

## STATISTICAL ANALYSIS PLAN

**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<sup>®</sup>) in Subjects with Primary Immunodeficiency**

**Investigational Medicinal Product: IgPro20 (Hizentra<sup>®</sup>)**

**Protocol Number: IgPro20\_4004**

**Version: 1.0**

**Version Date: 26 JUL 2018**

**Sponsor:**

CSL Behring LLC

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## 1 Modification History

<b>Version</b>	<b>Effective Date</b>	<b>Author of Modification</b>	<b>Reason for Change</b>
1.0	26 Jul 2018		N/A – New document.



## 2 Abbreviations and Definitions

### 2.1 Abbreviations

<b>Abbreviation</b>	<b>Definition</b>
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ESP	External Service Provider
EOS	End of Study
FAS	Full Analysis Set
h	Hour
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
kg	Kilogram
m	Meter
mg	Milligram
mL	Milliliter
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of Subjects
PAFR	Pump-Assisted Flow Rate
PID	Primary Immunodeficiency
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
ScAS	Screened Analysis Set
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class

<b>Abbreviation</b>	<b>Definition</b>
TEAEs	Treatment-Emergent Adverse Events
TFLs	Tables, Figures, and Listings
WHO-DDE	World Health Organization Drug Dictionary Enhanced

## 2.2 Definitions

<b>Item</b>	<b>Definition</b>
<b>Analysis Sets</b>	
Screened Analysis Set (ScAS)	Subjects who provided written informed consent and who undergo study screening procedures
Full Analysis Set (FAS)	Subjects of the ScAS who are included in the study, i.e. who undergo study procedures after Screening.
Safety Analysis Set (SAF)	Subjects in the FAS who received at least 1 dose or a partial dose of IgPro20 in the study.
<b>Cohorts</b>	
Pump-Assisted Volume Cohort	Weekly infusions: volume per injection site of <u>infusion parameter levels</u> : 25 mL, 40 mL, and 50 mL; each <u>infusion parameter level</u> for 4 weeks
Pump-Assisted Flow Rate Cohort	Weekly infusions: flow rate per injection site of <u>infusion parameter levels</u> : 25 mL/h, 50 mL/h, 75 mL/h, and 100 mL/h; each <u>infusion parameter level</u> for 4 weeks
Manual Push Flow Rate Cohort	2 to 7 infusions per week: flow rate per injection site of <u>infusion parameter levels</u> : 30 mL/h, 60 mL/h, and 120 mL/h (equivalent of approximately 0.5 mL/minute, 1 mL/minute, and 2 mL/minute) ; each <u>infusion parameter level</u> for 4 weeks
<b>Responder Analysis</b>	
<b>Criteria for Valid Infusion Definition Per Protocol</b>	
Pump-Assisted Volume Cohort	<ul style="list-style-type: none"> <li>• Maximum volume administered per injection site is at least 95% of the planned maximum volume (i.e., 25 mL, 40 mL or 50 mL) for at least one injection site and</li> <li>• Infusion was not interrupted or stopped prematurely for any reason as documented in the diary and</li> </ul>

Item	Definition
	<ul style="list-style-type: none"> <li>• No prohibited concomitant medication and</li> </ul> Total dose administered over all injection sites is at least 95% of the planned dose
Pump-Assisted Flow Rate Cohort	<ul style="list-style-type: none"> <li>• Injection site flow rate is at least 95% of the planned flow rate (i.e., 25 mL/h, 50 mL/h, 75 mL/h or 100 mL/h) for at least one injection site.</li> <li>and</li> <li>• Infusion was not interrupted or stopped prematurely for any reason as documented in the diary</li> <li>and</li> <li>• No prohibited concomitant medication and</li> </ul> Total dose administered over all injection sites is at least 95% of the planned dose
Manual Push Flow Rate Cohort	<ul style="list-style-type: none"> <li>• The actual infusion duration is no more than 1 minute or 10% (whichever is longer) longer than the calculated infusion duration based on the desired flow rate (i.e., 30 mL/h [0.5 mL/min], 60 mL/h [1 mL/min], or 120 mL/h [2 mL/min]) and the actual volume infused</li> <li>and</li> <li>• No prohibited concomitant medication and</li> </ul> The actual infusion volume is at least 95% of the planned infusion volume for that infusion day over all infusion sites.
<b>Criteria for Valid Infusion Modified Definition</b>	
Pump-Assisted Volume Cohort	<ul style="list-style-type: none"> <li>• Maximum volume administered per injection site is at least 95% of the planned maximum volume (i.e., 25 mL, 40 mL or 50 mL) for at least one injection site</li> <li>and</li> <li>• Infusion may be stopped for technical reasons* only; no related AEs started during interrupted or stopped infusion.</li> <li>and</li> <li>• No prohibited concomitant medication and</li> </ul> Total dose administered over all injection sites is at least 95% of the planned dose. (*Technical reason: technical problem with any part of equipment [pump, syringe, tubing, needle, including needle placement] used for infusion.)

Item	Definition																					
Pump-Assisted Flow Rate Cohort	<ul style="list-style-type: none"> <li>• Injection site flow rate is at least 95% of the planned flow rate (i.e., 25 mL/h, 50 mL/h, 75 mL/h or 100 mL/h) for at least one injection site. and</li> <li>• Infusion may be stopped for technical reasons* only; no related AEs started during interrupted or stopped infusion. and</li> <li>• No prohibited concomitant medication and</li> </ul> <p>Total dose administered over all injection sites is at least 95% of the planned dose.                      (*Technical reason: technical problem with any part of equipment [pump, syringe, tubing, needle, including needle placement] used for infusion.)</p>																					
Manual Push Flow Rate Cohort	<ul style="list-style-type: none"> <li>• The actual infusion duration is no more than 1 minute or 10% (whichever is longer) longer than the calculated infusion duration based on the desired flow rate (i.e., 30 mL/h [0.5 mL/min], 60 mL/h [1 mL/min], or 120 mL/h [2 mL/min]) and the actual volume infused and</li> <li>• No prohibited concomitant medication and</li> </ul> <p>The actual infusion volume is at least 95% of the planned infusion volume for that infusion day over all infusion sites.</p>																					
<b>Definition of Responder per Infusion Parameter Level</b>																						
Pump-Assisted Volume Cohort	≥ 3 valid infusions in any order (out of 4 infusions)																					
Pump-Assisted Flow Rate Cohort	≥ 3 valid infusions in any order (out of 4 infusions)																					
Manual Push Flow Rate Cohort	<p>≥ k valid infusions in any order during the 4 weeks planned for that infusion parameter level, with k being</p> <table border="1" data-bbox="548 1549 1393 1814"> <thead> <tr> <th data-bbox="548 1549 802 1619">Manual push infusions per week</th> <th data-bbox="802 1549 1133 1619">Total number of infusions scheduled for parameter set</th> <th data-bbox="1133 1549 1393 1619">Minimum number of valid infusions (k)</th> </tr> </thead> <tbody> <tr> <td data-bbox="548 1619 802 1654">2</td> <td data-bbox="802 1619 1133 1654">8</td> <td data-bbox="1133 1619 1393 1654">5</td> </tr> <tr> <td data-bbox="548 1654 802 1690">3</td> <td data-bbox="802 1654 1133 1690">12</td> <td data-bbox="1133 1654 1393 1690">7</td> </tr> <tr> <td data-bbox="548 1690 802 1726">4</td> <td data-bbox="802 1690 1133 1726">16</td> <td data-bbox="1133 1690 1393 1726">10</td> </tr> <tr> <td data-bbox="548 1726 802 1761">5</td> <td data-bbox="802 1726 1133 1761">20</td> <td data-bbox="1133 1726 1393 1761">12</td> </tr> <tr> <td data-bbox="548 1761 802 1797">6</td> <td data-bbox="802 1761 1133 1797">24</td> <td data-bbox="1133 1761 1393 1797">15</td> </tr> <tr> <td data-bbox="548 1797 802 1814">7</td> <td data-bbox="802 1797 1133 1814">28</td> <td data-bbox="1133 1797 1393 1814">17</td> </tr> </tbody> </table>	Manual push infusions per week	Total number of infusions scheduled for parameter set	Minimum number of valid infusions (k)	2	8	5	3	12	7	4	16	10	5	20	12	6	24	15	7	28	17
Manual push infusions per week	Total number of infusions scheduled for parameter set	Minimum number of valid infusions (k)																				
2	8	5																				
3	12	7																				
4	16	10																				
5	20	12																				
6	24	15																				
7	28	17																				

Item	Definition
Success Criterion	Percentage responder for infusion parameter $p$ in cohort $c$ $R_{c,p}(\%) = \frac{100 * (\text{Number of responder for } p \text{ in cohort } c)}{\text{Number of subjects in the SAF for cohort } c}$ with the success criterion for any $R_{c,p}$ being fulfilled if $R_{c,p} \geq 33\%$ .
Start Date of Non-Response	Date of the next infusion after a subject was classified as non-responder.
<b>Terms</b>	
AE Rate per Infusion	Number of Adverse Events for a Particular PT / Number of Infusions Within Cohort
Baseline	Most recent non-missing value prior to or on the first study treatment dose date
Body Mass Index (kg/m <sup>2</sup> )	Body weight (kg) / Height (m) <sup>2</sup>
Compliance per Infusion (%)	(Actual amount per infusion/prescribed or planned amount per infusion)*100, where amount is dose (mg/kg) or volume (mL)
Duration of Event	End date of the event – start date of the event + 1
Elapsed Time Until Event	Event date – reference date
Local TEAEs	TEAEs identified by MedDRA high level terms “administration site reactions NEC”, “infusion site reactions”, and “injection site reactions”
Tolerability of an Infusion Parameter Within Cohort	Number of infusions without severe local reactions within cohort / number of infusions within cohort (irrespective of their validity); an infusion without severe local reactions is defined as no occurrence of a severe local reaction from the start date and time of an infusion until the start date and time of the next infusion or study end if this was the last infusion.
Treatment-Emergent	Event which started on or after the date (and time) of first administration of study treatment

### 3 Purpose

This SAP provides a detailed and complete description of the planned statistical analyses for the final analysis of the study IgPro20\_4004 to support the Clinical Study Report (CSR). Mock tables, figures, and listings (TFLs) shells are provided in separate supporting documents.

This SAP complies with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline Topic E9, Statistical Principles for Clinical Trials. It is based upon the following study documents:

- Study Protocol (dated 15 Aug 2016);
- Study Protocol Amendment 1 (dated 1 Feb 2017);
- Study Protocol Amendment 2 (dated 31 May 2017);
- Study protocol Amendment 3 (dated 2 Dec 2017);
- Annotated electronic Case Report Form (eCRF) (dated 02 Feb 2017);
- Annotated eCRF (dated 29 Jan 2018);
- Annotated eCRF (dated 26 Jun 2018);
- Screen Report for eDiary (dated 14 Mar 2017).

All decisions regarding the final analysis of the study results, as defined in this SAP document, have been made prior to Database Freeze of the study data.

## 4 Study Design

### 4.1 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 primary immunodeficiency (PID). A target of 45 evaluable subjects (i.e., 15 subjects per cohort) is needed. Enrolled subjects will include a target of 14 (30%) pediatric subjects  $\leq 17$  years of age and a target of 9 (20%) obese subjects with body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup>.

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..

Assignment to one of the cohorts will take place at the Screening visit and subjects cannot be

changed later to another cohort. 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 (h) up to 100 mL/h
- Manual Push Flow Rate Cohort (2 to 7 infusions per week): Flow rate per injection site of 25 to 30 mL/h up to 120 mL/h (equivalent of approximately 0.5 mL/minute up to 2 mL/minute)

Each cohort will test 3 infusion parameter levels (for Pump-Assisted Flow Rate Cohort – 4 levels) 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, subjects may switch to the next infusion parameter level, if the current level has been tolerated (e.g., 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 (i.e., is a non-responder at that level, for definition see Section 11.2), the subject will continue study participation at the individually previously tolerated infusion parameter level for the remaining full study duration, to collect safety information.

The final analysis to support the CSR will take place after all subjects have completed or terminated the study.

The schedule of assessments planned for the study can be found in the protocol.

## 4.2 Objectives and Endpoints

Objectives	Endpoints
<b>Primary</b>	
The primary objective of this study is to determine the responder rate at higher infusion parameters of IgPro20 under the following conditions:	The primary endpoints are as follows: <ul style="list-style-type: none"> <li>• Pump-Assisted Volume Cohort: Percentage of responders for each</li> </ul>

Objectives	Endpoints
<ul style="list-style-type: none"> <li>• Pump-Assisted: Volume per injection site of 25 mL, 40 mL, and 50 mL;</li> <li>• Pump-Assisted: Flow rate per injection site of 25 mL/h, 50 mL/h, 75 mL/h and 100 mL/h;</li> <li>• 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/minute, 1 mL/minute, and 2 mL/minute, correspondingly).</li> </ul>	<p>planned volume (i.e., 25 mL, 40 mL and 50 mL per injection site).</p> <ul style="list-style-type: none"> <li>• Pump-Assisted Flow Rate Cohort: Percentage of responders for each planned flow rate (i.e., 25 mL/h, 50 mL/h, 75 mL/h and 100 mL/h per injection site).</li> <li>• Manual Push Flow Rate Cohort: Percentage of responders for each planned flow rate (i.e., 30 mL/h [0.5 mL/minute], 60 mL/h [1 mL/minute], and 120 mL/h [2 mL/minute] per injection site).</li> </ul>
<b>Secondary</b>	
<ul style="list-style-type: none"> <li>• To evaluate the safety of pump-assisted IgPro20 infusions at higher infusion parameters (volume and flow rate).</li> <li>• To evaluate the safety of manual push IgPro20 infusions.</li> <li>• To evaluate the tolerability of higher infusion parameters of IgPro20.</li> </ul>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• The rate of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.</li> <li>• 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.</li> <li>• Severity of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.</li> <li>• Duration of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.</li> <li>• For all cohorts: Tolerability of a certain infusion parameter, i.e. percentage of infusions per cohort by volume/flow rate subgroup experiencing no severe local reactions for each of the infusion parameter levels.</li> </ul>



Objectives	Endpoints
<b>Exploratory</b>	
<ul style="list-style-type: none"> <li>CCI [REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> </ul>	<ul style="list-style-type: none"> <li>CCI [REDACTED]</li> <li>[REDACTED]</li> <li>[REDACTED]</li> </ul>

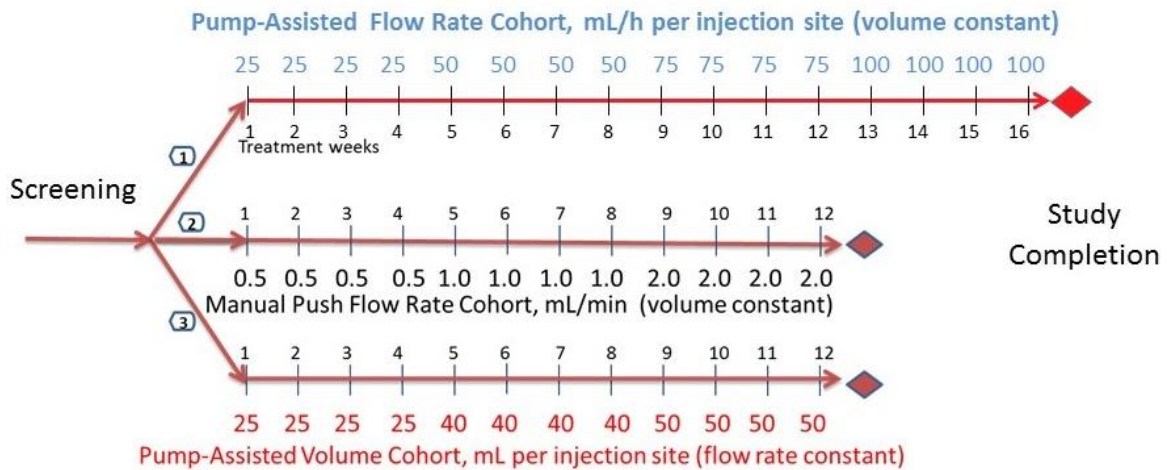
### 4.3 Study Treatments

The study treatment, IgPro20 (trade name Hizentra®), will be manufactured by CSL and will be labelled as investigational medicinal product for this study.

The active substance is human normal immunoglobulin in a ready-to-use formulation for subcutaneous injection. The same dose as prescribed by the subject’s healthcare provider prior to study entry will be used throughout the study, usually within 100-200 mg/kg per week range.

Subjects will administer infusions following the schedule below:

**Figure 1 Study Flowchart**



Subjects in the Pump-Assisted Cohorts will administer weekly treatment and subjects in the Manual Push Cohort will administer frequent infusions (i.e., 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 one month prior to Day 1 (date of Week 1 visit at the

site). The infusion parameters not under test (e.g., volume per injection site in the Flow Rate Cohort) should not exceed the levels used before the study.

#### **4.4 Randomization Procedures and Blinding**

This study is open-label and not randomized. Each study cohort requires specific entry criteria. However, these criteria are not mutually exclusive, and if a subject qualifies to be enrolled into more than one of the study cohorts, he/she may be assigned to either cohort at the investigator's discretion.

#### **4.5 Determination of the Sample Size**

The sample size for this study is not determined based on hypothesis testing considerations. 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% (i.e., 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  $\geq 33\%$ .

#### **4.6 Planned Interim Analyses and Reviews**

##### **4.6.1 Interim Analyses Other Than Sample Size Re-estimation**

No formal interim analysis will be performed. Safety and IgG data will be examined by the study team in an ongoing fashion while the study is being conducted.

##### **4.6.2 Interim Sample Size Re-estimation**

Sample size re-estimation is not planned for this study.

### **5 Changes in the Conduct of Planned Analyses**

Changes in the conduct of the analysis as compared to the most recent protocol or protocol amendments will be covered in the SAP. Changes in the conduct of the analysis after the finalization of the SAP will be covered by a SAP amendment. All changes in the analysis as compared to the protocol or protocol amendments will be described in the CSR. Any post hoc analyses after database lock will clearly be labelled as post hoc.

There will be a separate column "Missing" in the AE summary tables if the assessment for severity is missing. Missing severity will not be imputed as "Severe" as stated in the protocol.

## 6 Study Analysis Sets

### 6.1 Screened Analysis Set

The Screened Analysis Set (ScAS) will comprise all subjects who provided written informed consent and who undergo study screening procedures.

### 6.2 Full Analysis Set

The Full Analysis Set (FAS) will comprise all subjects who provided written informed consent and who are included in the study, i.e. who undergo study procedures after Screening. Screening failures will not be included in the FAS.

### 6.3 Safety Analysis Set

The Safety Analysis Set (SAF) will comprise all subjects in the FAS who received at least 1 dose or a partial dose of IgPro20 in the study.

## 7 General Considerations

### Database Format

Datasets will be provided in Study Data Tabulation Model (SDTM) format. Analysis datasets will be created according to Clinical Data Interchange Standards Consortium standards.

For each subject, data up to the time of study completion, loss to follow-up, or withdrawal from study, whichever is latest, will be included in the appropriate analysis sets defined in Section 6. If a subject withdraws consent, the subject's data will only be used until the time when consent is withdrawn.

### Statistical Analysis System (SAS) Version

SAS version 9.3 or higher will be used to perform all data analyses and to generate TFLs.

### Reporting Standards for Continuous and Categorical Variables

Continuous variables will be summarized in terms of the number of observations, mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum. Other descriptive statistics (e.g., 95% confidence intervals [CIs]) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Missing values will be presented as separate category. Percentages will be based

on the non-missing values. Analyses that use other descriptive statistics will have the specific descriptive statistics required identified with the analysis in the applicable SAP section.

**TFLs Format**

All ICH required data in the database will be presented in data listings.

Data will be displayed as described in this SAP and in the supporting, separate TFL shells document(s).

Tables will be presented by cohort and infusion parameter within cohort (Pump-Assisted Volume: Volume per Site 25 mL, 40 mL, 50 mL, and Total; Pump-Assisted Flow Rate: 25 mL, 50 mL, 75 mL, 100 mL, and Total; and Manual Push Flow Rate: 30 mL/h [0.5 mL/minute], 60 mL/h [1 mL/minute], 120 mL/h [2 mL/minute], and Total) as specified in the respective sections. As subjects may participate in more than one infusion parameter group, the total column may not be the sum of the infusion parameter columns. Subjects and events will be counted once in the total column. Events and assessments will be assigned to the infusion parameter level under which they occur. There will be total columns within cohorts, but no total column over cohorts. Details will be specified in the TFL shells document and in the corresponding SAP section.

Listings will include cohort and infusion parameter, site number, subject number, and basic demographics (age, sex, BMI at Screening). Events and assessments will be assigned to the infusion parameter under which they occurred or were assessed. In subject-level listings, the subjects will be assigned to the highest infusion parameter which they successfully reached. Listings will be presented for a specific analysis set or for all available data depending on the nature of the information listed. In the listings for all available data, a column will be inserted showing the smallest analysis set the subject is assigned to (hierarchy of analysis sets in terms of size/subset: SAF  $\leq$  FAS  $\leq$  ScAS, analysis sets may comprise the same subjects).

Unless otherwise stated, listings will be sorted by treatment status (not treated subjects followed by treated subjects), and within treatment status by cohort and infusion parameter, site-subject number, and by visit date and time or by event date and time. In case of partial dates, date sorting will be by year, month, and day. If any of these variables does not apply to a listing, then that listing will use only those variables which are applicable in the order given here.

Unless otherwise stated, summary tables including figures will be reported by cohort and infusion parameter. The cohort/infusion parameter will be labelled as specified in Section 0. Tables presented by cohort and infusion parameter may contain a total column or block.

If there is no data available for a table or listing (e.g., no deaths occurred in the study), the planned output will be displayed as “No data to report”.

### **Decimal Places**

Summary statistics of mean, median, and quartiles (location parameters) will be reported to one more decimal place than the collected data. For derived data, the maximum number of decimal places of the variables used in the derivation will determine the number of decimal places of the derived variable. For example, BMI uses 2 collected variables, height in meters (m) and weight in kilograms (kg). If the height is collected in centimeters, height in m will have 2 decimal places. Weight may be collected with 1 decimal place. Thus BMI will be considered to have 2 decimal places on observation level. The SD (parameter for variability) will be reported to one more decimal place than the mean. For example, the mean and median for age will be reported to one decimal place because it is collected in full years. The SD of age will then be reported to 2 decimal places. Descriptive percentages and proportions will be displayed to one decimal place. Duration of AEs will be displayed to 1 decimal place.

### **Formatting for Dates and Times**

- Dates only – ddmmmyyyy;
- Times only – hh:mm or hh:mm:ss (as appropriate);
- Dates and times – ddmmmyyyy hh:mm or ddmmmyyyy hh:mm:ss (as appropriate).

### **Planned and Actual Times in Summaries**

Planned times for study treatment dosing will be used in all tables and summary figures.

Generally, only pre-specified planned times will be used in the summaries, statistical analyses, and calculations of any derived parameters; unscheduled assessments will be included in the listings. However, both unscheduled and scheduled assessments will be included in worst-case post-baseline shift displays for laboratory data and in any summary or listing of potential clinical importance values for vital signs.

The infusion start date and time will be mapped to study weeks in the following way: The infusions will be sorted by start date and time and will be consecutively numbered. The infusions will be mapped to study weeks using the consecutive numbers.

Study Week	Pump-Assisted Cohorts	Manual Push Flow Rate Cohort			
		Infusions Per Week			
		2	3	4	5
1	Infusion 1	Infusion 1-2	Infusion 1-3	Infusion 1-4	Infusion 1-5
2	Infusion 2	Infusion 3-4	Infusion 4-6	Infusion 5-8	Infusion 6-10
3	Infusion 3	Infusion 5-6	Infusion 7-9	Infusion 9-12	Infusion 11-15
4	Infusion 4	Infusion 7-8	Infusion 10-12	Infusion 13-16	Infusion 16-20
5	Infusion 5	Infusion 9-10	Infusion 13-15	Infusion 17-20	Infusion 21-25
...	...				
9	Infusion 9	Infusion 17-18	Infusion 25-27	Infusion 33-36	Infusion 41-45
...	...				
12	Infusion 12	Infusion 23-24	Infusion 34-36	Infusion 45-48	Infusion 56-60
...	...				
16	Infusion 16 (PAFR)				

PAFR: Pump-Assisted Flow Rate Cohort

### 7.1 Multicenter Studies

Data from all participating sites will be pooled prior to analysis. Listings will include site information. The site will not be considered in any analysis.

### 7.2 Treatment Descriptors

For output displayed by cohort the following labels and order will be used:

- Pump-Assisted Volume Cohort;
- Pump-Assisted Flow Rate Cohort;
- Manual Push Flow Rate Cohort;
- Total (optional).

For output displayed by infusion parameters within cohort the following labels and order will be used:

- Pump-Assisted Volume Cohort: 25 mL, 40 mL, 50 mL, Total (optional);
- Pump-Assisted Flow Rate Cohort: 25 mL/h, 50 mL/h, 75 mL/h, 100 mL/h, Total (optional);

- Manual Push Flow Rate Cohort: 30 mL/h [0.5 mL/minute], 60 mL/h [1 mL/minute], 120 mL/h [2 mL/minute], Total (optional).

The display of the output will be specified in the TFL shells document.

### 7.3 Multiple Comparisons and Multiplicity

Type I error rate adjustment is not applicable as there is no confirmatory test planned in this study. **CCI**

## 8 Data Handling Conventions

In the event that the study is terminated, all available data will be listed and a review carried out by the study team to assess which statistical analyses are to be performed.

### 8.1 Missing Data

#### 8.1.1 Imputation of Non-Date Missing Data

Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a “blank” in subject listing displays. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

Subjects with the designation of treatment relationship for AEs and serious AEs (SAEs) missing will have the worst realistic case assumed to impute the relationship: if relationship to study treatment is missing and the AE started on or after the first infusion of study treatment it will be assumed to be “Related” (worst case). If the AE with missing relationship to treatment started before the first infusion of study treatment, it will be considered as “Not Related” (realistic case). There will be no other imputation for missing data.

For variables which determine the proportion of subjects, all subjects in the SAF will be included in the denominator when calculating the percentages irrespective of whether their outcome may be missing.

#### 8.1.2 Imputation of Partial Dates

A worst-case approach will be used to assign AE flags or concomitant medication flags if start dates of AEs or concomitant medications are missing or partially missing. Details are given in the respective sections. Study day, durations, or other time variables based on dates

cannot be calculated for partially missing start dates and thus will be missing. Except for the calculation of the duration of an AE for which the following approach will be used: For the calculation of the duration of an AE, missing end dates will not be imputed for AEs which are ongoing. For ongoing AEs the end date and thus the duration will not be available by definition. If the outcome of the AE indicates that the AE is resolved but the end date is still completely missing, the data entry date for this information will be used as AE end date. If only the end day is unavailable, the last day of the month or the subject's study end date whatever occurs first will be imputed as AE end date for the calculation of the AE duration. This approach will be followed in order to avoid underestimation of durations of AEs.

Missing infusion end date and time will be imputed by adding the infusion duration to the infusion start date and time.

## 8.2 Derivation Rules

Separate analysis dataset specifications will provide full details on all data derivations and transformations. The following sections provide a general description of the derived variables for data analyses.

### 8.2.1 Reference Dates

Reference dates are used to assign study periods relative to treatment.

- Because age is an eligibility requirement, the reference date for age will be the date of informed consent;
- Reference date for time since PID diagnosis will be the informed consent date;
- The safety reference date will be the treatment start date, and will be used to calculate study day for safety measures;
- The efficacy reference date will also be the treatment start date as the study is not randomized.

### 8.2.2 Study Day for Efficacy and Safety Measures

If the date of interest occurs on or after the reference date then the study day will be calculated as (date of interest - reference date) + 1. If the date of interest occurs before the



reference date then the study day will be calculated as (date of interest –reference date). There will be no study day 0.

### 8.2.3 Durations

Durations of an event (e.g., the duration of an AE) will be calculated in days as:

- event end date – event start date + 1;

Thus, there will be no duration of 0. If start and end time is available, it will also be used to calculate the duration. For AEs with missing end date, the approach as specified in Section 8.1.2 will be followed.

For elapsed time (e.g., the time since PID diagnosis) use

- event date – reference date.

Thus, an event which happens on the same date as the reference date will have an elapsed time of 0.

To transform durations in days into months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25. These algorithms return decimal numbers, and ignore the actual calendar days in the months or years between start date and end date.

Age will be calculated as the number of complete years between a subject's birth date and the date of informed consent. If the birth date is incomplete, the subject's birth year will be used to calculate age.

### 8.2.4 Baseline Definition

Baseline data is defined as the most recent, non-missing value prior to or on the first study treatment dose date.

### 8.2.5 Change from Baseline

Change from baseline will be calculated as:

- visit value – baseline value

If either the baseline or visit value is missing, the change from baseline will be missing as well.

#### 8.2.6 Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation and the visit will not be re-allocated if the actual visit date deviates from the planned date according to the visit schedule in the protocol). If multiple assessments for the same visit occur, it will be distinguished why this is the case. If a laboratory sample was repeated due to technical problems the results from the valid sample(s) for this visit – the non-missing results – will be used in the analysis. If a laboratory sample was repeated as safety follow-up to monitor abnormal values of the initial sample, the initial sample (revealing the abnormal values) of this visit will be used in the analysis.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

#### 8.2.7 Actual Treatment

All subjects will receive the same study treatment (IgPro20) in individual doses. This is an open-label non-randomized study in which the actual treatment will be identical to the assigned treatment.

#### 8.2.8 Derived Variables

##### **Derivation of BMI**

BMI will be calculated using the following formula:

$$\text{BMI (kg/m}^2\text{)} = \text{Weight (kg)} / [\text{Height (m)}]^2.$$

##### **Derivation of flow rate per injection site**

For the Pump-Assisted Cohort the pump flow rate is to be recorded in the eDiary. The flow rate per injection site will be calculated depending on the catheter type used for injection:

Type of catheter used	Flow rate per injection site
Straight	= Pump flow rate (mL/h)
Bifurcated	= Pump flow rate (mL/h) / 2
Trifurcated	= Pump flow rate (mL/h) / 3
Quadrifurcated	= Pump flow rate (mL/h) / 4

For the purposes of this study, equal flow rate in every catheter branch will be assumed.

#### Derivation of infusion volume per injection site

The infusion volume per injection site will be calculated based on the infusion volume administered via a specific pump depending on the catheter type used for injection:

Type of catheter used	Volume per injection site
Straight	= Pump volume (mL)
Bifurcated	= Pump volume (mL) / 2
Trifurcated	= Pump volume (mL) / 3
Quadrifurcated	= Pump volume (mL) / 4

For the purposes of this study, equal distribution of total volume into every catheter branch will be assumed.

#### 8.2.9 Subgroups

The study design does not include any stratification factors, and there are no plans for post hoc stratification. There are no formal plans for investigating any covariates.

The analysis of infusion parameters will be presented stratified by

- Age class ( $\leq 17$  years,  $> 17$  years);
- BMI class ( $< 30$  kg/m<sup>2</sup>,  $\geq 30$  kg/m<sup>2</sup>).

It will be specified in the respective sections which tables will be affected.

### **8.3 Study Periods Relative to Treatment**

Not applicable.

### **8.4 Values of Potential Clinical Importance**

Not applicable.

## **9 Study Population**

Unless otherwise stated, tables will be based on the SAF. Listings will usually show all data available (i.e. based on the ScAS); listing for derived variables may be based on a particular analysis set which will be specified in the corresponding section. Summaries and data listings will use labels as specified in Section 7.2.

### **9.1 Disposition of Subjects**

A summary table based on the ScAS will be provided by cohort and Total showing the number of subjects with the following information:

- Number of subjects screened;
- Number of screening failures and reason for screening failure;
- Number of subjects enrolled into the study;
- Number of subjects who entered each infusion parameter level;
- Number of subjects who completed the study;
- Number of subjects who discontinued from the study prematurely with reason for discontinuation;
- Infusion parameter level at which subjects discontinued from the study.

Reasons for study discontinuation will be presented in descending order of their frequency.

A by-subject listing for all available data with the information as described in Section 7 as well as screening status, reason for screening failure (in- or exclusion criterion numbers), date of enrollment, date of informed consent, date of eligibility, date of first and last treatment, maximum tolerated infusion parameter level, date of study completion or discontinuation, and reason for study discontinuation will be presented. Another listing for all available data will present the individual visit dates for all visits (scheduled and unscheduled) which the subject attended.

## 9.2 Protocol Deviations

In this study, the ScAS, the FAS, and the SAF are defined. Thus, protocol deviations will not have any impact on the statistical analysis of the study as no subjects will be excluded from the defined analysis sets because of protocol deviations. From a clinical perspective, there is still an interest to report protocol deviations.

A summary table by cohort and Total with the number and percentages of subjects in the analysis sets Screened, FAS, and Safety will be provided.

The following by-subject listings for all available data with the information as described in Section 7 as well as the information listed below will be provided:

- Inclusion and exclusion protocol deviations;
- Other protocol deviations.

## 9.3 Demographic and Baseline Characteristics

The following summaries will be provided for the SAF; tables will be presented by cohort and Total:

- Demographic characteristics: sex, age (years), age category, race, ethnicity, height (cm), weight (kg), and BMI ( $\text{kg}/\text{m}^2$ ) at Screening. Age, height, weight, and BMI will be summarized as continuous variables. Age and BMI will also be categorized and summarized (Age: < 18 years,  $\geq 18 - \leq 65$  years, > 65 years; 0 -  $\leq 27$  days, > 27 days - < 2 years,  $\geq 2 - < 12$  years,  $\geq 12 - < 18$  years,  $\geq 18 - \leq 65$  years, > 65 -  $\leq 84$  years, > 84 years;  $\leq 17$  years and > 17 years. BMI: <  $30 \text{ kg}/\text{m}^2$  and  $\geq 30 \text{ kg}/\text{m}^2$ );
- Disease characteristics: PID category, time since first PID diagnosis (years), historic IgG levels at diagnosis (g/L), and pre-study trough levels (g/L);

- Medical history: coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher will be presented by System Organ Class (SOC) and Preferred Term (PT) – include medical history terms with Medical History Start Date Type “Historical Condition” as entered in the eCRF or medication end date / evidence for end date prior to or on the informed consent date;
- Concomitant diseases (by SOC and PT) will be presented along with concomitant therapies and method of contraception (by Anatomical Therapeutic Chemical [ATC] Class level 4 and unique term) – include medical history terms with Medical History Start Date Type “Concomitant Disease” as entered in the eCRF or end date / evidence for end date after the informed consent date or flagged “Ongoing” and concomitant medication terms which are flagged ongoing, have end date missing, or end date / evidence for end date after the informed consent date.

By-subject listings for all available data with the information as described in Section 7 will be provided for:

- Demographic data: sex, age (years), age group, race, ethnicity, height (cm), body weight (kg), and BMI (kg/m<sup>2</sup>) at Screening;
- Disease characteristics: PID category, time since first PID diagnosis (years), historic IgG level at the time of diagnosis (g/L), pre-study IgG level (g/L);
- Medical history and concomitant diseases (medical history term, SOC, PT, start and end date, medical history term type);
- Reproductive system findings (childbearing potential, method of birth control, pregnancy during the study, date of pregnancy test, and pregnancy test result).

#### **9.4 Concomitant Medications**

Concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) B2 version March 2016 or more recent version. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by ATC class and unique term. ATC Level 4 will be used for the summary tables and listing unless coding is not available at level 4. In these cases level 3 ATC name will be used. Similarly, if the level 3 ATC name is not available then the level 2 ATC name will be used and if the level 2 ATC name is not available then the level 1 ATC

name will be used. ATC Level 1 information will be included in the dataset created but will not appear in the listing or summary except when all other levels are not available.

The following classification of concomitant medication related to start date of study treatment will be applied:

- Assign to ‘Prior Only’ if the concomitant medication start date and end date is prior to study treatment start date; if the subject has not taken any study treatment; or the concomitant medication start date is missing and the concomitant medication end date is before the study treatment start date. If the concomitant medication start or end date is partially missing, the concomitant medication will only be assigned to ‘Prior Only’ if the partial dates give clear evidence that the concomitant medication stopped prior to study treatment start date;
- Assign to ‘Prior and Concomitant’ if the concomitant medication start date is prior to study treatment start date and the concomitant medication end date is on or after study treatment start date or missing (ongoing treatment). If the concomitant medication start or end date is partially missing, the concomitant medication will only be assigned to ‘Prior and Concomitant’ if the partial start date gives clear evidence that the concomitant medication started prior to study treatment start date;
- Assign to ‘Concomitant Only’ if the concomitant medication start date is on or after the study treatment start date or the concomitant medication start date is partially or completely missing and there is no clear evidence from the partial date that the concomitant medication falls into one of the other categories above.

In the summary of concomitant medications, each subject will be counted once within each unique term (Any Medication, ATC Class, and unique term). For example, if a subject takes Amoxicillin on two separate occasions, the subject will be counted only once under the medication “Amoxicillin”, once in the corresponding ATC class, and once for “Any Medication”. The number and percentages of subjects based on the SAF along with the number of reports will be presented for ‘Prior and Concomitant’ and for ‘Concomitant Only’ medications by cohort and Total.

A by-subject listing for all available data with the information as described in Section 7 as well as medication/therapy, start and end date and time or ongoing, dose, route, frequency, primary indication for the concomitant medication, AE term if applicable, medical history

term if applicable, and concomitant medication flag (Prior Only, Prior and Concomitant, Concomitant Only) will be provided.

## 10 Efficacy

CCI [REDACTED]

CCI [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

A by-subject listing for the FAS with the information as described in Section 7 CCI [REDACTED] will be provided.

(Note: details for the primary safety endpoint are described in Section 11.1).

### 10.1.1 Sensitivity Analyses

Not applicable.

### 10.1.2 Subgroup Analyses

The analysis of infusion parameters will be stratified by subgroups as specified in Section 8.2.8.

## 10.2 Treatment Compliance

Treatment compliance will be monitored by reviewing the subject's diary and counting the used vials.

### Dose and Volume Compliance from Subject's Diary:

Treatment compliance will be analyzed by comparing the actual administered dose (mg/kg) and the actual administered volume (mL) over all infusion sites to the prescribed dose (mg/kg) prior to the study and the planned volume (mL) as in the diary, respectively.

- Compliance per Infusion (%) =  $\frac{\text{actual amount per infusion}}{\text{planned amount per infusion}} * 100$ ;
- Overall Compliance (%) =  $\frac{\text{cumulative actual amount over all infusions}}{\text{cumulative planned amount over all infusion}} * 100$ ;



where amount is either the dose (mg/kg) or the volume (mL).

In the Pump-Assisted Cohorts, the compliance per infusion equals the weekly compliance as one infusion per week is scheduled. In the Manual Push Flow Rate Cohort, subject’s weekly compliance will be calculated as the mean over all infusions in the particular week.

The following summaries will be provided by cohort and infusion parameter level based on the SAF:

- Descriptive statistics for overall compliance and subject’s weekly compliance;
- Percentage overall compliance categorized by < 90%, 90% - 110%, and > 110%.

A by-subject listing for the SAF with the information as described in Section 7 as well as prescribed and actual dose per infusion, planned and actual volume per infusion, compliance for dose and volume per infusion, subject’s weekly dose compliance, and overall dose compliance will be provided.

## 11 Safety Analyses

All safety analyses will be based on the SAF as defined in Section 6.

### 11.1 Responder (Primary Endpoint)

For each cohort the percentage of responders will be calculated for each infusion parameter level. The infusion parameter levels per cohort are displayed in Table 1.

**Table 1: Infusion parameter levels per cohort**

Cohort (c)	Infusion Parameter Levels (p)
Pump-Assisted Volume Cohort	Planned maximum volume per injection site <ul style="list-style-type: none"> <li>• 25 mL</li> <li>• 40 mL</li> <li>• 50 mL</li> </ul>

Cohort (c)	Infusion Parameter Levels (p)
Pump-Assisted Flow Rate Cohort	Planned maximum flow rate per injection site <ul style="list-style-type: none"> <li>• 25 mL/h</li> <li>• 50 mL/h</li> <li>• 75 mL/h</li> <li>• 100 mL/h</li> </ul>
Manual Push Flow Rate Cohort	Planned flow rate per injection site <ul style="list-style-type: none"> <li>• 30 mL/h [0.5 mL/min]</li> <li>• 60 mL/h [1 mL/min]</li> <li>• 120 mL/h [2 mL/min]</li> </ul>

The definition of responder is based on the definition of valid infusions. Both definitions are provided in the following.

**Definition of valid infusions**

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. [Table 2](#) specifies for each cohort when an infusion is considered valid.

**Table 2: Minimum criteria for a valid infusion**

<b>Pump-Assisted Volume Cohort</b>		
<b>Infusion Parameter</b>	<b>Definition Per Protocol</b>	<b>Modified Definition</b>
Volume	Maximum volume administered per injection site is at least 95% of the planned max volume (i.e., 25 mL, 40 mL or 50 mL) for at least 1 injection site.	No modification
Flow rate	Not applicable	Not applicable
Dose	Total dose administered is at least 95% of the planned dose.	No modification

<b>Pump-Assisted Volume Cohort</b>		
Interruptions or stops	Not interrupted or stopped prematurely for any reason as documented in the eDiary.	May be stopped for technical reasons* only.
AEs	Not addressed.	No related AEs started during interrupted or stopped infusion.
*Technical reason: technical problem with any part of equipment (pump, syringe, tubing, needle, including needle placement) used for infusion.		

<b>Pump-Assisted Flow Rate Cohort</b>		
<b>Infusion Parameter</b>	<b>Definition Per Protocol</b>	<b>Modified Definition</b>
Volume	Not applicable	Not applicable
Flow rate	Injection site flow rate is at least 95% of the planned flow rate (i.e., 25 mL/h, 50 mL/h, 75 mL/h, or 100 mL/h) for at least one injection site.	No modification
Dose	Total dose administered is at least 95% of the planned dose.	No modification
Interruptions or stops	Not interrupted or stopped prematurely for any reason as documented in the eDiary.	May be stopped for technical reasons* only.
AEs	Not addressed.	No related AEs started during interrupted or stopped infusion.
*Technical reason: technical problem with any part of equipment (pump, syringe, tubing, needle, including needle placement) used for infusion.		

<b>Manual Push Flow Rate Cohort</b>		
<b>Infusion Parameter</b>	<b>Definition Per Protocol</b>	<b>Modified Definition</b>
Volume	The actual infusion volume is at least 95% of the planned infusion volume for that infusion day.	No modification
Flow rate	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 (i.e., 0.5 mL/minute, 1 mL/minute, or 2 mL/minute) and the actual volume infused.	No modification

Any deviation from the above defined criteria for each infusion parameter step will be considered a ‘failure’ (i.e. invalid infusion) in the analysis of this set of infusion parameters. However, if it is conducted as stated in the protocol but at a lower parameter level, it can be evaluated for the actual parameter as conducted. For example, if a subject was scheduled to a test volume of 50 mL/injection site, but for some reasons tested 45 mL/injection 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/injection site level, even though it was not planned. These unplanned parameter levels will be summarized in a separate column “Other” in the tables depending on the scenario. The data may not be summarized if the unplanned level only occurs in one subject. If all subjects have the same unplanned infusion parameter level, a column labelled with this unplanned level will be added. This unplanned column will not be included in the table shell but will only be inserted into the table output as necessary.

Protocol deviations may result in an invalid infusion even if there is adherence to the criteria as stated in [Table 2](#). The following protocol deviations will lead to invalidation of an infusion (this will have no impact on the assignment of a subject to the analysis sets):

- Prohibited concomitant medication
  - Any medications with the primary purpose of masking local or systemic AEs (including but not limited to analgesics and anesthetics  $\pm$  12h around the infusion).
  - Any Ig product other than the study medication

These protocol deviations will be assessed on an infusion basis, not on a subject basis. Prior to DB lock, the infusion data will be merged with the concomitant medication data so that the start date of an infusion can be compared with the start date of concomitant medication. This list will be provided to CSL as an Excel file. CSL will manually review this file and flag the infusions which will have to be considered invalid due to prohibited concomitant medication. Only concomitant medication with complete start dates can be considered in the merge to infusion data.

### Definition of responder

For the Pump-Assisted Cohorts, a subject is considered as a ‘responder’ for a certain infusion parameter if he/she has performed  $\geq 3$  valid infusions for that infusion parameter in any order (i.e., not necessarily consecutive).

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 for that infusion parameter in any order (i.e., not necessarily consecutive) during the 4 weeks planned for that infusion parameter level, where  $k$  is specified in [Table 3](#):

**Table 3: Responder requirements in Manual Push Flow Rate Cohort**

Manual push infusions per week	Total number of infusions scheduled for parameter set	Minimum number of valid infusions ( $k$ )
2	8	5
3	12	7
4	16	10
5	20	12
6	24	15
7	28	17

Rationale for number of valid infusions to qualify a responder in the Manual Push Flow Rate 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, i.e. identical to the assumed response rate in Clinical Study Protocol 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  $\geq 3$  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 Flow Rate Cohort the minimum number of successes (k) in Table 3 corresponds to a probability for a subject to be a responder of at least 50%.

**Calculation of percentage of responder**

The percentage of subjects with response  $R_{c,p}$  in cohort  $c$  to a certain infusion parameter  $p$ ,  $R_{c,p}$ , will be calculated as:

$$R_{c,p}(\%) = \frac{100 * (\text{Number of responder for } p \text{ in cohort } c)}{\text{Number of subjects in the SAF for cohort } c}$$

where response is defined as outlined above.

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<sup>®</sup> label. No formal statistical testing will be performed.

All subjects included in the SAF of a cohort will be included in the denominator for calculation of  $R_{c,p}$ .

Number of infusions and number and percentage of valid infusions and number and percentage of responder will be presented by cohort and infusion parameter level. The base for the percentages will be the number of infusions and the number of subjects within the cohort.

Subgroup analyses for

- Age class ( $\leq 17$  years,  $> 17$  years) and
- BMI class ( $< 30$  kg/m<sup>2</sup>,  $\geq 30$  kg/m<sup>2</sup>)

will be produced (Table 14.3.2).

A by-subject listing with the information as described in Section 7 as well as start and end date and time of infusion, depending on the cohort and planned infusion parameter level: actual parameter level and percentage of planned and for manual push actual infusion duration and calculated infusion duration, for all cohorts: infusion interrupted or stopped, prohibited concomitant medication administered, validity of the infusion, and responder (no/yes) will be provided. In this listing, the data which is collected after a subject has been classified as non-responder will be flagged.

## 11.2 Non-Responder

If a subject is unable to tolerate a certain infusion parameter level (i.e., is a non-responder at that level), the subject will continue study participation at the highest individually tolerable infusion parameter level for the remaining full study duration to collect safety information.

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

The start date of non-response is the start date of the next infusion after the subject has been classified as non-responder. If a subject is a non-responder at the last infusion parameter level, the start date of non-response will be missing as no further data will be collected after the last infusion parameter level.

### 11.3 Extent of Exposure

Actual dose in mg/kg will be taken as entered in the database. For the Manual Push Flow Rate Cohort, the planned weekly volume will be derived from the planned weekly dose as entered in the eCRF assuming the nominal IgG content of IgPro20 being 200 mg/mL:

planned volume (mL) = planned dose (mg/kg) \* body weight (kg) / 200 mg/mL.

Subject's duration of exposure (days) in each infusion parameter level will be calculated as

(minimum of (treatment end date in parameter level [i] + 7 days, treatment start date in parameter level [i+1] – 1 day, study completion date) – treatment start date in parameter level [i]) + 1.

Subject's overall duration of exposure (days) will be calculated as

study completion date – date of first treatment + 1.

Duration in weeks will be derived by dividing the above item by 7.

Descriptive statistics for duration of exposure in weeks for each infusion parameter level and overall will be presented. In addition, the subject-years of exposure for each infusion parameter level and cohort will be given.

Subject's prescribed and actual dose (mg/kg) and total planned and actual volume (mL) per week will be summarized descriptively by cohort and infusion parameter level.

Number and percentage of incomplete infusions or infusions stopped will be presented. The base for the percentage will be the total number of infusions within the cohort.

### 11.4 AEs

AEs starting on or after the date (and time if available) of the first administration of study treatment will be considered treatment-emergent AEs (TEAEs). This is the formal definition of a TEAE. It should be kept in mind that all subjects have been on a stable Hizentra® dose prior to study start.

When the AE start date is missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study treatment. For the assignment of AEs within 72 hours after administration of treatment (temporally associated AEs), only AEs



with complete start dates will be considered. The start time will also be considered if available. AEs which start during infusion or within 72 hours after the end of an infusion will be considered temporally associated AEs.

Only TEAEs occurring until EOS visit will be included in the summary tables. All AEs will be listed.

For non-responder subjects at a certain infusion parameter level, AEs reported at the individually tolerable infusion parameter level after the non-response in the subject, i.e., AEs starting at or after the next infusion following the infusion leading to non-response, will be listed and flagged. These AEs will be analyzed separately from the AEs reported prior to that time.

AEs will be coded using the MedDRA version 20.0 or higher. AEs will be primarily classified by MedDRA PT. Analyses will be performed by SOC and PT. Aggregated incidences at SOC level and Any TEAE will also be provided.

Summaries of TEAEs will count the number of subjects, that is, subjects with multiple occurrences of the same PT will be counted once. Summaries of TEAEs will also include the number of events for each PT. Summaries will be presented for each infusion parameter and total within cohort. TEAEs will be assigned to the infusion parameter level under which they occurred. In the Total column within cohort, each subject will only be counted once with all events experienced.

AE rates per infusion will be calculated within cohort in the following way for each infusion parameter level:

- $$\text{AE Rate per Infusion} = \frac{\text{Number of Events for a Particular PT}}{\text{Number of Infusions}}$$

where number of infusions will be the sum of all infusions that subjects received within infusion parameter level irrespective of their validity as defined in Section 11.1.

Each AE summary table will present the number of subjects, percentage of subjects based on the SAF, number of events, and AE rate per infusion.

One overview summary of TEAEs table with entries for:

- any TEAE;

- causally related TEAEs;
- temporally associated TEAEs within 72 h;
- causally related or temporally associated TEAEs within 72 h
- deaths;
- causally related deaths;
- serious TEAEs;
- causally related serious TEAEs;
- study discontinuation due to TEAE;
- causally related study discontinuation due to TEAE;
- study drug withdrawal due to TEAE;
- causally related study drug withdrawal due to TEAE;
- local TEAEs;
- causally related local TEAEs;
- maximum severity of TEAEs.

will be produced.

The following summary tables of TEAEs will be produced:

- by SOC and PT;
- SAEs by SOC and PT;
- by SOC, PT, and maximum severity (missing severity will be presented as separate category);
- by SOC, PT, and causality (missing causality will be considered “Related” as outlined in Section [8.1.1](#));
- by SOC and PT temporally associated within 72 hours after treatment;
- by SOC and PT causally related or temporally associated within 72 hours after treatment;

- time to onset of TEAEs (descriptive statistics and categories 0 days, 1 day, 2 days, 3 days, > 3 days);
- duration of TEAEs (descriptive statistics and categories 1 day, 2 days, 3 days, > 3 days);
- tolerability of the infusion parameter (number of infusions without severe local reactions / number of all infusions).

Time to onset of TEAE will be calculated as

TEAE start date and time – infusion start date and time.

For the categories, the time will be rounded to days.

Duration of TEAEs will be calculated as defined in Section 8.2.3.

Tolerability of a certain infusion parameter within a cohort will be calculated as

number of infusions without severe local reactions / number of infusions

and will be presented by infusion parameter and cohort. The number of infusions irrespective of their validity as defined in Section 11.1 will be used as denominator for the assessment of tolerability. The total number of infusions within infusion parameter level and within cohort will be considered as denominator for the tolerability within infusion parameter level and within cohort, respectively. An infusion without severe local reactions is defined as no occurrence of a severe local reaction from the start date and time of an infusion until the start date and time of the next infusion or study end if this was the last infusion.

Local TEAEs will be identified by the MedDRA high level terms “administration site reactions NEC”, “infusion site reactions”, and “injection site reactions”. The MedDRA high level terms will be reviewed prior to database lock and the list of terms to be included into Local TEAEs will be updated. Local TEAEs will be included in all tables by using a virtual SOC called “Local Adverse Events”. In addition, the local TEAEs will also be presented by their MedDRA SOC “General disorders and administration site conditions”.

TEAEs will be sorted in descending order of total incidence by SOC and PT.

The summary will report for the Any TEAE row, each SOC, and each PT, the number of subjects with at least one TEAE, counted for the maximum reported severity in the table by severity. Local TEAEs will be reported only once in the Any row.

A listing of MedDRA SOC, PT, and verbatim text will be provided.

All AEs will be listed. TEAEs will be listed for the SAF. Other AE listings will use all available data. The listings will include the variables as specified in Section 7 and in addition MedDRA SOC, PT, and the verbatim, AE start and end date and time if available, duration of AE in days, severity, serious (yes or no), relationship to treatment (yes or no), outcome, action taken, and AE flags (TEAE, SAE, temporal relationship within 72h [AE72h]). Additionally, a listing of subject IDs for each individual PT will be produced.

The following listings will be provided:

- Non-TEAEs – all available data;
- TEAEs – SAF;
- Deaths – all available data;
- SAEs – all available data;
- AEs leading to study discontinuation – all available data;
- Local TEAEs – SAF;
- MedDRA SOC and PT with all AE verbatim – all available data;
- Subject IDs for each PT – all available data.

In all listings, the data which is collected after a subject has been classified as non-responder will be flagged.

#### 11.4.1 AEs of Special Interest

Not applicable.

#### 11.4.2 Deaths and SAEs

An entry in the overall summary table will show the number of subjects who died and the number of subjects with SAEs. SAEs and local SAEs will be summarized by SOC and PT.

Deaths will be listed. A by-subject listing for SAEs will be produced which will contain the information as specified in Section 11.4 and in addition information for criteria for SAE, hospitalization admission and discharge date, alternative cause for SAE not related to study treatment. These listings will be produced for all available data.

#### 11.4.3 AE Leading to Discontinuation from the Study, and Other Significant AEs

AEs leading to study discontinuation will be listed for all available data. An entry in the overview table will show the number of subjects who discontinued the study due to AE.

#### 11.4.4 Public Disclosure of Clinical Trials Requirements

To support post-study reporting of study results on public sites, the following will be provided:

- A summary of non-serious TEAEs that occurred in at least 5% of the subjects in at least one cohort (no rounding for the percentage will be used in terms of the 5% threshold, i.e., an event with 4.9% incidence rate will not be included in this table). The summary will be displayed by SOC and PT and will be sorted in descending frequency by total incidence of PTs;

Each of these summaries will include the number and percentage of subjects who experienced the TEAE and the number of TEAEs.

### 11.5 Pregnancies

See Section 9.7.2 of the study protocol.

### 11.6 Clinical Laboratory Evaluations

The laboratory tests in Section 8.1 of the protocol, Clinical Procedures, will be summarized as described in this section.

Laboratory data will be presented in standard units and in the order presented in the protocol:

- Hematology: Hemoglobin, Hematocrit, Mean Corpuscular Volume, Erythrocytes, Leukocytes, Platelets, Neutrophils, Eosinophils, Lymphocytes, Monocytes, and Basophils;
- Biochemistry: Sodium, Potassium, Chloride, Bicarbonate, Urea or Blood Urea Nitrogen, Creatinine, Gamma Glutamyl Transferase, Alkaline Phosphatase, Alanine Aminotransferase, Aspartate Transaminase.

For hematology and biochemistry tests, descriptive statistics as specified in Section 7 by visit (Screening and EOS) will be presented by cohort using results from scheduled visits. The change between EOS visit and Screening will also be presented descriptively.

Laboratory data will be listed using all available data with the variables as described in Section 7 as well as study visit, date and time of sampling, test result, and comments. Scheduled and unscheduled visits will be included in the listings. In these listings, the data which is collected after a subject has been classified as non-responder will be flagged.

Abnormal laboratory results for all available data will be provided in a separate listing. A listing of laboratory data for subjects with abnormal range changes will also be provided. Scheduled and unscheduled visits will be considered. In these listings, the data which is collected after a subject has been classified as non-responder will be flagged.

- Laboratory values which were normal or above normal range (high) at Screening and below normal range (low) at any post-Screening visit;
- Laboratory values which were normal or below normal range (low) at Screening and above normal range (high) at any post-Screening visit.

## 11.7 Other Safety Measures

### 11.7.1 Vital Signs

Vital signs will be summarized descriptively by scheduled visit along with change from baseline at each scheduled post-baseline visit by cohort. The following summaries will be provided:

- Systolic and diastolic blood pressure;
- Pulse rate;
- Respiratory rate;
- Body temperature;
- Body weight and height (at Screening and EOS).

Vital signs results will be presented in a listing for all available data with variables as specified in Section 7 at scheduled and unscheduled visits. In this listing, the data which is collected after a subject has been classified as non-responder will be flagged.

### **11.7.2 Physical Examination**

Physical examination dates for all available data will be listed along with the information whether or not the physical examination was done. In this listing, the data which is collected after a subject has been classified as non-responder will be flagged.

## **12 Pharmacokinetic Analyses**

Not applicable.

## **13 Pharmacodynamics and Biomarkers Analyses**

Not applicable.

## **14 Pharmacokinetic/Pharmacodynamic Analyses**

Not applicable.

## **15 Pharmacogenetic Data Analyses**

Not applicable.

## **16 References**

ICH Harmonised Tripartite Guideline Topic E9, Statistical Principles for Clinical Trials

## Appendices

### 16.1 Display Conventions

Visit names:

<b>Pump-Assisted Flow Rate Cohort</b>	<b>Pump-Assisted Volume Cohort &amp; Manual Push Flow Rate Cohort</b>
Screening	Screening
Day 1	Day 1
Day 8	Day 8
Day 15	Day 15
Day 22	Day 22
Day 29	Day 29
Day 36	Day 36
Day 43	Day 43
Day 50	Day 50
Day 57	Day 57
Day 64	Day 64
Day 71	Day 71
Day 78	Day 78
Day 85	
Day 92	
Day 99	
Day 106	
Day 113 (EOS)	Day 85 (EOS)