 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study; all subjects will receive the same IP (IGSC 20%) via SC infusion.

3.3.4.1 Subject Numbering

Within each study site, subjects in the study will receive a consecutive subject number. Subject numbers are generated beginning with the study center number (3 digits, assigned by the Sponsor) followed consecutively with a unique number for each subject (4 digits). For example, if the Investigator's center number is [redacted], subject numbers will be [redacted], [redacted], [redacted], etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.

3.3.4.2 Randomization

This is a single-arm study with no randomization.

3.3.4.3 Blinding

This is an open-label, single-arm study with no blinding.

3.3.4.4 Administration and Timing of Investigational Product for Each Subject

Subjects will receive a total of 52 weekly SC infusions of IGSC 20% IP (13 weekly SC infusions in Treatment Stage 1 and 39 weekly SC infusions in Treatment Stage 2). See Section 3.3.2 for details on Treatment Stage 1 dosing guidance and calculation. During

Treatment Stage 1, if considered medically necessary, weekly infusions may be given at the Investigator's study site or, if deemed appropriate, at an alternate site under the care and supervision of trained healthcare personnel.

The first 3 IGSC 20% infusions in Treatment Period 1 (SC#1, SC#2, and SC#3) will be given under supervision at the study site before any subsequent IP SC infusions are administered away from the study site. Thereafter, IGSC 20% infusions may be at home except for designated clinic visits at which IGSC 20% will be infused in the clinic (SC#5, 9, 13, 17, 20, 24, 28, 32, 36, 40, 44, 48, 52 [for those subjects who are in the PK subset, 5 additional blood samples for IgG level testing will also be required between SC#17 and #18]). A pump specifically designed for SC infusions will be provided for individual use to each subject prior to the beginning of IGSC 20% Treatment Stage 1. Subjects and, in the case of children, parents or legal guardians will be trained thoroughly on its use. The exact IGSC 20% total infusion dose administered will be recorded for each infusion.

3.3.4.5 Subcutaneous Administration Procedures of Investigational Product

Details regarding infusion rate and infusion administration are located in the pharmacy/study manual. Subjects may use the same anatomical area or rotate anatomical areas for SC infusions throughout the study. No more than 8 infusion sites per infusion will be used. The minimum distance between infusion sites is recommended to be no less than 2 inches (5.1 cm). The target infusion rate will be no greater than 25 mL/hour/site as tolerated by the subject and per the Investigator's discretion; the Investigator will tailor the infusion configuration for each subject. Subjects who are naïve to SC infusion for IgG replacement (i.e., receiving IVIG at study entry) should start at a lower SC infusion rate per site initially while transitioning from the IV to SC route of administration. Once the target infusion rate is achieved, it should not be changed in the middle of an infusion unless the subject experiences tolerability issues at that infusion rate. In the event that the subject is not able to tolerate the set infusion rate, the rate may be decreased for better tolerability. Conversely, if the target infusion rate is well tolerated during 2 infusions an increase of 20% in infusion rate and volume per site is allowed at the discretion of the Investigator at the time of the clinic visit. The volume infused, infusion start date/time, infusion end date/time, and initial and final infusion rates will be recorded.

The number of infusion sites, the location(s) and rate of infusion for each infusion site, and other SC infusion information will be recorded in the SC infusion diary by the subject/parents or legal guardians, site personnel as appropriate and subsequently recorded in the electronic case report form (eCRF). In addition, SC infusion local site reactions will be recorded in the diary. Full details regarding the SC infusion diary are in Section 3.6.2.2.

Refer to the pharmacy manual/study manual for detailed instructions for IGSC 20% preparation and administration.

3.3.4.6 Treatment Compliance

Reasons for any deviation from the administration of less than 100% of the IP dose as prepared by the pharmacist, or designee, must be recorded in the eCRF and in the subject's source documents.

3.4 Prior and Concomitant Therapy

Concomitant medications must be recorded in the subject's source documents and in the eCRF from time of consent, including the trade or generic names of the medication, the dose, the route of administration, duration, and frequency. All IgG treatments administered for the past 12 months prior to screening should be recorded.

3.4.1 Prohibited Medications Prior to Study Participation

Use of the following medications, as specified below, would exclude a subject from participating in this study:

- At the time of Screening, receiving systemic corticosteroids (long-term daily doses of > 1 mg of prednisone equivalent/kg/day for > 30 days) (intermittent courses of not more than 10 days would not exclude subject). Note: Inhaled or topical corticosteroids are allowed.
- At the time of Screening, receiving immunosuppressants including chemotherapeutic agents or immunomodulators
- At the time of Screening, receiving anti-coagulation therapy which would make SC administration inadvisable (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [e.g., dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], parenteral anticoagulants [e.g., fondaparinux]).

3.4.2 Prohibited Concomitant Medications during the Study

Use of the following during the study (from Screening to Week 53 Final Visit) is prohibited:

- After the Previous Regimen Phase, any IgG replacement therapy other than IGSC 20% provided in this study
- Corticosteroids in excess of stipulations delineated in Section 3.4.1
- Anti-coagulant therapy as outlined in Section 3.4.1
- Immunosuppressants including chemotherapeutic agents or immunomodulators
- Investigational products not part of this study

3.4.3 Restricted Concomitant Medications during the Study

For subjects receiving a permissible stable dose of systemic steroids (defined above), it is recommended to maintain the same dose throughout the study.

The medications listed below are not allowed during the study as premedication to an SC infusion; however, these medications are allowed during the study for general use (e.g., to treat an AE):

Oral medications:

- Ibuprofen
- Acetaminophen
- Antihistamines

Topical medications:

- Steroids
- Antihistamines

3.4.4 Drug Interactions

In the setting of a PI disease state, live viral vaccines have various contraindications and specific risks/degrees of effectiveness dependent on the type/category of the immune deficiency (Medical Advisory Committee of the Immune Deficiency Foundation [44]). Passive transfer of antibodies from IGSC 20% may transiently interfere with the immune response to live viral vaccines such as measles, mumps, rubella, and varicella in the normal host with an intact immune system. Best medical practices should be followed regarding immunization requirements, particularly for children during the course of this protocol.

3.5 Study Variables

3.5.1 Efficacy and Pharmacokinetic Variables

3.5.1.1 Primary Efficacy Variable

The primary efficacy variable is the number of SBIs. Also, the percentage of subjects with SBIs will be summarized. SBI definitions (FDA/EMA diagnostic criteria) are provided in Appendix 3 (34,35).

3.5.1.2 Secondary Variables

One of the secondary endpoints of this study is trough concentrations of total IgG of previous regimen during the Screening/Previous Regimen Phase and the IGSC 20% Treatment Stages.

It is measured to determine if IGSC 20% replacement therapy maintains mean trough IgG levels that are comparable to the mean trough blood levels with the previous IgG replacement regimen.

Other secondary variables include the rate of infection of any kind (serious and non-serious), antibiotic treatment (oral, parenteral, oral plus parenteral, prophylactic, and therapeutic), hospitalizations due to infection, and days lost from work/school/daily activities due to infections and related treatment. The infection of any kind includes acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "Is this an infection? (verbatim term delineating nature of infection).

3.5.1.3 Other Variables

Additional PK parameters include average trough concentration of IgG subclasses (IgG1, IgG2, IgG3, and IgG4), and concentration of antibody levels to *S. pneumoniae, H. influenzae*, and *C. tetani* (tetanus). Trough measles antibody titers (functional assay) are an exploratory variable for informational purposes.

For the adult (n~20) PK subset, serial samples will be collected immediately before and after SC#17 infusion at steady state. The PK profile will include total IgG concentrations at timepoints over a 7-day period. PK parameters including $AUC_{0\text{-}7days}$, C_{max}, and t_{max} will be determined by a noncompartmental model using WinNonlin.

Another efficacy variable is validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen test) will be analyzed separately.

3.5.2 Safety Variables

The following safety variables will be assessed in this study:

- AEs, suspected adverse drug reactions (suspected ADRs), serious AEs (SAEs), and discontinuations due to AEs and SAEs

  Note: All local infusion site reactions will be recorded in the eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator will be considered as AEs.
- Vital signs during clinic visits (temperature [T], respiratory rate [RR], heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]).
- Physical assessments: physical exams will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded.
- Laboratory assessments including chemistry, hematology, and urinalysis.

3.6 Assessments

3.6.1 Assessment Periods

An overview of the study schedule is provided as Appendix 1. The study consists of Screening/Previous Regimen Phase of up to 8 weeks in duration, IGSC 20% Treatment Stage 1 of 13 weeks duration, and IGSC 20% Treatment Stage 2 of 39 weeks duration, followed by a Final Visit at Week 53 one week after Week 52. The total duration of study participation may be up to 60 weeks.

3.6.2 Observations and Measurements

The following sections describe the procedures/assessments to take place at each study visit. See the Schedule of Study Procedures table in Appendix 1 for a summary of study visits and the procedures to be conducted at each visit. Visits occurring after the Baseline Visit should be scheduled at the protocol-specified week relative to the date of the Week 1 (Baseline) Visit; a ± 1 day window is allowed with the exception of the serial PK sampling (non-dosing) visits (only applicable to the PK subset). If there are logistical issues requiring schedule adjustment for weekly IGSC 20% administration, SC#1 may be scheduled 6 to 9 days after pIV#2. Schedule adjustment may also be made after SC#3 or later (± 2 days from last infusion) when home infusion is initiated. Unscheduled visits may be conducted if deemed necessary for the purpose of subject safety.

3.6.2.1 Screening Visit and Previous Regimen Phase

Subjects who initially fail to meet eligibility criteria may be re-screened once upon consultation with the Sponsor. Subjects who fail to meet eligibility criteria upon re-screen are screen failures and will not be eligible to participate in the study.

The Previous Regimen Phase for subjects may be between 4 weeks (for subjects entering study on SCIG) and up to 8 weeks (for subjects entering study on IVIG). At the Screening Visit, if a prospective subject is also being dosed (mandatory in-clinic dosing) with their pIV/pSC infusion, in such instances the Screening Visit also becomes a pIV#1 or pSC#1 Visit which shortens the overall duration of this phase. The duration of this phase is also dependent on the need for the HIV screening results that are required prior to Baseline/Week 1 of Treatment Stage 1, which may take up to 2 weeks to report. Another factor which may impact the duration of this phase is the previous IgG dosing frequency (i.e., weekly, biweekly, once every 3 or 4 weeks) in order to ensure 2 previous regimen C_{trough} blood samples are obtained prior to initiation of IGSC 20% dosing in Treatment Stage 1.

ASSESSMENTS AND PROCEDURES DURING SCREENING VISIT AND PREVIOUS REGIMEN PHASE

Screening Visit Assessments for all subjects

- Informed consent
- Assess inclusion and exclusion criteria (Section 3.2) to determine subject eligibility
- Assign subject number
- Medical history (record relevant medical history defined as any history impactful on the subject's condition in terms of current functioning, disability, treatment, or management)
- Demography
- Record specific diagnosis of type of PI, date of diagnosis, and date and dose of current IgG replacement regimen initiated
- AEs (including infusion reactions [see Section 4.3.1 for definitions]), prior and concomitant medications assessments (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection)
- Full physical exam (excludes breast and genitourinary exam)
- Record any SBIs (defined in Appendix 3) and hospitalizations due to infections (*if this occurs during the Screening/Previous Regimen Phase, the subject will be a Screen Failure*)
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including for example acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "Is this an infection? (verbatim term delineating nature of infection). Also record validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen test). The specific evaluations performed to validate infections must be recorded in the eCRF.
- Height and weight
- Vital signs (T, RR, HR, SBP, DBP)
- Record results of most recent chest X-ray within 12 months (A chest X-ray will be necessary if not performed within 12 months of the Screening visit for adult subjects only as permitted per local requirements.) Note: at least one radiographic view (anterior-posterior [AP] or posterior-anterior [PA] is required)
- Sample for IgG subclass levels, and antibody titers for bacterial pathogens (*H. influenzae*, *S. pneumoniae*, *C. tetani* [tetanus])
- Blood and urine samples for clinical laboratory assessments (e.g., clinical chemistry, hematology, urinalysis, pregnancy testing) (see Section 3.6.3).
  - Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential; absolute reticulocyte count (ARC)

- Additional Special Tests: haptoglobin
- HIV NAT test sample
- Sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, lactate dehydrogenase (LDH), AST, ALT, alkaline phosphatase (ALP), glucose, total bilirubin, indirect bilirubin
- Serum pregnancy test (potential child-bearing females only)
- Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)

For subjects who will also receive a previous regimen SCIG or IVIG dose at the Screening Visit, perform the following:

- Blood sample for previous regimen IgG level (C_{trough} for subjects receiving pIV#1/pSC#1)
- pIV/pSC dose in the clinic (mandatory)

For subjects who will NOT receive a previous regimen SCIG or IVIG dose at the Screening Visit, schedule a pIV#1/pSC#1 Visit during this stage.

Previous Regimen Phase pIV or pSC Visit #1 or #2

- Vital signs (T, RR, HR, SBP, DBP)
- **Trough (pre-dose of previous IgG replacement regimen) PK IgG sampling at 2 time points. Please note:**
  - For subjects receiving SCIG therapy as their previous regimen, the pSC#1 dose will occur during the Screening/Previous Regimen Phase with an IgG trough level drawn pre-dose. The second IgG trough level may be drawn at Baseline prior to the first dose of IGSC 20% (a separate pSC#2 visit is not required). These samples do not have to be consecutive; however, they must be collected pre-dose.
  - For subjects receiving IVIG therapy as their previous regimen, trough IgG levels will be drawn prior to each pIV dose. The pIV#1 dose can coincide with the Screening Visit. The pIV#2 dose will occur 3 to 4 weeks later during the Previous Regimen Phase. Please note a separate pIV#2 visit is required in all cases.
  - Note the IgG trough values drawn during the Previous Regimen Phase constitute the Pre-baseline trough values which will confirm the final eligibility for subjects entering the study (must be ≥ 500 mg/dL) with the exception of the pSC #2 trough result which will be reported after the Baseline visit.
- **Administration of the subject's current ("previous") IgG replacement regimen as detailed above and specifically in Sections 3.1 and 3.3.2**
- Record any SBIs (defined in Appendix 3) and hospitalizations due to infections (*if this occurs during the Screening/Previous Regimen Phase the subject will be a Screen Failure*)
- Record non-serious infections (by category) and antibiotic treatment.

These include infections of any kind including for example acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "Is this an infection?" (verbatim term delineating nature of infection). Also record validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen test). The specific evaluations performed to validate infections must be recorded in the eCRF.

- AEs (including infusion reactions [see Section 4.3.1 for definitions]), prior and concomitant medications assessments (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection)

3.6.2.2 Baseline/IGSC 20% SC#1/Week1 (Start of IGSC 20% Treatment Stage 1)

All Screening laboratory results and assessments must be available and all inclusion and exclusion criteria must have been satisfied prior to initiating treatment. Eligible subjects will enter IGSC 20% Treatment Stage 1. There should be no interruption in IgG dosing. The IGSC 20% Treatment Stage 1 should commence 7 days (1 week) after the last previous regimen dose of IVIG or SCIG, except if SCIG is given on a biweekly schedule, the interval would be 2 weeks (i.e., the timing of start of Treatment Stage 1 will match the SC dosing interval so that an accurately reflective, previous regimen IgG C_{trough} can be obtained at Baseline).

The first 3 SC infusions of IGSC 20% will be performed under medical supervision in the Investigator's clinic (SC#1, SC#2, and SC#3); weekly SC infusions may be administered at home thereafter, once the subject (or parent/guardian if the subject is a child) has been properly trained, and demonstrated to the treating physician his/her competence in administering infusion, use of the SC pump and collection of data on the SC diary.

BASELINE VISIT (WEEK 1)

Assessments to be performed prior to IGSC 20% infusion

- Re-assess inclusion and exclusion criteria (Section 3.2) to determine subject eligibility (e.g., assure HIV NAT result is negative)
- AEs (including infusion reactions [see Section 4.3.1 for definitions] and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Prior and concomitant medications assessments (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection)
- SC infusion diaries: SC/IgG infusion diaries will be provided to each subject at the Baseline visit which may be used to record items including but not limited to: local infusion site reactions, concomitant medications (including antibiotics [prophylactic and therapeutic]), and details of IgG drug administration (location and number of sites,

date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). All local infusion site reactions will be recorded in the eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator will be considered as AEs. The SC infusion diary may also be used to record days of missed work/school/daily activities due to infections and related treatment.

- Full physical exam (excludes breast and genitourinary exam)
- Weight and height
- Vital signs (T, RR, HR, SBP, DBP)
- Pre-dose PK IgG sampling which may also be the pSC#2 trough sample for subjects on a previous SC regimen.
- Blood sample for IgG subclass levels, and antibody titers for bacterial pathogens (*H. influenzae*, *S. pneumoniae*, *C. tetani* [tetanus])
- Blood draw for trough measles antibody titer
- Collection of virus safety retain samples as detailed in Table 3-1 and Section 3.6.3.1 (collect samples but test *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or parvovirus B19 [B19V] infection while participating in the study.)

  Note: For young pediatric subjects, at the discretion of the Investigator, virus safety retain samples may be drawn the day prior to Baseline instead of combining with other baseline blood draws on a single day.
- Blood and urine samples for clinical laboratory assessments (clinical chemistry, hematology, urinalysis, additional special tests) (see Section 3.6.3):
  - Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential; ARC
  - Additional Special Test: haptoglobin
  - Sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, ALP, glucose, total bilirubin, indirect bilirubin
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)
- Urine pregnancy test for women of childbearing potential (to be performed locally at the investigative site)
- Record any SBIs (defined in Appendix 3), hospitalizations due to infections (if this occurs during the Screening/Previous Regimen Phase and prior to first dose of Grifols IGSC 20%, the subject will be a Screen Failure)
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including for example acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: “Is this an infection? (verbatim term delineating nature of infection). Also record validated infections documented by positive radiograph,

fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen test). The specific evaluations performed to validate infections must be recorded in the eCRF.

- Record days lost from work/school/daily activities due to infections and treatment

Following completion of Baseline assessments (pre-dose), the subject will receive the first IGSC 20% infusion (SC#1) at the Investigator's site during the same visit.

- IGSC 20% dosage (mg/kg) will be based on the subject's prior (pre-study) IgG replacement regimen as described in Section 3.3 and will be ≥ 100 mg/kg/week
- Site personnel will train subjects/caregivers to administer IGSC 20% during this visit using an infusion SC pump
- Document total infusion volume prepared, infusion start date/time and stop date/time, total volume infused, and, if necessary, any infusion interruption with explanation
- Record AEs including infusion reactions (see Section 4.3.1 for definitions) and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Record concomitant medications (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection)

3.6.2.3 IGSC 20% Treatment Stage 1: Weeks 2 through 13; SC#2 through SC#13

After SC#3 (Week 3), subsequent clinic visits will be at monthly intervals through SC#13 and will include trough (pre-dose) PK IgG levels. **The IGSC 20% mg/kg dose will be adjusted if the trough level is below 500 mg/dL since this level is considered as ineffective against bacterial infection.**

IGSC 20% SC#2 – VISIT IN CLINIC

The second IGSC 20% infusion (SC#2) will be administered at the Investigator's site 1 week post Baseline to provide additional training for the subject. The subject or caregiver should administer the infusion under supervision by site personnel. The following assessments/procedures will be performed:

- Pre-infusion: Draw trough (pre-dose) PK IgG sample
- IGSC 20% dosage will be based on the subject's weight measured in the clinic at Baseline and any adjustment necessary based on the subject's most recent IgG trough level from last visit
- Site personnel will observe (or re-train) subjects/caregivers to self-administer IGSC 20% during this visit using an SC pump
- Document total infusion volume prepared, infusion start date/time and stop date/time, total volume infused, and, if necessary, any infusion interruption with explanation

- Record AEs including infusion reactions (see Section 4.3.1 for definitions) and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Record concomitant medications (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection)
- Record any SBIs (defined in Appendix 3) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 3 must be recorded in the eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind, including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "Is this an infection?" (verbatim term delineating nature of infection). Also record validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen test). The specific evaluations performed to validate infections must be recorded in the eCRF.
- Record days lost from work/school/daily activities due to infections and treatment

IGSC 20% SC#3 – VISIT IN CLINIC

The third IGSC 20% infusion (SC#3) will also be administered at the Investigator's site to provide additional experience for the subject/caregiver. The subject or caregiver should administer the infusion under supervision by site personnel. The following assessments/procedures will be performed:

- IGSC 20% dosage will be based on the subject's weight measured in the clinic at Baseline and any adjustment necessary based on the subject's most recent IgG trough level from last visit
- Site personnel will observe (or re-train) subjects/caregivers to self-administer IGSC 20% during this visit using an SC pump
- Document total infusion volume prepared, infusion start date/time and stop date/time, total volume infused, and, if necessary, any infusion interruption with explanation
- Record AEs including infusion reactions (see Section 4.3.1 for definitions) and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Record concomitant medications (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection)
- Record any SBIs (defined in Appendix 3) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 3 must be recorded in the eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

These include infections of any kind including for example acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "Is this an infection? (verbatim term delineating nature of infection). Also record validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen test). The specific evaluations performed to validate infections must be recorded in the eCRF.

- Record days lost from work/school/daily activities due to infections and treatment

IGSC 20% SC#5, 9, AND 13 – VISITS IN CLINIC

Assessments to be performed prior to IGSC 20% infusion at all Visits:

- Full physical exam (excludes breast and genitourinary exam) at SC#13 Visit only
- Weight
- Vital signs (T, RR, HR, SBP, DBP)
- Trough (pre-dose) PK IgG sampling
- Review of trough (pre-dose) PK IgG level to assure C_{trough} is not less than 500 mg/dL. Adjustment in dose of IGSC 20% will be necessary if IgG C_{trough} is below this threshold. The dose adjustment (mg/kg) should not be more than a 15% to 20% increase from the dose producing the low IgG trough, per the Investigator's discretion. Any dose adjustments beyond this range will require consultation with Grifols. Use weight from current visit to calculate the total dose of IGSC 20% to be administered on-site and subsequently at home at weekly intervals.
- Review SC infusion diary and infusion details from IGSC 20% administered weekly at home with subjects/caregivers. All local infusion site reactions will be recorded in the eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator will be considered as AEs.
- Record any SBIs (defined in Appendix 3) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories in Appendix 3 must be recorded in the eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including for example acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "Is this an infection? (verbatim term delineating nature of infection). Also record validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal

antigen test). The specific evaluations performed to validate infections must be recorded in the eCRF.

- Record days lost from work/school/daily activities due to infections and treatment

IP infusion in clinic at Visits SC#5, SC#9, and SC#13

- IGSC 20% dose will be based on the subject's weight measured in the clinic at SC#5, SC#9, and SC#13 Visits and any adjustment necessary based on the subject's most recent IgG trough level from last visit
- An infusion pump (designed for SC infusion) will be used to deliver IGSC 20%
- Site personnel will observe subjects/caregivers administering IGSC 20% and retrain if needed. This will be documented.
- Document total infusion volume prepared, infusion start date/time and stop date/time, total volume infused, and, if necessary, any infusion interruption with explanation
- Record AEs including infusion reactions (see Section 4.3.1 for definitions) and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Record concomitant medications (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection)

IP infusion may be administered at home for intervening weekly infusions, specifically infusion numbers SC#4, SC#6, SC#7, SC#8, SC#10, SC#11, and SC#12. The SC infusion diary must be completed with all relevant information pertaining to infusion particulars as detailed in Section 3.6.2.2. The weight that will be used to determine the infusion dose will be the most recent weight obtained at the last clinic visit.

Laboratory draw and height at SC#13 visit only prior to IGSC 20% infusion:

- Height
- Sample for IgG subclass levels, and antibody titers for bacterial pathogens (*H. influenzae*, *S. pneumoniae*, *C. tetani* [tetanus])
- Blood and urine samples for clinical laboratory assessments (clinical chemistry, hematology, urinalysis, additional special tests) (see Section 3.6.3):
  - Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential, ARC
  - Additional Special Tests: Direct antiglobulin test (DAT), serum free hemoglobin, haptoglobin
  - Sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, ALP, glucose, total bilirubin, indirect bilirubin
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)

3.6.2.4 IGSC 20% Treatment Stage 2 (Weeks 14 through 52, SC#14 through SC#52)

During IGSC 20% Treatment Stage 2, the mg/kg IGSC 20% dose (ratio of mg per kg) will now remain constant with no dose adjustment permitted, unless it is absolutely medically necessary to change the dose, and such change requires previous consultation with the Grifols Medical Monitor. Weight will be measured at every in-clinic visit and dosing will be based on the subject's current weight. For the subsequent at home IGSC 20% infusions between clinic visits, the dose will be the same as the total infusion dose calculated at the previous clinic study visit where weight was measured at the clinical site. IgG trough levels will be measured monthly (every 4 weeks). After 16 weeks of IGSC 20% treatment (including Stage 1), at SC#17, PK profiles in approximately 20 adult subjects will be measured. Where possible, the first available 20 adult subjects reaching the visit designated SC#17 in this study will constitute the PK subset. Blood draws for steady-state PK analyses will be collected after the 17th SC dose for up to 7 days post dose.

IGSC 20% SC# 17, 20, 24, 28, 32, 36, 40, 44, 48, AND 52 – VISITS IN CLINIC

Assessments to be performed prior to IGSC 20% infusion at all visits:

- Full physical exam (excludes breast and genitourinary exam) at SC#24 and #36 only
- Weight
- Vital signs (T, RR, HR, SBP, DBP)
- Trough (pre-dose) PK IgG sampling for all subjects. **Note for PK subset profiling IgG trough should be within 0.5 hour of start of infusion on SC#17.** Review of trough (pre-dose) PK IgG level. Use weight from current visit to calculate total dose of IGSC 20% to be administered on-site and subsequently at home at weekly intervals.
- Blood draw for trough measles antibody titer at SC#20 and SC#52 only
- Review SC infusion diary and infusion details from IGSC 20% administered weekly at home with subjects/caregivers. All local infusion site reactions will be recorded in the eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator, will be considered as AEs.
- Record any SBIs (defined in Appendix 3) and hospitalizations due to infections. The evaluations performed to fulfill the diagnostic categories in Appendix 3 must be recorded in the eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including for example acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "Is this an infection? (verbatim term delineating nature of infection). Also record validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal

antigen test). The specific evaluations performed to validate infections must be recorded in the eCRF.

- Record days lost from work/school/daily activities due to infections and treatment

Laboratory draw and height at SC#24 and SC#36 visits only prior to IGSC 20% infusion:

- Height
- Blood and urine samples for clinical laboratory assessments (clinical chemistry, hematology, urinalysis, additional special tests) (see Section 3.6.3):
  - Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential, ARC
  - Additional Special Tests: DAT, serum free hemoglobin, haptoglobin
  - Sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, ALP, glucose, total bilirubin, indirect bilirubin
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)
- Sample for IgG subclass levels and antibody titers for bacterial pathogens (*H. influenzae*, *S. pneumoniae*, *C. tetani* [tetanus])

IP infusion in clinic at SC#17, 20, 24, 28, 32, 36, 40, 44, 48, and 52 visits:

- IGSC 20% net total dose will be determined on the subject's current weight
- Site personnel will observe (and re-train as needed) subjects administering IGSC 20% using the SC pump
- Document total infusion volume prepared, infusion start date/time and stop date/time, total volume infused, and, if necessary, any infusion interruption with explanation
- Record AEs including infusion reactions (see Section 4.3.1 for definitions) and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Record concomitant medications (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection)

IP infusion may be administered at home for intervening weekly infusions, specifically infusion numbers SC#14, SC#15, SC#16, (SC#18 except for PK subset see Section 3.6.2.5), SC#19, SC#21, SC#22, SC#23, SC#25, SC#26, SC#27, SC#29, SC#30, SC#31, SC#33, SC#34, SC#35, SC#37, SC#38, SC#39, SC#41, SC#42, SC#43, SC#45, SC#46, SC#47, SC#49, SC#50, and SC#51. The SC infusion diary must be completed with all relevant information pertaining to infusion particulars as detailed in Section 3.6.2.2. The weight that will be used to determine the infusion dose will be the most recent weight obtained at the last clinic visit.

3.6.2.5 IGSC 20% Treatment Stage 2 – PK Subset Only

Subjects agreeing to participate in the serial PK sampling portion of the study (preferably the first 20 adults enrolled) will have additional PK profiling starting at SC#17 (Week 17) and ending at SC#18 (Week 18). While all subjects will have a SC#17 (Week 17) visit (described above), only subjects in the PK subset will have an additional clinic visit at SC#18.

To participate in the PK subset, a subject must not have required an mg/kg dose level adjustment in IGSC 20% at or after SC#9. Details are provided in Appendix 2 and below.

ADDITIONAL IGSC 20% SC#17 AND SC#18 ASSESSMENTS – FOR PK SUBSET ONLY

After IGSC SC#17 visit infusion – Serial PK sampling to be done for PK subset only

- PK serial blood samples for serial IgG levels will be drawn at the following time points after completion of the IGSC 20% SC#17 infusion:
  - Immediately at the completion of the 17th SC infusion
  - 1 day ± 4 hours post SC#17 infusion
  - 3 days ± 4 hours post SC#17 infusion
  - 5 days ± 4 hours post SC#17 infusion
  - 7 days ± 1 day post SC#17 infusion (within 0.5 hour prior to the SC#18 IGSC 20% infusion)

Assessments to be performed prior to IGSC 20% infusion at additional clinic visit at SC#18 (Week 18) for PK subset subjects only :

- Weight
- Vital signs (T, RR, HR, SBP, DBP)
- **Trough (pre-dose) PK IgG sampling *(within 0.5 hour of the start of infusion)***
- Review of trough (pre-dose) PK IgG level. Use weight from current visit to calculate total dose of IGSC 20% to be administered on-site and subsequently at home at weekly intervals**. If a dose adjustment (in mg/kg dose) occurred at or after SC#9 then the subject is not appropriate for the PK subset study and should not undergo the PK profiling. An additional subject should be designated for PK profiling.**
- Record any SBIs (defined in Appendix 3) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories in Appendix 3 must be recorded in the eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including for example acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: “Is this an infection?” (verbatim term delineating nature of infection). Also record validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms

e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen test). The specific evaluations performed to validate infections must be recorded in the eCRF.

- Record days lost from work/school/daily activities due to infections and treatment

IP infusion in clinic for PK subset only (SC#18 Visit):

- IGSC 20% dose will be based on the subject's current weight
- An infusion pump (designed for SC infusion) will be used to deliver IGSC 20%
- Site personnel will observe subjects/caregivers administering IGSC 20% and retrain if needed. This will be documented.
- Document total infusion volume prepared, infusion start date/time and stop date/time, total volume infused, and, if necessary, any infusion interruption with explanation
- Record AEs, including infusion reactions (see Section 4.3.1 for definitions) and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Record concomitant medications (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection)

3.6.2.6 Final Visit – Week 53 (1 Week Post Final IGSC 20% Infusion) – Visit in Clinic

The final infusion of IGSC 20% will be SC#52. One week post last SC infusion a Final Visit will occur.

The following assessments will be performed:

- Full physical exam (excludes breast and genitourinary exam)
- Height
- Vital signs (T, RR, HR, SBP, DBP)
- Trough (pre-dose) PK IgG sampling
- Sample for IgG subclass levels and antibody titers for bacterial pathogens (*H. influenzae*, *S. pneumoniae*, *C. tetani* [tetanus])
- Blood and urine samples for clinical laboratory assessments (clinical chemistry, hematology, urinalysis, additional special tests, pregnancy testing) (see Section 3.6.3):
  - Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential, ARC
  - Additional Special Tests: DAT, serum free hemoglobin, haptoglobin
  - Sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, ALP, glucose, total bilirubin, indirect bilirubin
  - Serum pregnancy test (potential child-bearing females only)
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)

- Record AEs including infusion reactions (see Section 4.3.1 for definitions) and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Record concomitant medications (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection)
- Perform final SC infusion diary review for infusion details with subjects/caregivers. All local infusion site reactions will be recorded in the eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator will be considered as AEs.
- Record any SBIs (Appendix 3) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories in Appendix 3 must be recorded in the eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including for example acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "Is this an infection?" (verbatim term delineating nature of infection). Also record validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen test). The specific evaluations performed to validate infections must be recorded in the eCRF.
- Record days lost from work/school/daily activities due to infections and treatment

3.6.2.7 Early Termination Visit

If a subject discontinues at any point during the study after Baseline, the subject will be requested to return to the Investigator's study site for an Early Termination Visit. The assessments at this visit will be the same as the Final Visit in the case of a subject who prematurely discontinues the study.

The following procedures and assessments will be performed during the Early Termination Visit:

- Full physical exam (excludes breast and genitourinary exam)
- Height
- Vital signs (T, RR, HR, SBP, DBP)
- Trough PK IgG sampling
- Sample for IgG subclass levels, and antibody titers for bacterial pathogens (*H. influenzae*, *S. pneumoniae*, *C. tetani* [tetanus])
- Blood and urine samples for clinical laboratory assessments (clinical chemistry, hematology, urinalysis, additional special tests, pregnancy testing) (see Section 3.6.3):

  - Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential, ARC
  - Additional Special Tests: DAT, serum free hemoglobin, haptoglobin
  - Sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, ALP, glucose, total bilirubin, indirect bilirubin
  - Serum pregnancy test (potential child-bearing females only)
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)
- Record AEs including infusion reactions (see Section 4.3.1 for definitions) and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])
- Record concomitant medications (for antibiotics distinguish between prophylactic use and use for treatment of an episode of infection)
- Perform final SC infusion diary review for infusion details with subjects/caregivers. All local infusion site reactions will be recorded in the eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator will be considered as AEs.
- Record any SBIs (Appendix 3) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories in Appendix 3 must be recorded in the eCRF
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including for example acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: “Is this an infection?” (verbatim term delineating nature of infection). Also record validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen test). The specific evaluations performed to validate infections must be recorded in the eCRF
- Record days lost from work/school/daily activities due to infections and treatment

3.6.3 Description of Laboratory Tests and Procedures

Detailed descriptions of laboratory test procedures are located in the study Laboratory Manual. Table 3-1 provides a summary of the laboratory tests conducted for this study.

Table 3-1 Name, Description, and Location of Laboratory Tests and Procedures

Test Panel	Description	Location
Hematology [a]	Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential, ARC	Central
Additional special tests [a]	DAT, serum free hemoglobin, haptoglobin	Central
Chemistry [a]	Sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, ALP, glucose, total bilirubin, indirect bilirubin	Central
IgG levels [a]	Total IgG levels will consist of trough (pre-dose) measurements in all subjects, and for the PK subset, serial PK sampling for PK profiling of IGSC 20%	Central
IgG subclass levels and antibody titers [a]	Measurement of IgG subclasses (IgG1, IgG2, IgG3, IgG4). Measurement of levels of selected specific antibodies against *H. influenzae,* anti-pneumococcal polysaccharide (*S. pneumoniae*), and *C. tetani* [tetanus]	Specialty
Trough measles antibody titers (functional assay) [a]	Trough samples for measles antibody titer will be collected at Baseline (before the first infusion of Grifols IGSC 20%), SC#20, and SC#52	Specialty
Serum pregnancy test [a]	Qualitative serum β-HCG for females of child-bearing potential will be performed at Screening and Final Visit	Central
Urine pregnancy test [a]	Qualitative urine β-HCG will be performed at Baseline	Local
Viral NAT testing [a, b, c]	Screening: HIV RNA testing Baseline: Collect retain samples for hepatitis A virus (HAV) RNA, HBV DNA, HCV RNA, HIV RNA, and B19V DNA testing	Central
Viral serology testing [a, b, c]	Baseline [c]: Collect retain samples for hepatitis A antibody differential (IgM/IgG), hepatitis B core antibody differential (IgM/IgG), hepatitis C antibody, HIV-1/-2 + Group O antibody, and B19V antibody differential (IgM/IgG) testing	Central
Urinalysis [a]	Microscopic evaluation is done only with cause. pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of the urine if abnormal)	Central

[a] Samples collected for laboratory analyses that are non-analyzable due to any factor (i.e., lost, quantity not sufficient, laboratory error) need to be recollected by contacting the subject and arranging for re-sampling.

[b] These samples will be retained until all analyses in support of the study are complete.

[c] See Section 3.6.3.1.

3.6.3.1 Virus Safety Testing

At Screening, a sample for HIV NAT testing will be collected and tested for determination of subject eligibility. The subject must be negative for HIV by NAT based on a Screening blood sample. The subject may enter the Previous Regimen Phase while the Screening blood sample is being tested, but will be a Screen Failure and will not undergo Baseline assessments if the HIV result is positive.

Virus safety (viral NAT and viral serology) retain samples collected at the Baseline Visit, prior to IGSC 20% infusion, will be tested only if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or B19V infection while participating in the study. Virus safety samples will be retained until all analyses in support of the study are complete. Additional samples for viral NAT and viral serology testing may be collected and tested during the study only if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or B19V infection while participating in the study.

Note: For young pediatric subjects, at the discretion of the Investigator, virus safety retain samples may be drawn the day prior to Baseline instead of combining with other baseline blood draws on a single day.

3.6.3.2 Immunoglobulin G Assessments

All subjects will have trough (pre-dose) total IgG measurements performed at each visit (except SC#3). These measurements are important as a guide to dose level adjustment in Treatment Stage 1 to assure that adequate IgG levels are maintained at a sufficient concentration (not less than 500 mg/dL) to avoid serious infection. Samples will be retained until all analyses in support of the study are complete.

In addition, IgG subclass antibody levels (IgG1, IgG2, IgG3, and IgG4) will be measured at Screening, Baseline (prior to first dose of IGSC 20%), SC#13, SC#24, SC#36, and Final Visit in all subjects. Specific antibody levels to the following pathogens will also be measured at these time points: *H. influenzae*, anti-pneumococcal polysaccharide (*S. pneumoniae*), and tetanus *(C. tetani)*. Trough samples for measles antibody titer will be collected at Baseline (before the first infusion of Grifols IGSC 20%) at SC#20 and at SC#52.

In the adult PK subset, total IgG PK profiling will be performed as described in Section 3.6.2.5. Samples will be drawn at the following time points:

- Trough (pre-dose) PK IgG sampling (within 0.5 hour of the start of the 17th SC infusion)
- Immediately at the completion of the 17th SC infusion
- 1 day ± 4 hours post infusion
- 3 days ± 4 hours post infusion
- 5 days ± 4 hours post infusion

- 7 days ± 1 day post infusion (within 0.5 hour prior to the 18th IGSC 20% dose)

3.7 Removal of Subjects

Subjects may withdraw or be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative
- If, in the Investigator's opinion, continuation in the study would be detrimental to the subject's well-being
- At the specific request of the Sponsor

Also, subjects may be withdrawn from IP or the study for the following reasons:

- Subjects with an occurrence of a concomitant disease, or any medical condition which, either because of its severity or duration or necessary change in treatment, contravenes the condition of the study or puts the subject at unnecessary risk or harm
- Subjects with an occurrence of an AE which in the opinion of the Investigator and/or subject requires termination of treatment
- Subjects who are noncompliant with the protocol (including noncompliance with weekly IGSC 20% dosing) per the Investigator’s discretion
- Pregnancy (Note: Subject must be withdrawn from IP administration and the study prior to dosing with a commercially available IgG product.)

In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's source documentation.

3.8 Follow-Up of Subjects Withdrawn from Study

Subjects who receive any amount of IP and discontinue early from the study will be requested to return to have all assessments completed for the Early Termination Visit (see Section 3.6.2.7 and Appendix 1) as close as practical to 1 week after their last administration of the IP.

3.9 Subject Recruitment

A PK subject who undergoes a dose adjustment (in mg/kg) at or after SC#9 is not appropriate for the PK subset study and should not undergo the PK profiling. The subject will be permitted to continue within the study. However, an additional PK subject may be recruited; similarly an additional PK subject may be enrolled if a subject in the PK subset cannot adequately complete the PK profiling.

3.10 Premature Termination of Study/Closure of Center

The Sponsor, IRB/EC, and/or regulatory authorities have the right to close this study or a study center, and the Investigator/Sponsor has the right to close a center, at any time, although this should occur only after consultation between involved parties. The IRB/EC must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at the site) must be returned to the Sponsor. The Investigator will retain all other documents until notification given by the Sponsor for destruction.

A study center can be closed for the following reasons:

- Lack of enrollment
- Non-compliance with the requirements of the study protocol
- Non-compliance with International Conference on Harmonization Good Clinical Practice (ICH GCP)

4 ADVERSE EVENTS

4.1 Warnings/Precautions

For complete information on IGSC 20%, refer to the IB.

4.2 Adverse Event Monitoring

Subjects must be carefully monitored for AEs. This monitoring includes clinical and laboratory tests and physical signs. Adverse events should be assessed in terms of their seriousness, severity, and causal relationship to the IP.

4.3 Adverse Event Definitions

4.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product or study treatment and which does not necessarily have a causal relationship with this administration. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any AE that occurs at any time between the signing of the ICF and the last day of the subject's participation in the clinical trial must be reported and recorded in the AE eCRF.

All local infusion site reactions will be recorded in the eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator will be considered as AEs.

4.3.2 Suspected Adverse Drug Reactions/Adverse Reactions

All noxious and unintended responses to a medicinal product or study treatment related to any dose should be considered suspected ADRs. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product or study treatment and an AE is at least a reasonable possibility, that is, the relationship cannot be ruled out.

4.3.3 Causality of Adverse Event

The Investigator is required to provide a causality assessment for each AE reported to the Sponsor. The Sponsor will consider the Investigator's causality assessment and also provide its own assessment for SAEs. Assessment of the causal relationship to the study drug will be made according to the following classifications based on Karch FE et al. (45):

Definite: An event that follows a reasonable temporal sequence from administration of the treatment or in which the treatment level has been established in body fluids or tissues; that follows a known response pattern to the suspected treatment and that is confirmed by improvement on stopping the treatment (dechallenge), and reappearance of the event on repeated exposure (rechallenge).

Probable: An event that follows a reasonable temporal sequence from administration of the treatment; that is confirmed by dechallenge; that follows a known response pattern to the suspected treatment; that is confirmed by dechallenge and that could not be reasonably explained by the known characteristics of the subject's clinical state.

Possible: An event that follows a reasonable temporal sequence from administration of the treatment; that follows a known response pattern to the suspected treatment; but that could have been produced by the subject's clinical state or other modes of therapy administered to the subject.

Doubtful/Unlikely: An event that follows a reasonable temporal sequence from administration of the treatment; that does not follow a known response pattern to the suspected treatment; but that could not be reasonably explained by the known characteristics of the subject's clinical state.

Unrelated: Any event that does not meet the criteria above.

The operational tool to decide the AE causal relationship is based on algorithms by Karch FE et al. and Naranjo CA et al. (46,47).

When an AE is classified, assessing causal relationship by the Investigator, as “definitive”, i.e., “probable”, “possible” or “doubtful/unlikely”, the event will be defined as a suspected ADR. When the causal relationship is labeled “unrelated”, then it will be considered that the AE is not imputable to the study treatment and it is not a suspected ADR.

In addition, when a causal relationship between the study treatment and the AE cannot be ruled out by the Investigator and/or Sponsor, it means that the AE cannot be labeled “unrelated”.

For any subject, all AEs that occur at any time from the beginning of IP administration until the final visit of the clinical trial will be considered as treatment emergent AEs (TEAEs).

4.3.4 Severity of Adverse Event or Suspected Adverse Drug Reaction

AEs and suspected ADRs will be classified depending on their severity according to the following definitions:

1. Mild: an AE which is well tolerated by the subject, causing minimum degree of malaise and without affecting normal activities.
2. Moderate: an AE that interferes with the subject’s normal activities.
3. Severe: an AE that prevents the subject from performing their normal activities.

AE and suspected ADR severity gradation must be distinguished from AE and suspected ADR seriousness gradation, which is defined according to event consequence. For example, headache can be mild, moderate or severe but not necessarily serious in all these cases.

The Investigator will be responsible for assessing the AE and suspected ADR intensity during the clinical trial, taking into account current criteria included in this section.

4.3.5 Expectedness of Adverse Event or Suspected Adverse Drug Reaction

An AE or suspected ADR is considered “unexpected” if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information. The expectedness shall be determined by the Sponsor according to the reference document (i.e., IB) for any serious ADRs (potentially related SAEs) for expedited safety reporting purposes.

4.3.6 Seriousness of Adverse Event or Suspected Adverse Drug Reaction; Serious Adverse Event

An AE or suspected ADR is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

1. Death

2. Life-threatening AE (life-threatening in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
3. In-patient hospitalization or prolongation of existing hospitalization
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect
6. An important medical event (important medical event in the definition of "serious" refers to those events which may not be immediately life-threatening, or result in death, or hospitalization, but from medical and scientific judgment may jeopardize the subject or/and may require medical or surgical intervention to prevent one of the other outcomes listed above).

This definition permits either the Sponsor or the Investigator to decide whether an event is "serious". If either the Sponsor or the Investigator believes that the event is serious, the event must be considered "serious" and evaluated by the Sponsor for expedited reporting.

A distinction should be drawn between serious and severe AEs. The term "severe" is used to describe the intensity (severity) of a specific event; the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious", which is defined on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) is a medical term while severity is a subjective term.

According to the medical criteria, an AE or a suspected ADR can be classified as serious, although it does not fulfill the conditions fixed in this section, if it is considered important from a medical point of view.

4.3.7 Adverse Event Documentation

All AEs and SAEs occurring after the subject has **signed the ICF through the Final Visit (i.e., end of study)** must be fully recorded in the subject's eCRF or SAE form and medical record. If no AE has occurred during the study period, this should also be indicated in the eCRF.

It is the responsibility of the Investigator to ensure that AEs are appropriately recorded.

At each visit, AEs will be elicited by asking the individual a non-leading question such as "Do you feel different in any way since the last visit?" Moreover, AEs will also be collected through directly observed events or spontaneously volunteered by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome wherever possible.

The following variables must be recorded in the AE eCRF:

1. The verbatim term (a diagnosis is preferred)
2. Date/time of onset
3. Date/time of resolution
4. Severity (mild, moderate, severe)
5. Causality (unrelated, doubtful/unlikely, possible, probable, definite)*
6. Seriousness (yes, no)
7. Action taken (with regard to IP)
8. Other action (to treat the event)
9. Outcome and sequel (follow-up on AE)

   **Causality assessment will be made only when the AE occurs after the subject has initiated at least one infusion of the IP. An AE occurring before subject's exposure to IP will be always labeled as "unrelated".*

For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE, the time of onset of the AE and the time of AE change materially in intensity and/or resolve will be captured in the eCRF.

In addition to the Investigator's own description of the AEs, each AE will be encoded according to the Medical Dictionary for Regulatory Activities (MedDRA).

For example, a laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the Investigator, should be reported as an AE. Each event must be described in detail along with start and stop dates, severity, relationship to IP, action taken and outcome. Each event must be adequately supported by documentation as it appears in the subject's medical or case file.

4.3.8 Type and Duration of the Follow-Up of Subjects after Adverse Events

In so far as is possible, all individuals will be followed up until the AE or suspected ADR has been resolved. If an AE/suspected ADR/SAE is present when the subject has completed the study, the course of the event must be followed until the final outcome is known or the event has been stabilized, no further change is expected, and the Investigator decides that no further follow-up is necessary.

4.4 Reporting of Serious Adverse Events or Pregnancy

4.4.1 Reporting Serious Adverse Event

Any SAE (see Section 4.3.6) that occurs after **signing the study ICF through the Final Visit (i.e., end of study)** must be expeditiously reported whether or not considered attributable to the study drug. Each SAE must be fully recorded in the subject's eCRF and SAE Report Form.

SAEs will be reported using the designated SAE Report Form. When the Investigator becomes aware of an SAE, she/he must submit a completed, signed and dated SAE Report Form (in English) within 24 hours to the Sponsor by email/fax. The date of this SAE discovery by the site staff should be documented in the source documents (ie, medical records).

Each SAE must be followed up until resolution or stabilization. After the initial report, all relevant information for SAE follow up and the outcome must also be supplied to the Sponsor in a timely manner (within 3 days from its identification or within 24 hours for relevant new information) by means of the SAE Report Form. In addition, the Sponsor or contract research organization (CRO) may request additional information and/or reports.

All SAE Report Forms must be reported by email to:

Grifols Global Pharmacovigilance for Reporting SAEs and Pregnancy

Email: [redacted]
FAX (back-up only): [redacted] (International)

When required, and according to local law and regulations, SAEs must be reported to the IRB/EC and regulatory authorities.

4.4.2 Reporting Pregnancy

Pregnancies occurring during the course of the study will not be considered an AE unless a relation to the study drug is suspected. In any case, a *Pregnancy Report Form* must be completed and sent as soon as possible to the Sponsor for any pregnancies that occur in a female subject or partner of a male subject from time of consent through the Final Visit (i.e., end of study). A copy of the form should be filed at the study site for follow-up until the end of the pregnancy. Any pregnancy must be followed by the Investigator until delivery or to the end of pregnancy. Any anomalies, complications, abnormal outcomes, or birth defects observed in the child must be reported as an SAE (see email address or fax number in Section 4.4.1) within 24 hours of the Investigator or study personnel's first knowledge.

5 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

5.1 Statistical and Analytical Plans

Unless otherwise specified, descriptive statistics will include the number, mean, standard deviation (SD), median, minimum and maximum values for the continuous/quantitative data or absolute and relative frequency counts and percentages for categorical/qualitative data.

Data handling and evaluation procedures will be described as detailed in the Statistical Analysis Plan.

5.1.1 Subject Population(s) for Analysis

Safety Population

The safety population will include all subjects who have received any amount of IGSC 20% and will be used for safety analysis.

Efficacy Evaluable Population

The efficacy evaluable population will include all subjects who have received at least one dose of IGSC 20% and will be used for efficacy analysis.

IgG Population

The IgG population will consist of all subjects who receive any amount of IGSC 20% and have total IgG concentration data to facilitate the comparison of mean trough IgG concentration during the IGSC 20% phase versus the pre-treatment phase.

Pharmacokinetic Population

The PK population will consist of all adult subjects who have received IGSC 20% and have sufficient serial IgG concentration vs. time data to facilitate calculation of AUC PK parameters.

5.1.2 Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized. For quantitative variables, mean, SD, median, and minimum/maximum will be provided. For qualitative variables, the frequency and percentage will be provided.

5.1.3 Efficacy Analysis

The primary efficacy variable of SBIs will be analyzed using the efficacy evaluable population. The number of SBIs from Week 1 to Week 53 during the IGSC 20% treatment period and percentage of subjects with SBIs will be summarized.

The SBI rate will be compared to the recommended standard rate of 1 SBI per person per year. The following hypothesis testing is performed with one-sided test at alpha = 0.01 level:

$$H_0 : \lambda \geq 1 \; SBI \; per \; person \; per \; year$$
$$versus$$
$$H_A : \lambda < 1 \; SBI \; per \; person \; per \; year$$

Where λ is the SBI rate during IGSC 20% treatment. Occurrence of SBI is assumed to follow the Poisson distribution.

The generalized linear model procedure for Poisson regression with log link will be used to estimate the SBI rate for IGSC 20% and its one-sided 99% upper confidence bound. Person-year will be calculated for each subject and will be used in the generalized linear model as offset variable. No covariates but the intercept term are included in the model. The estimated intercept term and the upper limit of its confidence interval (CI) will be transformed by using the natural exponential function.

Secondary Efficacy Assessments:

- All infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "Is this an infection?" (verbatim term delineating infection).
- Number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic). Use of prophylactic antibiotics will be distinguished from antibiotics for treatment of acute infection
- Number of hospitalizations due to infection
- Number of days of work/school/daily activities missed per subject year due to infections and their treatment

Other Efficacy Assessments

- Validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, *or* diagnostic testing for microorganisms e.g., bacterial, viral, fungal or protozoal pathogens (for instance, rapid streptococcal antigen detection test)

The secondary and other efficacy variables will be summarized descriptively. Annualized rate of all infections, days missed work/school/daily activities, days on antibiotics, and hospitalizations will be calculated and the 95% CI will be provided.

5.1.4 Pharmacokinetic Analysis

Trough concentrations of total IgG during the Screening/Previous Regimen Phase and the IGSC 20% Treatment Stages will be summarized by week for the efficacy evaluable population. Mean trough for IGSC 20% treatment phase will be calculated as the average of

all steady state trough concentrations measured during the IGSC 20% Treatment Stage 2, i.e., IgG trough levels measured at the following visits: SC#17, #18, #20, #24, #28, #32, #36, #40, #44, #48, #52, and #53. Comparison will be made to the mean of 2 troughs for previous IgG treatment (either IVIG or other SCIG products) obtained from the Screening/Previous Regimen Phase. Mean trough data will be summarized. Mean trough summary and analysis will be based on the IgG population.

For samples collected after SC#14 infusion (start of Treatment Stage 2), total IgG concentrations will be summarized by time point. For subjects in the PK subset with an IgG PK profile, individual and mean/median IgG concentrations vs. time curves will be plotted. PK parameters for total IgG including $AUC_{0\text{-}7days}$, C_{max}, and t_{max} will be determined by noncompartmental model using WinNonlin software. All PK parameters will be tabulated and summarized descriptively. The analyses will be based on the PK population.

Summaries will be provided for average trough concentration of IgG subclasses (Screening, Baseline, before the 13th, 24th, 36th IGSC 20% infusion, and Final Visit). Summaries of average trough level concentration of antibody titers against *S. pneumoniae, H. influenzae*, and *C. tetani* (tetanus) will also be provided (collected at these same time points).

Trough measles antibody titers (functional assay at Baseline, SC#20 Visit, and SC#52 Visit) are an exploratory variable for informational purposes.

5.1.5 Safety Analysis

The safety analyses are based on the safety population.

All AEs, suspected ADRs, SAEs and discontinuations due to AEs and SAEs will be summarized by presenting the number of events and the number and percentage of subjects with the events. The summaries will be presented by MedDRA system organ class and preferred term. AE summaries by severity will also be provided. Local infusion site reactions will be similarly summarized.

Subjects with deaths, SAEs, and AEs leading to premature discontinuation from the study will be listed and presented in a narrative form.

Adverse events temporally associated with SC administration of study drug will be defined as those occurring during or within 72 hours of completion of an infusion. Additionally, local infusion site reactions will be tabulated and summarized for the total duration of the study and by IGSC 20% infusion week.

For all laboratory tests and vital signs, the original value and the change from Baseline will be summarized for numeric results and frequency/percentage will be summarized for qualitative results. For laboratory tests with normal ranges, out of normal range values will be flagged and shift tables will be provided.

5.2 Determination of Sample Size

Assuming that the true rate of the SBIs is 0.25 per subject per year, 40 subjects treated for one year for IGSC 20% will provide at least 90% power to reject the null hypothesis of a SBI rate greater than or equal to 1.0 per person per year, using a one-sided test at the 0.01 level.

In order to obtain a total of 40 PI subjects including 20 adult and 20 pediatric evaluable subjects, approximately 60 subjects will be enrolled and treated in the study. This sample size is to allow for a moderate to high early discontinuation rate seen in other similar studies (13,36).

6 ADMINISTRATIVE

6.1 Investigator(s), Other Study Personnel and External Committees

Information regarding additional key personnel involved in the conduct of the study, including names and contact details of participating Investigators, monitors, clinical laboratories, technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the Sponsor and at the Investigator sites within the study reference manual/file.

Investigators and staff will receive training via an Investigators meeting, site initiation visit or other appropriate individual site training session(s).

6.2 Data Quality

Monitoring and auditing procedures defined/agreed by the Sponsor will be followed in order to comply with ICH GCP guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, ICH GCP, and legal aspects. The on-site verification of the eCRF for completeness and clarity will include cross checking with source documents and clarification of administrative matters. Query verification of data will be described in the Data Management Plan.

6.3 Documentation

The study data will be recorded and kept current in the eCRF by the site study personnel directly responsible for the information. Entries made in the eCRF must be verifiable against source documents, or have been directly entered into the eCRF, in which case the entry in the eCRF will be considered the source data.

The data in the eCRF will be monitored at the site by Grifols Therapeutics Inc. representatives at regular intervals and reviewed for completeness and compared with the source documents. Examples of source documents include individual subject medical records, which are separate from the eCRFs.

All AEs and SAEs must be recorded. All SAEs must be recorded on the SAE form. The SAE form must be kept in the site records with a copy provided to the designated person as detailed in the study file.

6.3.1 Record Retention

At study completion, all study data will be transferred to Grifols Therapeutics Inc. according to ICH GCP guidelines, local laws, regulations, and Grifols Therapeutics Inc. requirements. The study file and all source data should be retained until notification is given by the Sponsor for destruction.

An Investigator is required by ICH GCP guidelines to retain the study files. If an Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person (e.g., other Investigator). Grifols Therapeutics Inc. must be notified in writing of the person responsible for record retention and the notification will be retained in the Sponsor study file and the Investigator site file.

6.3.2 Access to Information for Monitoring

The data will be recorded and kept current in eCRFs by the study site personnel directly responsible for the information and reviewed for completeness by the monitor. Grifols Therapeutics Inc. personnel or designee can review the records.

In accordance with ICH GCP guidelines, the monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the eCRFs for consistency and to verify adherence to the protocol, and the completeness, consistency, and accuracy of data entered. "Source documentation" includes individual subject files, separate from the eCRFs, which should be maintained and include visit dates, laboratory results, concomitant treatment, vital signs, medical history, examinations, AEs, IP dispensing logs, and other notes as appropriate. The Investigator agrees to cooperate with the monitor to ensure that any problems noted during the course of these monitoring visits are resolved.

6.3.3 Access to Information for Audits or Inspections

Representatives of regulatory authorities or of Grifols Therapeutics Inc. may conduct audits or inspections of the Investigator study site. If the Investigator is notified of an audit or inspection by a regulatory authority, the Investigator agrees to notify the Grifols Therapeutics Inc. Medical Monitor immediately. The Investigator agrees to provide to representatives of a Regulatory Agency or Grifols Therapeutics Inc. access to records, facilities, and personnel for the effective conduct of an audit or inspection.

7 ETHICAL AND LEGAL ASPECTS

7.1 Institutional Review Board/Ethics Committee

Documented approval from appropriate IRBs/ECs will be obtained for all participating centers/countries prior to study start, according to ICH GCP guidelines, local laws, regulations, and organizations. When necessary, an extension, amendment or renewal of the IRBs/ECs approval must be obtained and also forwarded to the Sponsor. The IRBs/ECs must supply to the Sponsor, upon request, a list of the IRBs/ECs members involved in the vote and a statement to confirm that the IRB/EC is organized and operates according to ICH GCP guidelines and applicable laws and regulations.

7.2 Ethical Conduct of the Study

The procedures set out in this protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor and Investigator abide by ICH GCP guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an audit by the Sponsor representatives and/or an inspection by Regulatory Authority representatives at any time. The Investigator must agree to the audit or inspection of study-related records by the Sponsor representatives and/or Regulatory Authority representatives and must allow direct access to source documents to the Sponsor and/or Regulatory Authority representatives.

Modifications to the study protocol will not be implemented by either the Sponsor or the Investigator without agreement by both parties. However, the Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IRB/EC/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and if appropriate the proposed protocol amendment should be submitted to the IRB/EC/Sponsor. Any deviations from the protocol must be fully explained and documented by the Investigator.

7.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, must be in place and fully documented prior to study start. Study information including contact information for Investigator sites responsible for conducting the study will be posted on a publicly accessible clinical registry(ies) as required by local law.

7.4 Subject Information and Consent

Subject information, ICF, and Assent Form will be provided to Investigator sites. Prior to the beginning of the study, the Investigator must have the IRB/EC written approval/favorable opinion of the written ICF, Assent Form, and any other written information to be provided to subjects. The written approval of the IRB/EC together with the approved subject

information/Assent Form/ICF must be filed in the study files and a copy of the documents must also be provided to Sponsor by the Investigator site.

Written ICF by the subject or a parent and/or legal guardian along with subject assent, if applicable, must be obtained before any study specific procedure takes place. Participation in the study and date of ICF given by the subject should be documented appropriately in the subject's files. A signed copy of the subject ICF and Assent Form, if applicable, will be provided to the subject or subject's authorized representative (i.e., parent or legal guardian).

7.5 Insurance

Sponsor shall maintain comprehensive general liability insurance or self-insurance in amounts adequate to cover any damage, demand, claim, loss, or liability caused or incurred by Sponsor, or as otherwise required by applicable laws and/or regulations.

7.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number and subject initials will be recorded in the eCRF, and if the subject’s name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. Subjects will be informed in writing that representatives of the Sponsor, IRB/EC, or Regulatory Authorities may inspect their medical records to verify the information collected and that all personal information made available for an audit or inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject’s identity will remain confidential.

The Investigator will maintain a list to enable subjects’ records to be identified.

8 USE OF DATA AND PUBLICATION

Sponsor is committed to honoring the principles of academic freedom while, at the same time, protecting its confidential information, the subjects, and the integrity of the study, and the study documentation all in compliance with applicable law. Institution and/or Investigator recognize that, with respect to any study that is part of a multi-site study, there is a need for a coordinated approach to any publication or presentation of results from the sites. Accordingly, the Institution/Investigator shall not publish or present any results from this study to any third parties until: (1) Sponsor publishes the results; (2) Institution and/or Investigator receives written notification from Sponsor that publication of the results is no

longer planned; or (3) twelve (12) months following the close of Study, whichever occurs first.

Institution and/or Investigator shall submit to Sponsor for its review a copy of any proposed publication at least thirty (30) calendar days prior to the planned date of submission for publication or presentation. Institution and Investigator shall consider in good faith all comments received from Sponsor during the review period and shall delete Sponsor's confidential information (other than study results).

If Sponsor determines that the publication contains patentable subject matter which requires protection, Sponsor may require the delay of submission for publication or presentation for an additional period of time for the purpose of filing patent applications or otherwise take measures to protect such information.

Institution and/or Investigator shall acknowledge Sponsor's support in all publications and presentations.

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10 APPENDICES

Appendix 1 Schedule of Study Procedures

Procedures and Evaluation	Previous Regimen Phase			IGSC 20% Treatment Stage 1			IGSC 20% Treatment Stage 2			Final Visit (Week 53)/ Early Termination 1 Week post last IGSC 20% Dose
Visit Designations:	**Screening[a]**	**pIV#1[a] /pSC#1[a]**	**pIV#2**	**Baseline/ SC#1**	**SC#2 & 3**	**SC#5, 9, 13**	**SC#17**	**SC#18 in clinic only for PK subset**	**SC#20, 24, 28, 32, 36, 40, 44, 48, 52**	
Study Weeks				Week 1	Weeks 2&3	Weeks 5, 9, 13	Week 17	Week 18	Weeks 20, 24, 28, 32, 36, 40, 44, 48, 52	Week 53
Informed consent/assent (if applicable)	X									
Inclusion/exclusion criteria (confirm eligibility)[b]	X			X[c]						
Medical history, demography	X									
Record specific diagnosis of type of PI	X									
Full physical exam[d]	X			X[c]		SC#13[c]			SC#24[c], SC#36[c]	X
Weight[e]	X			X[c]		X[c]	X[c]	X[c]	X[c]	
Height	X			X		SC#13			SC#24, SC#36	X
Record results of most recent chest X-ray within 12 months[f]	X[f]									
Vital signs	X	X	X	X[c]		X[c]	X[c]	X[c]	X[c]	X
Record any serious bacterial infections (defined in Appendix 3), hospitalizations due to infections	X	X	X	X	X	X	X	X	X	X
Record non-serious infections as AEs & antibiotic treatment	X	X	X	X	X	X	X	X	X	X
Record days lost from work/school/daily activities due to infections and treatment		X	X	X	X	X	X	X	X	X
Laboratory assessments (chemistry, hematology, special tests, urinalysis)[g]	X			X[c]		SC#13[c]			SC#24[c], SC#36[c]	X[c]
Serum pregnancy test[h]	X	X[c, g]								X
Urine pregnancy test[h] (at site)				X[c]						
Trough (pre-dose) PK IgG sampling	X	X[c]	X[c]	X[c]	SC#2 only[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Sample for IgG subclass levels & antibody titers for bacterial pathogens (*H. influenzae, S. pneumoniae*, *C. tetani* [tetanus])	X			X[c]		SC#13[c]			SC#24[c], SC#36[c]	X[c]

Procedures and Evaluation Visit Designations:	Previous Regimen Phase			IGSC 20% Treatment Stage 1			IGSC 20% Treatment Stage 2			Final Visit (Week 53)/ Early Termination 1 Week post last IGSC 20% Dose
	Screening[a]	pIV#1[a] /pSC#1[a]	pIV#2	Baseline/ SC#1	SC#2 & 3	SC#5, 9, 13	SC#17	SC#18 in clinic only for PK subset	SC#20, 24, 28, 32, 36, 40, 44, 48, 52	
Study Weeks				Week 1	Weeks 2&3	Weeks 5, 9, 13	Week 17	Week 18	Weeks 20, 24, 28, 32, 36, 40, 44, 48, 52	Week 53
Blood draw for trough measles antibody titer				X[c]					SC#20, SC#52[c]	
HIV NAT testing	X									
Collection of virus safety retain samples[i]				X[c]						
Previous (p)IV/SC infusions		X	X							
IGSC 20% infusion intervals				X	X	q weekly 4-13	q weekly 14-17	X	q weekly 18-52	
IGSC 20% given in clinic infusion number[j]				SC#1	SC#2, 3	SC#5, 9, 13	SC#17	SC#18	SC#20, 24, 28, 32, 36, 40, 44, 48, 52	
Serial PK sampling							X[k]----------X[k]			
Prior and concomitant medications[l]	X	X	X	X	X	X	X	X	X	X
Adverse events including infusion reactions (see Section 4.3.1 for definitions) and clinical observation of signs and symptoms suggestive of any significant disease or condition [e.g., thrombosis, anemia, etc.])	X	X	X	X	X	X	X	X	X	X
Review SC infusion diary & infusion details with subjects/caregivers				X		X	X		X	X

Note: Please see Appendix 3 for serious bacterial infections diagnostic tests and requirements (e.g., chest X-ray, cultures) that are required per FDA Guidance to meet criteria for this primary endpoint. If a SBI occurs, additional testing is needed to validate and must be recorded in the eCRF.

Similarly, for validated non-serious infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, or diagnostic testing for microorganisms the specific evaluations performed to validate infections must be recorded in the eCRF.

[a] The Screening Visit can coincide with the previous (p)IV#1 or pSC#1 visit. After the pIV#1 infusion, subjects will receive the pIV#2 infusion. After previous (p)SC#1 infusion, subjects will enter IGSC 20% Treatment Stage 1 directly.

[b] Inclusion/exclusion criteria must be satisfied before the subject receives the first IGSC 20% infusion.

[c] **Must be performed prior to IgG replacement product administration at designated study visits**.

[d] Excludes breast and genitourinary exam.

[e] The recorded weight will be used to calculate the IGSC 20% dose for this study visit and subsequent weekly infusions until next in clinic study visit where weight is measured.

[f] Record results of most recent chest X-ray within 12 months (A chest X-ray will be necessary if not performed within 12 months of the Screening visit for adult subjects as permitted per local requirements).

[g] Laboratory Assessments (chemistry, hematology, haptoglobin, & urinalysis) will be performed at the Screening and Baseline Visits. Additional testing of all laboratory assessments will be prior to IGSC 20% infusion clinic visits coinciding with SC#13, #24, and #36, and the Final Visit. Laboratory testing includes **Hematology**: Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential; ARC. **Additional Special Tests**: DAT, serum free hemoglobin, haptoglobin (during Screening and Baseline, only haptoglobin will be measured. At all other time points specified, all additional special tests will be performed). **Chemistry**: Sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, ALP, glucose, total bilirubin, indirect bilirubin. **Urinalysis**: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal).

[h] Potential child-bearing females only; results must be negative to participate in the study or continue on IP. Qualitative serum β-HCG will be performed at Screening Visit and repeated during the Screening/Previous Regimen Phase for subjects entering study on a prior IVIG regimen who do not have Screening Visit and pIV#1 coincide (pre-dose pIV#1) given the potential for an 8-week time interval before Baseline. A qualitative urine pregnancy test will be performed at Baseline at the investigative site.

[i] Collect blood samples at Baseline, prior to IGSC 20% infusion but test *only* if the subject exhibits clinical signs and symptoms consistent with hepatitis A, hepatitis B, hepatitis C, HIV, or parvovirus B19 infection while participating in the study. See Section 3.6.3 and Table 3-1 for details. **Note: For young pediatric subjects, at the discretion of the Investigator, virus safety retain samples may be drawn the day prior to Baseline instead of combining with other baseline blood draws on a single day**.

[j] During Treatment Stage 1 and Treatment Stage 2 IGSC 20% infusions will be given in the clinic with observation of self-administration technique (subject/caregiver) of SC infusion at Visit Designations SC#1, 2, 3, 5, 9, 13, 17, (18 for PK subset), 20, 24, 28, 32, 36, 40, 44, 48, and 52. The remaining weekly IGSC 20% doses should be administered at home.

[k] Blood draws for PK assessment will be taken in approximately 20 adults subjects at the following time points: prior to the 17th IGSC 20% infusion (within 0.5 hour of the start of infusion); immediately at the completion of the 17th SC infusion; 1 day ± 4 hours post infusion; 3 days ± 4 hours post infusion; 5 days ± 4 hours post infusion and 7 days ± 1 day post infusion (within 0.5 hour prior to the 18th IGSC 20% dose) for IgG trough level.

[l] For antibiotics distinguish between prophylactic use and use for treatment of an episode of infection.

Appendix 2 PK Subset Group Detail Commencing at SC#17 IGSC 20% Treatment Stage 2 (~20 adults)

	SC#17	1 day ± 4 hours post SC#17	3 days ± 4 hours post SC#17	5 days ± 4 hours post SC#17	SC#18
Serial PK profile total IgG post IGSC 20% SC#17	**X** prior to the 17th IGSC 20% infusion (within 0.5 hour of the start of infusion)	**X**	**X**	**X**	**X** 7 days ± 1 day post SC#17 (within 0.5 hour prior to the 18th IGSC 20% dose) for IgG trough level
	X immediately at the completion of the 17th SC infusion				

Appendix 3 Diagnostic Criteria for Serious Infection Types

Infection: Bacteremia/sepsis[a]

- *Symptoms:* chills, rigors
- *Physical findings:* fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure < 90 mmHg or a reduction of ≥ 40 mmHg 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 (MRI) scan, or computed tomography (CT) scan showing bony destruction with radiolucent areas; for chronic osteomyelitis: sequestra, involucra**

Note: 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 mmHg; WBC count > 12,000/mm^3, < 4,000/mm^3, or > 10% immature (band) forms (48). For pediatric subjects, we recommend you employ the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis (49).

[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 subjects without indwelling catheters or vascular access devices, a single blood culture positive for a pathogenic organism will meet the diagnostic criteria for bacteremia. (Multiple blood cultures are typically obtained in cases of suspected bacteremia/sepsis, as per standard medical practice, and the finding of a single positive culture should prompt additional confirmatory cultures). Subjects 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 *S. pneumoniae*, *Neisseria meningitides*, or *H. influenzae*, in combination with CSF leukocytosis and/or decrease in CSF glucose, can serve to confirm the diagnosis of acute bacterial meningitis (50).

Infection: Bacterial Pneumonia[d] • *Symptoms*: productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgias • *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 (PaO_2 < 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 (CXR)** (new in comparison with Baseline CXR)
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, CT scan, MRI scan, or radionuclide scan**

Note: Items in bold are considered essential diagnostic features.

[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 infection episodes in a clinical trial of IVIG, the finding of a new pulmonary infiltrate with consolidation on CXR 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 (51).

[e] We recommend 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 (51).

Appendix 4 Blood Pressure Percentiles for Pediatric Patients

Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in Table 3 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.