Clinical Study Protocol

Protocol Title:	An open-label, multi-center study to evaluate the safety and pharmacokinetics of IGSC 20% administered for 6 months 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]
Study Number/Protocol Version Number/Date:	GTI1502/Version 3.0/15 Mar 2016 Includes GTI1502/Version 2.0/20 Aug 2015 and GTI1502/Version 1.0/16 Jun 2015
IND Number:	16528
Development Phase:	3

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

Medical Monitor: [redacted]

Signature: [redacted] **Date:** 15 March 2016

Confidentiality Statement:

Summary of Changes for Amendment 2

Protocol Version	Date of Approval
3.0 Amendment 1 + Integrated Protocol	15 Mar 2016
2.0 Amendment 1 + Integrated Protocol	20 Aug 2015
1.0 Original	16 Jun 2015

Protocol Amendment 2

The protocol for GTI1502 (Version 2.0, dated 20 Aug 2015) has been amended and reissued as Protocol Amendment 2, Version 3.0, dated 15 Mar 2016.

SUMMARY OF CHANGES FOR AMENDMENT 2

Sections	Change From: (Strikethrough is added to highlight deleted text)	Change To: (Underline is added to highlight new text)	Rationale:
Global change	Approximately 50 subjects will be enrolled in order to have approximately 30 adult subjects and 12 to ~~15~~ pediatric subjects (age 2-16 years) completing treatment with subcutaneously administered IGSC 20%.	Approximately 50 subjects will be enrolled in order to have approximately 30 adult subjects and 12 to 18 pediatric subjects (age 2-16 years) completing treatment with subcutaneously administered IGSC 20%.	For internal consistency.
Global change	Screening Phase: ~~7~~ to 28 days	Screening Phase: up to 28 days	To clarify that a minimum Screening duration is not required.
Protocol Synopsis, Sections 3.3.2.3, 3.5.4, 3.6.2.4, and 4.3.1	~~local~~ infusion site reactions	infusion site reactions	To provide clarification.
Protocol Synopsis: Inclusion Criteria Section 3.2.1	3. The subject has not had an SBI within the last 3 months prior to Screening. 4. Currently on IgG replacement therapy (via IV or SC infusion) for ≥3 ~~consecutive~~ months. ~~Subjects receiving IVIG prior to study must receive a dosage of 300 to 800 mg/kg per infusion.~~ 5. ~~Documented (at least once within previous 3 months) IgG trough level of ≥500 mg/dL on current IgG replacement therapy regimen.~~ 6. Screening trough IgG levels must be ≥500 mg/dL. Note: If Screening trough levels are not above this threshold, the subjects 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.	3. The subject has not had an SBI within the last 3 months prior to or during Screening. 4. Currently on IgG replacement therapy (via IV or SC infusion) for ≥3 months. 5. Note: This inclusion criterion is removed in protocol amendment 2. 6. Screening trough IgG levels must be ≥500 mg/dL. Note: If Screening trough levels are not above this threshold, the subjects 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 months prior to Screening a second time.	(4) IVIG dose inclusion stipulation removed due to Run-in Phase which adjusts to the required dose range. (5) Historical IgG trough criterion removed since not evaluated frequently in medical practice.

Sections	Change From: (Strikethrough is added to highlight deleted text)	Change To: (Underline is added to highlight new text)	Rationale:
Protocol Synopsis: Exclusion Criteria Section 3.2.2	7. The subject has significant proteinuria (dipstick proteinuria ≥3+ or known urinary protein loss >1~~-2~~ g/24 h or nephrotic syndrome) and/or has a history of acute renal failure and/or severe renal impairment (blood urea nitrogen [BUN] or creatinine more than 2.5 times the upper limit of normal [ULN]) and/or on dialysis 18. 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 20. Mentally challenged subjects who cannot give independent informed consent	7. The subject has significant proteinuria (dipstick proteinuria ≥3+ or known urinary protein loss >1 g/24 h or nephrotic syndrome) and/or has a history of acute renal failure and/or severe renal impairment (blood urea nitrogen [BUN] or creatinine more than 2.5 times the upper limit of normal [ULN]) and/or on dialysis 18. 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 <u>with the exception of other IgG products</u> within the previous 3 months 20. Mentally challenged subjects who cannot give independent informed consent <u>or assent</u>	(7, 20) To further clarify other exclusions (18) To allow patients on previous investigational IgG studies to participate without a 3 month minimum time stipulation to avoid potential treatment hiatus.
Protocol Synopsis: Determination of Sample Size Section 5.2	…Also a sample size of 42 to ~~45~~ with at least 24 scheduled administrations of IGSC 20% would provide the clinical experience data on a total of more than 1008 to 1080 IGSC 20% dosing administrations for safety assessment. The planned enrollment of 42 subjects should be more than adequate to establish that the AUC for total IgG for IGSC 20% is non-inferior to that achieved by IGIV-C 10%.	…Also a sample size of 42 to <u>48</u> with at least 24 scheduled administrations of IGSC 20% would provide the clinical experience data on a total of more than 1008 to 1080 IGSC 20% dosing administrations for safety assessment. The planned <u>minimum</u> enrollment of 42 <u>completing</u> subjects should be more than adequate to establish that the AUC for total IgG for IGSC 20% is non-inferior to that achieved by IGIV-C 10%.	To provide clarification for the requirements for number of subjects
Section 3.1.2 Run-In Phase	Group 2 - Three (3)-month Run-In Phase: Those subjects who prior to screening are receiving IVIG therapy (at a dose between 300 and 800 mg/kg per infusion every 3 or 4 weeks) but who are not receiving IGIV-C 10% specifically (ie, a different commercially available IVIG) will be required to receive IGIV-C 10% intravenously (at an equivalent dose and dosing interval as in their previous IVIG therapy) for a total duration of a 3-month Run-In Phase.	Group 2 - Three (3)-month Run-In Phase: Those subjects who prior to screening are receiving IVIG therapy (at a dose between 300 and 800 mg/kg per infusion every 3 or 4 weeks) but who are not receiving IGIV-C 10% specifically (ie, a different commercially available IVIG) will be required to receive IGIV-C 10% intravenously (at an equivalent dose and dosing interval as in their previous IVIG therapy) for a total duration of a 3-month Run-In Phase. <u>Subjects receiving infusions</u>	To add clarification

Sections	Change From: (Strikethrough is added to highlight deleted text)	Change To: (Underline is added to highlight new text)	Rationale:
		every 3 weeks will have 4 Run-In visits and subjects receiving infusions every 4 weeks will have 3 Run-In visits. Group 3 - Four (4)-month Run-In Phase: Subjects meeting any of the criteria for Group 3 will be scheduled to begin receiving IGIV-C 10% intravenously at a dose of 300 to 800 mg/kg every 3 to 4 weeks (dose and interval to be determined based on the investigator's clinical judgment) for a period of up to 4 months prior to the IV#1 visit. Subjects receiving infusions every 3 weeks will have 5 Run-In visits and subjects receiving infusions every 4 weeks will have 4 Run-In visits.	
	Group 3 - Four (4)-month Run-In Phase: Subjects meeting any of the criteria for Groups 2 and 3 will be scheduled to begin receiving IGIV-C 10% intravenously at a dose of 300 to 800 mg/kg every 3 to 4 weeks (dose and interval to be determined based on the investigator's clinical judgment) for a period of up to 4 months prior to the IV#1 visit. The number of visits (up to 5) during the Run-In Phase will be determined based on each subject's previous IgG treatment regimen.		
Section 3.3.1.4	IGSC 20% and IGIV-C 10% must be stored at temperatures of 2°C to 8°C (36°F to 46°F) and protected from light. Do not freeze. Investigators, or designees, are responsible for maintaining storage temperature records and for immediately reporting deviations in temperature to the study monitor.	IGSC 20% and IGIV-C 10% 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.	Wording to be consistent with the Pharmacy manual
Section 3.3.2.2	The IV and SC dose of study drug will be individualized based on each subject's current IgG regimen which is assumed to be an effective dose. Subjects are required to have been clinically stable for at least 3 months on this pre-determined dose (between 300-800 mg/kg administered every 3 or 4 weeks) of an approved IgG product. The IV IGIV-C 10% dose will be the same as this established dose and dosing interval. For those subjects currently on SCIG, the initial IV IGIV-C 10% dose should be between 300 and 800 mg/kg in conjunction with investigator judgment.	The IV and SC dose of study drug will be individualized based on each subject's current IgG regimen which is assumed to be an effective dose. Subjects are required to have been clinically stable for at least 3 months on an IgG product. The IV IGIV-C 10% dose will be between 300 and 800 mg/kg during the Run-in phase and IV#1 and IV# 2. See Table 3-1.	For internal consistency and simplicity
Section 3.3.2.3	Details regarding infusion rate and infusion administration are located in the pharmacy/study manual. Subjects may use the same anatomical area or rotate	Details regarding infusion rate and infusion administration are located in the pharmacy/study manual. Subjects may use the same anatomical area or rotate	Corrects inconsistency since there is allowance

Sections	Change From: (Strikethrough is added to highlight deleted text)	Change To: (Underline is added to highlight new text)	Rationale:
	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. The ~~maximum~~ 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.	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. 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.	to increase the infusion rate.
Section 3.3.3.1	Within each study site, subjects in the study will receive a consecutive subject number at Screening Visit. Subject numbers are generated beginning with the study center number (3 digits, assigned by the Sponsor starting at 100) followed consecutively with a unique number for each subject (4 digits~~, including leading zeros~~). For example, if the Investigator's center number is 301, subject numbers will be ~~3010001~~, ~~3010002~~, ~~3010003~~, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.	Within each study site, subjects in the study will receive a consecutive subject number at Screening Visit. Subject numbers are generated beginning with the study center number (3 digits, assigned by the Sponsor starting at 100) followed consecutively with a unique number for each subject (4 digits). For example, if the Investigator's center number is 301, subject numbers will be 3012001, 3012002, 3012003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.	To reflect the actual numbering convention used.
Section 3.3.4	All dose calculations will be done by the~~ study clinic personnel~~ and the dose preparation procedures will be provided to each subject for in-home SC administration.	All dose calculations will be done by the Interactive Web Response (IWR) system and the dose preparation procedures will be provided to each subject for in-home SC administration.	To reflect the actual system used.
Section 3.4	Concomitant medications must be recorded in the subject's source documents and in the eCRF, including the trade or generic names of the medication, the dose, the route of administration, duration, and frequency.	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.	To specify the starting time for concomitant medications recording
Section 3.4.2	Use of the following during the study (from Screening to SC Week#25 Final Visit) is prohibited: • Any IgG replacement therapy other than IGIV-C 10% or IGSC 20% provided in this study	Use of the following during the study (from Screening to SC Week#25 Final Visit) is prohibited: • Any IgG replacement therapy other than IGIV-C 10% or IGSC 20% provided in this study once the first dose of study treatment is administered	To specify the starting point for the prohibition of any non-study IgG replacement therapy

Sections	Change From: (Strikethrough is added to highlight deleted text)	Change To: (Underline is added to highlight new text)	Rationale:
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 (eg, 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 (eg, to treat an AE):	To provide clarification
Section 3.6.2	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. For ~~all~~ visits, a ± 1 day window is allowed~~, with the exception of~~ the serial PK sampling visits, ~~and t~~he SC#2 and SC#3 visits ~~which~~ must be performed with a +1 day visit window (ie, these 2 visits cannot be performed 1 day early). Unscheduled visits may be conducted if deemed necessary for the purpose of subject safety.	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. For most clinic visits, a ± 1 day window is allowed. For the serial PK sampling visits, see specific PK windows in Section 3.6.2.3 and 3.6.2.4. If there are logistical issues requiring schedule adjustment for weekly subcutaneous IGSC 20% administration, SC#1 may be scheduled 6 to 9 days after IV#2. The SC#2 and SC#3 visits must be performed with a +1 day visit window (ie, these 2 visits cannot be performed 1 day early). Unscheduled visits may be conducted if deemed necessary for the purpose of subject safety.	To clarify the timing of visit windows.
Section 3.6.2.1	The subject's medical records will be reviewed to confirm a documented diagnosis of PI. Subjects who are interested in participating will undergo the following tests and procedures: • Written informed consent and assent if applicable will be obtained prior to initiation of any screening procedures • Eligibility will be checked by careful assessment of the inclusion and exclusion criteria • Demographics and medical history will be recorded including age, gender, age at diagnosis of PI, previous /current IgG treatments.	The subject's medical records will be reviewed to confirm a documented diagnosis of PI. Subjects who are interested in participating will undergo the following tests and procedures: • Written informed consent and assent if applicable will be obtained prior to initiation of any screening procedures • Eligibility will be checked by careful assessment of the inclusion and exclusion criteria • Demographics and medical history will be recorded including age, gender, age at diagnosis of PI, and past 12 months of previous /current IgG treatments. Record relevant medical history defined as any history impactful on the subject's condition in terms of current functioning, disability, treatment, or management.	To clarify requirements for medical history documentation and chest X-ray

Sections	Change From: (Strikethrough is added to highlight deleted text)	Change To: (Underline is added to highlight new text)	Rationale:
	• Chest X-ray (if chest X-ray or CT have not been performed within past 6 months prior to screening) • Total IgG trough level determination: participants will be required to have a ~~documented~~ total IgG level of ≥500 mg/dL to enroll	• Chest X-ray (if chest X-ray or CT have not been performed within past 6 months prior to screening) Note: at least one radiographic view (anterior-posterior [AP] or posterior- anterior [PA] is required.) • Total IgG trough level determination: participants will be required to have a screening total IgG level of ≥500 mg/dL to enroll	
Section 3.6.2.3 IV#1 VISIT & PK ASSESSMENT FOR IV DOSING	• Predose urine pregnancy test	• Predose urine pregnancy test (child-bearing potential females only)	To clarify the pregnancy test is for women of child-bearing potential
Section 3.6.2.4 SC Week #1 Clinical Visit Appendix 1 footnote [m]	• Predose virus safety retain samples Note: For children at the discretion of the Investigator, virus safety retain samples may be drawn ~~the~~ day prior to SC Week#1 instead of combining with other blood draws on a single day.	• Predose virus safety retain samples Note: For children at the discretion of the Investigator, virus safety retain samples may be drawn 1 or 2 days prior to SC Week#1 instead of combining with other blood draws on a single day	To clarify the window for virus safety retain samples
Section 3.6.2.4 Section 3.6.2.5	b. ……Or any single alarm symptom such as hemoptysis or cyanosis (36,37,38).	c. Any single alarm symptom such as hemoptysis or cyanosis (36,37,38).	Format change
Section 3.6.2.5	If the results of the interim PK analysis do not indicate a need for a dose adjustment factor change, subjects will be brought into the clinic and end of study procedures will be performed.	If the results of the interim PK analysis do not indicate a need for a dose adjustment factor change, subjects will be brought into the clinic (within one week following the confirmation of the initial dose adjustment factor) and end of study procedures will be performed.	To specify a timeframe for bringing subjects back for end of study procedures
Section 3.6.3 Table 3-2	Additional special tests[a] DAT, serum free hemoglobin, haptoglobin Central ~~(central DAT if feasible)~~	Additional special tests[a] DAT, serum free hemoglobin, haptoglobin Central	To provide clarification that this testing will be performed at the

Sections	Change From: (Strikethrough is added to highlight deleted text)	Change To: (Underline is added to highlight new text)	Rationale:
			central laboratory
Section 3.6.2.3	Note: For pediatric subjects, at the discretion of the Investigator, virus safety retain samples may be drawn ~~the~~ day prior to SC Week#1 instead of combining with other blood draws on a single day.	Note: For pediatric subjects, at the discretion of the Investigator, virus safety retain samples may be drawn 1 or 2 days prior to SC Week#1 instead of combining with other blood draws on a single day.	To clarify the window for virus safety retain samples
Section 3.7	Subjects ~~may~~ withdraw or be withdrawn from the study for the following reasons: Also, subjects ~~may~~ be withdrawn from IP/study drug or the study for the following reasons: • Subjects who develop an SBI ~~during the IV Run-In Phase or IGIV-C 10% IV Phase~~ prior to the first dose of IGSC 20% If a subject discontinues study after receiving IGIV-C 10% but prior to receiving the first dose of IGSC 20%, an additional subject may be recruited into the study to assure that 30 adults and 12 children ~~receive at least one dose of~~ IGSC 20%.	Subjects will withdraw or be withdrawn from the study for the following reasons: Also, subjects will be withdrawn from IP/study drug or the study for the following reasons: • Subjects who develop an SBI prior to the first dose of IGSC 20% If a subject discontinues study after receiving IGIV-C 10% but prior to receiving the first dose of IGSC 20%, an additional subject may be recruited into the study to assure that 30 adults and 12 children complete IGSC 20% treatment.	To provide clarification for subject discontinuation and subject completion target
Section 4.3.1	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.	An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product or study treatment and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.	To provide clarification
Section 4.4.1	Any SAE (see Section 4.3.6) that occurs after signing the study ICF through the Final Visit (ie, end of study) must be expeditiously reported whether or not considered attributable to the study drug. Each SAE must be fully	Any SAE (see Section 4.3.6) that occurs after signing the study ICF through the Final Visit (ie, end of study) must be expeditiously reported whether or not considered attributable to the study drug. Each SAE must be fully	To provide clarification for SAE reporting

Sections	Change From: (Strikethrough is added to highlight deleted text)	Change To: (Underline is added to highlight new text)	Rationale:
	recorded in the subject's eCRF ~~or~~ 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 ~~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. Each SAE must be followed up until resolution or stabilization. After the initial report, all relevant information for SAE follow up, and for 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 and Pregnancy Report Forms must be reported to ~~Grifols electronically through the EDC system or when the EDC system is not available, reported to~~:	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. Each SAE must be followed up until resolution or stabilization. After the initial report, all relevant information for SAE follow up, and for 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 and Pregnancy Report Forms must be reported to:	procedures
Section 4.4.2	(No previous text)	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 from time of consent through the Final Visit (ie, 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	To provide procedures for reporting pregnancy

Sections	Change From: (Strikethrough is added to highlight deleted text)	Change To: (Underline is added to highlight new text)	Rationale:
		Section 4.4.1) within 24 hours of the Investigator or study personnel's first knowledge.	
Appendix 1	Pre-dose laboratory assessments (hematology, chemistry, ~~special tests,~~ urinalysis)[i] Special tests ~~only~~ (DAT, serum free hemoglobin, haptoglobin) Footnotes: [f] Only if chest X-ray or CT have not been performed in the past 6 months at Screening [j] Pregnancy testing will be repeated at any time if pregnancy is suspected. [n] Weekly SC dosing may be 7 days ± 1 day. ~~except for~~ SC#2 and SC#3 ~~which~~ must be performed with a +1 day window.~~; the~~ first 3 SC infusions of IGSC 20% will be performed in the clinic where site personnel will instruct on/observe proper SC dosing technique using the pump. Subsequent monthly SC infusions will also occur and be observed in the clinic after labs and total IgG trough levels are obtained. Other SC infusions will be performed at home for interim weeks starting after the SC Week #3 visit.	Pre-dose laboratory assessments (hematology, chemistry, urinalysis)[i] Special tests (DAT, serum free hemoglobin, haptoglobin) *Special tests assessment added at Screening, IV#1 Baseline, SC Week #1, SC Week #9, SC Weeks #17, Final Visit (Week #25)/Early Termination, and Monthly Extension Visit* Footnotes: [f] Only if chest X-ray or CT have not been performed in the past 6 months at Screening (Note: at least one radiographic view (AP or PA) is required.) [j] Pregnancy testing will be repeated at any time if pregnancy is suspected. Pregnancy testing including serum and urine tests will be performed for child-bearing potential females only. [n] Weekly SC dosing may be 7 days ± 1 day. If there are logistical issues requiring schedule adjustment for weekly subcutaneous IGSC 20% administration, SC#1 may be scheduled 6 to 9 days after IV#2. SC#2 and SC#3 visits must be performed with a +1 day window. The first 3 SC infusions of IGSC 20% will be performed in the clinic where site personnel will instruct on/observe proper SC dosing technique using the pump. Subsequent monthly SC infusions will also occur and be observed in the clinic after labs and total IgG trough levels are obtained. Other SC infusions will be performed at home for interim weeks starting after the SC Week #3 visit.	Changes made to be consistent with the changes in the protocol text body

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

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:
An open-label, multi-center study to evaluate the safety and pharmacokinetics of IGSC 20% administered for 6 months in subjects with primary immunodeficiency

Study Number:
GTI1502

Phase:
3

Number of Subjects Planned:
Approximately 50 subjects

Study Centers Planned:
Approximately 30 study centers

Study Objectives:

Primary Pharmacokinetic (PK) Objective

To determine a dose of weekly subcutaneously administered Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (Grifols) (IGSC 20%) that produces steady-state AUC of total IgG that is non-inferior to that of the regularly administered IV dose of Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified (Grifols) (IGIV-C 10%) in primary immunodeficiency (PI) subjects

Secondary Objective

To determine if IGSC 20% replacement therapy maintains mean steady-state trough total IgG levels that are comparable to the mean trough total IgG levels with the IGIV-C 10% replacement therapy in PI subjects

Safety Objective

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

Overall Study Description:

This is a prospective, multi-center, open-label, single-sequence, 6-month, PK and safety and tolerability study of IGSC 20% in subjects with PI. Approximately 50 subjects will be enrolled in order to have approximately 30 adult subjects and 12 to 18 pediatric subjects (age 2-16 years) completing treatment with subcutaneously administered IGSC 20%. Pediatric enrollment will be stratified by age category with a target of 4 to 6 children for each group: 2 to 5 years, >5 to 12 years, and >12 to 16 years of age. The PK profiles of total IgG following administration of both IV (IGIV-C 10%) administration and SC (IGSC 20%) administration under approximate steady-state conditions will be determined and compared.

This study will include 3 treatment phases: Run-In Phase, IV Phase (IV administration of

IGIV-C 10% treatment), and SC Phase (SC administration of IGSC 20%). Before a subject is to be enrolled (entering either the Run-In or IV Phase) into the study, the subject will be screened during the Screening Phase of up to 28 days (following the first assessment of subject eligibility).

Subjects, depending on their current IgG treatment regimen, may be required to enter the Run-In Phase to receive IV IGIV-C 10% treatment (Sponsor provided) to achieve an approximately steady-state condition prior to entering the IV Phase. They will then enter the IV Phase to determine the AUC profiles of IV infusions of IGIV-C 10%.

Subjects with a qualifying IV IGIV-C 10% treatment regimen (on stable IGIV-C 10% doses of 300-800 mg/kg) can enter the IV Phase directly where they will receive IGIV-C 10% (Sponsor provided). In the IV Phase, steady-state IV PK assessments including AUC will be performed.

After completing the IV Phase, subjects will enter the SC Phase to receive weekly SC doses of IGSC 20% for at least 24 weeks. The IGSC 20% dose will be determined by using an initial IV to SC dose adjustment factor of 1.37. After reaching an approximately steady-state condition, the SC PK profiles including AUC at SC Week #13 will be determined.

Comparison of the IV PK profiles and IGSC 20% PK profiles in the first 6 adult/adolescent subjects will be performed through an interim PK analysis. If the dose adjustment factor is deemed acceptable (SC dose of IGSC 20% is non-inferior to the subject's IV dose) (Section 3.1.5), all subjects will continue to complete treatment and assessments through Week#25 (no further monthly extension visits). Otherwise, a new dose adjustment factor will be employed for all subjects following the procedures described in Section 3.1.5, and subjects will receive 24 weeks of IGSC 20% treatment at the new IGSC 20% dose. In this study, the PK profiles will be assessed in all subjects. Subjects aged 2 to 5 years old will be assessed using an abbreviated sampling schedule for PK profiles.

The interim serial PK samples (for both the IGIV-C 10% IV and the IGSC 20% SC dosing phases) may be obtained at an alternate location. If an outside agency is utilized for sample collection, the samples will be drawn and processed per protocol and laboratory manual instructions.

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. 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.

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. Subjects 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 (eg, X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (eg, 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 or during Screening.
4. Currently on IgG replacement therapy (via IV or SC infusion) for ≥3 months.
5. *Note: This inclusion criterion is removed in protocol amendment 2.*
6. Screening trough IgG levels must be ≥500 mg/dL.

   Note: If Screening trough levels are not above this threshold, the subjects 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 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

<u>Exclusion Criteria:</u>

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)
6. Females of childbearing potential who are pregnant, have a positive pregnancy test at

Screening (serum) or IV#1 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 [eg, 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+ or known urinary protein loss >1 g/24 h or nephrotic syndrome) and/or has a history of acute renal failure and/or severe renal impairment (blood urea nitrogen [BUN] or creatinine more than 2.5 times the upper limit of normal [ULN]) and/or on dialysis
8. The subject has Screening Visit values of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding more than 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 history of or current diagnosis of deep venous thrombosis or thromboembolism (eg, deep vein thrombosis, myocardial infarction, cerebrovascular accident or transient ischemic attack); history refers to an incident in the year prior to Screening or 2 episodes over lifetime.
11. The subject is currently receiving anti-coagulation therapy which would make SC administration inadvisable (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [eg, dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], parenteral anticoagulants [eg, fondaparinux]).
12. The subject currently has a known hyperviscosity syndrome.
13. 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).
14. 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.
15. 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 3) or the adult subject has non-controlled arterial hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg)
16. 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.

17. The subject has known substance or prescription drug abuse
18. 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
19. The subject/caregiver is unwilling to comply with any aspect of the protocol, including the home SC infusions, blood sampling, and completion of a SC infusion diary for the duration of the study
20. Mentally challenged subjects who cannot give independent informed consent or assent
21. 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:

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

IGSC 20% is a sterile liquid formulation of immunoglobulin that has been purified from human plasma via a multi-step process. IGSC 20% is manufactured using the same process as for IGIV-C 10% (Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified [IGIV-C]), with the addition of a nanofiltration step and is further concentrated by ultrafiltration to a higher IgG concentration (20%). IGSC 20% vials will be supplied in a 50 mL vial size or smaller containing a 20% solution of immunoglobulin, ie, a concentration of 20 g/100 mL, with a nominal 10 grams immunoglobulin per vial.

In the current study, the initial IV to SC dose adjustment calculation formula used is:

$$\frac{\text{300 to 800 mg/kg (IV dose)}}{\text{3 or 4 (regular IV dosing interval in week)}} \times 1.37 \text{ (IV to SC dose adjustment factor)}$$

Reference Therapy, Dose and Mode of Administration:

Grifols Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified (IGIV-C 10%)

IGIV-C 10% is a sterile liquid formulation of immunoglobulin that has been purified from human plasma. IGIV-C 10% is a licensed product. IGIV-C 10% vials may be supplied in the vial sizes of 10, 25, 50, 100, and 200 mL. In this study, administration of IGIV-C 10% will be via the IV route only.

The IV IGIV-C 10% dose and dosing interval will be individualized based on the treatment each subject is receiving for their PI at screening.

Duration of Treatment:

Total duration of study participation: up to 50 weeks

Screening Phase: up to 28 days

Treatment duration:

Run-In Phase: 3 to 4 months

IV Phase: 4 to 5 weeks

SC Phase: 24 weeks

If the initial dose adjustment factor is deemed insufficient at the time of the interim PK analysis (please see synopsis section below), a new dose adjustment factor will be calculated and implemented. In this case, all subjects will complete 24 weeks of IGSC 20% treatment with a dose determined using the new dose adjustment factor.

Study Variables:

Primary PK Variable

- AUC in the IV Phase: Steady-state AUC of total IgG over a regular dosing interval (τ), either every 3 weeks or every 4 weeks (ie, $AUC_{0-\tau,IV}$ or $AUC_{0\text{-}21days,IV}$ or $AUC_{0\text{-}28\ days,IV}$, respectively) in PI subjects
- AUC in the SC Phase: Steady-state AUC of total IgG over a weekly SC dosing interval (τ) (ie, $AUC_{0-\tau,SC}$ or $AUC_{0\text{-}7days,SC}$) in PI subjects

Secondary Variables

- Mean steady-state trough (pre-dose) concentration of total IgG following IV administration of IGIV-C 10% or SC administration of IGSC 20%

Exploratory Variables

- t_{max} (time to reach C_{max}) and C_{max} in PI subjects at steady state
- Trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Antibody levels for *S. pneumoniae*, *H.influenzae*, and *C. tetani* (tetanus)
- Rate of serious bacterial infection (SBI)
- 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
- Validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms eg, bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test)
- 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 due to infections and their treatment
- Trough measles antibody titers (functional assay) for informational purposes

Safety Variables

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

  Note: All infusion site reactions will be recorded in the eCRF. For local infusion site reactions where the signs/symptoms 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, they will be considered as AEs.
- Vital signs during clinic visits (systolic blood pressure [SBP] and diastolic blood pressure [DBP], heart rate [HR], temperature [T], respiratory rate [RR])
- Physical assessments: physical examinations 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.
- Total number of non-serious infections and proportion of subjects who experience non-serious infections of any kind (including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator.

Key Assessments and Procedures:

IgG trough levels will be measured for all subjects during the Screening Visit, Run-In Phase, IV Phase, and SC Phase as detailed in Appendix 1.

The sampling for determining PK profiles for IV administered IGIV-C 10% will commence at the IV#1 (IV Phase) visit for all enrolled subjects.

The sampling for determining PK profiles for the SC administration of IGSC 20% will commence at the SC Week #13 visit for all enrolled subjects.

Subjects between the ages of 2 and 5 years of age will undergo serial PK sampling using an abbreviated sampling schedule.

SC infusion diary: An IGSC 20% infusion diary will be provided to each subject prior to the first IGSC 20% infusion which may be used to record items including but not limited to: infusion site reactions, concomitant medications (including antibiotics [prophylactic and therapeutic]), and details of study drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume of each SC dose, 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.

Note: All infusion site reactions will be recorded. For the subset of local infusion site reactions where the signs/symptoms 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, these will be considered as AEs.

Statistical Methods:

Study Populations:

Safety Population

The safety population will include all subjects who received any amount of study drugs (IGIV-C 10% and/or IGSC 20%) and will be used for safety analysis.

PK Population

The PK population will consist of all subjects who receive study drugs and have sufficient and valid total IgG concentration vs. time data for either the IV or SC Phase to allow calculation of $AUC_{0-\tau,SC}$ or $AUC_{0-\tau,IV}$ (the primary PK endpoint).

The validity of total IgG concentrations will be reviewed and determined before the database lock based on consideration of treatment compliance and blood sampling/testing issues (such as collection problem). Any invalid total IgG concentrations will be flagged with the reason for invalidity in the listing.

IgG Population

The IgG population will consist of all subjects who receive study drugs and have any total IgG concentration data. The summary of total IgG concentration data will be based on IgG Population.

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.

Study Analyses:

Primary PK Analyses

The Primary PK endpoint is the steady-state AUC over a dosing interval defined as follows:

- $AUC_{0-\tau,SC}$, the AUC over a weekly dosing interval (τ) at an approximate steady-state condition following weekly SC infusion, ie, $AUC_{0\text{-}7\ days}$.
- $AUC_{0-\tau,IV}$, the AUC over a regular dosing interval (τ) at an approximate steady-state condition following the regular IV infusion, either every 3 weeks or every 4 weeks, ie, $AUC_{0\text{-}21\ days}$ or $AUC_{0\text{-}28\ days}$, respectively.

$AUC_{0-\tau,SC}$ is to be obtained after the 13th SC dose of IGSC 20% at the weekly dose calculated using the final dose adjustment factor, and $AUC_{0-\tau,IV}$ is to be obtained following IV infusion of IGIV-C 10% at the IV#1 visit. Since the dosing interval (τ) is 7 days for the SC dose, $AUC_{0-\tau,SC}$ is determined as $AUC_{0\text{-}7\ days}$. For IV dosing, the dosing interval (τ) is 21 or 28 days for the 3-week or 4-week subjects, $AUC_{0-\tau,IV}$ is determined as $AUC_{0\text{-}21}$ days or

$AUC_{0\text{-}28\ days}$, respectively.

Prior to statistical comparison of $AUC_{0\text{-}\tau's}$ between the IV IGIV-C 10% and SC IGSC 20% doses, the $AUC_{0\text{-}21}$ days from the IV infusion in subjects on a 3-week IV dosing interval will be divided by 3 or the $AUC_{0\text{-}28}$ days from IV dosing in subjects on a 4-week IV dosing interval divided by 4 for comparison with $AUC_{0\text{-}7}$ days from the weekly SC infusion.

The hypothesis to be tested is that the weekly SC dose of IGSC 20% will achieve an approximate steady-state $AUC_{0\text{-}\tau,\ SC}$ of total IgG that is non-inferior to that achieved by a regular IV dose of IGIV-C 10% ($AUC_{0\text{-}\tau,\ IV}$ divided by 3 or 4 depending on the IV dosing intervals). Non-inferiority of steady-state IgG AUC between SC dose of IGSC 20% and IV IGIV-C 10% administration will be tested based on established regulatory guidelines for bioequivalence testing. The 90% confidence interval (CI) of the geometric LSM ratio of SC AUC to IV AUC will be calculated. The SC dose is considered to be non-inferior to the IV dose if the low bound of the 90% CI for the geometric LSM AUC ratio is above 0.80 based on loge-transformed data.

Secondary and Exploratory PK Analysis

Secondary and exploratory PK endpoints include the steady-state mean trough concentration of total IgG and the C_{max}, t_{max} of total IgG. Descriptive statistics will be calculated for the steady-state mean trough concentration of total IgG and for C_{max} and t_{max} of total IgG. All pre-infusion total IgG concentrations obtained before and at the 13th SC dose of IGSC 20% will be evaluated to determine if an approximate steady-state condition has been achieved by the 13th SC dose. The steady-state mean trough concentrations of total IgG following SC administrated IGSC 20% will be determined as the average value of C_{trough} measurements obtained at Weeks#13, #14, #17, and #21. The mean steady-state trough concentrations of total IgG following IV administrated IGIV-C 10% will be determined as the average value of C_{trough} measurements obtained at the IV#1 visit and at 21 or 28 days after the IV#1 IGIV-C 10% dose (depending on dosing interval), ie, immediately prior to the administration of IV dose at IV#2 visit.

Summaries will be provided for trough concentration of total IgG and each of its subclasses between IV infusion of IGIV-C 10% and SC administration of IGSC 20%. Summaries of trough level concentration of antibody titers against *S. pneumonia*, *H.influenza*, and *C. tetani* will also be provided.

Depending on the number of subjects being dosed on IGIV-C 10% at 3- or 4-week dosing interval, subgroup analyses may be performed to evaluate PK variables by IV dosing interval. Subgroup analyses will additionally include age, sex, race, ethnicity and other factors as appropriate.

Additional exploratory variables will be summarized descriptively. The number and proportion of subjects having SBI, infections, days on antibiotics, hospitalizations due to infection, and days of work/school/daily activities missed due to infections will be calculated and summarized. Furthermore, the total number of events or days and corresponding annualized rate per subject of SBIs, infections, days on antibiotics, hospitalizations due to infection, and days of work/school/daily activities missed due to infections will be calculated

and summarized.

Interim PK Analysis

An interim PK analysis will be performed as soon as practical after the first 6 adult/adolescent subjects (age ≥12-75 years) have completed the PK sampling schedule for both the IV and SC (after the 13th SC dose) phases of the trial. PK data from these 6 adult/adolescent subjects will be analyzed using procedures as described above under primary efficacy analysis. A decision on whether to modify the dose adjustment factor for calculating the SC dose will be made based on this interim PK analysis.

Final PK and statistical analysis will be based on the PK data obtained after the final (or adjusted, if any) SC dose administered in all completed subjects.

Safety Analysis

The safety analyses are based on the safety population.

All AEs, suspected ADRs, AR, and SAEs, and discontinuations due to AEs and SAEs will be summarized by presenting the number of AEs and the number and percentage of subjects with AEs. 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 and non-serious infections 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 IV or 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.

Determination of Sample Size

The planned number of subjects (50 enrolled to provide 30 completing adult subjects and 12 to 18 completing pediatric subjects). This sample size is primarily based on safety assessment consideration. Also a sample size of 42 to 48 with at least 24 scheduled administrations of IGSC 20% would provide the clinical experience data on a total of more than 1008 to 1080 IGSC 20% dosing administrations for safety assessment.

The planned minimum enrollment of 42 completing subjects should be more than adequate to establish that the AUC for total IgG for IGSC 20% is non-inferior to that achieved by IGIV-C 10%.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

GLOSSARY AND ABBREVIATIONS

ADR	Adverse drug reaction
AP	Anterior-posterior
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Adverse reaction
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
DVT	Deep venous thrombosis
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)
IWR	Interactive Web Response
kg	Kilogram
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
NAT	Nucleic acid amplification technology
PA	Posterior- anterior
PE	Pulmonary embolus
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
SRC	Safety Review Committee
SSC	Specific Signs/Symptoms Check
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 infections (SBIs) 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).

IVIG infusions produce an immediate rise in the 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 to 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 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 (eg, IGIVnex in Canada) for both IV and SC administration. The advantage of higher concentration SCIG products (20%) is primarily reduced infusion volume and shorter infusion time thereby significantly increasing ease of administration.

1.3 Study Rationale

The investigational product (IP) in this study 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%. The second study drug is Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified, henceforth referred to as IGIV-C 10% which is approved for the indication of PI and will be employed in this trial to standardize IV immune globulin administration during the initial Run-In Phase and IV Phase (Section 3.1).

The primary objective of this study is to determine a dose of subcutaneously administered IGSC 20% that produces steady-state area under the concentration-time curve (AUC) of total IgG by weekly SC administration that is not inferior to that of a regularly administered IV dose of Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified (Grifols IGIV-C 10%). IGIV-C 10% is a 10% Grifols immunoglobulin product, licensed in the US as GAMUNEX® and some other countries (eg, IGIVnex in Canada) for both IV and SC administration. The additional objective of the trial is to assess the safety of the new IGSC 20% formulation.

In addition to the information provided here, please also refer to the Investigator's Brochure (IB) of IGSC 20% and IGIV-C 10%.

1.3.1 Dose Rationale

AUC-based IVIG to SCIG dose adjustments have historically been in the range of 1.37 to 1.53 across products (eg, Gamunex-C, Hizentra, Gammagard), and this study will commence with an IVIG:IGSC 20% dose adjustment ratio of 1.37, which is the same ratio used for the SC IGIV-C 10%.

For IGSC 20% preclinical data support an IVIG:IGSC 20% dose adjustment factor of 1.37. In a single dose study in New Zealand White rabbits, the AUC plasma fractional availability was calculated for IGSC 20% vs. IGIV-C 10%. A single 100 mg/kg IV bolus injection was compared with IGSC 20% at doses of 1.0, 1.15, 1.3, and 1.5 times the IV dose level. IGSC 20% produced an AUC that was 74%, 80%, 89%, and 95%, respectively, of the AUC produced by 100 mg/kg IV IGIV-C 10%. Thus, it is expected, that an IGSC 20% dose in the range of 1.3 to 1.5 times the IGIV-C 10% dose level will produce comparable AUC (see IGSC 20% IB).

The new product, IGSC 20%, is manufactured in a similar manner to IGIV-C 10% with an additional nanofiltration step and a higher final IgG concentration (20%). As such, it is anticipated that the clinical dosing strategy, safety, and efficacy attributes of IGSC 20% will be similar to IGIV-C 10% in patients with PI. IGIV-C 10% is currently approved for SC administration in PI in various geographic regions. The dose adjustment ratio employed in this protocol (1.37) for the transition from IV to SC route has been successfully evaluated with IGIV-C 10% in 2 Grifols clinical studies (06001 and T5004-401). Accordingly in this study, a 1:1.37 IV to SC dose adjustment factor will be initially employed for the transition from IVIG to IGSC 20% treatment and will be evaluated in the interim PK analysis.

Grifols Study 060001 showed that weekly SC administration of IGIV-C 10% in 32 adult/adolescents PI subjects resulted in a relatively constant steady-state trough concentration of total IgG (1140 mg/dL). The steady-state trough levels of IgG following SC infusions were found to be 19% higher than those from IV infusions. There were no SBIs reported in the 24-week SC treatment phase (34). This study demonstrated that the 1:1.37 IV to SC dose adjustment factor produced a point estimate for the geometric least squares mean (LSM) ratio of AUC_{SC} vs. AUC_{IV} of 0.888, with a 90% confidence interval (CI) of 0.861 to 0.917 (analysis of variance [ANOVA]). The lower bound of the 90% CI was above 0.80 indicating that the SC dose was non-inferior to the IV dose in terms of AUC. In addition, the 90% CI was within the limit of 0.80 to 1.25, a criterion for concluding “bioequivalence” between the 2 treatments (SC and IV doses of IGIV-C 10%).

Additionally, a recently completed pediatric study (Grifols Study T5004-401) of weekly SC administration of IGIV-C 10% in 11 pediatric subjects (age range 4-15 years) also resulted in no SBI reported in the 12-week SC treatment period. The mean steady-state minimum concentration (C_{trough}) of total IgG was 1325 mg/dL following weekly SC infusion of IGIV-C 10% which was 31% higher than that of the IV dosing C_{trough} (997 mg/dL) (1.37 dose adjustment factor relative to IV). The mean of the ratios of SC AUC vs. IV AUC was also favorable (mean ± SD: 1.05 ± 0.104).

Accordingly in this study, a 1:1.37 IV to SC dose adjustment factor will be initially employed for the transition from IVIG to IGSC 20% treatment and will be evaluated in the interim PK analysis (Section 3.1.5).

2 STUDY OBJECTIVES

2.1 Primary Pharmacokinetic Objective

- To determine a dose of weekly subcutaneously administered IGSC 20% that produces steady-state AUC of total IgG that is non-inferior to that of the regularly administered IV dose of IGIV-C 10% in PI subjects

2.2 Secondary Objective

- To determine if IGSC 20% replacement therapy maintains mean steady-state trough total IgG levels that are comparable to the mean trough total IgG levels with the IGIV-C 10% replacement therapy in PI subjects

2.3 Exploratory Objectives

- To evaluate t_{max} (time to reach C_{max}) and C_{max} in PI subjects at steady state
- 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 rate of SBIs
- 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 validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, or diagnostic testing for microorganisms, eg, bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test)
- 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 due to infections and their treatment
- Trough measles antibody titers (functional assay) are an exploratory variable for informational purposes

2.4 Safety Objective

- 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-sequence, 6-month, PK and safety and tolerability study of IGSC 20% in subjects with PI. Approximately 50 subjects will be enrolled in order to have approximately 30 adult subjects and 12 to 18 pediatric subjects (age 2-16 years) completing treatment with subcutaneously administered IGSC 20%. Pediatric enrollment will be stratified by age category with a target of 4 to 6 children for each group: 2 to 5 years, >5 to 12 years, and >12 to 16 years of age. The PK profiles of total IgG following administration of both IV (IGIV-C 10%) administration and SC (IGSC 20%) administration under approximate steady-state conditions will be determined and compared. The primary objective is to determine a weekly SC dose of IGSC 20% that achieves an AUC of total IgG that is non-inferior to that achieved by a subject's IV dose of immune globulin.

This study will include 3 treatment phases: Run-In Phase, IV Phase (IV administration of IGIV-C 10% treatment), and SC Phase (SC administration of IGSC 20%). Before a subject is to be enrolled (entering either the Run-In or IV Phase) into the study, the subject will be screened during the Screening Phase, which is up to 28 days. The specific inclusion and exclusion criteria for this study are described in Section 3.2.

Subjects, depending on their current IgG treatment regimen, may be required to enter the Run-In Phase to receive IV IGIV-C 10% treatment (Sponsor provided) to achieve an approximately steady-state condition prior to entering the IV Phase. They will then enter the IV Phase to determine the AUC profile of IV infusions of IGIV-C 10%.

Subjects with a qualifying IV IGIV-C 10% treatment regimen (on stable IGIV-C 10% doses of 300-800 mg/kg) can enter the IV Phase directly where they will receive IGIV-C 10% (Sponsor provided). In the IV Phase, steady-state IV PK assessments including AUC will be performed.

After completing the IV Phase, subjects will enter the SC Phase to receive weekly SC doses of IGSC 20% for at least 24 weeks. The IGSC 20% dose will be determined by using an initial IV to SC dose adjustment factor of 1.37. After reaching an approximate steady-state condition, the SC PK profiles including AUC at SC Week#13 will be determined.

The interim serial PK samples (for both the IGIV-C 10% IV and the IGSC 20% SC dosing phases) may be obtained at an alternate location. If an outside agency is utilized for sample collection, the samples will be drawn and processed per protocol and laboratory manual instructions.

Comparison of the IV PK profiles and IGSC 20% PK profiles in the first 6 adult/adolescent subjects will be performed through an interim PK analysis. If the dose adjustment factor is deemed acceptable (SC dose of IGSC 20% is non-inferior to the subject's IV dose) (Section 3.1.5), all subjects will continue to complete treatment and assessments through Week#25 (no further monthly extension visits). Otherwise, a new dose adjustment factor will be employed for all subjects following the procedures described in Section 3.1.5, and subjects will receive 24 weeks of IGSC 20% treatment at the new IGSC 20% dose. In this study, the PK profiles will be assessed in all subjects. Subjects aged 2 to 5 years old will be assessed using an abbreviated sampling schedule for PK profiles.

The overall study diagram is depicted in Figure 3-1 and Figure 3-2. The subject entry criteria are described in Table 3-1.

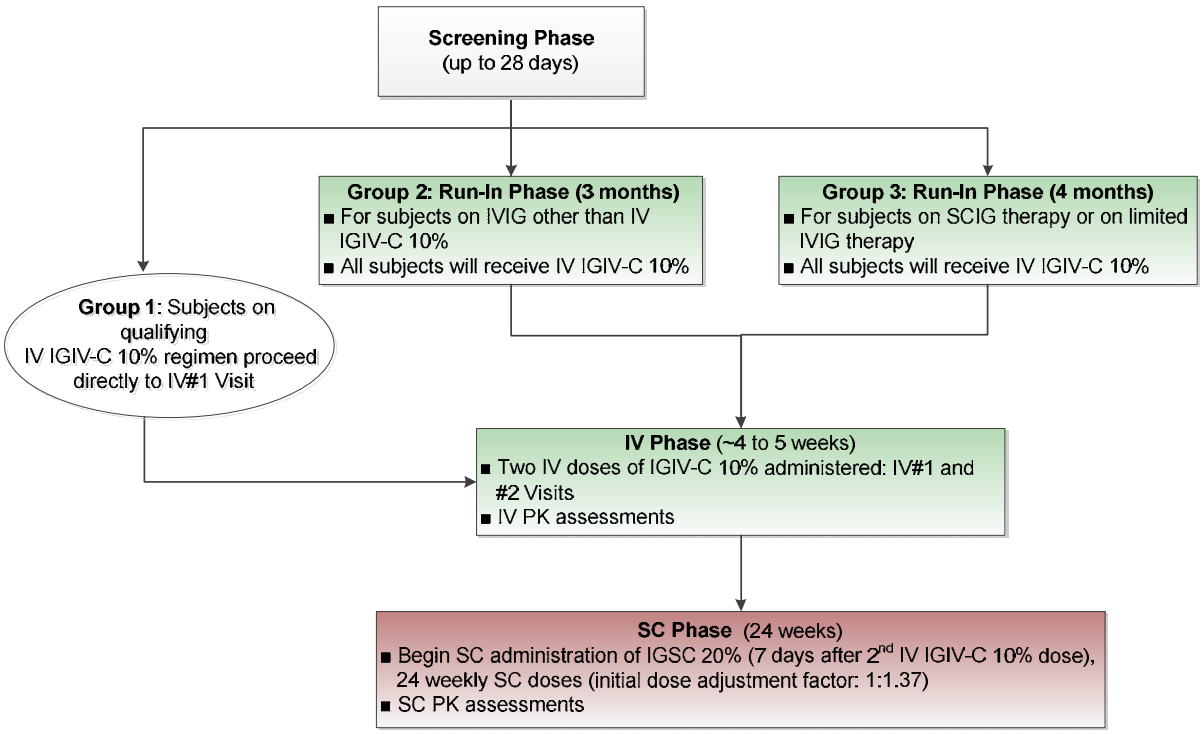


Figure 3-1 Overall study design

3.1.1 Screening Phase

At screening, subjects will be categorized into 3 groups: 1) those subjects who can directly enter the IV Phase of the study, 2) those who will require a 3-month Run-In Phase, and 3) those who will require a 4-month Run-In Phase (Figure 3-1 and Table 3-1). The Screening Phase is up to 28 days long.

Table 3-1 Study entry of subjects

	Subject Populations at Screening Based upon Most Recent IgG Treatment History (All must have confirmed diagnosis of PI)	Required Study Entry Point	IGIV-C 10% Dose and Interval during Study
1	Receiving stable (≥3 months) dose of IV IGIV-C 10% between 300 and 800 mg/kg, every 3 or 4 weeks	**IV Phase** (IV#1)	Same dose and interval as at screening.
2	Receiving IVIG other than IGIV-C 10% with doses between 300 and 800 mg/kg, every 3 or 4 weeks	**Run-In Phase** (3 month)	Same dose and interval as at screening.
3	Receiving IVIG other than IGIV-C 10%, but either not on stable dose (≥ 3 months) OR dose is not between 300 and 800 mg/kg OR interval is not every 3 or 4 weeks	**Run-In Phase** (4 month)	Dose (300-800 mg/kg) and interval (3 or 4 weeks) to be determined by Investigator.
	Receiving SCIG	**Run-In Phase** (4 month)	Dose (300-800 mg/kg) and interval (3 or 4 weeks) to be determined by Investigator.

3.1.2 Run-In Phase

Group 1 - Subjects are eligible for direct entry into the IV Phase:

Subjects who are already receiving a stable (≥3 months) dose of IV IGIV-C 10% between 300 and 800 mg/kg per infusion every 3 or 4 weeks, do not need to enter the Run-In Phase and may proceed directly to the IV Phase. These subjects will have their IV#1 Visit scheduled to coincide with the date for their next IV infusion according to their regular dosing interval. The subjects will come to the clinic for this visit.

Group 2 - Three (3)-month Run-In Phase:

Those subjects who prior to screening are receiving IVIG therapy (at a dose between 300 and 800 mg/kg per infusion every 3 or 4 weeks) but who are not receiving IGIV-C 10% specifically (ie, a different commercially available IVIG) will be required to receive IGIV-C 10% intravenously (at an equivalent dose and dosing interval as in their previous IVIG therapy) for a total duration of a 3-month Run-In Phase. Subjects receiving infusions every 3 weeks will have 4 Run-In visits and subjects receiving infusions every 4 weeks will have 3 Run-In visits.

Group 3 - Four (4)-month Run-In Phase:

The following subjects will be required to participate in a 4-month Run-In Phase:

- Subjects who are currently receiving IVIG therapy but have not been on a stable dose for the 3 months prior to screening OR where the dose is not between 300 and 800 mg/kg OR who receive IVIG infusions that are not administered at a frequency of every 3 or 4 weeks
- Subjects who prior to screening are receiving SCIG

Subjects meeting any of the criteria for Group 3 will be scheduled to begin receiving IGIV-C 10% intravenously at a dose of 300 to 800 mg/kg every 3 to 4 weeks (dose and interval to be determined based on the investigator's clinical judgment) for a period of up to 4 months prior to the IV#1 visit. Subjects receiving infusions every 3 weeks will have 5 Run-In visits and subjects receiving infusions every 4 weeks will have 4 Run-In visits.

3.1.3 IV Phase

In the IV Phase, subjects will receive 2 IV infusions of IGIV-C 10%. At the IV#1 visit, subjects who have at screening entered directly into the IV Phase of the study will receive a dose of IV IGIV-C 10% equivalent to their current IgG dose. Subjects who have been required to go through a Run-In Phase will receive the same dose of IV IGIV-C 10% as have been administered during that pre-requisite Run-In period. Blood draws for PK profiling will begin just prior to the first IGIV-C 10% infusion (IV#1) and will continue throughout the subject's normal dosing period (3 or 4 weeks total). At the end of this period and in order to ensure that the subjects have adequate total IgG levels prior to initiating study drug by SC, a second dose of IV IGIV-C 10% will be administered (IV#2). **The SC Phase will begin 1 week after the IV#2 visit.**

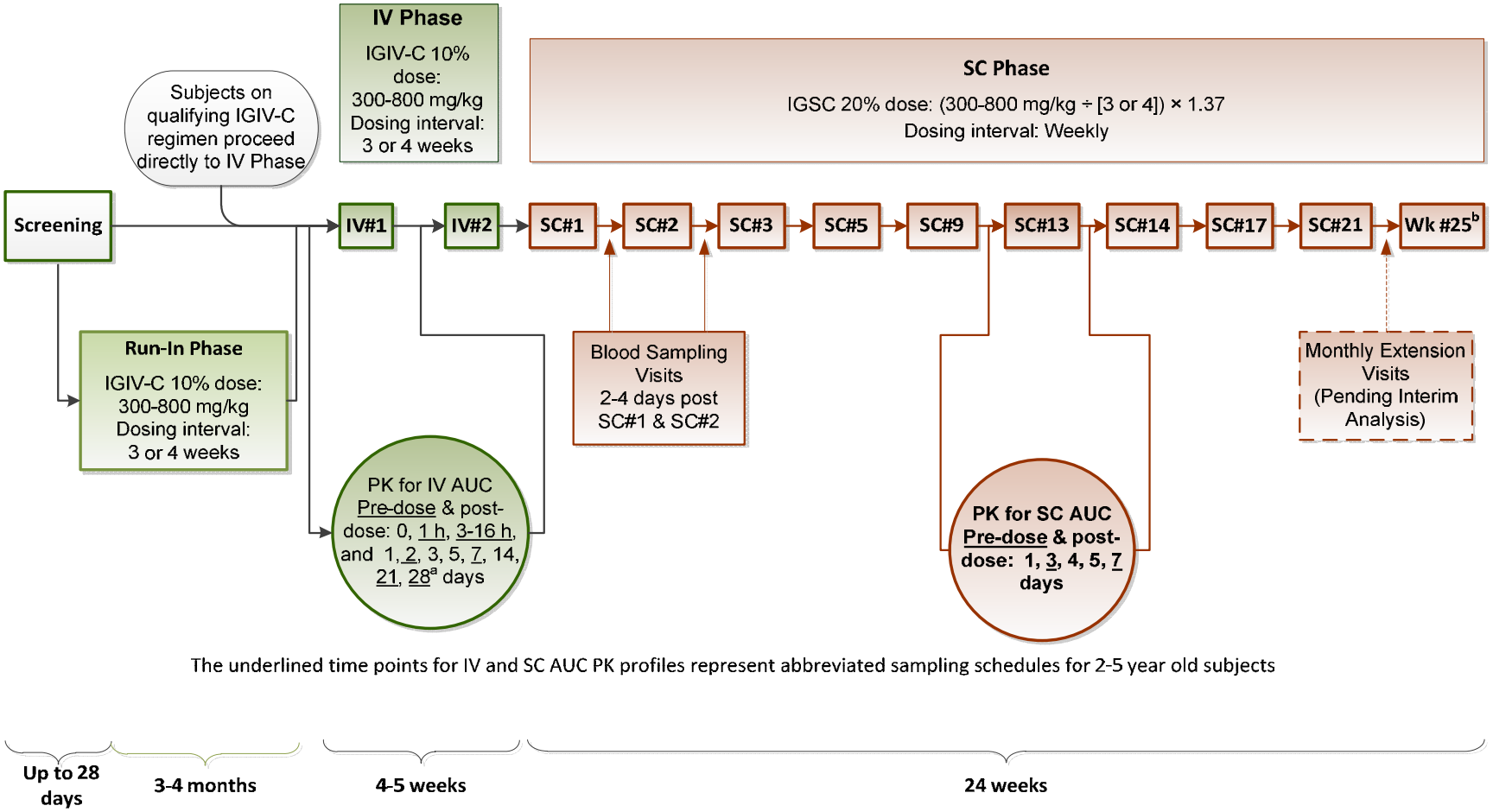
3.1.4 SC Phase

One week (7 days) after the second IV dose (IV#2), subjects will return to the clinic to begin the weekly SC administrations of IGSC 20%. The SC Phase will continue for a total of 24 weeks (6 months). The initial weekly SC dose is calculated as described in Section 3.3.2. Briefly, the SC dose is calculated using the following formula:

$$\frac{\text{300 to 800 mg/kg (IV dose)}}{\text{3 or 4 (regular IV dosing interval in week)}} \times 1.37 \text{ (IV to SC dose adjustment factor)}$$

After 12 weeks (3 months) of weekly SC therapy, determination of PK profiles for total IgG during the SC Phase will begin at the blood draw just prior to the 13th SC infusion with the last sample collected immediately prior to the 14th SC infusion (7 days total).

The detailed study flow chart and specific time points for PK sampling for IV IGIV-C 10% and SC IGSC 20% administration are outlined in Figure 3-2.



[a] Only applicable to subjects who are on a 4-week dosing interval

[b] Wk#25 = Final Visit (Week #25)/Early Termination Visit

Figure 3-2 IV dosing of IGIV-C 10% and SC dosing of IGSC 20% Clinic Visits and PK sampling schedules (Also see Sections 3.6.2.3 and 3.6.2.4)

3.1.5 Interim PK Analysis

The dosing regimen for SC administration of IGSC 20% is based on literature data of the bioavailability of subcutaneous administered IgG and prior experience with SC IGIV-C 10%. The weekly IGSC 20% dosing regimen to be evaluated herein (1.37 times the currently stable IV IgG dose divided by 4 for subjects on an every-4-week dosing schedule or divided by 3 for subjects on an every-3-week dosing schedule) is predicted to provide an steady-state AUC of total IgG levels not inferior to that of the prior IV dose based on the established bioequivalence acceptance data.

While it is believed that a dose adjustment factor of 1.37 for determining an SC dose of IGSC 20% (from an IV dose) is suitable, an interim PK analysis is planned to confirm that this SC dose adjustment factor calculation is adequate and to allow for potential modification of the dose adjustment factor if necessary. The interim PK analysis will be performed as soon as practical after the first 6 adult/adolescent subjects (age ≥12-75 years) have completed the steady-state PK sampling schedule for both the IV (IV#2) and SC Phases (SC#14) of the trial. Data from these 6 adult/adolescent subjects will be analyzed using standard PK and statistical methodology (Section 5) to evaluate and compare the $AUC_{0\text{-}\tau's}$ of total IgG from the IV administration of IGIV-C 10% and SC administration of IGSC 20%.

The outcome of this interim analysis will determine whether the dose adjustment factor will be modified. If the ratio of geometric LSM for $AUC_{0\text{-}7,\ SC}$ vs. adjusted $AUC_{0\text{-}7,\ IV}$ falls below 10% of the desired 1.0 (ie, <0.9), and the mean trough concentrations for the SC administration of IGSC 20% falls below the target level in more than 3 of the 6 adult/adolescent subjects, then a dose adjustment factor increase would be implemented to ensure that the subjects receive an optimal IGSC 20% and are not susceptible to potential bacterial infections.

If the ratio of geometric LSM for $AUC_{0\text{-}7,\ SC}$ vs. adjusted $AUC_{0\text{-}7,\ IV}$, achieves ≥0.9, there will be no change in the dose adjustment factor.

Subjects enrolled early in the trial may complete their regularly scheduled 24 weeks of SC therapy on the initial IGSC 20% dose before a decision from the interim analysis is available. In this event, these subjects will continue to receive weekly SC infusions of IGSC 20% until the interim PK analysis deems whether or not a new dose adjustment factor would be required. Subjects will return to the study center every 4 weeks for evaluation and have the same study procedures performed as those at SC Week#21 with (at less frequent intervals) safety laboratory assessments, IgG subclass levels, and specific antibody titers for *S. pneumoniae*, *H. influenzae*, and *C. tetani* (tetanus) every 8 weeks as detailed in Section 3.6.2.5. This will continue until the interim analysis is completed. If the results of the interim analysis do not indicate a need for a dose adjustment factor change, subjects will be brought into the clinic and end of study procedures will be performed.

If the need for changing the dose adjustment factor arises, the revised dose adjustment factor will be calculated based on the ratio of the geometric LSM for $AUC_{0\text{-}7,\ SC}$ vs. adjusted $AUC_{0\text{-}7,\ IV}$ with consideration of mean trough levels obtained from the SC administration of IGSC 20%.

The revised dose adjustment factor will be communicated to sites and the revised dose adjustment factor would be applied to the subjects' next SC infusion of IGSC 20% in the clinic, which should be scheduled as soon as possible, upon receiving formal notification from the Sponsor. These subjects will re-commence at SC#1 with the new dose adjustment factor. All subjects will be required to have a minimum of 24 weekly SC infusions of IGSC 20% with the new dose adjustment factor. For subjects currently in the SC Phase or who have completed the 24 weeks of the SC Phase and are continuing on treatment until the results of the interim PK analysis are available, subjects will be required to continue in the SC Phase with the revised dose adjustment factor for 24 weekly SC infusions. In both of the above situations, all subjects will have a repeat complete IGSC 20% PK profile after 12 weeks on the new dose adjustment factor (same assessment as initial SC Week #13). The time points for PK blood sample collection will be those outlined in Figure 3-2 and Section 3.6.2.4.

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 Sponsor. 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. Subjects 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 (eg, X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (eg, hyper immunoglobulin M [IgM] immunodeficiency syndrome). Please also refer to Exclusion Criteria.
3. The subject has not had a SBI within the last 3 months prior to or during Screening.
4. Currently on IgG replacement therapy (via IV or SC infusion) for ≥3 months.
5. *Note: This inclusion criterion is removed in protocol amendment 2.*
6. Screening trough IgG levels must be ≥500 mg/dL.

   Note: If Screening trough levels are not above this threshold, the subjects 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 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)
6. Females of childbearing potential who are pregnant, have a positive pregnancy test at Screening (serum) or IV#1 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 [eg, 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+ or known urinary protein loss > 1 g/24 h or nephrotic syndrome) and/or has a history of acute renal failure and/or severe renal impairment (blood urea nitrogen [BUN] or creatinine more than 2.5 times the upper limit of normal [ULN]) and/or on dialysis
8. The subject has Screening Visit values of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding more than 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 history of or current diagnosis of deep venous thrombosis (DVT) or thromboembolism (eg, deep vein thrombosis, myocardial infarction, cerebrovascular

accident or transient ischemic attack); history refers to an incident in the year prior to Screening or 2 episodes over lifetime.

11. The subject is currently receiving anti-coagulation therapy which would make SC administration inadvisable (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [eg, dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], parenteral anticoagulants [eg, fondaparinux]).
12. The subject currently has a known hyperviscosity syndrome.
13. 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).
14. 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.
15. 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 3) or the adult subject has non-controlled arterial hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg)
16. 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.
17. The subject has known substance or prescription drug abuse
18. 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
19. The subject/caregiver is unwilling to comply with any aspect of the protocol, including the home SC infusions, blood sampling, and completion of a SC infusion diary for the duration of the study
20. Mentally challenged subjects who cannot give independent informed consent or assent
21. 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

IGSC 20% (IP) and IGIV-C 10% (study drug) are provided by the Sponsor for this study.

3.3.1.1 IGSC 20%

Grifols Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) is a sterile liquid formulation of immunoglobulin that is purified from human plasma via a multi-step process. IGSC 20% is manufactured using the same process as for IGIV-C 10% (Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified [IGIV-C]), with the addition of a nanofiltration step and is further concentrated by ultrafiltration to a higher IgG concentration (20%). IGSC 20% vials will be supplied in a 50 mL vial size or smaller containing a 20% solution of immunoglobulin, ie, a concentration of 20 g/100 mL, with a nominal 10 grams immunoglobulin per vial.

3.3.1.2 IGIV-C 10%

IGIV-C 10% is a sterile liquid formulation of immunoglobulin that is purified from human plasma via a multi-step process. IGIV-C 10% is a licensed product. IGIV-C 10% vials may be supplied in the vial sizes of 10, 25, 50, 100, and 200 mL. In this study, administration of IGIV-C 10% will be via the IV route only.

3.3.1.3 Labeling of Investigational Products

IGSC 20% and IGIV-C 10% 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.

3.3.1.4 Storage of Investigational Products

IGSC 20% and IGIV-C 10% 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 IP/study drug.

IGSC 20% and IGIV-C 10% 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.

3.3.1.5 Preparation

The volume (ie, total infusion dose administered) of IGSC 20% to be prepared for each SC infusion will be individualized for each subject based on an IV to SC dose adjustment factor of 1:1.37 using body weight-based dosing. IGIV-C 10% dose will be based on subject's previous IGIV-C 10% or other IVIG product regimen. See Table 3-1.

IGSC 20% and IGIV-C 10% must be inspected visually before being administered. The solution must not be used if turbid or if it contains visible particles. Solution which has been

frozen should not be used. The Investigator, or designee, is responsible for immediately reporting any issues noted with IGSC 20% and IGIV-C 10% to the study monitor.

Reference the pharmacy manual/study manual for detailed instructions for IGSC 20% and IGIV-C 10% preparation and administration.

3.3.1.6 Accountability for Investigational Products

IGSC 20% and IGIV-C 10% are 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/study drug 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% and IGIV-C 10% for his/her site. IP/study drug inventory/dispensing documentation, verifying the receipt, dispensing, 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% and IGIV-C 10% supplies must be accounted for by the monitor and inventory/dispensing logs must be verified by the monitor prior to IGSC 20% and IGIV-C 10% 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.

3.3.2 Rationale for Selection of Doses/Timing of Investigational Products

3.3.2.1 Selection of Doses and Timing of Dosing in the Study

In the current study, the initial IV to SC dose adjustment calculation formula used is:

$$\frac{\text{300 to 800 mg/kg (IV dose)}}{\text{3 or 4 (regular IV dosing interval in week)}} \times 1.37 \text{ (IV to SC dose adjustment factor)}$$

The selection of dosing regimen for SC administration of IGSC 20% is based on literature data of the bioavailability of SC administered IgG and prior experience with other products (Section 1.3.1). The weekly IGSC 20% SC dosing regimen to be evaluated herein (1.37 times the currently stable IV IGIV-C 10% dose divided by 4 for subjects on an every-4-week dosing interval or divided by 3 for subjects on an every-3-week dosing interval) should provide a steady-state AUC of total IgG levels not inferior to that of the approved IV dose based on the established bioequivalence acceptance data.

The initial SC dose selected based on a dose adjustment factor of 1.37 will be evaluated in an interim PK analysis after the first 6 adult/adolescent subjects have completed both the IV and SC PK sampling schedule. If the interim PK analysis suggests that modification of the SC dose adjustment factor is needed, a new SC dose adjustment factor will be calculated and the procedures in Section 3.1.5 will be followed.

As described in Section 3.1, the initial IV IGIV-C 10% dose (Run-In or IV Phase) and dosing interval will be individualized based on the treatment each subject is receiving for their PI at screening (see Table 3-1).

3.3.2.2 Selection and Timing of Dose for Each Subject

The IV and SC dose of study drug will be individualized based on each subject's current IgG regimen which is assumed to be an effective dose. Subjects are required to have been clinically stable for at least 3 months on an IgG product. The IV IGIV-C 10% dose will be between 300 and 800 mg/kg during the Run-in phase and IV#1 and IV# 2. See Table 3-1.

Subjects currently on stable IV IGIV-C 10% (for at least 3 months) will receive their first IV dose of IGIV-C 10% at the IV#1 visit. Subjects currently on IVIG therapy other than IV IGIV-C 10% will receive IV IGIV-C 10% for at least 3 months (during Run-In Phase) prior to the IV#1 visit. Subjects currently on SCIG therapy, or whose IVIG dose is not stable for the 3 months prior to Screening, or IVIG dose is not between 300 and 800 mg/kg per infusion or not receiving infusions every 3 or 4 weeks at Screening will receive IV IGIV-C 10% for at least 4 months in Run-In Phase prior to the IV#1 visit. Subjects will return to the clinic at their next scheduled IV dosing interval (ie, 3 or 4 weeks later) to receive a 2nd IV IGIV-C 10% dose (IV#2 Visit).

The first SC administered IGSC 20% will be initiated 7 days after the 2nd IV IGIV-C 10% dose (at the SC Week#1 visit). Weekly (q 7 days ± 1 day) SC administrations of IGSC 20% will continue for a total of 24 weeks. The weekly SC dose will be one quarter of the current IV monthly dose if the subject is on a 4 week dosing regimen or one third of the current IV dose if the subject is on a 3 week dosing regimen multiplied by 1.37 as previously described.

If the interim PK analysis suggests that modification of the SC dose adjustment factor is needed, a new SC dose adjustment factor will be calculated and the procedures in Section 3.1.5 will be followed.

3.3.2.3 Subcutaneous Administration Procedures for IGSC 20%

The number of injection sites, infusion rate, and the specific times of the day for the SC infusion may be individualized by the subject and Investigator. The first 3 SC infusions will be given under supervision in the clinic before self-administration at home will be allowed. The selected pump specifically designed for SC infusions will be provided for individual use to each subject prior to the SC Phase and each subject will be trained thoroughly on its use. The PK focus of the study will be emphasized to all the subjects/caregivers. Subjects will be instructed to closely adhere to their individualized dosing regimen accurately and cautioned not to round-up to the whole vial or to under dose. The exact IGSC 20% dose (and dose volume) based on the predetermined adjustment factor and the stable IV dose of IGIV-C 10% will be administered and recorded.

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. 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. 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, number of infusion sites, infusion start date/time, infusion end date/time, the location(s) of infusions, and the initial and final 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. In addition, SC infusion site reactions may be recorded in the diary. Full details regarding the SC Infusion Diary are in Section 3.6.2.4.

3.3.3 Method of Assigning Subjects to Treatment Groups

3.3.3.1 Subject Numbering

Within each study site, subjects in the study will receive a consecutive subject number at Screening Visit. Subject numbers are generated beginning with the study center number (3 digits, assigned by the Sponsor starting at 100) followed consecutively with a unique number for each subject (4 digits). For example, if the Investigator's center number is 301, subject numbers will be 3012001, 3012002, 3012003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.

3.3.3.2 Randomization

This is a single-sequence, crossover study with no randomization.

3.3.3.3 Blinding

This is an open-label study with no blinding.

3.3.4 Treatment Compliance

Reasons for any deviation from the administration of less than 100% of all protocol-specified doses of IGIV-C 10% or IGSC 20% as prepared by the pharmacist, or designee, must be recorded in the eCRF and in the subject's source documents.

All IV infusions during the Run-In and IV Phases and the first 3 SC infusions will be administered in the clinic under the supervision of the treating investigator or designee. Subjects will be instructed on SC dosing techniques during the first 3 SC dosing infusions in the clinic. All dose calculations will be done by the Interactive Web Response (IWR) system and the dose preparation procedures will be provided to each subject for in-home SC administration. The actual date/clock time, location of the infusions, number of infusion sites, volume, and duration of dosing will be recorded.

A SC Infusion Diary will be provided to document SC infusions self-administered away from the clinic. These data will be used to calculate infusion compliance, dosing compliance, and overall drug compliance.

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.

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 >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 [eg, dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], parenteral anticoagulants [eg, fondaparinux]).

3.4.2 Prohibited Concomitant Medications during the Study

Use of the following during the study (from Screening to SC Week#25 Final Visit) is prohibited:

- Any IgG replacement therapy other than IGIV-C 10% or IGSC 20% provided in this study once the first dose of study treatment is administered
- 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 (as defined in Section 3.4.1), 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 (eg, 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 [35]). Passive transfer of antibodies from IGIV-C 10% or 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 Primary Pharmacokinetic Variables

- AUC in the IV Phase: Steady-state AUC of total IgG over a regular dosing interval (τ), either every 3 weeks or every 4 weeks (ie, $AUC_{0\text{-}\tau,\,IV}$ or $AUC_{0\text{-}21days,IV}$ or $AUC_{0\text{-}28days,IV}$, respectively) in PI subjects
- AUC in the SC Phase: Steady-state AUC of total IgG over a weekly SC dosing interval (τ) (ie, $AUC_{0\text{-}\tau,SC}$ or $AUC_{0\text{-}7days,SC}$) in PI subjects

3.5.2 Secondary Pharmacokinetic Variables

- Mean steady-state trough (pre-dose) concentration of total IgG following IV administration of IGIV-C 10% or SC administration of IGSC 20%

3.5.3 Exploratory Variables

- t_{max} (time to reach C_{max}) and C_{max} in PI subjects at steady state
- Trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)

- Antibody levels for *S. pneumoniae*, *H.influenzae*, and *C. tetani* (tetanus)
- Rate of SBIs
- 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
- Validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms, eg, bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test)
- 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 due to infections and their treatment
- Trough measles antibody titers (functional assay) for informational purposes

3.5.4 Safety Variables

The following safety variables will be assessed in this study:

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

  Note: All infusion site reactions will be recorded in the eCRF. For 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, they will be considered as AEs.
- Vital signs during clinic visits (systolic blood pressure [SBP] and diastolic blood pressure [DBP], heart rate [HR], temperature [T], respiratory rate [RR])
- 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.
- Total number of non-serious infections and proportion of subjects who experience non-serious infections of any kind (including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator.

3.6 Assessments

3.6.1 Assessment Periods

Study phases in this study are described in Section 3.1. The study consists of Screening (up to 28 days), Run-In (3-4 months), IV (4-5 weeks), and SC Phases (24 weeks). The total

duration of study participation may be up to 50 weeks. If there is a revision to the IV to SC dose adjustment factor, there may be an additional 24 weeks added to the study participation.

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. For most clinic visits, a ± 1 day window is allowed. For the serial PK sampling visits, see specific PK windows in Section 3.6.2.3 and 3.6.2.4. If there are logistical issues requiring schedule adjustment for weekly subcutaneous IGSC 20% administration, SC#1 may be scheduled 6 to 9 days after IV#2. The SC#2 and SC#3 visits must be performed with a +1 day visit window (ie, these 2 visits cannot be performed 1 day early). Unscheduled visits may be conducted if deemed necessary for the purpose of subject safety.

3.6.2.1 Screening Visit

The subject's medical records will be reviewed to confirm a documented diagnosis of PI. Subjects who are interested in participating will undergo the following tests and procedures:

- Written informed consent and assent if applicable will be obtained prior to initiation of any screening procedures
- Eligibility will be checked by careful assessment of the inclusion and exclusion criteria
- Demographics and medical history will be recorded including age, gender, age at diagnosis of PI, and past 12 months of previous/current IgG treatments. Record relevant medical history defined as any history impactful on the subject's condition in terms of current functioning, disability, treatment, or management.
- A full physical exam will be performed (excluding breast and genitourinary exam)
- Wells Score will be performed as a pretreatment benchmark for all subjects (Appendix 4 provides Wells Score and management details; see also Section 3.6.3.3)
- Chest X-ray (if chest X-ray or CT have not been performed within past 6 months prior to screening) Note: at least one radiographic view (anterior-posterior [AP] or posterior-anterior [PA]) is required)
- Vital signs: SBP and DBP, HR, T, RR after 5 minutes at rest
- Body weight and height
- Blood and urine samples for clinical laboratory assessments (eg, hematology, clinical chemistry, special tests, urinalysis, pregnancy testing) (see Section 3.6.3).
    - Hematology: Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential; absolute reticulocyte count (ARC)
    - Clinical chemistry: Sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, lactate dehydrogenase (LDH), AST, ALT, alkaline phosphatase (ALP), glucose, total bilirubin, indirect bilirubin
    - Special tests: Direct antiglobulin (DAT), serum free hemoglobin, and haptoglobin
    - D-dimer sample as a pretreatment benchmark for all subjects

  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)
  - Serum pregnancy test (potential child-bearing females only)
- Total IgG trough level determination: participants will be required to have a screening total IgG level of ≥500 mg/dL to enroll
- Prior and concomitant medications
- Adverse events and history of serious infections

Subjects who are eligible for study entry will have their first Run-In Phase visit or IV Phase (IV#1) visit scheduled to coincide with the date for their next IV or SC infusion according to their regular dosing interval.

3.6.2.2 Run-In Phase (If Required) – IV Administration of IGIV-C 10%

The following procedures and tests will be completed **at each visit (every 3 or 4 weeks)** for those subjects who are required to enter either the 3-month or 4-month Run-in Phase (see Section 3.1.2 and Appendix 1):

- Vital signs (pre-infusion: SBP and DBP, HR, T, RR)
- Body weight
- Predose blood draw for trough total IgG prior to IV infusion (within 0.5 hour prior to the start of infusion).
- IV IGIV-C 10% infusions
- Adverse events including SBIs (subjects with an SBI will discontinue from the study)

  Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category*) as detailed in Section 3.6.3.1. (*The site is to record non-serious infections [by category] which 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 eg, 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.)
- Concomitant medications
- Record days lost from work/school/daily activities due to infections and treatment

3.6.2.3 IV Phase – IV Administration of IGIV-C 10%

IV#1 VISIT & PK ASSESSMENT FOR IV DOSING

The following procedures and tests (Also see Appendix 1) will be completed for all subjects at the IV#1 Baseline visit:

- Vital signs (pre-infusion: SBP, DBP, HR, T, RR)
- Body weight and height
- Predose laboratory assessments (as outlined in Screening Visit [Section 3.6.2.1] including hematology, clinical chemistry, special tests, and urinalysis) prior to IV infusion
- Predose blood draw for trough total IgG, IgG subclass, and antibody titer levels for *S. pneumoniae*, *H.influenzae*, and *C. tetani* (tetanus) prior to IV infusion (within 0.5 hour prior to the start of infusion).
- Predose urine pregnancy test (child-bearing potential females only)
- IV IGIV-C 10% infusion and initiate serial PK sampling as detailed below
- Concomitant medications
- Adverse events including SBIs (subjects with an SBI will discontinue from the study)

  Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category as detailed in Section 3.6.3.1.
- Record days lost from work/school/daily activities due to infections and treatment

The PK sampling for IV administered IGIV-C 10% will commence at the IV#1 (IV Phase) visit for all enrolled subjects. Subjects who are between 2 and 5 years of age will undergo an abbreviated sampling schedule for serial PK sampling.

IV PK Sampling for subjects >5 years of age: Blood draws for PK assessment will be taken at the following time points:

- Prior to IV#1 (IV Phase) infusion (within 0.5 hour of the start of infusion)
- Immediately at the completion of IV infusion
- 1 h after completion of infusion
- 3 to 16 hours post-infusion with a window of 2 hours around the 16-hour time point if required by site
- 1 day ± 2 h post-infusion
- 2 days ± 2 h post-infusion
- 3 days ± 4 h post-infusion
- 5 days ± 4 h post-infusion
- 7 days ± 1 day post-infusion
- 14 days ± 1 day post-infusion
- 21 days ± 1 day post-infusion (last sample for subjects on a 3-week dosing schedule and is also the pre-dose trough sample for IV#2)
- 28 days ± 1 day post-infusion (only for subjects on a 4-week dosing schedule and is also the pre-dose trough sample for IV#2)

IV PK Sampling for subjects ≤5 years of age: Blood draws for PK assessments will be taken at the following time points:

- Prior to IV #1 (IV phase) infusion (within 0.5 hour of the start of infusion)
- 1 h after completion of infusion
- 3 to 16 hours post-infusion with a window of 2 hours around the 16-hour time point if required by site
- 2 days ± 2 h post-infusion
- 7 days ± 1 day post-infusion
- 21 days ± 1 day post-infusion (last sample for subjects on a 3-week dosing schedule and is also the pre-dose trough sample for IV#2)
- 28 days ± 1 day post-infusion (only for subjects on an every-4-week dosing schedule and is also the pre-dose trough sample for IV#2)

The actual date/clock time of the start and end of the IV infusion, the volume/amount of dose infused, and the rate of infusion will be recorded.

All efforts will be made to obtain all PK samples in the time frame specified above. The final PK blood sample will be drawn prior to the subject receiving the next dose of study drug (ie, the second IV dose) in the clinic. If an outside agency is utilized in sample collection, the sample will be drawn and processed per protocol instructions to ensure sample integrity.

IV#2 VISIT

This visit for the second IV infusion (IV#2) will be conducted at the next scheduled dosing interval (ie, 3 or 4 weeks from IV#1). The following procedures and tests will be performed at the IV#2 visit:

- Vital signs (pre-infusion: SBP and DBP, HR, T, RR)
- Predose blood draw for trough total IgG, IgG subclass, and antibody titer levels for *S. pneumoniae, H.influenzae,* and *C. tetani* (tetanus) prior to SC infusion (within 0.5 hour prior to the start of infusion).

  Note: This trough IgG sample is the same one that is used for PK blood draw at the 21 or 28 day post-infusion time points.
- Pre-dose measles antibody titer
- IV IGIV-C 10% infusion
- Concomitant medications
- Adverse events including SBIs (subjects with an SBI will discontinue from the study)

  Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category) as detailed in Section 3.6.3.1.
- Record days lost from work/school/daily activities due to infections and treatment

Subjects will return to the clinic 7 days after the IV#2 visit to start the SC Phase of the study which includes weekly infusions of IGSC 20% that will continue for a total 24 weeks.

3.6.2.4 SC Phase – SC Administration of IGSC 20%

CONSIDERATIONS FOR SC ADMINISTRATION

The first 3 weekly doses of SC study drug will be administered in the clinic by medical site personnel. During these clinic visits, subjects will be instructed and informed regarding all aspects of the techniques and procedures needed for self-administration of study drug (which is to begin at SC Week #4). The SC dose calculations will be performed by study clinic personnel and will be verified (double-checked) by another study staff member. The exact SC dose volume to be administered and rate of infusion will be provided to each subject by the clinic personnel. The number and location of SC infusion sites will be determined by the subjects in consultation with the investigator.

SC infusion diary: An IGSC 20% infusion diary will be provided to each subject prior to the first IGSC 20% infusion which may be used to record items including but not limited to: infusion site reactions, concomitant medications (including antibiotics [prophylactic and therapeutic]), and details of study drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume of each SC dose, 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.

Note: All infusion site reactions will be recorded. For 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, these will be considered as AEs.

SC WEEK #1 CLINIC VISIT

Subjects with an SBI identified prior to SC#1 administration will discontinue study. The following procedures and tests will be completed at the SC Week #1 visit:

- A full physical exam prior to IGSC 20% infusion (excluding breast and genitourinary exam)
- Predose Wells Score will be performed as a benchmark prior to first IGSC 20% dose for all subjects (Appendix 4 provides Wells Score and management details; see also Section 3.6.3.3)
- Vital signs (pre-infusion: SBP, DBP, HR, T, RR)
- Body weight (will be used for SC dose calculation)
- Predose laboratory assessments (as outlined in Screening Visit [Section 3.6.2.1] including hematology, clinical chemistry, special tests, and urinalysis)
- Predose D-dimer sample as a benchmark prior to first IGSC 20% infusion for all subjects
- Predose virus safety retain samples

  Collection of virus safety retain samples prior to IGSC 20% infusion as detailed in Table 3-2. Collect samples but test only if the subject exhibits clinical signs and symptoms consistent with hepatitis A virus (HAV), HBV, HCV, HIV, or parvovirus B19 (B19V) infection while participating in the study.

Note: For children at the discretion of the Investigator, virus safety retain samples may be drawn 1 or 2 days prior to SC Week#1 instead of combining with other blood draws on a single day. Collected samples will be tested only if the subject exhibits clinical signs and symptoms consistent with HAV, HBV, HCV, HIV, or B19V infection while participating in the study.

- SC infusion of IGSC 20%
- Concomitant medications
- Adverse events including SBIs

  Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category) as detailed in Section 3.6.3.1.
- Record days lost from work/school/daily activities due to infections and treatment

  IGSC 20% dosage (mg/kg) will be based on the subject's prior IgG replacement regimen and current body weight as described in Section 3.3.
- Site personnel will train subjects/caregivers how to administer IGSC 20% using an infusion SC pump
- Train and distribute SC Infusion Diary with subjects/caregivers (See Section 3.6.2.4)

POST SC#1 DAY 2-4 BLOOD SAMPLING VISIT ONLY

Obtain a sample for DAT, serum free hemoglobin, and haptoglobin 2-4 days post SC#1.

No other assessments are needed for this blood draw visit.

SC WEEKS #2, #3 CLINIC VISITS

The objective of these 2 visits is for safety monitoring, for the subject/caregiver to self-administer SC infusions at the clinic, and for additional self-SC administration training and support by the clinical site staff to assure capability for full independent home administration.

- Abbreviated physical exam defined as targeted to symptoms and to include examination of heart, lungs, ears/nose/throat, and with inspection of previous injection sites, and Specific Signs/Symptoms Check for DVT or pulmonary embolus (PE).

  If the following specific signs/symptoms are present, perform Wells Score and blood draw for D-dimer testing (Appendix 4; see also Section 3.6.3.3):

  a. Clinical suspicion of possible DVT with unilateral symptomatic leg swelling, accompanied by any of the following pain, warmth, and/or redness
  b. Medical suspicion of possible PE in a subject presenting with new or worsening dyspnea, tachypnea, chest pain, syncope, and cough in the appropriate clinical setting (cough should not be due to infection, lung disease [eg, asthma, emphysema], or angiotensin-converting enzyme inhibitors)
  c. Any single alarm symptom such as hemoptysis or cyanosis (36,37,38)
- Vital signs (pre-infusion: SBP, DBP, HR, T, RR)

- Predose Special tests (DAT, serum free hemoglobin, haptoglobin) will be performed at both SC Week #2 and SC Week #3 visits. (These visits represent a 7-day time point after the prior IGSC 20% infusion). Note that additional special tests (DAT, serum free hemoglobin, haptoglobin) will be performed 2-4 days *post SC #2 only* (also noted below as a separate Blood Sampling Visit).
- Observe subject/caregiver self-administration of SC infusion of IGSC 20% in the clinic

  Note: Site personnel will observe (and re-train if needed) subjects/caregivers on administration IGSC 20% using the infusion SC pump
- Concomitant medications
- Adverse events including SBIs

  Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category) as detailed in Section 3.6.3.1.
- Record days lost from work/school/daily activities due to infections and treatment
- Review SC infusion diary and infusion details with subjects/caregivers

POST SC#2 DAY 2-4 BLOOD SAMPLING VISIT ONLY

Obtain a sample for DAT, serum free hemoglobin, and haptoglobin 2-4 days post SC#2.

No other assessments are needed for this blood draw visit.

SC WEEKS #5, #9, #17, AND #21 CLINIC VISITS

The following procedures and tests will be completed at the SC Weeks #5, #9, #17, and #21visits:

- Abbreviated physical exam with inspection of SC injection sites, and Specific Signs/Symptoms Check.

  If the following Specific signs/symptoms are present, perform Wells Score and blood draw for D-dimer testing (Appendix 4; see also Section 3.6.3.3):

  a. Clinical suspicion of possible DVT with unilateral symptomatic leg swelling, accompanied by any of the following pain, warmth, and/or redness
  b. Medical suspicion of possible PE in a subject presenting with new or worsening dyspnea, tachypnea, chest pain, syncope, and cough in the appropriate clinical setting (cough should not be due to infection, lung disease [eg, asthma, emphysema], or angiotensin-converting enzyme inhibitors)
  c. Any single alarm symptom such as hemoptysis or cyanosis (36,37,38)
- Vital signs (pre-infusion: SBP and DBP, HR, T, RR)
- Body weight (will be used for SC dose calculation)
- Height SC Week #9, SC Week #17, and SC Week #21 only
- **SC Week #9, SC Week#17only:** Predose laboratory assessments drawn prior to SC infusion (as outlined in Screening Visit [Section 3.6.2.1] including hematology, clinical chemistry, special tests, and urinalysis)

- Predose blood draw for trough total IgG (all visits)
- **SC Week #9, SC Week#17 only:** IgG subclass, and antibody titer levels prior to SC infusion (within 0.5 hour prior to the start of infusion).
- Review SC infusion diary and infusion details with subjects/caregivers
- Observe subject/caregiver self-administration of SC infusion of IGSC 20% in the clinic
- Concomitant medications
- Adverse events including SBIs

  Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category) as detailed in Section 3.6.3.1.
- Record days lost from work/school/daily activities due to infections and treatment

AWAY FROM CLINIC (SC WEEKS #4, #6, #7, #8, #10, #11, #12, #15, #16, #18, #19, #20, #22, #23, #24)

Subjects will begin home self-administration of SC infusions of IGSC 20% beginning with the 4th SC infusion. If it is felt by the subject or Investigator that the subject requires additional educational training for administering the study drug SC, additional clinic visits will be scheduled to further train the subject. Subjects will be directed to adhere closely to their individualized dosing regimen and cautioned not to round-up to the whole vial or under dose.

SC infusion diary: The IGSC 20% infusion diary may be used to record items including but not limited to: infusion site reactions, concomitant medications (including antibiotics [prophylactic and therapeutic]), and details of study drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume of each SC dose, 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.

SC WEEK #13 CLINIC VISIT & PK ASSESSMENT FOR SC DOSING

The following procedures and tests will be completed at the SC Week #13 visit:

- Abbreviated physical exam with inspection of SC injection sites and Specific Signs/Symptoms Check.

  If the following Specific signs/symptoms are present perform Wells Score and blood draw for D-dimer testing (Appendix 4; see also Section 3.6.3.3):

  a. Clinical suspicion of possible DVT with unilateral symptomatic leg swelling, accompanied by any of the following pain, warmth, and/or redness
  b. Medical suspicion of possible PE in a subject presenting with new or worsening dyspnea, tachypnea, chest pain, syncope, and cough in the appropriate clinical setting (cough should not be due to infection, lung disease [eg, asthma, emphysema], or angiotensin-converting enzyme inhibitors)
  c. Any single alarm symptom such as hemoptysis or cyanosis (36,37,38)
- Vital signs (pre-infusion: SBP, DBP, HR, T, RR)

- Predose blood draw for trough total IgG
- Body weight
- Observe patient/caregiver self-administration of SC infusion of IGSC 20% in the clinic and initiate serial PK sampling as detailed below
- Concomitant medications
- Adverse events including SBIs

  Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category) as detailed in Section 3.6.3.1.
- Record days lost from work/school/daily activities due to infections and treatment
- Review SC infusion diary and infusion details with subjects/caregivers.

PK samples associated with the SC administration of IGSC 20% will commence at the SC Week #13 visit for all enrolled subjects including those ≤5 years of age. Subjects between the ages of 2 to 5 years of age will undergo an abbreviated schedule for serial PK sampling.

Blood draws for PK assessment **for subjects >5 years of age** will be taken at the following times:

- Prior to the 13th SC infusion (within 0.5 h of the start of infusion and this is the same sample for predose trough total IgG level)
- 1 day ± 4 h post-infusion
- 3 days ± 4 h post-infusion
- 4 days ± 4 h post-infusion
- 5 days ± 4 h post-infusion
- 7 days ± 1 day post-infusion (within 0.5 hour prior to the 14th SC dose) for IgG trough level

Blood draws for PK assessment **for subjects ≤5 years of age** will be taken at the following times:

- Prior to the 13th SC infusion (within 0.5 h of the start of infusion and this is the same sample for predose trough total IgG level)
- 3 days ± 4 h post-infusion
- 7 days ± 1 day post-infusion (within 0.5 hour prior to the 14th SC dose) for IgG trough level

The actual date/clock time of the start and end of the SC infusion, volume/amount of dose infused, rate of infusion, and location and number of infusion sites will be recorded. The actual date/clock time for each blood sample for either PK or trough level assessment will be collected and recorded. The interim PK samples may be obtained at an alternate location. If an outside agency is utilized for sample collection, the sample will be drawn and processed per protocol and laboratory manual instructions.

SC WEEK #14 CLINIC VISIT

The following procedures and tests will be completed at the SC Week #14 visit:

- Abbreviated physical exam with inspection of SC injection sites and Specific Signs/Symptoms Check.

  If the following Specific signs/symptoms are present perform Wells Score and blood draw for D-dimer testing (Appendix 4; see also Section 3.6.3.3):

  a. clinical suspicion of possible DVT with unilateral symptomatic leg swelling, accompanied by any of the following pain, warmth, and/or redness
  b. medical suspicion of possible PE in a subject presenting with new or worsening dyspnea, tachypnea, chest pain, syncope, and cough in the appropriate clinical setting (cough should not be due to infection, lung disease [eg, asthma, emphysema], or angiotensin-converting enzyme inhibitors)
  c. Any single alarm symptom such as hemoptysis or cyanosis (36,37,38)
- Vital signs (pre-infusion: SBP, DBP, HR, T, RR)
- Predose blood draw for trough total IgG prior to SC infusion (within 0.5 hour prior to the start of infusion). Note: This trough IgG sample is the same one that is used for PK blood draw at 7 days post-infusion timepoint (SC Week#13).
- Observe subject/caregiver self-administration of SC infusion of IGSC 20% in the clinic
- Concomitant medications
- Adverse events including SBIs

  Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category) and antibiotic treatment as detailed in Section 3.6.3.1.
- Record days lost from work/school/daily activities due to infections and treatment
- Review SC Infusion Diary and infusion details with subjects/caregivers

3.6.2.5 Monthly Extension Visits

The monthly extension visits will occur only for subjects enrolled early in the trial who may complete their regularly scheduled 24 weeks of SC therapy on the initial IGSC 20% dose before a decision from the interim PK analysis is available. In this event, these subjects will continue to receive weekly SC infusions of IGSC 20% until the interim PK analysis deems whether or not a new dose adjustment factor would be required. Subjects will return to the study center every 4 weeks for evaluation and have the same study procedures performed as those at SC Week#21. At every 8 weeks, safety laboratory assessments, IgG subclass levels, and specific antibody titers for *S. pneumoniae, H. influenzae*, and *C. tetani* (tetanus) will be performed. This will continue until the interim PK analysis is completed (See Section 3.1.5).

The following procedures and tests will be completed at the Monthly Extension Visit:

- Abbreviated physical exam with inspection of SC injection sites and Specific Signs/Symptoms Check.

If the following Specific signs/symptoms are present perform Wells Score and blood draw for D-dimer testing (Appendix 4; see also Section 3.6.3.3):

a. Clinical suspicion of possible DVT with unilateral symptomatic leg swelling, accompanied by any of the following pain, warmth, and/or redness
b. Medical suspicion of possible PE in a subject presenting with new or worsening dyspnea, tachypnea, chest pain, syncope, and cough in the appropriate clinical setting (cough should not be due to infection, lung disease [eg, asthma, emphysema], or angiotensin-converting enzyme inhibitors)
c. Any single alarm symptom such as hemoptysis or cyanosis (36,37,38)

- Vital signs (pre-infusion: SBP, DBP, HR, T, RR)
- Body weight (will be used for SC dose calculation) and height
- **Every 8 week intervals only:** Predose laboratory assessments drawn prior to SC infusion (as outlined in screening visit [Section 3.6.2.1] including hematology, clinical chemistry, special tests, and urinalysis) ***and*** IgG subclass, and antibody titers for *S. pneumoniae, H. influenzae*, and *C. tetani* (tetanus) prior to SC infusion (within 0.5 hour prior to the start of infusion)
- Predose blood draw for trough total IgG
- Observe subject/caregiver self-administration of SC infusion of IGSC 20% in the clinic
- Concomitant medications
- Adverse events including SBIs

  Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category) as detailed in Section 3.6.3.1.
- Record days lost from work/school/daily activities due to infections and treatment
- Review SC infusion diary and infusion details with subjects/caregivers

If the results of the interim PK analysis do not indicate a need for a dose adjustment factor change, subjects will be brought into the clinic (within one week following the confirmation of the initial dose adjustment factor) and end of study procedures will be performed.

3.6.2.6 Final Visit (Week #25)/Early Termination Clinic Visit

The Final Visit (Week #25) visit will be scheduled one week after the final SC infusion. If a subject discontinues at any point during the study after the first Run-In visit or IV#1 for those who enter the IV Phase directly, 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 a subject who prematurely discontinues the study.

The following procedures and tests will be completed (note that no study-related infusion will be scheduled):

- Full physical exam (excludes breast and genitourinary exam)
- Vital signs (SBP, DBP, HR, T, RR)

- Laboratory assessments (as outlined in Screening Visit [Section 3.6.2.1] including hematology, clinical chemistry, special tests, and urinalysis)
- Blood draw for trough total IgG, IgG subclass, and antibody titers for *S. pneumoniae, H. influenzae*, and *C. tetani* (tetanus)
- Serum pregnancy test (for females of childbearing potential)
- Measles antibody titer
- Concomitant medications
- Adverse events including SBIs

  Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category) as detailed in Section 3.6.3.1.
- Record days lost from work/school/daily activities due to infections and treatment
- Review SC infusion diary and infusion details with subjects/caregivers

3.6.3 Description of Laboratory Tests and Procedures

Detailed descriptions of laboratory test procedures are located in the study Laboratory Manual. Table 3-2 provides a summary of the laboratory tests conducted for this study.

Table 3-2 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
D-dimer	D-dimer	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 PK profiling of IGIV-C 10% (IV Phase) and IGSC 20% (SC Phase)	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 IV#2 (before the first SC infusion of IGSC 20%) and at SC Week#25	Specialty
Serum pregnancy test[a]	Qualitative serum β-HCG for females of child-bearing potential will be performed at Screening and Final Visit	Central

Table 3-2 Name, Description, and Location of Laboratory Tests and Procedures

Test Panel	Description	Location
Urine pregnancy test	Qualitative urine pregnancy test for females of child-bearing potential will be performed at IV #1 Baseline	Local
Viral nucleic acid amplification technology (NAT) testing[a, b]	SC Week#1 prior to IGSC 20% infusion: Collect retain samples for hepatitis A virus (HAV) RNA, HBV DNA, HCV RNA, HIV RNA, and parvovirus B19 (B19V) DNA testing	Central
Viral serology testing[a, b]	SC Week#1 prior to IGSC 20% infusion: 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 (ie, lost, quantity not sufficient, laboratory error) need to be recollected by contacting the subject and arranging for re-sampling.

[b] See Section 3.6.3.2 for details.

3.6.3.1 Assessment and Recording of Infections

The site is to record non-serious infections (by category), which 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 eg, 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.

3.6.3.2 Virus Safety Testing

Virus safety (viral NAT and viral serology) retain samples collected at SC Week#1 prior to IGSC 20% infusion will be tested only if the subject exhibits clinical signs and symptoms consistent with HAV, HBV, HCV, 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 blood 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 HAV, HBV, HCV, HIV, or B19V infection while participating in the study. Note: For pediatric subjects, at the discretion of the Investigator, virus safety retain samples may be drawn 1 or 2 days prior to SC Week#1 instead of combining with other blood draws on a single day.

3.6.3.3 D-dimer and Wells Score

The Wells Score for DVT and PE with associated citations is described in Appendix 4 which provides full details for assigning point score for each of these individual conditions. At Screening and prior to administering IGSC 20% for the first time at the SC Week #1 Clinic Visit, Wells Score and blood draw for D-dimer will be performed to establish a pretreatment benchmark (prior to receiving IGIV-C 10% and prior to beginning IGSC 20%, respectively). At subsequent visits during the SC Phase, the Wells Score and blood draw for D-dimer will be performed only if the abbreviated physical exam and Specific Signs/Symptoms Check (defined in Section 3.6.2.4) raises any clinical/medical concerns regarding possible presence of DVT or PE.

As delineated in Appendix 4, any subject with a total Wells prediction score >1 for the DVT assessment or >4 for the PE assessment should have further diagnostic testing per study site standard of care if medically indicated - unless the D-dimer is negative since this test has a high negative predictive value. If the D-dimer is positive at any time after the Screening time point (ie, above Screening value, exceeding cutoff range of the reporting laboratory), redraw a blood sample for repeat D-dimer testing at the central laboratory within one week to confirm. In all situations, the Investigator should use best medical judgment to evaluate the subject as medically indicated.

3.7 Removal of Subjects

Subjects will 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 will be withdrawn from IP/study drug 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 develop an SBI prior to the first dose of IGSC 20%
- Subjects who are noncompliant with the protocol per the Investigator’s discretion
- Pregnancy

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

If a subject discontinues study after receiving IGIV-C 10% but prior to receiving the first dose of IGSC 20%, an additional subject may be recruited into the study to assure that 30 adults and 12 children complete IGSC 20% treatment.

3.8 Follow-up of Subjects Withdrawn from Study

Subjects who receive any amount of IP/study drug and discontinue early from the study will be requested to return clinic to have all assessments completed for the Early Termination Visit (see Section 3.6.2.6 and Appendix 1) as close as practical to 1 week after their last administration of the IP/study drug.

3.9 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 among 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 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)

STOPPING RULES FOR THE STUDY AS A WHOLE:

As a conservative measure, if 5 subjects on IGSC 20% develop an SAE of exactly the same type (ie, the same MedDRA [Medical Dictionary for Regulatory Activities] preferred term) which is not an infection or manifestation of an underlying disorder documented in medical history, then this would constitute an unanticipated clustering which could signal a potential safety concern. If this situation were to arise, the Sponsor will constitute a Safety Review Committee (SRC) whose members (from Grifols) will be impartial and independent of the clinical trial team. In cases where there is a clear medical plausibility supporting an uncommon clustering of SAEs of the same type (not including infections), and these sentinel SAEs are designated as ‘definitely related’, ‘probably related’, or ‘possibly related’ by both the Investigator and the SRC, consideration would be given to possibly discontinuing the study.

4 ADVERSE EVENTS

4.1 Warnings/Precautions

For complete information on IGSC 20% or IGIV-C 10%, refer to their respective IBs.

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/study drug.

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 that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding), 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 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.

All infusion site reactions will be recorded. For 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, these 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. In the framework of this study, a suspected ADR with a causal relationship of "definite" will be labeled as an AR; thus, ARs are a subset of suspected ADRs.

The Sponsor is responsible for assessing the suspected ADR expectedness during the clinical trial.

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. Assessment of the causal relationship to the study drug will be made according to the following classifications based on Karch FE et al. (39):

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; 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; 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 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; 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. (40,41).

When an AE is classified, assessing causal relationship by the Investigator, as definitive, ie, "probable", "possible" or "doubtful/unlikely", the event will be defined as a suspected ADR. A suspected ADR with a causal relationship of "definite" will be defined as an AR. 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/study drug administration until the final visit of the clinical trial will be considered as treatment emergent AEs (TEAEs).

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.

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 of an AR shall be determined by the Sponsor according to the reference document (ie, IB).

Events not listed for the particular drug under investigation in the IB are considered "unexpected" and those listed are considered "expected." When new Serious ADRs (potentially related SAEs) are received, it is the Sponsor's responsibility to determine whether the events are "unexpected" 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 and Pregnancy Documentation

All AEs and SAEs occurring after the subject has signed the ICF through the Final Visit (ie, 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/study drug)
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/study drug. An AE occurring before subject's exposure to IP/study drug 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, eg, 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/study drug, action taken, and outcome. Each event must be adequately supported by documentation as it appears in the subject's medical or case file.

A pregnancy not verified before the screening visit but occurring during the course of the study will not be considered an AE unless a relation to the study drug is at least suspected. In any case, a Pregnancy Report Form must be completed and sent within 24 hours to the Sponsor, and the study treatment must be discontinued. A copy of the form should be filed at the study site for follow-up until the end of the pregnancy.

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 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.

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 (ie, 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.

Each SAE must be followed up until resolution or stabilization. After the initial report, all relevant information for SAE follow up, and for 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 and Pregnancy Report Forms must be reported to:

Grifols Global Pharmacovigilance for Reporting SAEs and Pregnancy

Email: [redacted]

FAX (back-up only): [redacted] (US/Canada) and [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 from time of consent through the Final Visit (ie, 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 of observations, 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 Populations for Analysis

Safety Population

The safety population will include all subjects who received any amount of study drugs (IGIV-C 10% and/or IGSC 20%) and will be used for safety analysis.

PK Population

The PK population will consist of all subjects who receive study drugs and have sufficient and valid total IgG concentration vs. time data for either the IV or SC Phase to allow calculation of $AUC_{0\text{-}\tau,SC}$ or $AUC_{0\text{-}\tau,IV}$ (the primary PK endpoint).

The validity of total IgG concentrations will be reviewed and determined before the database lock based on consideration of treatment compliance and blood sampling/testing issues (such as collection problem). Any invalid total IgG concentrations will be flagged with the reason for invalidity in the listing.

IgG Population

The IgG population will consist of all subjects who receive study drugs and have any total IgG concentration data. The summary of total IgG concentration data will be based on IgG Population.

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 Pharmacokinetic Analysis

All subjects in the PK Population as defined above will be included in the PK analysis. Total IgG concentrations will be summarized for IV and SC by each timepoint. Individual and mean total IgG concentrations vs. time curves will be plotted. PK parameters of total IgG will be determined by noncompartmental PK methods using WinNonlin Professional version 6.4 or above (Pharsight Corporation, Cary, NC). Steady-state PK parameters to be calculated, as appropriate, or as permitted by data, will include AUC, C_{max}, and t_{max}. All PK parameters will be calculated separately for IV and SC administration and will be tabulated and summarized descriptively. The mean and the lower and upper bounds of the 90% CI will be calculated on ln-transformed AUC parameters. These mean and lower and upper bounds will be back-transformed (exponentiated) to provide the geometric mean and 90% CI on the original scale.

The Primary PK endpoint is the steady-state AUC over a dosing interval defined as follows:

- $AUC_{0-\tau,SC}$, the AUC over a weekly dosing interval (τ) at an approximate steady-state condition following weekly SC infusion, ie, $AUC_{0\text{-}7\ days}$.
- $AUC_{0-\tau,IV}$, the AUC over a regular dosing interval (τ) at an approximate steady-state condition following the regular IV infusion, either every 3 weeks or every 4 weeks, ie, $AUC_{0\text{-}21\ days}$ or $AUC_{0\text{-}28\ days}$, respectively.

$AUC_{0-\tau,SC}$ is to be obtained after the 13th SC dose of IGSC 20% at the weekly dose calculated using the final dose adjustment factor, and $AUC_{0-\tau,IV}$ is to be obtained following IV infusion of IGIV-C 10% at the IV#1 visit. Since the dosing interval (τ) is 7 days for the SC dose, $AUC_{0-\tau,SC}$ is determined as $AUC_{0\text{-}7\ days}$. For IV dosing, the dosing interval (τ) is 21 or 28 days for the 3-week or 4-week subjects, $AUC_{0-\tau,IV}$ is determined as $AUC_{0\text{-}21\ days}$ or $AUC_{0\text{-}28\ days}$, respectively.

Prior to statistical comparison of $AUC_{0-\tau}$'s between the IV IGIV-C 10% and SC IGSC 20% doses, the $AUC_{0\text{-}21\ days}$ from the IV infusion in subjects on a 3-week IV dosing interval will be divided by 3 or the $AUC_{0\text{-}28\ days}$ from IV dosing in subjects on a 4-week IV dosing interval divided by 4 for comparison with $AUC_{0\text{-}7\ days}$ from the weekly SC infusion.

The hypothesis to be tested is that the weekly SC dose of IGSC 20% will achieve an approximate steady-state $AUC_{0-\tau,SC}$ of total IgG that is non-inferior to that achieved by a regular IV dose of IGIV-C 10% ($AUC_{0-\tau,IV}$ divided by 3 or 4 depending on the IV dosing intervals). Non-inferiority of steady-state IgG AUC between SC dose of IGSC 20% and IV IGIV-C 10% administration will be tested based on established regulatory guidelines for bioequivalence testing. The 90% CI of the geometric LSM ratio of SC AUC to IV AUC will be calculated. The SC dose is considered to be non-inferior to the IV dose if the low bound of the 90% CI for the geometric LSM AUC ratio is above 0.80 based on loge-transformed data.

Secondary and Exploratory PK Analysis

Secondary and exploratory PK endpoints include the steady-state mean trough concentration of total IgG and the $C_{max,}$ t_{max} of total IgG. Descriptive statistics will be calculated for the steady-state mean trough concentration of total IgG and for the $C_{max,}$ and t_{max} of total IgG. All pre-infusion total IgG concentrations obtained before and at the 13th SC dose of IGSC 20% will be evaluated to determine if an approximate steady-state condition has been achieved by the 13th SC dose. The steady-state mean trough concentrations of total IgG following SC administrated IGSC 20% will be determined as the average value of C_{trough} measurements obtained at Weeks#13, #14, #17, and #21. The average steady-state trough concentrations of total IgG following IV administrated IGIV-C 10% will be determined as the average value of C_{trough} measurements obtained at the IV#1 visit and at 21 or 28 days after the IV#1 IGIV-C 10% dose (depending on dosing interval), ie, immediately prior to the administration of IV dose at IV#2 visit.

Summaries will be provided for trough concentration of total IgG and each of its subclasses between IV infusion of IGIV-C 10% and SC administration of IGSC 20%. Summaries of trough level concentration of antibody titers against *S. pneumonia, H.influenza,* and *C. tetani* will also be provided.

Depending on the number of subjects being dosed on IGIV-C 10% at 3- or 4-week dosing intervals, subgroup analyses may be performed to evaluate PK variables by IV dosing interval. Subgroup analyses will additionally include age, sex, race, ethnicity and other factors as appropriate.

5.1.4 Interim PK Analysis

An interim PK analysis will be conducted as described in Section 3.1.5. This analysis will be performed as soon as practical after the first 6 adult/adolescent subjects (aged ≥12-75 years) have completed the PK sampling schedule for both the IV and SC (after the 13th SC dose) Phases of the trial. PK data from these 6 adult/adolescent subjects will be analyzed using procedures as described in Section 5.1.3 above. A decision on whether to modify the dose adjustment factor for calculating the SC dose will be made based on this interim PK analysis.

Final PK and statistical analysis will be based on the PK data obtained after the final (or adjusted, if any) SC dose administered in all completed subjects.

5.1.5 Exploratory Analysis

Other exploratory variables include the following:

- Serious bacterial infections
- 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).
- Validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms, eg, bacterial, viral, fungal or protozoal pathogens (for instance, rapid streptococcal antigen detection test).
- 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 due to infections and their treatment.

These parameters will be summarized descriptively. The number and proportion of subjects having any SBI, infections, days on antibiotics, hospitalizations due to infection, and days of work/school/daily activities missed due to infections will be calculated and summarized. Furthermore, the total number of events or days and corresponding annualized rate per subject of SBIs, infections, days on antibiotics, hospitalizations due to infection, and days of work/school/daily activities missed due to infections will be calculated and summarized.

5.1.6 Safety Analysis

The safety analyses are based on the safety population.

All AEs, suspected ADRs, ARs, SAEs, and discontinuations due to AEs and SAEs will be summarized by presenting the number of AEs and the number and percentage of subjects with AEs. 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. Non-serious infections of any kind (including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator will also be considered a safety endpoint and 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 IV or 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

The planned number of subjects is 50 enrolled to provide 30 completing adult subjects and 12 to 18 completing pediatric subjects. This sample size is primarily based on safety assessment consideration. Also a sample size of 42 to 48 with at least 24 scheduled administrations of IGSC 20% would provide the clinical experience data on a total of more than 1152 to 1080 IGSC 20% dosing administrations for safety assessment.

The planned minimum enrollment of 42 completing subjects should be more than adequate to establish that the AUC for total IgG for IGSC 20% is non-inferior to that achieved by IGIV-C 10%.

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 (eg, 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, to verify adherence to the protocol, and to verify 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/study drug 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 IRB's/EC's approval must be obtained and also forwarded to the Sponsor. The IRB/EC 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 (ie, 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 where it is permitted will be recorded in the eCRF, and if the subject’s name appears on any other document (eg, 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.

9 REFERENCES

1. Rosen F. Primary immunodeficiency diseases report of an IUIS Scientific Committee. Clinical & Experimental Immunology. 1999;118(S1):1-28.

2. Boyle J, Buckley R. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. Pharmaceuticals Policy and Law. 2008;10:99-108.

3. Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova J-L et al. Primary immunodeficiency diseases worldwide: more common than generally thought. J Clin Immunol. 2013;33: 1-7.

4. Buckley R, Schiff RI. The use of intravenous immune globulin in immunodeficiency diseases. N Engl J Med. 1991;11(2):110-7.

5. Sacher RA. Intravenous immunoglobulin consensus statement. J Allergy Clin Immunol. 2001;(4 Suppl):S139-S146.

6. Gardulf A. Immunoglobulin treatment for primary antibody deficiencies advantages of the subcutaneous route. Biodrugs. 2007;21(2):105-16.

7. Helbert M, Farragher A. Subcutaneous immunoglobulin for patients with antibody deficiency. British Journal of Hospital Medicine. 2007;68(4):206-10.

8. Ochs H, Gupta S, Kiessling P, Nicolay U, Berger M, the Subcutaneous IgG Study Group. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. Journal of Clinical Immunology. 2006;26(3):265-73.

9. Boyle ML, Scalchunes C. Impact of intravenous immunoglobulin (IVIG) treatment among patients with primary immunodeficiency diseases. Pharmaceuticals Policy and Law. 2008;10:133–146.

10. Stiehm E, Casillas A, Finkelstein J, Gallagher K, Groncy P, Kobayashi R et al. Slow subcutaneous human intravenous immunoglobulin in the treatment of antibody immunodeficiency: Use of an old method with a new product. J Allergy Clin Immunol. 1998;101:848-9.

11. Radinsky S, Bonagura V. Subcutaneous immunoglobulin infusion as an alternative to intravenous immunoglobulin. J Allergy Clin Immunol. 2003;112 (3):630-3.

12. Thomas M, Brennan V, Chapel H. Rapid subcutaneous immunoglobulin infusions in children. The Lancet. 1993;342:1432-3.

13. Hagan JB, Fasano M, Spector S, Wasserman R, Melamed I, Rojavin M et al. Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPRo20, in patients with Primary Immunodeficiency. J Clin Immunol 2010;30(5): 734-45.

14. Jolles S, Bernatowska E, de Gracia J, Borte M, Cristea V, Peter HH et al. Efficacy and safety of Hizentra® in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. Clinical Immunology. 2011a;141:90–102.

15. Jolles S, Borte M, Nelson RP, Rojavin M, Bexon M, Lawo J-P at el. Long-term efficacy, safety, and tolerability of Hizentra® for treatment of primary immunodeficiency disease. Clinical Immunology. 2014;150:161-169.

16. Abrahamsen TG, Sandersen H, Bustnes A. Home therapy with subcutaneous immunoglobulin infusions in children with congenital immunodeficiencies. Pediatrics. 1996;6:1127-1131.

17. Gaspar J. Gerritsen B, Jones A. Immunoglobulin replacement treatment by rapid subcutaneous infusion. Arch Dis Child. 1998;79:48-51.

18. Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. Clin Immunol. 2004;112:1-7.

19. Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM et al. The Comparison of the Efficacy and Safety of Intravenous Versus Subcutaneous Immunoglobulin Replacement Therapy. Journal of Clinical Immunology. 2000;20(2):94-100.

20. Chinen J, Shearer WT. Subcutaneous immunoglobulins: Alternative for the hypogammaglobulinemic patient? J Allergy Clin Immunol. 2004;114:934-5.

21. Chouksey A, Duff K, Wasserbauer N, Berger M. Subcutaneous immunoglobulin-G replacement therapy with preparations currently available in the United States for intravenous or intramuscular use: reasons and regimens. Allergy, Asthma, and Clinical Immunology. 2005;1(3):120-30.

22. Gardulf A, Björvell H, Gustafson R, Hammarström L, Smith CI. Safety of rapid subcutaneous gammaglobulin infusions in patients with primary antibody deficiency. Immunodeficiency. 1993;4:81-4.

23. Gardulf A, Björvell H, Gustafson R, Hammarström L, Smith CI. The life situations of patients with primary antibody deficiency untreated or treated with subcutaneous gammaglobulin infusions. Clin Exp Immunol. 1993;92(2):200-4.

24. Gardulf A, Andersen V, Björkander J, Ericson D, Frøland S, Gustafson R et al. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. The Lancet. 1995;345:365-9.

25. Gardulf A, Nicolay U, Math D, Asensio O, Bernatowska E, Böck A et al. Children and adults with primary antibody deficiencies gain quality of life by subcutaneous IgG self-infusions at home. J Allergy Clin Immunol. 2004;114 (4):936-42.

26. Gardulf A, Nicolay U. Replacement IgG therapy and self-therapy at home improve the health-related quality of life in patients with primary antibody deficiencies. Curr Opin Allergy Clin Immunol. 2006;6:434-42.

27. Gardulf A, Nicolay U, Asensio O, Bernatowska E, Böck A, Carvalho BC et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies — a prospective, multi-national study. J Clin Immunol. 2006;26(2):177-85.

28. Hansen S, Gustafson R, Smith CI, Gardulf A. Express subcutaneous IgG infusions: decreased time of delivery with maintained safety. Clin Immunol. 2002;104 (3):237-41.

29. Nicolay U, Haag S, Eichmann F, Herget S, Spruck D, Gardulf A. Measuring treatment satisfaction in patients with primary immunodeficiency diseases receiving lifelong immunoglobulin replacement therapy. Qual Life Res. 2005;14:1683-91.

30. Nicolay U, Kiessling P, Berger M, Gupta S, Yel L, Roifman CM et al. Health-related quality of life and treatment satisfaction in North American patients with primary immunodeficiency diseases receiving subcutaneous IgG self-infusions at home. J Clin Immunol. 2006;26(1):65-72.

31. Waldmann TA, Strober W, Blaese RM. Metabolism of immunoglobulins. Prog Immunol. 1972;891-903.

32. Orange JS, Belohradsky BH, Berger M, Borte M, Hagan J, Jolles S, et al. Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy. Clinical and Experimental Immunology. 2012;169:172–181.

33. Wanieski J, Gardulf A, Hammarstrom L. Bioavailability of gamma-globulin after subcutaneous infusions in patients with common variable immunodeficiency.J Clin. Immunology. 1994;14:90-97.

34. Wasserman RL, Irani A-M, Tracy J, Tsoukas C, Stark D, Levy R, et al. Pharmacokinetics and safety of subcutaneous immune globulin (human), 10% caprylate/chromatography purified in patients with primary immunodeficiency disease. British Society for Immunology, Clinical and Experimental Immunology. 2010;161:518–526.

35. Shearer WT, Fleisher TA, Buckley RH, Ballas Z, Ballow M, Blaese RM et al. Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts. J Allergy Clin Immunol. 2014;133(4):961-966.

36. Levin D. Seo JB, Kiely DG, Hatabu H, Gefter W, van Beek EJR, Schiebler ML on behalf of the 2013 International Workshop for Pulmonary Functional Imaging (IWPFI). Triage for suspected acute pulmonary embolism: think before opening Pandora's box. European Journal of Radiology 2015; 84: 1202-1211.

37. Wilbur J, Shian B. Diagnosis of deep venous thrombosis and pulmonary embolism. Am Fam Physician 2012; 86(10):913-919.

38. Oudega R, Moons KGM, Hoes AW. Ruling out deep venous thrombosis in primary care. Thromb Haemost 2005; 94: 200-205.

39. Karch FE, Lasagna L. Adverse drug Reactions. A critical review. JAMA. 1975;234: 1236-1241.

40. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. Clin Pharmacol Ther. 1977;21:247-54.

41. Naranjo CA, Busto U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45.

42. Levy MM, Fink MP, Marshall JC et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31:1250-1256.

43. International Consensus Conference on Pediatric Sepsis. Pediatric Crit Care Med. 2005; 6:2-8.

44. FDA Guidance for Industry "Acute Bacterial Meningitis – Developing Antimicrobial Drugs for Treatment," Draft Guidance, July 1998. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070937.pdf. Last checked: 13 Feb 2015.

45. FDA Guidance for Industry "Community Acquired Pneumonia – Developing Antimicrobial Drugs for Treatment," Draft Guidance, July 1998. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm123686.pdf. Last checked: 13 Feb 2015.

46. Anderson DR, Kovacs MJ, Kovacs G, et al. Combined use of clinical assessment and D-dimer to improve the management of patients presenting to the emergency department with suspected deep vein thrombosis (the EDITED Study). J Thromb Haemost 2003;1(4):645-51.

47. Wells PS, Anderson, DR, Rodger M, et al. Evaluation of D-dimer in the Diagnosis of Suspected Deep-Vein Thrombosis. N Engl J Med 2003;349:1227-35.

48. Wells PS. Integrated strategies for the diagnosis of venous thromboembolism. J Thromb Haemost 2007; 5 Suppl 1: 41-50.

49. Adam SS, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. Blood 2009; 113(13): 2878-2887.

50. Wells PS, Anderson, DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost 2000;83(3):416-20.

10 APPENDICES

Appendix 1 Schedule of Study Procedures

Phase / Clinic Visits / Procedures and Evaluation	Screening (up to 28 days)	Run-In (if required) (IGIV-C 10%) (3 to 4 months)	IV Phase[a] (IGIV-C 10%)		SC Phase[b] (IGSC 20%)												
			IV#1 Baseline	IV#2	SC Week #1	+2-4 days post SC#1	SC Week #2	+2-4 days post SC#2	SC Week #3	SC Week #5	SC Week #9	SC Week #13	SC Week #14	SC Week #17	SC Week #21[p]	Final Visit (Week #25)/ Early Term	Monthly Extension Visit[c]
Informed consent/assent (if applicable)	X																
Inclusion and exclusion criteria (confirm eligibility)	X																
Medical history, demographics	X																
Full physical exam[d]	X				X											X	
Abbreviated physical exam and Specific Signs/Symptoms Check (SSC)[e]							X		X	X	X	X	X	X	X		X
Pre-dose Wells Score and D-dimer testing (at subsequent visits only if indicated per Specific SSC)[e]	X				X		SSC[e]		SSC[e]	SSC[e]	SSC[e]	SSC[e]	SSC[e]	SSC[e]	SSC[e]		SSC[e]
Chest X-ray[f]	X																
Vital signs[g]	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
Body weight[h]	X	X	X		X					X	X	X		X	X		X
Height	X		X								X			X	X		X
Pre-dose laboratory assessments (hematology, chemistry, urinalysis)[i]	X		X		X						X			X		X	X[c]
Special tests (DAT, serum free hemoglobin, haptoglobin)	X		X		X	X	X	X	X		X			X		X	X[c]
Serum pregnancy test[j]	X															X	
Urine pregnancy test[j]			X														
Pre-dose sample for total IgG level[k]	X	X	X	X						X	X	X	X	X	X	X	X

Phase / **Clinic Visits** / **Procedures and Evaluation**	**Screening (up to 28 days)**	**Run-In (if required)** (IGIV-C 10%) **(3 to 4 months)**	**IV Phase**[a] (IGIV-C 10%)		**SC Phase**[b] **(IGSC 20%)**												
			IV#1 Baseline	**IV#2**	**SC Week #1**	**+2-4 days post SC#1**	**SC Week #2**	**+2-4 days post SC#2**	**SC Week #3**	**SC Week #5**	**SC Week #9**	**SC Week #13**	**SC Week #14**	**SC Week #17**	**SC Week #21**[p]	**Final Visit (Week #25)/ Early Term**	**Monthly Extension Visit**[c]
Pre-dose sample for IgG subclass levels and antibody titers[l]			X	X							X			X		X	X[c]
Pre-dose measles antibody titer samples				X												X	
Pre-dose virus safety retain samples[m]					X												
IGIV-C 10% infusions		X	X	X													
IGSC 20% infusions[n] & infusion number					X		q weekly #2		q weekly #3	q weekly #4-8	q weekly #9-12	q weekly #13	q weekly #14-16	q weekly #17-20	q weekly #21-24		q weekly
Serial PK sampling (subjects age ≤5 years, abbreviated schedule)			X[o]									X[p]					
Concomitant medications	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
AE Assessments including SBIs[q]	X	X	X	X	X		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	X	X	X	X	X
Subject SC Infusion Diary review and infusion details					X		X		X	X	X	X	X	X	X	X	X

[a] Time between IV#1 and #2 visits (IV Phase) will be dependent upon subject's IV dosing interval (3 or 4 weeks) upon entering the IV Phase.

[b] SC week number = SC infusion number with the exception of Week#25 which is the Final Visit/Early Termination Visit.

[c] In the event that subjects complete their regularly scheduled 24 weeks of SC infusions prior to the results of the interim PK analysis, they will continue to receive weekly SC infusions of IGSC 20% and return to the clinic for monthly (every 4 weeks) visits which will have the same assessments as SC Week#21 visit including (at less frequent intervals) safety laboratory assessments, IgG subclass levels, and specific antibody titers for *S. pneumoniae, H. influenzae*, and *C. tetani* (tetanus) every 8 weeks. They will continue to be followed monthly until the results of the interim PK analysis are available. If a dose adjustment modification is not required, subjects will return to the clinic for a final visit.

[d] A full physical exam will be performed (excluding breast and genitourinary exam)

[e] Abbreviated physical exam (targeted to symptoms and to include examination of heart, lungs, ears/nose/throat, and inspection of previous injection sites.). Specific Signs/Symptoms Check: If the following Specific Signs/Symptoms are present, perform Wells Score and blood draw for D-dimer testing (Appendix 4; see also Section 3.6.3.3): (a) clinical suspicion of possible DVT with unilateral symptomatic leg swelling, accompanied by any of the following pain, warmth, and/or redness; (b) medical suspicion of possible PE in a subject presenting with new or worsening dyspnea, tachypnea, chest pain, syncope, and cough in the appropriate clinical setting (cough should not be due to infection, lung disease [eg, asthma, emphysema], or angiotensin-converting enzyme inhibitors), (c) Any single alarm symptom such as hemoptysis or cyanosis (36,37,38).

[f] Only if chest X-ray or CT have not been performed in the past 6 months at Screening (Note: at least one radiographic view (AP or PA) is required.)

[g] Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, temperature, and respiration rate) will be measured prior to infusion.

[h] Body weight is measured to determine the IV or SC study drug dose.

[i] Laboratory assessments to be obtained prior to infusion of any study drug (IV IGIV-C 10% or IGSC 20%) at all specified visits. Additional special tests include DAT, serum free hemoglobin, and haptoglobin. Laboratory testing includes Hematology: Hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential; ARC. 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).

[j] Pregnancy testing will be repeated at any time if pregnancy is suspected. Pregnancy testing including serum and urine tests will be performed for child-bearing potential females only.

[k] Blood samples for total IgG trough level to be obtained prior to infusion of study drug (IGIV-C 10% or IGSC 20%) where indicated.

[l] IgG subclasses IgG1, IgG2, IgG3, IgG4, and antibody levels for *S. pneumoniae*, *H. influenzae*, and *C. tetani* (tetanus).

[m] Collect virus safety retain samples at SC Week#1 prior to IGSC 20% infusion but test *only* if the subject exhibits clinical signs and symptoms consistent with HAV, HBV, HCV, HIV, or B19V infection while participating in the study. See Section 3.6.3.2 and Table 3-2 for details. Note: For children at the discretion of the investigator, virus safety retain samples may be drawn 1 or 2 days prior to SC Week #1 instead of combining with other blood draws on a single day.

[n] Weekly SC dosing may be 7 days ± 1 day. If there are logistical issues requiring schedule adjustment for weekly subcutaneous IGSC 20% administration, SC#1 may be scheduled 6 to 9 days after IV#2. SC#2 and SC#3 visits must be performed with a +1 day window. The first 3 SC infusions of IGSC 20% will be performed in the clinic where site personnel will instruct on/observe proper SC dosing technique using the pump. Subsequent monthly SC infusions will also occur and be observed in the clinic after labs and total IgG trough levels are obtained. Other SC infusions will be performed at home for interim weeks starting after the SC Week #3 visit.

[o] Blood samples for IV#1 (IV Phase) PK assessments are at the following time points **for subjects >5 years of age**: prior to the IV#1 IGIV-C 10% infusion (within 0.5 hour of the start of infusion); immediately at the completion of the IV# 1 infusion; 1 hour after completion of infusion; 3 to 16 hours with a window of 2 hours around the 16-hour time point if required by site; 1 day ± 2 hours post infusion; 2 days ± 2 hours post infusion; 3 days ± 4 hours post infusion; 5 days ± 4 hours post infusion; 7 days ± 1 day post infusion; ; 14 days ± 1 day post infusion; 21 days ± 1 day post infusion; 28 days ± 1 day post infusion (only for subjects on a 4-week dosing schedule; within 0.5 hour prior to the IV#2 dose) for total IgG trough level. **Subjects who are between 2 to 5 years of age will undergo abbreviated serial PK sampling**: Prior to IV #1 IGIV-C 10% infusion (within 0.5 hour of the start of infusion); 1 hour after completion of infusion; 3 to 16 hours with a window of 2 hours around the 16-hour time point if required by site; 2 days±2 hours post infusion;7 days±1 day post infusion; 21 days±1 day post infusion; 28 days±1 day post infusion (only for subjects on a 4-week dosing schedule; within 0.5 hour prior to the IV#2 dose).

[p] Blood samples for SC Week#13 PK assessments are at the following time points **for subjects >5 years of age**: prior to the 13th IGSC 20% infusion (within 0.5 hour of the start of infusion); 1 day ± 4 hours post 13th infusion; 3 days ± 4 hours post 13th infusion; 4 days ± 4 hours post 13th infusion; 5 days ± 4 hours post 13th infusion and 7 days ± 1 day post 13th infusion (within 0.5 hour prior to the 14th IGSC 20% dose) for total IgG trough level. **Subjects who are between 2 to 5 years of age will undergo abbreviated serial PK sampling:** prior to the 13th IGSC 20% infusion (within 0.5 hour of the start of infusion); 3 days± 4 hours post 13th infusion; 7 days ± 1 day post 13th infusion (within 0.5 hour prior to the 14th IGSC 20% dose).

[q] Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category) as detailed in Section 3.6.3.1.

Appendix 2 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 (42). 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 (43).

[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 (44).

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 (45).

[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 (45).

Appendix 3 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.

Appendix 4 Wells Score

Deep Vein Thrombosis (46,47)

Clinical Characteristic	Score
Active cancer (treatment ongoing, within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within previous 12 weeks requiring general or regional anesthesia	1
Previously documented DVT	1
Localized tenderness along distribution of deep venous system	1
Entire leg swollen	1
Calf Swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis at least as likely as DVT	-2
Total Score:	

Any subject with a total Wells prediction score >1 for DVT assessment should have further diagnostic testing per study site standard of care if medically indicated - unless the D-dimer is negative since this test has a high negative predictive value. If the D-dimer is positive at any time after the Screening time point (ie, above Screening value, exceeding cutoff range of the reporting laboratory), redraw a blood sample for repeat D-dimer testing at the central laboratory within one week to confirm. In all situations, the investigator should use best medical judgment to evaluate the subject as medically indicated (48,49).

Pulmonary Embolism (50)

Clinical Characteristic	Score
Previous DVT or PE	1.5
Surgery or bedridden for 3 days during past 4 weeks	1.5
Active cancer (treatment within 6 months or palliative)	1
Hemoptysis	1
Heart rate > 100 beats/min	1.5
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3
Total Score:	

Any subject with a total Wells prediction score >4 for the PE assessment should have further diagnostic testing per study site standard of care if medically indicated - unless the D-dimer is negative since this test has a high negative predictive value. If the D-dimer is positive at any time after the Screening time point (ie, above Screening value, exceeding cutoff range of the reporting laboratory), redraw a blood sample for repeat D-dimer testing at the central laboratory within one week to confirm. In all situations, the investigator should use best medical judgment to evaluate the subject as medically indicated (48,49).