



CLINICAL STUDY PROTOCOL

An Open-Label Multicenter Study to Evaluate the Safety and Tolerability of Higher Infusion Parameters of Immune Globulin Subcutaneous (Human), 20% Liquid (Hizentra[®]) in Subjects with Primary Immunodeficiency

Study Number:	IgPro20_4004
Study Product:	IgPro20 (Hizentra [®])
Development Phase:	IV
Sponsor:	CSL Behring LLC 1020 1 st Avenue King of Prussia PA 19406-1310 USA
Protocol Version:	Amendment 3
EudraCT Number:	Not applicable
IND Number:	CCI
Protocol Date:	2 December 2017
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Conference on Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national and local regulations.

This protocol includes information and data that contain trade secrets and privileged or confidential information that is the property of the sponsor ("CSL"). This information must not be made public without written permission from CSL. These restrictions on disclosure will apply equally to all future information supplied to you. This material may be disclosed to and used by your staff and associates as may be necessary to conduct the clinical study.



Study Number :

IgPro20_4004

Study Product:

IgPro20

List of Personnel and Organizations Responsible for Conduct of the Study

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator's Study File. This list will be updated by CSL (or delegate) and provided to the study sites as needed.

Signature on Behalf of Sponsor

Study Title: An Open-Label Multicenter Study to Evaluate the Safety and Tolerability of Higher Infusion Parameters of Immune Globulin Subcutaneous (Human), 20% Liquid (Hizentra®) in Subjects with Primary Immunodeficiency

Protocol Number: IgPro20_4004

I have read the protocol titled “An Open-Label Multicenter Study to Evaluate the Safety and Tolerability of Higher Infusion Parameters of Immune Globulin Subcutaneous (Human), 20% Liquid (Hizentra®) in Subjects with Primary Immunodeficiency” and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

PPD

PPDDate
(DD MMM YYYY)



Study Number :

IgPro20_4004

Study Product:

IgPro20

Signature of Investigator

Study Title: An Open-Label Multicenter Study to Evaluate the Safety and Tolerability of Higher Infusion Parameters of Immune Globulin Subcutaneous (Human), 20% Liquid (Hizentra[®]) in Subjects with Primary Immunodeficiency

Protocol Number: IgPro20_4004

I have read the protocol titled “An Open-Label Multicenter Study to Evaluate the Safety and Tolerability of Higher Infusion Parameters of Immune Globulin Subcutaneous (Human), 20% Liquid (Hizentra[®]) in Subjects with Primary Immunodeficiency”.

By signing this protocol, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki (2008), the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation) and applicable regulatory requirements.

Changes to the protocol will only be implemented after written approval is received from CSL Behring LLC (CSL) and the Institutional Review Board or Independent Ethics Committee (as appropriate), with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the protocol.

Name of investigator

Affiliation of investigator

Date

(DD MMM YYYY)

Protocol Synopsis

Title An Open-Label Multicenter Study to Evaluate the Safety and Tolerability of Higher Infusion Parameters of Immune Globulin Subcutaneous (Human), 20% Liquid (Hizentra[®]) in Subjects with Primary Immunodeficiency

Study Number IgPro20_4004

Sponsor CSL Behring LLC (CSL)

Development Phase IV

Study Product IgPro20 (Hizentra[®])

Indication Primary immunodeficiency

Study Summary This multicenter, open-label, parallel-arm, non-randomized study is designed to evaluate safety and tolerability of higher infusion parameters of IgPro20 in subjects with primary immunodeficiency (PID). The study will include 3 cohorts with a minimum of 15 subjects each as follows:

- Pump-Assisted Volume Cohort (weekly infusions): Volume per injection site of 25 mL up to 50 mL.
- Pump-Assisted Flow Rate Cohort (weekly infusions): Flow rate per injection site of 25 mL/hour up to 100 mL/hour.
- Manual Push Flow Rate Cohort (2 to 7 infusions per week): Flow rate per injection site of 25 to 30 mL/hour up to 120 mL/hour (equivalent of approximately 0.5 mL/minute up to 2 mL/minute).

Each cohort will test 3 (for pump-assisted flow rate cohort – 4) infusion parameter levels, repeated at least 4 times over a duration of 12 (for flow rate cohort – 16) weeks. After 4 infusion weeks at each level, qualifying subjects (responders) will switch to the next infusion parameter level (eg, from 25 to 50 mL/h). During the study, the weekly dose will remain unchanged (as prescribed by treating healthcare provider, usually within 100 to 200 mg/kg per week range); only the respective infusion parameter under evaluation will change.

Primary Objective(s) The primary objective of this study is to determine the responder rate at higher infusion parameters of IgPro20 under the following conditions:

- Pump-Assisted: Volume per injection site of 25 mL, 40 mL, and 50 mL.
- Pump-Assisted: Flow rate per injection site of 25 mL/h, 50 mL/h, 75 mL/h and 100 mL/h.
- Manual Push (manual infusion using syringe without a pump): Flow rate per injection site of 30 mL/h, 60 mL/h, and 120 mL/h (0.5 mL/min, 1 mL/min, and 2 mL/min, correspondingly).

Primary Endpoint(s) The primary endpoints are as follows:

- Pump-Assisted Volume Cohort: Percentage of responders for each planned volume (ie, 25 mL, 40 mL and 50 mL per injection site).
- Pump-Assisted Flow Rate Cohort: Percentage of responders for each planned flow rate (ie, 25 mL/h, 50 mL/h, 75 mL/h and 100 mL/h per injection site).
- Manual Push Flow Rate Cohort: Percentage of responders for each planned flow rate (ie, 30 mL/h [0.5 mL/min], 60 mL/h [1 mL/min], and 120 mL/h [2 mL/min] per injection site).

Secondary Objective(s) The secondary objectives of the study are:

- To evaluate the safety of pump-assisted IgPro20 infusions at higher infusion parameters (volume and flow rate).
- To evaluate the safety of manual push IgPro20 infusions.
- To evaluate the tolerability of higher infusion parameters of IgPro20.

Secondary Endpoint(s) The secondary endpoints are as follows:

- The rate of total adverse events (AEs) per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- The rate of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- The time to onset of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- Severity of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- Duration of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- For all cohorts: Tolerability of a certain infusion parameter, ie, percentage of infusions per cohort by volume/flow rate subgroup experiencing no severe local reactions for each of the infusion parameter levels.

Exploratory Objective(s)

CCI

Exploratory Endpoint(s)

CCI

Study Design	This multicenter, open-label, parallel-arm, non-randomized study is designed to evaluate safety and tolerability of higher infusion parameters of IgPro20 in subjects with PID.
Number of Subjects	Approximately 50 subjects will be enrolled into the study. A target of 45 evaluable subjects (ie, 15 subjects per cohort) is needed. Enrolled subjects will include a target of 14 (30%) pediatric subjects ≤ 17 years of age and a target of 9 (20%) obese subjects with BMI of ≥ 30 kg/m ² . Pediatric and obese subjects may be distributed across any or all of the treatment cohorts without respect to balanced enrollment within the cohorts for these subpopulations.
Study Duration	The duration of the study for an individual subject is expected to be 3 months per subject in the Manual Push Flow Rate and Pump-Assisted Volume Cohorts, and 4 months in the Pump-Assisted Flow Rate Cohort. The overall study duration (ie, first subject's Screening visit to last subject's End of Study visit) will be approximately 18 months.
Study Population and Main Criteria for Eligibility	<p>Subjects meeting all of the following inclusion criteria may be enrolled into the study:</p> <ol style="list-style-type: none"> 1. Capable of providing informed consent/assent and willing and able to adhere to all protocol requirements. The subject's parent(s) or legally acceptable representative(s) capable of providing written informed consent. 2. Male or female on stable dose of IgPro20 (Hizentra) therapy. 3. Women of childbearing potential must be using and agree to continue using medically approved contraception (which must be discussed with the study doctor) and must have a negative pregnancy test at Screening. 4. Subjects with PID, eg, with a diagnosis of common variable immunodeficiency or X-linked agammaglobulinemia, as defined by the Pan American Group for Immune Deficiency and the European Society of Immune Deficiencies or by the International Union of Immunological Societies Expert Committee. 5. With infusion parameters as specified below: <ul style="list-style-type: none"> <u>Pump-Assisted Flow Rate Cohort subjects only*</u> 5a. Experience with pump-assisted infusions of IgPro20 at the tolerated flow rate of 25 mL/h** per injection site for at least 1 month prior to Day 1. <u>Pump-Assisted Volume Cohort subjects only*</u> 5b. Total weekly IgPro20 dose of ≥ 50 mL (≥ 10 g). 5c. Experience with pump-assisted infusions of IgPro20 at tolerated volumes of 25 mL/injection site for at least 1 month

prior to Day 1.

Manual Push Flow Rate Cohort subjects only

5d. Experience with frequent (2-7 times per week) infusions of IgPro20 at the tolerated flow rate of approximately 0.5 mL/min (equivalent of 25-30 mL/h) per injection site for at least 1 month prior to Day 1. The dose (volume) per injection site should not exceed 25 mL.

*Subjects who tolerated higher infusion parameters relevant for their study cohort prior to the study based on their chart records will not be allowed to participate in the study. If records are not available, information may be obtained by asking the subject.

**Subjects who use an infusion pump that operates by maintaining a constant pressure as opposed to a constant flow rate, may not have experienced flow rates that are exactly 25 mL/h. Flow rates for constant pressure pumps (adjusted for needle gauge and infusion tubing size) that are within $\pm 20\%$ of 25 mL/h per injection site are acceptable for study entry.

Study Product Dose, Dosing Regimen and Administration

IgPro20 will be administered subcutaneously at a dose prescribed by subject's healthcare provider prior to study entry (usually 100 to 200 mg/kg per week). Subjects in the Pump-Assisted Cohorts will administer weekly treatment and subjects in the Manual Push Cohort will administer more frequent than weekly treatment (ie, 2 to 7 times per week).

Comparator Product, Dose, Dosing Regimen and Administration

Not applicable.

Efficacy Assessments

CCI [REDACTED]

- **CCI** [REDACTED]

Safety Assessments

Safety will be assessed by:

- The frequency and severity of AEs.
- Local reactions (injection site reactions).
- Tolerability of a certain infusion parameter (ie, percentage of subjects and infusions per cohort by volume/flow rate subgroup experiencing no severe local reactions for each of the infusion parameter levels).
- Physical examination.
- Vital signs.
- Clinical laboratory tests.

- Biochemistry
- Hematology

Pharmacokinetics Not applicable.

Pharmacodynamics Not applicable.

Other Assessments Not applicable.

Statistical Analyses

Subject Disposition

The number of subjects who were screened, enrolled into the study, and completed the study, will be presented in summary tables by treatment group and total subjects. The reason for discontinuing the study product or withdrawing a subject from the study will be listed by subject.

Subject Characteristics

At a minimum, subject characteristics will be presented in summary tables. Continuous data will be summarized by descriptive statistics (number of observations, mean, standard deviation, minimum, maximum, median, Q1, Q3) and categorical data will be summarized by frequency distributions. Age will be described as both a continuous and a discrete variable.

Efficacy Analyses

CCI

Safety Analyses

All safety endpoints will be summarized descriptively only within each of the 3 cohort separately. Adverse events will be further summarized by the values of infusion parameters within each cohort; rates per injection will be presented as well. Adverse events will be presented including a virtual System Organ Class comprising local reaction (identified by Medical Dictionary for Regulatory Activities high level terms: “administration site reactions NEC”, “infusion site reactions”, and “injection site reactions”) and by severity. Further, time to onset and duration will be presented descriptively. Tolerability of a certain infusion parameter within a cohort will be calculated as ‘number of infusions without severe local reaction / number of all infusions’ and be presented by infusion parameter and cohort.

Interim Analyses Not applicable.



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Study Product:

IgPro20

Schedule of Assessments – Pump-Assisted Flow Rate Cohort

Study Period	Screening	Forced Upward Titration																End of Study	
Study Day	-35 to -7	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113±1 day	
Week Number		1 ^f	2	3	4	5 ^f	6	7	8	9 ^f	10	11	12	13 ^f	14	15	16	17 ^f	
Informed consent/assent	X																		
Inclusion / exclusion criteria	X	X																	
Medical history and demographics	X																		
Pregnancy test	X																		X
Physical examination	X																		X
Systolic and diastolic blood pressure, respiratory rate, pulse rate, and body temperature	X	X				X				X				X					X
Body weight and height	X																		X
Hematology ^a & biochemistry ^b	X																		X
Infusion training / supervised infusion / supervised entry of infusion data in the subject eDiary		X				X				X				X					
IgPro20 dispensation and IRT update		X				X				X				X					
Subject eDiary ^c training and review		X				X				X				X					X ^g
IgPro20 administration (weekly for pump-assisted infusions)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum IgG trough level ^d		X																	X
Adverse events (including injection site assessments) ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies	X	X				X				X				X					X

eDiary = electronic diary; IgG = immunoglobulin G; IgPro20 = Hizentra; IRT = Interactive Response Technology.

- a. Hematology: hemoglobin, hematocrit, mean corpuscular volume, erythrocytes, leukocytes, differential count, platelets.
- b. Biochemistry: sodium, potassium, chloride, bicarbonate, urea, creatinine, gamma glutamyl transferase, alkaline phosphatase, alanine aminotransferase, aspartate transaminase.
- c. eDiary will be used for collecting infusion parameters and adverse events. A paper diary is available as a back-up if the eDiary is unavailable. As soon as the eDiary becomes available, the data from the paper diary must be transcribed into the eDiary and the paper diary retained as source.



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- d. Within approximately 1 hour before next infusion.
- e. Subjects who drop out of the study due to reasons other than 'consent withdrawn' or 'lost to follow-up' will be followed up by weekly telephone calls by site personnel for the full duration of their planned study participation, in order to collect information on AEs.
- f. Office visit at Weeks 1, 5, 9, 13, and End of Study.
- g. eDiary / back-up paper diary collection and review. The eDiary device will also be collected, if provisioned.



Study Number:

IgPro20_4004

Study Product:

IgPro20

Schedule of Assessments – Manual Push Flow Rate & Pump-Assisted Volume Cohorts

Study Period	Screening	Forced Upward Titration												End of Study
Study Day	-35 to -7	1	8	15	22	29	36	43	50	57	64	71	78	85±1 day
Week number		1 ^f	2	3	4	5 ^f	6	7	8	9 ^f	10	11	12	13 ^f
Informed consent/assent	X													
Inclusion / exclusion criteria	X	X												
Medical history and demographics	X													
Pregnancy test	X													X
Physical examination	X													X
Systolic and diastolic blood pressure, respiratory rate, pulse rate, and body temperature	X	X				X				X				X
Body weight and height	X													X
Hematology ^a & biochemistry ^b	X													X
Infusion training / supervised infusion / supervised entry of infusion data in the subject eDiary		X				X				X				
IgPro20 dispensation and IRT update		X				X				X				
Subject eDiary ^c training and review		X				X				X				X ^g
IgPro20 administration (weekly for pump-assisted infusion; 2 to 7 times per week for manual push)		X	X	X	X	X	X	X	X	X	X	X	X	
Serum IgG trough level ^d		X												X
Adverse events (including injection site assessments) ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies	X	X				X				X				X

eDiary = electronic diary; IgG = immunoglobulin G; IgPro20 = Hizentra; IRT = Interactive Response Technology.

- a. Hematology: hemoglobin, hematocrit, mean corpuscular volume, erythrocytes, leukocytes, differential count, platelets.
- b. Biochemistry: sodium, potassium, chloride, bicarbonate, urea, creatinine, gamma glutamyl transferase, alkaline phosphatase, alanine aminotransferase, aspartate transaminase.
- c. eDiary will be used for collecting infusion parameters and adverse events. A paper diary is available as a back-up for use if the eDiary is unavailable. As soon as the eDiary becomes available, the data from the paper diary must be transcribed into the eDiary and the paper diary retained as source.
- d. Within approximately 1 hour before next infusion.



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- e. Subjects who drop out of the study due to reasons other than 'consent withdrawn' or 'lost to follow-up' will be followed up by weekly telephone calls by site personnel for the full duration of their planned study participation, in order to collect information on AEs.
- f. Office visit at Weeks 1, 5, 9, and End of Study.
- g. eDiary / back-up paper diary collection and review. The eDiary device will be collected, if provisioned.

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AUC	Area under the concentration-time curve
BMI	Body mass index
eCRF	Electronic case report form
eDiary	Electronic diary
EAE	Experimental allergic encephalomyelitis
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ICH	International Conference on Harmonisation
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
IVIG	IV immunoglobulin
PID	Primary immunodeficiency
PK	Pharmacokinetic
SAE	Serious adverse event
SBIs	Serious bacterial infections
SC	Subcutaneous
SCIG	SC immunoglobulin
US	United States

Definition of Terms

Term	Definition
Eligible subject	Eligible subjects are subjects meeting the inclusion/exclusion criteria.
Enrolled subject	Enrolled subjects are eligible subjects who freely signed informed consent form and enrolled in the study.
Full Analysis Set	The Full Analysis Set (FAS) will comprise all subjects who provide informed consent and who are included in the study; ie, who undergo study procedures after Screening. Screening failures will not be included in the FAS. However, the number of Screening failures will be summarized in the disposition tables and all Screening failures will be listed.
Safety Population	The Safety Population will comprise all subjects in the Full Analysis Set who received at least 1 dose or a partial dose of IgPro20 in the study.
Treatment-emergent adverse event	Treatment-emergent adverse events are adverse events occurring after the start of the first IgPro20 infusion in the study and up to the End of Study visit.
Pump-Assisted Volume Cohort	Subjects testing volumes per injection site of 25 mL up to 50 mL.
Pump-Assisted Flow Rate Cohort	Subjects testing flow rates per injection site of 25 mL/hour up to 100 mL/hour.
Manual Push Flow Rate Cohort	Subjects testing flow rates per injection site of 25 to 30 mL/hour up to 120 mL/hour (equivalent of approximately 0.5 mL/minute up to 2 mL/minute)

1. Introduction

1.1 Background

1.1.1 Primary Immunodeficiency

Primary immunodeficiency (PID) represents a variety of disorders characterized by an intrinsic defect in the immune system that renders patients more susceptible to infections, which may be fatal if left untreated. Major clinical manifestations include multiple infections despite aggressive treatment, opportunistic infections and failure to thrive (Cooper et al, 2003). PID constitutes a spectrum of more than 300 innate defects in the body's immune system. They can be divided into 9 groups: disorders of humoral and cellular immunity, combined immunodeficiency with associated or syndromic features, predominantly antibody deficiency syndromes, diseases of immune dysregulation, congenital phagocyte defects, defects in intrinsic and innate immunity, auto-inflammatory disorders, complement disorders, and phenocopies of PID. Predominantly antibody deficiency syndromes are the most common PID subtype (Yong et al, 2008; Bousfiha et al, 2015; Picard et al, 2015). PID is considered to be a rare disease, with the prevalence depending on the type of immunodeficiency (Raje and Dinakar, 2015). Registry data from various countries estimated the overall prevalence of PID at 1.94/100,000 (United Kingdom) or 2.3/100,000 (Japan) to 5.38/100,000 (France) and up to 30.5/100,000 (Turkey) (Ishimura et al, 2011; Bousfiha et al, 2013; Kilic et al, 2013). However, current epidemiological data indicate a higher overall prevalence than previously thought, being estimated at up to 83.3/100,000 (Bousfiha et al, 2013).

Patients with PID are not only at a higher risk for infections, but also to develop other conditions such as chronic lung disease, gastrointestinal diseases, malignancies and autoimmune diseases (Morimoto and Routes, 2008). For the past 3 decades, immunoglobulin replacement therapy has been used for patients with all PID conditions, to prevent infections and infection-related complications (Sriaroon and Ballow, 2015).

1.1.2 Subcutaneous Immunoglobulin Replacement Therapy

Immunoglobulin replacement therapy is the lifelong treatment for patients with PID and can be administered through intravenous (IV) or subcutaneous (SC) routes (Sriaroon and Ballow,

2015), usually with special pumps. Providing passive immunity and maintaining consistent serum immunoglobulin G (IgG) concentrations controls most of the recurrent infections and results in an improved quality of life for these patients (Borte et al, 2011).

Although both IV and SC treatment regimens in equal doses provide a similar efficacy in the prevention of serious bacterial infections, there are some advantages of the SC route (Chapel et al, 2000; Sriaroon and Ballow, 2015). With SC treatment regimens, smaller doses of IgG are given more frequently, resulting in altered pharmacokinetics (PK) with lower peak and higher trough levels of IgG as compared to the large boluses given less frequently, usually once every 3-4 weeks, with IV infusions (Berger, 2004). This increased stability of IgG concentration improves the patients' well-being, since it reduces symptoms such as fatigue and myalgia at the end of the dosing cycle (Berger, 2008). Unlike IV immunoglobulin (IVIG), SC immunoglobulin (SCIG) does not require a good venous access and therefore does not lead to potential problems with venous access in the future due to frequent IV infusion (Jolles et al, 2015). Since an IV port is also not required for SC therapy, this is associated with lower risk of various infusion complications, from thrombo-embolic events to septicemia (Sriaroon and Ballow, 2015). Other important aspects of SCIG treatment, since it can be administered at home, are the improved quality of life, treatment satisfaction, and therapy convenience, in both children and adults (Gardulf et al, 2004; Nicolay et al, 2006).

1.1.3 Manual Push Technique

The conventional mode of SCIG administration has been an infusion pump, delivering IgG volumes of up to 25 mL per injection site, which can take up to 2 hours (Berger, 2008; Shapiro, 2010). Infusion pumps may be difficult to use for some patients and the potential costs might be unfavorable (Misbah et al, 2009). As an alternative, the manual push technique, also called rapid push, has been established in recent years for the administration of SCIG. It is a simple method where SCIG is given manually by injection using syringe and a short tubing with a butterfly needle. The total weekly dose is divided into several smaller doses, depending on each patient's dose and preference. Compared to weekly pump-assisted infusions, infusion times are much shorter, ranging from 5 to 20 minutes, and fewer injection sites are used. Furthermore, it provides effective and cost-efficient drug delivery, improved patient autonomy and convenience (Shapiro 2010; Shapiro 2013a; Martin et al, 2013). Based on a retrospective analysis comparing standard pump administration vs. rapid push

administration, it has been shown that serum IgG levels as well as the overall safety and tolerability profiles are comparable between the 2 SCIG infusion methods. In addition, manual push is well tolerated in both pediatric and obese adult patients and can be a practical treatment option in most PID patient subpopulations requiring SCIG replacement therapy, improving treatment satisfaction and supporting patient adherence (Shapiro 2013a; Misbah et al, 2009; Shapiro 2013b; Shapiro 2013c).

1.1.4 SCIG Infusion Parameters

The currently approved Hizentra® infusion parameters in the United States (US) and abroad include a volume per injection site of up to 25 mL, and a flow rate of up to 25 mL/h per site (US package insert, European Union [EU] package insert), as outlined below:

Volume – For the first infusion of Hizentra, do not exceed a volume of 15 mL per injection site. The volume may be increased to 20 mL per site for the fifth infusion and then to 25 mL per site as tolerated.

Rate – For the first infusion of Hizentra, the recommended flow rate is 15 mL per hour per site. For subsequent infusions, the flow rate may be increased to 25 mL per hour per site as tolerated.

Higher infusion parameters, such as an increased flow rate and volume per injection site, reduce the time needed for infusion and decrease the number of injection sites, independent of the method used. An infusion of up to 60 mL per site and a flow rate of more than 60 mL/h using the manual push method have been previously described. In retrospective analyses of adult and pediatric patients using the rapid push method, the majority of subjects reported an infusion time of 9 minutes or less. With a mean volume per site of 15.8 mL in adults, an average flow rate of 1.75 mL/min or 105 mL/h can be assumed. In the age group of 10 to 18 years, an even higher flow rate of 1.9 mL/min (114 mL/h) can be assumed with a mean volume per site of 17.1 mL. Furthermore, in obese adults (body mass index [BMI] ≥ 30 kg/m²) a mean volume per site of 17.8 mL was documented, providing an average flow rate of 1.97 mL/min (118.67 mL/h) without tolerability issues (Shapiro 2013a; Shapiro 2013b; Shapiro 2013c).

While the flow rate in manual push is not usually presented in mL/h due to small volumes and short infusion times, a more detailed analysis of average flow rates, based on data from available publications, is presented in Table 1.

Table 1. Average Flow Rates in Manual Push Infusions

Manual push flow rate as originally reported	Flow rate, mL/min	Flow rate, mL/h	References
15 min per 3 mL	0.2	12	Berger, 2008.
1-2 cc/min	1-2	60-120	Misbah et al. 2009.
9 min per 15 mL	1.7	100	Shapiro, 2013b.
5 min per 10 mL	2	120	Richter et al., 2013.
9 min per 20 mL	2.2	133	Shapiro, 2013b.

For pump-assisted infusions, higher infusion parameters have also been tested previously in clinical studies with IgPro20 (Hizentra). In the US PID extension study, IgPro20_3001, the protocol allowed for up to 40 mL per site and an infusion rate of up to 35 mL/h. In the EU PID pivotal study, ZLB06_001CR, the maximum infusion parameters allowed were 25 mL per site and 35 mL/h ([Jolles et al, 2015](#)). The same infusion parameters have been successfully tested in IgPro20 studies conducted in Japan ([Kanegane et al, 2014](#)). In all of these studies, there were no safety issues related to the higher injection site volumes or rates, although they were not evaluated in a systematic manner and there were not enough data collected to be able to draw robust conclusions. Additionally, in the recently completed IgPro20 study in subjects with chronic inflammatory demyelinating polyneuropathy, IgPro20_3003, injection site volumes and rates of 50 mL/site and 35 mL/h/site, respectively, were allowed. A substantial number of study subjects have already used these higher infusion parameters without safety issues.

In a recently published study of 20% SCIG administered to PID subjects in the US, the reported median infusion rate was 60 mL/h/site (range 4.4-180) and the median infusion volume per injection site was 39.50 mL (range 6.4-76.0), with 71.6% of subjects reaching a flow rate of at least 60 mL/h and 10.8% of subjects receiving a volume of at least 60 mL/site ([Suez Det al, 2016](#)). In the corresponding EU study, 41.6% of subjects reached a maximum infusion rate of ≥ 40 mL/h/site, with a number of study participants injecting 20% SCIG at 60 mL/h/site and with a volume of up to 48 mL/site ([Borte Met al, 2016](#)).

The above-mentioned publications, as well as numerous personal communications from immunologists treating PID patients demonstrate that, in current clinical practice, Hizentra infusions are sometimes conducted at significantly higher than currently approved flow rate and volume per injection site, with or without infusion pump (by manual push). The safety and tolerability of these new infusion parameters and techniques has not been evaluated in a systematic manner.

Therefore, the aim of this study is to obtain safety and tolerability data of higher infusion parameters of IgPro20 (Hizentra) in PID patients, for both pump-assisted and manual push techniques, allowing for greater flexibility and convenience of Hizentra infusions.

1.2 Background Information on IgPro20

1.2.1 Overview

IgPro20 is a ready-to-use formulation of polyvalent SCIG. The IgG portion represents all IgG subclasses present in human plasma and retains all IgG function (ie, Fc receptor interaction site [Fc] and antigen binding fragment [Fab] mediated activity). The sterile 20% IgG solution is stabilized with 250 mmol/L L-proline at pH 4.8. IgPro20 also contains 8 to 30 mg/L polysorbate 80 (P80). IgPro20 has a low sodium content (< 10 mmol/L) and an osmolality of approximately 390 mOsmol/kg.

The protein moiety of IgPro20 is highly purified IgG ($\geq 98\%$ purity). More than 90% of the IgG consists of monomers and dimers. IgPro20 is prepared from large donor pools and represents the antibody spectrum present in the donor population. Careful selection of donors, as well as testing of each individual donation and the plasma pool for viral markers, helps to ensure viral safety of the finished product.

The manufacturing process (IgG isolation) for IgPro20 is based on the manufacturing process for Privigen® (IgPro10). After production of the active substance solution, the final IgPro20 product is formulated and concentrated to the higher protein content of 20%.

IgPro20 was approved for PID in the US, the EU, Canada, Switzerland, Japan, Australia, and several other countries under the trade name Hizentra.

1.2.2 Nonclinical Evaluation

Human immunoglobulins are naturally occurring proteins with a well-established safety and tolerability record. The testing of human immunoglobulin preparations in animal models is of limited value because immunoglobulins are immunologically active and can cross-react between species. Nonclinical studies with IgPro20 focused on its SC use (local tolerance, PK), functionality (in vitro Fab and Fc function, in vivo efficacy in experimental allergic encephalomyelitis [EAE] rat model), safety regarding hypotensive effects, and repeated SC administrations.

Fab and Fc functions of IgPro20 are comparable to those of Privigen and other marketed IVIG products. In the EAE rat model (a nonclinical model of human multiple sclerosis) IgPro20 administered SC attenuated the symptoms of EAE and led to a lower mortality.

The bioavailability of IgPro20 was assessed after SC administration to rats on 5 consecutive days; a dose-dependent increase in area under the concentration-time curve (AUC) and maximum serum concentration of human IgG was found. In 2 repeated-dose toxicity studies in rats with SC administration of IgPro20 every other day for 28 days and 6 months, respectively, all animals developed antibodies against human IgG in a dose dependent manner. In spite of this antibody formation, human IgG was detected in the serum of the animals; serum concentrations increased to a steady-state (28-day study) with a slight decline in the second half of the in-life phase of the 6 months study. Thus antibody development against human IgG did not result in total removal of human IgG from the blood of the animals. The highest dose administered in this study resulted in IgG serum levels in the animals that are comparable to IgG levels obtained in patients treated with IgPro20, and was considered a no observed adverse effect level.

IgPro20 was also tolerated locally after SC, IV, paravenous, and intra-arterial application in rabbits.

IgPro20 contains 250 mmol/L of the non-essential amino acid L-proline as a stabilizer. Studies on L-proline in safety pharmacology, multiple dose toxicity, reproduction toxicity and in juvenile animals were conducted during development of Privigen. Studies with IV and SC administration of L-proline were included. L-proline is a suitable excipient of IVIGs at

the specified concentrations which was confirmed in clinical studies conducted with Privigen. These results were confirmed in a 28-day repeated-dose toxicity study in rats with daily SC administration of L-proline performed during IgPro20 development. Considering the lower amount of L-proline infused with IgPro20 compared with Privigen, due to smaller doses in average weekly SCIG vs. average 3- or 4-weekly IVIG dosing regimens and the good tolerability of IgPro20 administered SC to rabbits, it can be concluded that L-proline can be safely used as an excipient in IgPro20.

1.2.3 Previous Clinical Experience

The approval of IgPro20 for the treatment of patients with PID was based on data from 3 pivotal studies in the US, Europe, and Japan (ie, studies ZLB04_009CR, ZLB06_001CR, and ZLB06_002CR, respectively). In addition, extension studies to the 3 aforementioned phase 3 pivotal studies have been conducted and completed: 1 study each in the US (US extension study IgPro20_3001), in Europe (European extension study ZLB07_002CR), and in Japan (follow-up study ZLB07_001CR). A further long-term extension study in Japan (IgPro20_3006) has also been completed.

1.2.3.1 Phase 3 PID Study ZLB04_009CR (US Pivotal Study)

This prospective, open-label, phase 3 study was conducted in the US and investigated the efficacy, safety, local tolerability, and PK of SC IgPro20 in 49 subjects with PID. Subjects previously receiving monthly treatment with IVIG were switched to weekly SC administration of IgPro20 for 15 months. Subjects were initially treated with 1.30 times their previous IVIG dose during a 12-week wash-in/wash-out period and had their IgPro20 dose further adjusted based on the results of the PK substudy for the subsequent 12 month efficacy period. Doses were adjusted to ensure equivalent systemic IgG exposure to IVIG as measured by the serum IgG AUC.

The primary efficacy variable was the annualized rate of serious bacterial infections (SBIs, as defined in the Food and Drug Administration [FDA] Guidance for Industry [FDA, 2013]). None of the subjects had an SBI and the annualized rate of total infections per subject was 2.76. Overall, SC infusions with IgPro20 provided a high level of efficacy in subjects with PID in terms of passive immunity and maintaining adequate and consistent serum IgG levels. There were no safety concerns with the use of IgPro20.

1.2.3.2 Phase 3 PID Study ZLB06_001CR (European Pivotal Study)

This prospective, open-label phase 3 study was conducted in Europe that investigated the efficacy, safety, tolerability, and PK of SC IgPro20 in 51 subjects with PID. The study consisted of a 12-week wash-in/wash-out followed by a 28-week efficacy period. The IgPro20 weekly doses administered during this study were generally equal to the subjects' previous weekly equivalent IVIG or SCIG doses. The primary efficacy variable was a descriptive comparison of IgG trough levels at 6 consecutive weeks at steady-state within the study. During the study, the mean of individual median IgG trough levels increased by 8.1% with IgPro20 treatment (from 7.49 g/L with the previous IgG therapy to 8.10 g/L during Infusions 12 to 17). None of the subjects had an SBI during the efficacy period of this study (after washout of the previous IgG product), and only one subject had an SBI during the wash-in/wash-out period, resulting in an annualized rate of 0.03 SBIs/subject. The annualized rate of total infections was 5.18 infections/subject. Overall, it was demonstrated that SCIG therapy with IgPro20 is a highly effective treatment for adult and pediatric subjects with PID when administered at approximately 100% of the weekly equivalent doses during the subjects' preceding therapy. There were no safety concerns with the use of IgPro20.

1.2.3.3 Phase 3 PID study ZLB06_002CR (Japan Pivotal Study)

This phase 3 study was conducted in Japan including 25 subjects, with a PK sub-study including 8 subjects, to investigate the efficacy, safety, tolerability, and PK of IgPro20 in subjects with PID. The weekly dose of IgPro20 was the weekly equivalent dose of the previous IVIG treatment, and IgPro20 treatment included a 12-week wash-in/wash-out period followed by a 12-week efficacy period. The primary efficacy variable was maintenance of the mean of individual median IgG concentration at trough level (C_{trough}) values expressed via the ratio of geometric mean concentrations. IgG C_{trough} values increased by 9% with IgPro20 treatment, from 6.53 g/L in the IVIG period to 7.15 g/L during the SCIG efficacy period, meeting the primary objective. IgG C_{trough} values <5 g/L on IgPro20 therapy during the Japan pivotal study were seen in only 1 of 24 subjects. In this study, none of the subjects had an SBI. A total of 52.4% of subjects had an infection in the efficacy period, resulting in an annualized rate of 2.98 infections/subject. Overall, it was demonstrated that SCIG therapy with IgPro20 is an effective treatment for adult and pediatric subjects with PID in Japan when

administered at approximately 100% of the weekly equivalent doses of the subjects' preceding IVIG therapy. There were no safety concerns with the use of IgPro20.

Long-term extension and follow-up studies, as outlined in [Section 1.2.3](#), have further confirmed the high efficacy and safety of IgPro20 at steady-state dosing. In addition to safety data from the clinical development program, postmarketing experience with IgPro20 has shown the product to be well tolerated, with a similar safety profile in pediatric and geriatric patients as documented for adult patients.

1.3 Study Overview

This is a multicenter, open-label, parallel-arm, non-randomized study designed to evaluate safety and tolerability of higher infusion parameters of IgPro20 in subjects with PID.

The primary objective of this study is to characterize the responder rate at higher infusion parameters of IgPro20. Subjects will be assigned to 1 of 3 treatment cohorts: Pump-Assisted administration with 3 upward volume titrations (25 mL, 40 mL, and 50 mL); Pump-Assisted administration with 4 upward flow rates per injection site (25 mL/h, 50 mL/h, 75 mL/h and 100 mL/h) and Manual Push administration (manual infusion using syringe without a pump) with upward titration of flow rate per injection site of 30 mL/h, 60 mL/h, and 120 mL/h (0.5 mL/min, 1 mL/min, and 2 mL/min, correspondingly).

Further details of the study design can be found in [Section 3](#).

1.4 Potential Risks and Benefits

Safety data from the 3 pivotal studies performed by CSL for the authorization of IgPro20 in PID showed that almost all adverse events (AEs) (99%) were mild or moderate in intensity. There was no dose-dependent increase in the overall rate of AEs, within the range of doses and flow rates tested in these studies, and there was no evidence in either study of severe systemic AEs.

Adverse reactions such as local reactions, headache, fatigue, nausea, pain, pruritus, rash, vomiting, and pyrexia were observed during the clinical development program. In addition, in the postmarketing setting, reactions such as hypersensitivity, tremor, and burning sensation were reported, as well as rare events such as anaphylaxis, aseptic meningitis syndrome and

thrombotic events. SC infusions generally result in lower rates of headache and other systemic adverse reactions than IV infusions, which is attributed to the more stable serum IgG concentrations attained with SCIG treatment.

The risk that products manufactured from plasma could transmit an infectious agent has been reduced by screening plasma donors for prior exposure to pathogens and by testing the donations for the presence of certain markers of infections. In addition, different complementary virus elimination processes used during the manufacture of IgPro20 (incubation at pH 4, virus filtration, fractionation, and depth filtration) effectively reduce the potential for viral transmission. The manufacturing process was also investigated for its capacity to eliminate hamster-adapted scrapie agent 263K, which is considered to be a model for Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob disease. The results demonstrated substantial removal of the infectious agent by the manufacturing process in all model systems. To date, no viral infection related to the infusion of IgPro20 was reported. However, the possibility of transmitting infective agents cannot be totally excluded.

As previously noted, Hizentra infusions at higher than currently approved volume and flow rate parameters per injection site have been used in both clinical research and clinical practice without apparent safety signals (see [Section 1.1.4](#) [SCIG Infusion Parameters]). However, there are insufficient data to allow for objective quantification of any potential increase in safety risks associated with these higher infusion parameters.

The benefits of manual push include the use of smaller volumes per infusion compared to less frequent infusion schedules. Other advantages associated with manual push include the ability to maintain more even serum IgG concentrations with higher trough levels compared to weekly or twice weekly schedules, which could potentially confer better protection against infections, as well as lower time per infusion and total time per weekly/monthly dose compared to pump-assisted infusions. The use of manual push is also associated with a simpler infusion technique (ie, there is no requirement to load and handle a pump) and reduced healthcare costs as there is no expenditure on a pump. The benefits of the higher flow rates and volumes, as proposed for the current study, include reduced infusion time, and fewer injection sites per infusion.

A number of disadvantages are associated with use of the manual push technique, including the difficulty to control the syringe to deliver a stable flow rate and the manual strength required to operate the syringe for several minutes.

Overall, the associated benefit-risk assessment of the study is considered acceptable for subjects enrolled in the study.

2. Study Objectives and Endpoints

2.1 Primary Objective and Endpoints

2.1.1 Primary Objective

The primary objective of this study is to determine the responder rate at higher infusion parameters of IgPro20 under the following conditions:

- Pump-Assisted: Volume per injection site of 25 mL, 40 mL, and 50 mL.
- Pump-Assisted: Flow rate per injection site of 25 mL/h, 50 mL/h, 75 mL/h and 100 mL/h.
- Manual Push (manual infusion using syringe without a pump): Flow rate per injection site of 30 mL/h, 60 mL/h, and 120 mL/h (0.5 mL/min, 1 mL/min, and 2 mL/min, correspondingly).

2.1.2 Primary Endpoints

The primary endpoints are as follows:

- Pump-Assisted Volume Cohort: Percentage of responders for each planned volume (ie, 25 mL, 40 mL and 50 mL per injection site).
- Pump-Assisted Flow Rate Cohort: Percentage of responders for each planned flow rate (ie, 25 mL/h, 50 mL/h, 75 mL/h and 100 mL/h per injection site).
- Manual Push Flow Rate Cohort: Percentage of responders for each planned flow rate (ie, 30 mL/h [0.5 mL/min], 60 mL/h [1 mL/min], and 120 mL/h [2 mL/min] per injection site).

2.2 Secondary Objectives and Endpoints

2.2.1 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety of pump-assisted IgPro20 infusions at higher infusion parameters (volume and flow rate).
- To evaluate the safety of manual push IgPro20 infusions.
- To evaluate the tolerability of higher infusion parameters of IgPro20.

2.2.2 Secondary Endpoints

The secondary endpoints are as follows:

- The rate of total AEs per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- The rate of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- The time to onset of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- Severity of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- Duration of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- For all cohorts: Tolerability of a certain infusion parameter; ie, percentage of infusions per cohort by volume/flow rate subgroup experiencing no severe local reactions for each of the infusion parameter levels.

2.3 Exploratory Objective and Endpoints

2.3.1 Exploratory Objective

CCI



2.3.2 Exploratory Endpoints

CCI



3. Study Design

3.1 Study Design and Rationale

This multicenter, open-label, parallel-arm, non-randomized study is designed to evaluate safety and tolerability of higher infusion parameters of IgPro20 in subjects with PID. The study will include 3 cohorts with a minimum of 15 subjects each as follows:

- Pump-Assisted Volume Cohort (weekly infusions): Volume per injection site of 25 mL up to 50 mL.
- Pump-Assisted Flow Rate Cohort (weekly infusions): Flow rate per injection site of 25 mL/hour up to 100 mL/hour.
- Manual Push Flow Rate Cohort (2 to 7 infusions per week): Flow rate per injection site of 25 to 30 mL/hour up to 120 mL/hour (equivalent of approximately 0.5 mL/minute up to 2 mL/minute; see [Table 1](#)).

Each cohort will test 3 infusion parameter levels (for Pump-Assisted Flow Rate Cohort – 4) for at least 4 weeks each over a duration of 12 weeks (for Pump-Assisted Flow Rate Cohort – 16 weeks). After the fourth week on each level, qualifying subjects (responders) will switch to the next infusion parameter level (eg, from 25 to 50 mL/h). During the study the weekly dose will remain unchanged (as prescribed by treating healthcare provider, usually within 100-200 mg/kg per week range); only the respective infusion parameter under evaluation will change. If a subject is unable to tolerate the respective infusion parameter level (ie, is a non-responder at that level, for definition see [Section 11.3.5](#)), the subject will continue study

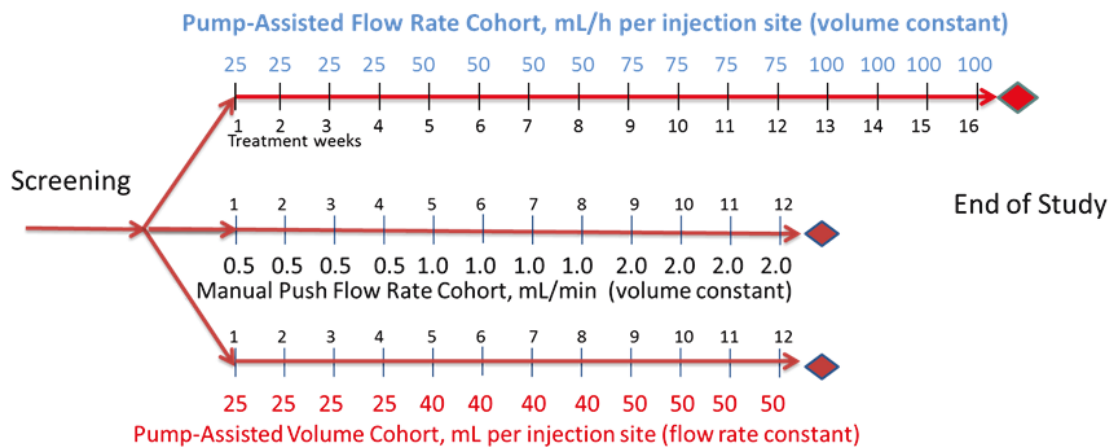
participation at the individually previously tolerated infusion parameter level for the remaining full study duration, to collect safety information.

If a subject within the Pump-Assisted Cohort is able to perform ≥ 3 out of 4 (75%) valid infusions at a certain infusion parameter level, he/she will be considered to be a responder for this infusion parameter level (eg, completed 3 infusions with 50 mL/h means responder for 50 mL/h). Valid infusions do not need to be consecutive. Determination of a responder in the Manual Push Cohort is more complex due to the expected variable frequency of infusions per week for different subjects (see [Section 11.3.5](#) for further details). Valid infusions in this cohort also do not need to be consecutive. However, each subject needs to adhere to the same schedule (number of infusions per week) throughout the study.

An infusion parameter will be considered successfully achieved if at least one third of the subjects in the corresponding cohort (5 of 15) are responders at that infusion parameter level, as defined above. The highest achieved infusion parameter level will be used for the label change. The rationale for this is based on medical experience (personal communications with several key opinion leaders and limited clinical research experience). A response rate for reaching the top infusion parameter for each endpoint of 50% is assumed. Using a binomial distribution with 15 evaluable subjects, there will be a 94% probability that the observed response rate for a single endpoint in the study is $\geq 33\%$.

Excluding the differences in infusion parameters/administration, all 3 cohorts have a similar overall study design (including AE collection). A schematic overview of the study is presented in [Figure 1](#).

Figure 1. Study Overview



3.2 Dose and Dosing Regimen

IgPro20 will be administered subcutaneously at a dose prescribed by subject’s healthcare provider prior to study entry (usually 100 to 200 mg/kg per week). Subjects in the Pump-Assisted Cohorts will administer weekly treatment and subjects in the Manual Push Cohort will administer more frequent infusions (ie, 2 to 7 times per week).

3.3 Planned Study Duration

The duration of the study for an individual subject is expected to be 3 months per subject in the Manual Push Flow Rate and Pump-Assisted Volume Cohorts, and 4 months in the Pump-Assisted Flow Rate Cohort. The overall study duration (ie, first subject’s Screening visit to last subject’s End of Study visit) will be approximately 18 months.

3.4 Planned Number of Sites

The study is planned to be conducted at approximately 15 sites in the US and Canada.

3.5 Planned Number of Subjects

Approximately 50 subjects will be enrolled into the study. A target of 45 evaluable subjects (ie, 15 subjects per cohort) is needed. Enrolled subjects will include a target of 14 (30%) pediatric subjects ≤ 17 years of age and a target of 9 (20%) obese subjects with BMI of ≥ 30

kg/m². Pediatric and obese subjects may be distributed across any or all of the treatment cohorts without respect to balanced enrollment within the cohorts for these subpopulations..

3.6 Study Monitoring Procedures

3.6.1 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board will be established to monitor safety events in this study. Further details will be described in the Data and Safety Monitoring Board Charter.

3.6.2 Other Monitoring Committees

Not applicable.

4. Selection and Withdrawal of Subjects

4.1 Eligibility Criteria

The study population will be selected on the basis of the inclusion and exclusion criteria described in the sections below. Subject eligibility should be reviewed and documented by an appropriately medically qualified member of the investigator's study team before subjects are included in the study.

4.1.1 Inclusion Criteria

Subjects meeting all of the following inclusion criteria may be enrolled into the study:

1. Capable of providing informed consent/assent and willing and able to adhere to all protocol requirements. The subject's parent(s) or legally acceptable representative(s) capable of providing written informed consent.
2. Male or female on stable dose of IgPro20 (Hizentra) therapy.
3. Women of childbearing potential must be using and agree to continue using medically approved contraception (which must be discussed with the study doctor) and must have a negative pregnancy test at Screening.
4. Subjects with PID, eg, with a diagnosis of common variable immunodeficiency or X-linked agammaglobulinemia, as defined by the Pan American Group for Immune

Deficiency and the European Society of Immune Deficiencies or by the International Union of Immunological Societies Expert Committee.

5. With infusion parameters as specified below:

Pump-Assisted Flow Rate Cohort subjects only*

5a. Experience with pump-assisted infusions of IgPro20 at the tolerated flow rate of 25 mL/h** per injection site for at least 1 month prior to Day 1.

Pump-Assisted Volume Cohort subjects only*

5b. Total weekly IgPro20 dose of ≥ 50 mL (≥ 10 g).

5c. Experience with pump-assisted infusions of IgPro20 at tolerated volumes of 25 mL/injection site for at least 1 month prior to Day 1.

Manual Push Flow Rate Cohort subjects only

5d. Experience with frequent (2-7 times per week) infusions of IgPro20 at the tolerated flow rate of approximately 0.5 mL/min (equivalent of 25-30 mL/h) per injection site for at least 1 month prior to Day 1. The dose (volume) per injection site should not exceed 25 mL.

*Subjects who tolerated higher infusion parameters relevant for their study cohort prior to the study based on their chart records will not be allowed to participate in the study. If records are not available, information may be obtained by asking the subject.

**Subjects who use an infusion pump that operates by maintaining a constant pressure as opposed to a constant flow rate, may not have experienced flow rates that are exactly 25 mL/h. Flow rates for constant pressure pumps (adjusted for needle gauge and infusion tubing size) that are within $\pm 20\%$ of 25 mL/h per injection site are acceptable for study entry.

4.1.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria must not be enrolled into the study:

1. Ongoing SBI at the time of Screening. Serious bacterial infections as defined by [FDA Guidance \(2008\)](#).
2. Other significant medical conditions that could increase the risk to the subject.
3. Females who are pregnant, breast feeding, or planning a pregnancy during the course of the study.
4. Participation in a study with an Investigational Medicinal Product (IMP) other than IgPro20 within three months prior to enrollment.

5. Evidence of uncooperative attitude or unable to complete scheduled visits for any reason.
6. Any condition that is likely to interfere with evaluation of the IMP or satisfactory conduct of the study.
7. Subjects who are employees at the investigational study site, or relatives or spouse of the investigator.
8. Female subject of childbearing potential either not using or not willing to use a medically reliable method of contraception or not sexually abstinent during the study, or not surgically sterile.
9. Alcohol, drug or medication abuse within 1 year before the study.
10. Currently receiving a therapy not permitted during the study, as defined in [Section 7.3](#).
11. Mental condition rendering the subject (or the subject's legally acceptable representative[s]) unable to understand the nature, scope and possible consequences of the study.
12. Known or suspected hypersensitivity to IgPro20, or to any excipients of IgPro20.
13. Any issue that, in the opinion of the investigator, would render the subject unsuitable for participation in the study.

4.2 Subject Withdrawal

4.2.1 Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or CSL for safety, behavioral or administrative reasons (eg, due to an AE, protocol deviation, loss to follow-up, subject noncompliance, and study termination).

In accordance with International Conference on Harmonisation (ICH) principles of Good Clinical Practice (GCP) the investigator always has the option to advise a subject to withdraw from the study if the subject's safety or well-being is compromised by his or her further participation in the study. Concern for the interests of the subject must always prevail over the interests of the study.

If a subject is withdrawn from the study or further participation is declined, they will continue to have access to medical care and will be treated as per routine medical practice.

4.2.2 Procedures for Handling Withdrawals

If a subject declines further participation or is withdrawn from the study, attempts will be made to complete and document the final assessment. If the subject is withdrawn from the study after receiving IgPro20, every effort will be made to ensure that the relevant safety assessments are completed. The subject may also be asked by the investigator to complete other study assessments.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, CSL may retain and continue to use any data collected before such withdrawal of consent.

In the event that a subject withdraws from the study, the investigator should record the reason and date of withdrawal in the electronic case report form (eCRF) and in the subject's medical records.

4.2.3 Replacement Policy

Subjects withdrawn from the study will not be replaced.

5. Study Interventions

5.1 Description of Investigational MEDICINAL Product

5.1.1 IgPro20

Substance number	IgPro20
Active substance	Human normal immunoglobulin
Trade name	Hizentra
Dosage form	Solution for SC injection (ready-to-use formulation of polyvalent SCIG)
Dose	As prescribed by subject's healthcare provider prior to study entry, usually within 100-200 mg/kg per week range.
Mode of administration	SC

SC=subcutaneous.

The study IMP, IgPro20, will be manufactured by CSL in accordance with Good Manufacturing Practice guidelines and local regulatory requirements, and will be labelled as the IMP for this study.

5.1.2 Comparator Product

Not applicable.

5.2 Packaging, Labeling, Supply and Storage

5.2.1 Packaging and Labeling

IgPro20 will be packaged and labeled according to current ICH Good Manufacturing Practice and GCP guidelines, and national legal requirements.

5.2.2 Supply and Storage

IgPro20 will be supplied to the study sites by external service providers on behalf of CSL. IgPro20 must be stored between 2°C and 25°C (36°F and 77°F) and protected from light, in a secure storage area as specified in the IMP Handling Instructions.

5.3 Accountability and Destruction

All supplies of IgPro20 must be accounted for throughout the study. At the end of the study, the original IMP Inventory Log, dated and signed by the investigator or delegate (eg, pharmacist), must be retained at the study site as verification of final accountability of IgPro20.

Records for the delivery of IgPro20 to the study site, the inventory at the study site, the use by each subject, and the destruction or return of IgPro20 to CSL's external service providers must be maintained by the investigator (or delegate). The records will include dates, quantities, lot numbers, kit numbers and unique code numbers assigned to IgPro20 and assigned to the subjects. The investigator must provide reasons for any discrepancies in IMP accountability.

Information on the destruction of IgPro20 is provided in the IMP Handling Instructions / Pharmacy Manual.

5.4 Other Intervention(s)

Not applicable.

5.5 Rescue Therapy

Not applicable.

6. Allocation, Dosing and Administration

6.1 Allocation to Treatment

6.1.1 Subject Assignment

After providing written informed consent, the subject will be issued with a study-level unique subject identification number. The subject identification number will be used to identify the subject for the duration of the study. Subject identification numbers will not be reassigned or reused.

6.1.2 Randomization Procedures

Each study cohort requires specific entry criteria ([Section 4.1.1](#)). However, these criteria are not mutually exclusive, and if a subject qualifies to be enrolled into more than 1 of the study cohorts, he/she may be assigned to either cohort at the investigator's discretion.

6.1.3 Blinding Procedures

Not applicable.

6.2 Dosing and Administration

6.2.1 Dosing and Administration

IgPro20 will only be administered by subjects included in this study following the procedures set out in this study protocol. An Interactive Response Technology (IRT) system will be utilized during the study for IMP accountability.

Enrolled subjects will administer SC IgPro20 at a dose prescribed by their healthcare provider prior to study entry (usually 100-200 mg/kg per week). Subjects in the Pump-Assisted Cohorts will administer weekly treatment and subjects in the Manual Push Cohort will administer frequent infusions (ie, 2-7 times per week). Subjects in the Manual Push Cohort should maintain the same frequency of infusions per week throughout the whole

study, including 1 month prior to Day 1. The infusion parameters not under test (eg, volume per injection site in the flow rate cohort) should not exceed the levels used before the study.

IgPro20 can be stored at room temperature between 2°C and 25°C (36°F and 77°F), protected from light. The IMP should be at room temperature before use. The IMP should not be shaken. Excessive shaking will cause foaming. For a more detailed description of the preparation of the IMP, refer to the handling instructions in the Subject IMP Handling Guide.

6.2.2 Infusion Rates

For pump-assisted infusions, the volume and flow rate will be determined according to the pump display readings. As it is physically not possible to perform manual push at a constant rate, and it is performed in clinical practice by series of short manual pushes on the syringe plunger with small breaks between them, average flow rate per infusion in this cohort will be estimated by dividing volume infused in milliliters by the time of infusion in minutes.

The subject electronic diary (eDiary) for study participants in the Manual Push Cohort will provide recommendations of infusion duration depending on the actual dose (volume) to be infused and the target flow rate in mL/min for every subject using the following calculations (Table 2). If the eDiary is not available, a back-up paper diary will be provided for patient use until the eDiary becomes available. As soon as the eDiary is available, the data in the back-up paper diary will be entered into the eDiary. The back-up paper diary, if used, will be retained as a source document. During the time period when a back-up paper diary is in use, designated site staff will contact the subject on a weekly basis to ensure recording of infusion data and any AEs.

Table 2. Infusion Time

Volume, mL \ Flow rate, mL/min	0.5	1	2
	Infusion Time, minutes		
2	4	2	1
3	6	3	1.5
4	8	4	2
5	10	5	2.5
6	12	6	3
7	14	7	3.5
8	16	8	4
9	18	9	4.5

Flow rate, mL/min Volume, mL	0.5	1	2
10	20	10	5
11	22	11	5.5
12	24	12	6
13	26	13	6.5
14	28	14	7
15	30	15	7.5
16	32	16	8
17	34	17	8.5
18	36	18	9
19	38	19	9.5
20	40	20	10

6.3 Treatment Compliance

All doses of IgPro20 will be administered by SC infusion, with an office visit every 4 weeks, where the dose will be administered by the subject under the observation of the study staff; the remainder of the infusions will be done at home after confirmed and observed training at the first infusion (office visit). Treatment compliance will be monitored by reviewing the subject eDiaries and counting the used vials, the results of which should be documented.

7. Contraindications, Permitted Therapies and PROHIBITED Therapies

7.1 Contraindications and Precautions to Further Dosing

IgPro20 is contraindicated in subjects:

- Who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin or to components of the immunoglobulin formulation, such as polysorbate 80 in IgPro20.
- With hypersensitivity to homologous immunoglobulins, especially in the rare cases of immunoglobulin A (IgA) deficiency when the subject has antibodies against IgA.
- With hyperprolinemia type I or II.

Full details of guidance on precautions for IgPro20 can be found in the Investigator's Brochure and Prescribing Information.

7.2 Permitted Therapies

The following therapies are PERMITTED during the study:

- Any medications that do not have the primary purpose of masking local or systemic AEs, and that are taken by the subject on a regular basis.
- Prescribed medications required for the management of chronic medical conditions
- Over the counter medications and dietary supplements.

7.3 Prohibited Therapies

The following therapies are NOT PERMITTED during the study:

- Any immunoglobulins other than IgPro20 provided for the study.
- Any other investigational product at any time during the study.
- Any medications with the primary purpose of masking local or systemic AEs (including but not limited to analgesics and anesthetics +/-12h around the infusion).
- Any systemic immunosuppressants that can affect serum IgG concentration (except for stable steroid doses required for pre-existing conditions).

Subjects are not to be enrolled into the study if they receive any prohibited therapy or any therapy in a prohibited dosage that cannot be discontinued or reduced to a permitted dose before enrollment.

If administration of any prohibited therapy becomes necessary during the study for medical reasons, the subject may be withdrawn from further study participation.

7.4 Dietary and Lifestyle Restrictions

Not applicable.

7.5 Overdose

Overdose is defined as the accidental or intentional infusion or ingestion of any dose of a product that is considered excessive. The effects of any potential overdose with IgPro20 have not been studied.

8. Study Procedures and Visit Schedule

8.1 Clinical Procedures

The clinical procedures related to demographics and safety are provided in Table 3. All other clinical procedures are provided in Table 4. Refer to the Laboratory Manual for detailed instructions on how the assessments should be performed.

Table 3. Clinical Procedures: Demographics and Safety Evaluation

Assessment	Description
Demographics	Date of birth, age, sex, and race.
Medical history	Relevant medical history. PID history, including specific PID diagnosis, date of diagnosis, and historic pre-treatment serum IgG level at the time of PID diagnosis. Contraception method. Current/concomitant therapies.
Pregnancy test	Blood test for beta-human chorionic gonadotropin.
Physical examination	As per the site's standard procedure
Vital signs	<ul style="list-style-type: none"> Blood pressure (systolic and diastolic) and respiratory rate after the subject has rested in a sitting or supine position ≥ 5 minutes Pulse rate (per minute) will be measured from the radial pulse counted manually or with an automatic blood pressure monitor over ≥ 15 seconds Body temperature using sublingual or tympanic measurement (consistent method to be throughout the study for a given subject) Body weight Height.
Hematology	<ul style="list-style-type: none"> Erythrocytes Leukocytes Differential count^a Hematocrit Mean corpuscular volume Hemoglobin Platelets
Biochemistry	<ul style="list-style-type: none"> Alanine aminotransferase Bicarbonate Gamma glutamyl transferase Urea or BUN Alkaline phosphatase Chloride Potassium Aspartate transaminase Creatinine Sodium

BUN = blood urea nitrogen; IgG = immunoglobulin G; PID = primary immunodeficiency.

^aDifferential count: neutrophils, eosinophils, lymphocytes, monocytes, basophils.

Table 4. Clinical Procedures

Procedure	Description
Serum IgG assessment	<ul style="list-style-type: none"> Blood samples will be collected for assessment of serum IgG trough levels.

IgG = immunoglobulin G.

The timing and frequency of all clinical procedures are described in the [Schedule of Assessments](#). Refer to the Laboratory Manual for details about the collection, storage, handling and transportation of biological specimens.

8.2 Retention of Samples

Samples will not be retained after the completion of the study.

8.3 Concomitant Therapies

All drugs and/or procedures currently being administered to a subject at the time of signing informed consent, and which continue to be taken in addition to IgPro20 during the study, are regarded as concomitant therapies and must be documented as such in the eCRF.

8.4 Visit Schedule

The timing and frequency of the study visits are described in the [Schedule of Assessments](#). Time windows for all assessments are detailed in Table 5.

Table 5. Time Windows for Assessments

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Screening	Between Day -35 and -7.
Vital signs	± 5 min
Blood collection for clinical laboratory tests	Between Day -35 and -7 and at the End of Study visit on Day 85 (±1) day (Day 113 [±1] day for the Pump-Assisted Flow Rate Cohort).
Blood collection for IgG	On Day 1 and End of Study visit (within approximately 1 hour before next infusion).

8.4.1 Screening

All subjects, or the subjects' parent(s) or legally acceptable representative(s), must provide written informed consent before any study-specific assessments or procedures are performed. Written informed consent is not required for assessments or procedures performed according to standard of care (eg, for diagnosis or treatment); results from such assessments may be used in the determination of study eligibility.

A Screening examination should be performed between Day -35 and -7. The following procedures will be conducted and documented at the Screening visit:

- Obtain written informed consent.
- Review inclusion/exclusion criteria.
- Record information regarding medical history and demographics.
- Collect blood sample for beta-human chorionic gonadotropin for females of child-bearing potential.
- Perform a physical examination.
- Measure vital signs:
 - Systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature
 - Body weight
 - Height
- Collect blood samples for laboratory safety evaluation (biochemistry and hematology).
- Start recording AEs and use of concomitant therapies.

Subjects who complete all of these assessments and who fulfil the eligibility criteria (ie, eligible subjects) will be enrolled into the study. If the subject is not eligible for the study, the primary reason for screen failure must be entered in the eCRF.

8.4.2 Pump-Assisted Flow Rate Cohort

8.4.2.1 Week 1 (Day 1)

The following procedures will be conducted and documented at this **office visit**:

- Review inclusion/exclusion criteria.
- Measure systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature.
- Collect blood sample for IgG trough level assessment (within approximately 1 hour before infusion).
- Train subjects on how to use pump for infusion of IgPro20.
- Train subjects on how to use the subject eDiary / back-up paper diary.
- Supervised infusion of IgPro20. Supervised entry of infusion data in the subject eDiary / back-up paper diary.
- IgPro20 dispensation and IRT update.

- Evaluate for AEs (including injection site reaction[s]), record any findings in the eCRF. Train subjects to record AEs in the subject eDiary / back-up paper diary. Confirm that AEs have been recorded in the subject eDiary / back-up paper diary.
- Record use of any concomitant therapy(ies).

8.4.2.2 Weeks 2 (Day 8±1), 3 (Day 15±1) & 4 (Day 22±1)

The following procedures will be conducted and documented **at home**:

- Administer IgPro20. Infusion data should be recorded in the subject eDiary / back-up paper diary.
- Evaluate for AEs (including injection site reaction[s]) and record any findings in the subject eDiary / back-up paper diary.

8.4.2.3 Week 5 (Day 29±1)

The following procedures will be conducted and documented at this **office visit**:

- Measure systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature.
- Review the subject eDiary / back-up paper diary and provide re-training, if necessary.
- Supervised infusion of IgPro20. Supervised entry of infusion data in the subject eDiary / back-up paper diary.
- IgPro20 dispensation and IRT update.
- Review instructions for how to use pump for infusion of IgPro20, if necessary.
- Evaluate for AEs (including injection site reaction[s]), record any findings in the eCRF, and confirm that AEs have also been recorded in the subject eDiary / back-up paper diary. Re-train subjects to record AEs in the subject eDiary / back-up paper diary, if necessary.
- Review if subject has met definition of non-responder for this infusion parameter level.
- Record use of any concomitant therapy(ies).

8.4.2.4 Weeks 6 (Day 36±1), 7(Day 43±1) & 8 (Day 50±1)

The following procedures will be conducted and documented **at home**:

- Administer IgPro20. Infusion data should be recorded in the subject eDiary / back-up paper diary.
- Evaluate for AEs (including injection site reaction[s]) and record any findings in the subject eDiary / back-up paper diary.

8.4.2.5 Week 9 (Day 57±1)

The following procedures will be conducted and documented at this **office visit**:

- Measure systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature.
- Supervised infusion of IgPro20. Supervised entry of infusion data in the subject eDiary / back-up paper diary.
- IgPro20 dispensation and IRT update.
- Review instructions for how to use pump for infusion of IgPro20, if necessary.
- Review the subject eDiary / back-up paper diary and provide re-training, if necessary.
- Evaluate for AEs (including injection site reaction[s]), record any findings in the eCRF, and confirm that AEs have also been recorded in the subject eDiary / back-up paper diary. Re-train subjects to record AEs in the subject eDiary / back-up paper diary, if necessary.
- Review if subject has met definition of non-responder for this infusion parameter level.
- Record use of any concomitant therapy(ies).

8.4.2.6 Weeks 10 (Day 64±1), 11 (Day 71±1), 12 (Day 78±1)

The following procedures will be conducted and documented **at home**:

- Administer IgPro20. Infusion data should be recorded in the subject eDiary / back-up paper diary.
- Evaluate for AEs (including injection site reaction[s]) and record any findings in the subject eDiary / back-up paper diary.

8.4.2.7 Week 13 (Day 85±1)

The following procedures will be conducted and documented at this **office visit**:

-
- Measure systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature.
 - Review the subject eDiary / back-up paper diary and provide re-training, if necessary.
 - Supervised infusion of IgPro20. Supervised entry of infusion data in the subject eDiary / back-up paper diary.
 - IgPro20 dispensation and IRT update.
 - Review instructions for how to use pump for infusion of IgPro20, if necessary.
 - Evaluate for AEs (including injection reaction[s]), record any findings in the eCRF, confirm that AEs have also been recorded in the subject eDiary / back-up paper diary. Re-train subjects to record AEs in the subject eDiary / back-up paper diary, if necessary.
 - Review if subject has met definition of non-responder for this infusion parameter level.
 - Record use of any concomitant therapy(ies).

8.4.2.8 Weeks 14 (Day 92±1), 15 (Day 99±1) & 16 (Day 106±1)

The following procedures will be conducted and documented **at home**:

- Administer IgPro20. Infusion data should be recorded in the subject eDiary / back-up paper diary.
- Evaluate for AEs (including injection site reaction[s]) and record any findings in the subject eDiary / back-up paper diary.

8.4.3 Manual Push Flow Rate & Pump-Assisted Volume Cohorts

8.4.3.1 Week 1 (Day 1)

The following procedures will be conducted and documented at this **office visit**:

- Review inclusion/exclusion criteria.
- Measure systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature.
- Collect blood sample for IgG trough level assessment (within approximately 1 hour before infusion).
- Train subjects on how to administer an infusion of IgPro20.

- Train subjects on how to use the subject eDiary / back-up paper diary.
- Supervised infusion of IgPro20 via whichever method the subject will use (either pump or manual push). Supervised entry of infusion data in the subject eDiary / back-up paper diary.
- IgPro20 dispensation and IRT update.
- Evaluate for AEs (including injection site reaction[s]) and record any findings in the eCRF. Train subjects to record AEs in the subject eDiary / back-up paper diary. Confirm that AEs have been recorded in the subject eDiary / back-up paper diary.
- Record use of any concomitant therapy(ies).

8.4.3.2 Weeks 2 (Day 8±1), 3 (Day 15±1) & 4 (Day 22±1)

The following procedures will be conducted and documented **at home**:

- Administer IgPro20 (weekly for pump-assisted infusions, more frequent than weekly [2-7 days per week] for manual push). Infusion data should be recorded in the subject eDiary / back-up paper diary.
- Evaluate for AEs (including injection site reaction[s]) and record any findings in the subject eDiary / back-up paper diary.

8.4.3.3 Week 5 (Day 29±1)

The following procedures will be conducted and documented at this **office visit**:

- Measure systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature.
- Review the subject eDiary / back-up paper diary and provide re-training, if necessary.
- Supervised infusion of IgPro20 (weekly for pump-assisted infusions, more frequent than weekly [2-7 days per week] for manual push). Supervised entry of infusion data in the subject eDiary / back-up paper diary.
- IgPro20 dispensation and IRT update.
- Review how to use pump for infusion of IgPro20, if necessary.
- Evaluate for AEs (including injection site reaction[s]), record any findings in the eCRF, and confirm that AEs have also been recorded in the subject eDiary / back-up paper diary. Re-train subjects to record AEs in the subject eDiary / back-up paper diary, if necessary.

- Review if subject has met definition of non-responder for this infusion parameter level.
- Record use of any concomitant therapy(ies).

8.4.3.4 Weeks 6 (Day 36±1), 7 (Day 43±1) & 8 (Day 50±1)

The following procedures will be conducted and documented **at home**:

- Administer IgPro20 (weekly for pump-assisted infusions, more frequent than weekly [2-7 days per week] for manual push). Infusion data should be recorded in the subject eDiary / back-up paper diary.
- Evaluate for AEs (including injection site reaction[s]) and record any findings in the subject eDiary / back-up paper diary.

8.4.3.5 Week 9 (Day 57±1)

The following procedures will be conducted and documented at this **office visit**:

- Measure systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature.
- Review the subject eDiary / back-up paper diary and provide re-training, if necessary.
- Supervised infusion of IgPro20 (weekly for pump-assisted infusions, more frequent than weekly [2-7 days per week] for manual push). Supervised entry of infusion data in the subject eDiary / back-up paper diary.
- IgPro20 dispensation and IRT update.
- Review instructions for how to use pump for infusion of IgPro20, if necessary.
- Evaluate for AEs (including injection site reaction[s]), record any findings in the eCRF, and confirm that AEs have also been recorded in the subject eDiary / back-up paper diary. Re-train subjects to record AEs in the subject eDiary / back-up paper diary, if necessary.
- Review if subject has met definition of non-responder for this infusion parameter level.
- Record use of any concomitant therapy(ies).

8.4.3.6 Weeks 10 (Day 64±1), 11 (Day 71±1) & 12 (Day 78±1)

The following procedures will be conducted and documented at **home**:

- Administer IgPro20 (weekly for pump-assisted infusions, more frequent than weekly [2-7 days per week] for manual push). Infusion data should be recorded in the subject eDiary / back-up paper diary.
- Evaluate for AEs (including injection site reaction[s]) and record any findings in the subject eDiary / back-up paper diary.

8.4.4 End of Study

The scheduled end of study participation for an individual subject occurs during Week 13 on Day 85 ± 1 day for the Manual Push Flow Rate & Pump Assisted Volume cohorts (Week 17 on Day 113 ± 1 day for the Pump-Assisted Flow Rate Cohort). After that no further study-related procedures will be performed. The following procedures will be performed and documented at this **office visit**:

- Collect blood sample for beta-human chorionic gonadotropin for females of child-bearing potential.
- Perform a physical examination.
- Measure vital signs:
 - Systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature
 - Body weight
 - Height
- Collect blood sample for IgG trough level assessment (within approximately 1 hour before infusion).
- Collect blood samples for laboratory safety evaluation (biochemistry and hematology).
- Review and collection of subject eDiary / back-up paper diary and collection of eDiary device, if provisioned.
- Evaluate for AEs (including injection site reaction[s]) and record any findings.
- Record use of any concomitant therapy(ies).

Subjects who discontinue the study early will be asked to complete the End of Study procedures.

9. Adverse Events

9.1 Definitions

9.1.1 Adverse Event

As per the ICH guidelines, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

The period of observation for AEs extends from the time the subject gives informed consent until the End of Study (see [Section 9.4](#) for further details).

Adverse events may include:

- Exacerbation (ie, an increase in the frequency or severity) of a pre-existing condition. Illness present before study entry should be recorded in the medical history section of the eCRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study.
- A clinical event occurring after consent but before IgPro20 administration.
- Intercurrent illnesses with an onset after administration of IgPro20.

Adverse events do not include:

- Events identified at Screening that meet exclusion criteria.
- Medical or surgical procedures (the condition that leads to the procedure is the AE).
- Situations where an untoward medical occurrence has not taken place. For example:
 - Planned hospitalizations due to pre-existing conditions, which have not worsened.
 - Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery).
 - Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 h in duration or for normal management procedures (eg, chemotherapy).
- Overdose of IgPro20 or any concomitant therapy that does not result in any adverse signs or symptoms.

For laboratory safety parameters, any instances of absolute values being outside the reference range or changes at any visit after study start that are considered by the investigator as clinically significant must be recorded in the eCRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:

- Laboratory parameters already beyond the reference range at Screening, unless a further increase/decrease can be considered an exacerbation of a pre-existing condition.
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (eg, in vitro hemolysis) and flagged as such by the laboratory in the laboratory report.
- Abnormal parameters that are obviously biologically implausible (eg, values that are incompatible with life or outside the measuring range).
- An abnormal laboratory value that cannot be confirmed after repeat analysis, preferably in the same laboratory (ie, the previous result could be marked as not valid and should not necessarily be reported as an AE).

9.1.2 Adverse Event of Special Interest

Not applicable.

9.1.3 Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion.
- **Is life-threatening** – The term “life-threatening” 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 that hypothetically might have caused death if it had been more severe.

- **Requires in-patient hospitalization or prolongation of existing hospitalization** – CSL considers “hospitalization or prolongation of existing hospitalization” for at least 24 h as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly or birth defect.**
- **Is medically significant** – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a qualified healthcare provider to potentially jeopardize the subject or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion.

Adverse events that do not fall into the above categories are defined as nonserious AEs.

9.2 Severity of Adverse Events

The severity of each AE (ie, nonserious and serious AEs) is to be assessed by the investigator as follows:

Severity	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

CDISC SDTM Severity Intensity Scale for Adverse Event Terminology.

AE = adverse event.

If AE severity is not reported (missing), it will be conservatively assessed as a severe AE.

9.3 Causality of Adverse Events

The causal relationship of an AE to IgPro20 must always be assessed by the investigator. All AEs will be classified as either **related** or **not related** to IgPro20. If a causality assessment is not provided for an AE (including an SAE), the AE will be considered related to IgPro20.

The degree of certainty with which an AE is attributed to IgPro20 or an alternative cause (eg, natural history of the underlying disease, concomitant therapy) will be determined by how well the event can be understood in terms of:

- Known pharmacology of IgPro20.
- Clinically and / or pathophysiologically plausible context.
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product-related (eg, headache, facial flushing, pallor).
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with IgPro20, IMP withdrawal or reproduced on rechallenge).

9.4 Observation Period for Adverse Events

The observation period for AE (and SAE) reporting in an individual subject will start at the time of giving written informed consent for participation in the current study and finish with the End of Study visit.

If the investigator becomes aware of an SAE that has started after the observation period has finished, and the event is considered to be associated with IgPro20, then this must be reported to CSL.

9.5 Adverse Event Reporting

9.5.1 Adverse Events

At each clinical evaluation, the investigator (or delegate) will determine whether any AEs have occurred. AEs will be recorded in the AE page of the eCRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs and symptoms. The investigator must follow up on the course of an AE until resolution or stabilization. If an AE is ongoing after the End of Study visit, the AE will continue to be followed up until resolution, stabilization, or the subject is lost to follow-up. Subjects who drop out of the study due to reasons other than ‘consent withdrawn’ or ‘lost to follow-up’ will be followed up by weekly telephone calls by site personnel for the full duration of their planned study participation, in order to collect information on AEs.

If, during the study period, a subject presents with a preexisting condition that was not noted at the time of study entry, the condition should be retrospectively recorded in the Medical History section of the eCRF.

9.5.2 Adverse Events of Special Interest

Not applicable.

9.6 Serious Adverse Event Reporting

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the eCRF.

All SAEs that occur during the course of the study, whether or not causally related to IgPro20, must be entered into the eCRF immediately (within 24 h of the investigator becoming aware of the event).

Adverse events occurring in the period between the time the subject gave written informed consent and the first exposure to IgPro20 that meet 1 or more of the seriousness criteria for AEs must be entered into the eCRF in the same manner as other SAEs and will be included in the clinical study database.

Any SAE that occurs after the End of Study visit that is considered to be causally related to IgPro20 must be **reported immediately (ie, within 24 h of the investigator becoming aware of the event) to CSL.**

9.6.1 Requirements for Reporting of Serious Adverse Events

The minimum reporting requirements for reporting of SAEs include:

- Identifiable subject.
- Suspected medicinal product and / or procedure.
- Event term.
- Identifiable reporting source.

In addition, the investigator must:

- Report all SAEs to the relevant Institutional Review Board / Independent Ethics Committee (IRB / IEC) within the timeframe specified by the IRB / IEC.
- Enter follow-up information in the eCRF until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
- Ensure that the causality assessment for all SAEs is entered in the eCRF.

If the minimum requirements for reporting are fulfilled, the investigator should not wait to receive additional information to fully document the event.

In cases of death, the investigator should supply CSL and the IEC / IRB (as applicable) with any additional information as it becomes available (eg, autopsy reports and detailed medical reports).

9.6.2 Unusual Failure of Efficacy (Canadian sites only)

For study sites located **in Canada only**, unusual failure of efficacy is also to be reported to CSL using the same process and requirements as for serious adverse events in order to comply with Health Canada's *Food and Drug Regulations*. The rationale for this is if a health product fails to produce the expected intended effect, there may be an adverse outcome for the patient, including an exacerbation of the condition for which the health product is being used. In cases where the investigator is uncertain whether an adverse event should be considered as a report of unusual failure in efficacy, the adverse event should be treated as such and reported accordingly.

9.7 Other Significant Event Reporting

9.7.1 Medication Compliance

Details of actual doses of IgPro20 administered (ie, volume, location of infusions, infusion rate) will be recorded in the subject eDiary or a back-up paper diary if the eDiary is not available. Once the eDiary becomes available, the data recorded in the back-up paper diary will be transcribed to the eDiary. The back-up paper diary will be retained as a source

document. Any overdose that is considered by the investigator to be medically significant must be reported as an SAE (see [Section 9.6](#)).

9.7.2 Pregnancy and Lactation

A female subject who becomes pregnant while participating in the study, or up to and including 20 weeks after the last study dose of IgPro20, must notify the investigator immediately.

If a female subject becomes pregnant, she must discontinue forced upward titration treatment regimen with IgPro20. Her study participation will be discontinued and the procedure for discontinuation of a subject will be followed, as described in [Section 4.2](#).

This requirement is not because IgPro20 is potentially harmful to pregnant women or the fetus, but because pregnancy is likely to alter IgG metabolism and may result in medical need to adjust the IgPro20 dose, which will affect her ability to follow the forced upward titration schedule.

CSL must be notified within 5 days of the investigator becoming aware of the pregnancy.

Whenever possible, a pregnancy in a subject exposed to IgPro20 should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator to CSL using a Pregnancy Reporting / Outcome Form.

9.8 IRB / IEC Reporting Requirements

The time frame within which an IRB / IEC must be notified of deaths and investigational product-related unexpected SAEs is stipulated by each IRB / IEC. It is the investigator's responsibility to comply with the requirements for IRB / IEC notification. CSL will provide investigators with all details of all SAEs reported to regulatory authorities.

9.9 Follow-up of Adverse Events

Every effort should be made to follow-up subjects who continue to experience an AE or an SAE on completion of the study until the AE resolves, is stabilized, or until the subject is lost

to follow-up. Further details on follow-up of subjects who drop out from the study are described in [Section 9.5.1](#). All follow-up information should be entered into the eCRF within 24 hours of awareness and documented in the subject's medical records. Information on attempted follow-up contacts should be documented in the subject's medical records.

If an ongoing AE becomes serious after completion of the study, this information should be sent as follow-up and must be reported immediately (within 24 hours of the investigator becoming aware of the event) to CSL as described in [Section 9.6](#).

All follow-up information (and attempted follow-up contacts) should be documented in the subject's medical records. Details of the subject's progress should also be submitted to CSL Global Clinical Safety and Pharmacovigilance.

10. Assessments

10.1 Subject Characteristics

Subject characteristics to be evaluated will include:

- Demographic data (eg, sex, race).
- Medical and surgical history.
- Details of diagnosis and disease status at enrollment into the study.
- Previous and concomitant therapy.

10.2 Efficacy Assessments

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- **CCI**

10.3 Safety Assessments

Safety will be assessed by:

- The frequency and severity of AEs.
- Local reactions (injection site reactions).
- Tolerability of a certain infusion parameter (ie, percentage of subjects and infusions per cohort by volume/flow rate subgroup experiencing no severe local reactions for each of the infusion parameter levels).
- Physical examination.

- Vital signs.
- Clinical laboratory tests:
 - Biochemistry
 - Hematology

Clinical laboratory tests will be performed at time points as detailed in the [Schedule of Assessments](#). More frequent evaluations may be performed, if clinically indicated, at the discretion of the investigator.

10.4 Pharmacokinetic and Pharmacodynamics

Not applicable.

10.5 Other Assessments

Not applicable.

11. Statistics

11.1 Sample Size Estimation

A minimum of 45 evaluable (15 per cohort) subjects will be needed. This is based on an assumed response rate for reaching the top infusion parameter for each endpoint of 50% (ie, 100 mL/h for the Pump-Assisted Flow Rate Cohort, 50 mL per injection site for the Pump-Assisted Volume Cohort, and 2 mL/min for Manual Push Flow Rate Cohort). Using a binomial distribution with 15 evaluable subjects, there will be a 94% probability that the observed response rate for a single endpoint in the study is $\geq 33\%$.

11.2 Description of Analysis Datasets

11.2.1 Full Analysis Set

The Full Analysis Set (FAS) will comprise all subjects who provide informed consent and who are included in the study; ie, who undergo study procedures after Screening. Screening failures will not be included in the FAS. However, the number of Screening failures will be summarized in the disposition tables and all Screening failures will be listed.

11.2.2 Safety Population

The Safety Population will comprise all subjects in the Full Analysis Set who received at least 1 dose or a partial dose of IgPro20 in the study.

11.3 Statistical Analyses and Methods

A complete description of the statistical analyses and methods will be available in a Statistical Analysis Plan, which will be finalized before the database is locked.

11.3.1 Subject Disposition and Characteristics

11.3.1.1 Subject Disposition

The number of subjects who were screened, enrolled into the study, and completed the study will be presented in summary tables by treatment group and total subjects. The reason for discontinuing the study product or withdrawing a subject from the study will be listed by subject.

11.3.1.2 Subject Characteristics

At a minimum, subject characteristics will be presented in summary tables. Continuous data will be summarized by descriptive statistics (number of observations, mean, standard deviation, minimum, maximum, median, Q1, Q3) and categorical data will be summarized by frequency distributions. Age will be described as both a continuous and a discrete variable. Supportive data will be listed by subject.

11.3.2 Efficacy Analyses

CC/



11.3.3 Safety Analyses

AEs, laboratory, and vital signs will be summarized descriptively only within each of the 3 cohorts separately. No analysis combining data from 3 separate cohorts or comparing safety outcomes between cohorts will be performed.

If a subject is a non-responder at a certain infusion parameter level, AEs reported at the individually tolerable infusion parameter level after the non-response in the subject, ie, AEs starting at or after the next infusion following the infusion leading to non-response, will be listed and flagged, and analysed separately from the AEs reported prior to that time.

AEs will be summarized by the values of infusion parameters within each cohort. Rates per infusion will be presented as well. Adverse events will be presented including a virtual System Organ Class comprising local reaction (identified by the Medical Dictionary for Regulatory Activities high level terms: “administration site reactions NEC”, “infusion site reactions”, and “injection site reactions”) and by severity. Further, time to onset and duration will be presented descriptively. Tolerability of a certain infusion parameter within a cohort will be calculated as ‘number of infusions without severe local reaction / number of all infusions’ and be presented by infusion parameter and cohort. All infusions, regardless of the validity of the procedure (see Section 11.3.5) will be considered.

11.3.4 Pharmacokinetics and Pharmacodynamic Data

Not applicable.

11.3.5 Other Analyses – Infusion Parameters

For the primary endpoints, number and percentage of subjects with response will be provided.

If a subject is a non-responder at a certain infusion parameter level, data collected up to the time of non-response are taken into account for the analysis of response. Data collected at the individually tolerable infusion parameter level after the non-response in the subject will not be included in the analysis of response but will only be listed and flagged.

Percentages will be calculated as follows:

- a) An infusion will be considered ‘valid’ if the subject completes the full dose per scheduled infusion parameter (volume or flow rate) under test without interruptions or decrease during that infusion as detailed in [Table 6](#). Other protocol deviations may also lead to invalidation of an infusion. Protocol deviations will be treated on an infusion basis, not on a subject basis.

Table 6. Criteria for Valid Infusions

Cohort	Criteria for a valid infusion
Pump assisted volume cohort	<ul style="list-style-type: none"> Maximum volume administered per injection site is at least 95% of the planned maximum volume (ie, 25 mL, 40 mL or 50 mL) for at least one injection site and Infusion was not interrupted or stopped prematurely for any reason as documented in the eDiary and Total dose administered is at least 95% of the planned dose
Pump assisted flow rate cohort	<ul style="list-style-type: none"> Injection site flow rate is at least 95% of the planned flow rate (ie, 25 mL/h, 50 mL/h, 75 mL/h or 100 mL/h) for at least one injection site. and Infusion was not interrupted or stopped prematurely for any reason as documented in the eDiary and Total dose administered is at least 95% of the planned dose
Manual push cohort	<ul style="list-style-type: none"> The actual infusion duration is not more than 1 minute or 10% (whichever is larger) longer than the calculated infusion duration based on the desired flow rate (ie, 0.5 mL/min, 1 mL/min, or 2 mL/min) and the actual volume infused. and The actual infusion volume is at least 95% of the planned infusion volume for that infusion day.

- b) For the Pump-Assisted Cohorts, a subject is considered as a ‘responder’ for a certain infusion parameter if he/she has performed ≥ 3 valid infusions (see a) for that infusion parameter in any order, ie, not necessarily consecutive).
- c) For the Manual Push Flow Rate Cohort, a subject is considered as a ‘responder’ for a certain infusion parameter if he/she has performed $\geq k$ valid infusions (see a) for that infusion parameter in any order, ie, not necessarily consecutive) during the 4 weeks planned for that infusion parameter level, where k is specified in Table 7.

Table 7. Responder Requirements in Manual Push Cohort

Manual push infusions /wk	Infusions scheduled for parameter set (n)	Minimum No. of valid infusions (k)
2	8	5
3	12	7
4	16	10
5	20	12
6	24	15
7	28	17

- d) For each cohort (c) the percentage of subjects with response to a certain infusion parameter (p), $R_{c,p}$, will be calculated as [%]:
- $$100 * (\text{Number of responders for } p \text{ in cohort } c) / (\text{number of subjects from the Safety Population in cohort } c)$$
- where response is defined as outlined in b) and c), respectively.

The success criterion for any $R_{c,p}$ will be considered fulfilled if $R_{c,p} \geq 33\%$. Within each cohort, the highest infusion parameter with fulfilled success criterion will be considered the new top infusion parameter to be recommended for the Hizentra label. No formal statistical testing will be performed. All subjects included in the Safety Population of a cohort will be included in the denominator for calculation of $R_{c,p}$.

Rationale for number of valid infusions to qualify a responder in the manual push cohort: The probability for a subject to be a responder for a certain infusion parameter is assumed to be 50% irrespective of the value of the infusion parameter itself, ie, identical to the assumed response rate in [Section 11.1](#). This assumption is based on the expectation that there will be no infusion-related reasons for a subject to interrupt the infusion or change the infusion parameters. To achieve ≥ 3 out of 4 valid infusions the probability for a single infusion to be valid has to be $\geq 61\%$ for pump assisted cohorts. Using this 61% success probability for a single infusion in the manual push cohort the minimum of successes (k) in above table corresponds to a probability for a subject to be a responder of at least 50%.

The primary endpoints will be considered and evaluated independently from each other.

No imputation of missing data will be performed.

Descriptive subgroup analyses will be performed for Infusion Parameters by:

- Age class (≤ 17 years, > 17 years).
- BMI class ($< 30 \text{ kg/m}^2$, $\geq 30 \text{ kg/m}^2$).

11.3.6 Interim Analysis

Not applicable.

12. Quality Assurance

The study may be subject to an audit by CSL, an authorized representative(s) of CSL and / or inspections by an authorized regulatory authority (eg, US FDA). Regulatory authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. CSL will immediately notify the investigator of an upcoming audit/inspection.

In the event of an audit, all pertinent study-related documentation must be made available to the auditor(s). If an audit or inspection occurs, the investigator at each study site will permit the auditor/inspector direct access to all relevant documents and allocate their time as well as the time of relevant staff to discuss the findings and any relevant issues.

13. Regulatory and Ethics Considerations

13.1 Regulatory Considerations

CSL or its agents will submit the appropriate documents to the local regulatory agencies and will await approval before study start.

This study will be conducted under a Clinical Trial Agreement between the sponsor (or delegate) and the respective institutions representing the study sites and documented in accordance with the applicable regulatory guidelines and requirements.

The procedures set out in this study protocol are designed to ensure that CSL and the investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic E6 (Guideline for GCP). The study will also be carried out according to all applicable international and national regulatory requirements.

13.2 Institutional Review Board / Independent Ethics Committee

The investigator must submit the protocol and informed consent forms (ICFs) for review by an authorized and properly constituted (according to local guidelines) IRB/IEC. Written approval must be received from the IRB/IEC before commencement of the study.

13.3 Subject Information and Informed Consent

The principles of informed consent in the Declaration of Helsinki must be implemented in this clinical study before protocol-specified procedures are carried out. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives (or if necessary, legally acceptable representatives) must be given ample opportunity to inquire about details of the study.

Should there be any amendments to the protocol that would directly affect the subject's participation in the study (eg, a change in any procedure), the ICF must be amended to incorporate this modification. Subject must be informed of the change and they must sign the amended ICF indicating that they re-consent to participate in the study.

13.4 Subject Identification and Confidentiality

All subject names and contact details will be kept confidential. Subjects will be identified throughout documentation and evaluation by the number allotted to them during the study. Each subject will be told that all study findings will be handled in the strictest confidence.

The investigator at the study site will be responsible for retaining sufficient information about each subject (eg, name, address, phone number and identity in the study) so that regulatory agencies or CSL may access this information should the need arise. These records should be retained in a confidential manner as long as legally mandated according to local requirements.

Subject medical records pertaining to the study may be inspected/audited at any time by CSL employees or their duly authorized representatives, a regulatory authority or the IRB/IEC. All records accessed will be strictly confidential. Consent to participate in the study includes consent to these inspections/audits.

13.5 Indemnity and Compensation

It is CSL policy that persons who participate in CSL's clinical studies should be no worse off for their having been involved in the study. These persons include the subjects/volunteers, the investigator, the hospital and the IRB/IEC.

CSL has taken out insurance to cover its obligations under both the Indemnity and the Compensation guidelines for injury to subjects involved in the study.

Other details regarding compensation and the obligations of the investigator/CSL are provided in the Clinical Trial Agreement for the study (see [Section 14.1](#)).

14. Administrative Considerations

14.1 Clinical Trial Agreement

This study will be conducted under a Clinical Trial Agreement between CSL (“Sponsor”) and the institution(s) representing the investigational study site(s) (“Authority”). Financial support to the investigational site(s) will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of investigator and CSL, and will form the contractual basis under which the clinical study will be conducted.

14.2 Clinical Study Registration and Results Disclosure

CSL will provide the relevant study protocol information in public database(s) before or at commencement of the study. CSL may also provide study information for inclusion in national registries according to local regulatory requirements.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record.

14.3 Implementation of the Protocol / Protocol Amendment(s)

With the exception of medical emergencies, no changes or deviations in the conduct of the signed protocol will be permitted without documented approval of the CSL Medical Monitor and the IRB/IEC. In the event of a medical emergency, the investigator at the study site will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the CSL Medical Monitor and the IRB/IEC.

Modifications to the protocol that may affect subject safety or the way the study is to be conducted will be documented in a protocol amendment, which must be approved by the IRB/IEC.

Administrative changes to the protocol, defined as minor corrections and/or clarifications that have no effect on the way the study is to be conducted, will not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information.

14.4 Protocol Deviations

All instances where the requirements of the study protocol were not complied with will be tracked. Corresponding subjects may be withdrawn from the study at the discretion of the investigator and/or CSL. Study protocol deviations arise when subjects who have been entered in the study deviate from the IRB/IEC -approved study protocol.

If a major protocol deviation (ie, a deviation that could have a significant effect on the subject's safety, rights, or welfare and/or on the integrity of the study data) occurs, the investigator must notify CSL and the appropriate IRB/IEC as soon as possible or as per local requirements.

An infusion will be considered 'valid' if performed according to the predefined time, total volume, and infusion rate. Any deviation from these for each infusion parameter step will disqualify the infusion and be considered a 'failure' in the analysis of this set of infusion parameters. However, if it is conducted as stated in [Section 11.3.5](#), it can be evaluated for the actual parameter as conducted. For example, if a subject was scheduled to a test volume of 50 mL/site, but for some reasons tested 45 mL/site, it will not count for the 50 mL level, but if that infusion was otherwise uneventful and performed in full without interruption, it will be considered valid for the 45 mL/site level, even though it was not planned.

Protocol deviations may result in an invalid infusion even if there is adherence to the infusion parameters, as stated above. These include, but are not limited to, prohibited concomitant medication use. Full details regarding validation failure will be included in the statistical analysis plan.

14.5 Documentation and Record Keeping

14.5.1 Data Collection

The investigator (or delegate) will maintain individual records for each subject. These records should include dates when a subject visited the study site, records of vital signs, medical history, or physical examinations, administration of IgPro20 or concomitant therapy, any AEs experienced, and other notes as appropriate. These records constitute source data.

An eCRF and eDiary will be provided by CSL (or delegate) for each subject enrolled into the study. The investigator is responsible for ensuring accurate and proper completion of the eCRF and eDiary in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study. All entries on the eCRF must be backed up by source data (ie, the eDiary). A paper diary is provided for use as a back-up if the eDiary becomes unavailable for use. Once the eDiary becomes available again, the data recorded in the back-up paper diary will be transcribed into the eDiary.

All source data will be kept according to all applicable regulatory requirements. Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate). The back-up paper diary, if used, will be retained as source.

The subject will enter infusion data into the eDiary under supervision by the study staff on Day 1. The subject will enter the infusion data into the eDiary for all home infusions and record if any AE occurred. It must be completed in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study. At office visits on Days 29, 57 or 85 (Flow Rate Cohort) and Days 29 and 57 (Manual Push and Pump-Assisted Volume Cohorts) as well as the End of Study visit, subjects will review the eDiary and back-up paper diary with study staff.

14.5.2 Data Quality Assurance

Subjects will receive mandatory, formal training for correct completion of the eDiary / back-up paper diary (including drug usage and AE reporting) before issuing the diary.

Data generated throughout the study will be monitored and the eCRFs checked against the subject records (including the eDiary / back-up paper diary) for completeness and accuracy. CSL's (or delegate) study monitor will perform this function.

Following completion of eCRF pages and entry of the data into a database, the data will be checked electronically for consistency and plausibility. Queries will be generated for questionable data and clarification sought from the investigator. These data queries must be resolved in a timely manner by the investigator (or delegate).

14.5.3 Record Retention

An investigator study file prepared by CSL (or delegate), containing all applicable documents for use at the study site, will be made available to the investigator before the start of the study. All study documentation and materials maintained in the investigator study file must be kept in conformance with applicable national laws and regulations.

All study documentation and materials maintained in the investigator study file at the study site must be available for inspection by the CSL's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited or inspected by qualified delegates from CSL or a competent regulatory authority.

Following completion of the study, the investigator is responsible for archiving the investigator's study file, the subject's records and the source data according to applicable regulatory requirements.

14.6 Study and Site Closure

CSL reserves the right to prematurely discontinue or suspend the study either at a particular site or at all study sites at any time and for any reason. If such action is taken, the CSL study monitor (or delegate) will discuss this with the investigator at each study site at that time and notify the investigators in writing. If the study is suspended or terminated for safety reasons all investigators and the relevant regulatory agencies will be immediately notified of the action as well as the reason for it. The investigator at each study site will advise the IRB/IEC overseeing the study at their site.

14.7 Clinical Study Report

A clinical study report will be written after the completion of the study. CSL or its agent will write the report in consultation with the investigator or, if applicable, a nominated coordinating investigator (or delegate). It is required by CSL that the coordinating investigator will sign the clinical study report.

Progress reports may be provided to the relevant regulatory bodies in accordance with their requirements.

14.8 Use of Data and Publications

The rights and obligations of investigators and CSL concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Agreement for the study.

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Signed By	Date (GMT)
PPD [redacted]	11-Dec-2017 15:34:50
Approved-PPD [redacted] Approval	
PPD [redacted]	12-Dec-2017 00:17:45
Approved-PPD [redacted] Approval	

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