STATISTICAL ANALYSIS PLAN

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Study Title: Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases

Study Number: 161504

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STATISTICAL ANALYSIS PLAN
Final Analysis

HYQVIA
PHASE 4

Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases

PROTOCOL IDENTIFIER: 161504

Study Sponsor(s): SHIRE (formerly Baxalta US, Inc)*
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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0 Draft	22 Jan 2020	N/A (New document)
2.0 Draft	29 Jan 2020	Trough IgG levels added as an additional endpoint/outcome measure for analysis
1.0 Final	31 Jan 2020	
1.0 Draft Final Analysis	04 Mar 2020	Expanded sections, content and structure of Interim Analysis SAP into Final Analysis SAP
2.0 Draft (Stable Draft)	13Mar2020	Editorial adjustments. Also, incorporated additional endpoints/outcome measures for a more complete and robust analysis
2.1 Draft	7 May 2021	Updated the author of the SAP. Updated and clarified the scope of analysis in adverse events. Clarification made on the analysis sets. Removed the per-protocol set in this analysis definition. Editorial adjustments to match the protocol endpoint order. Clarified the scope of the final analysis SAP. Editorial adjustments.
2.2 Draft	25 May 2021	Added the analysis in exposure. Clarification on the treatment duration. Added the age subgroup analysis for trough level IgG, IgG subclasses, and specific antibodies.

2.0 Final	25 May 2021	

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ABBREVIATIONS

Abbreviations	Descriptions
ADaM	Analysis Data Model
AE	Adverse Event
AR/SAR	Adverse Reaction or Suspected Adverse Reaction
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DMC	Data Monitoring Committee
EQ-5D	EuroQoL (Quality of Life)-5 Dimensions
FA	Final Analysis
HBV	Hepatitis B virus
HRQoL	Health-related Quality of Life
HRU	Healthcare Resource Utilization
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
I/E	Inclusion/Exclusion
IgG	Immunoglobulin G
IGI, 10%	Immune Globulin Infusion (Human), 10% Solution
IGIV or IVIg	Intravenous immunoglobulin G
IP	Investigational Product
ISMC	Internal Safety Monitoring Committee
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PedsQL	Pediatric Quality of Life
PIDD	Primary Immunodeficiency Diseases
PT	Preferred Term (MedDRA)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard Deviation
SEM	Standard Error of Mean
SDTM	Study Data Tabulation Model
SI	Système International
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Event
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures, and Listings
TSQM-9	Treatment Satisfaction Questionnaire for Medication
WHO	World Health Organization

1. INTRODUCTION

1.1 Study 161504

Study 161504 (SHP671-PIDD-161504) is a Phase 4 (post-authorization), open-label, non-randomized, non-controlled, multicenter, safety, tolerability and immunogenicity evaluation of HyQvia in pediatric subjects with primary immunodeficiency diseases (PIDD) who have received immunoglobulin therapy *before* enrollment into this study.

PIDD is a class of disorders that results in increased susceptibility to infection, including both recurrent pyogenic infections secondary to defects of humoral immunity and opportunistic infections resulting from defects in cell-mediated immunity.

The purpose of the Europe Study 161504 is to acquire additional data on safety, tolerability and immunogenicity of HyQvia in pediatric (age 2 to <18 years) subjects with PIDD.

This study comprises 3 epochs (parts):

Epoch 1 is Part 1 of the study. Subjects who were not treated with HyQvia by time of enrollment in the study but instead were on non-HyQvia intravenous (IV) or SC treatment with immunoglobulin (IV-pretreated, SC pretreated) will be enrolled in Epoch 1 and treated with HyQvia subcutaneously.

Epoch 2 is Part 2 of the study. Subjects already treated with HyQvia by time of enrollment in the study (HyQvia pretreated) will be enrolled directly in Epoch 2 and treated with HyQvia subcutaneously.

Epoch 3 is Part 3 of the study. Only subjects whose anti-rHuPH20 antibody titer was ≥160 during *either* Epoch 1 or Epoch 2 and who experience either a study drug-related serious adverse event (SAE) or a related severe adverse event (AE) will be enrolled in Epoch 3 and followed for safety purposes for approximately 1 year. Subjects in Epoch 3 will be treated with KIOVIG intravenously or Cuvitru subcutaneously.

The safety of subjects in Study 161504 and in a similar Study 161503 which is focused exclusively on U.S. subjects with PIDD, is monitored jointly by an independent, Internal Safety Monitoring Committee (ISMC).

1.2 Categories of Planned Deliverables

Three categories of deliverables are planned for Study 161504:

1. Periodic ISMC Subject-Level Listings *
2. Interim Analysis (IA)

3. Final Analysis (end-of-study analysis)

* Out of scope of this SAP and are documented in the study ISMC Charter, dated 09 Dec 2019, version 5.0 or most recent version.

1.3 Statistical Analysis Plan Overview

This document is the statistical analysis plan (SAP) for the study final analysis (end-of-study analysis) and is an expansion of the content and structure of the interim SAP which was approved on 31 Jan 2020, *before* data extraction for interim analysis, in accordance with Section 6.6 of the Shire Statistical Analysis Plan Work Instruction (RD JBA-0348). This final analysis SAP is planned to be approved *before* study database lock for final analysis, also in accordance with the Shire Statistical Analysis Plan Work Instruction.

This SAP provides a technical and detailed elaboration of the statistical analysis described in the approved study Protocol Amendment 2, dated 04 Dec 2019. All analyses planned are descriptive, unless otherwise specified, and will be performed externally by the sponsor-designated contract research organization (CRO), using SAS®, Version 9.4 or higher.

There are no statistical stopping criteria (go/no-go decision criteria) for this study.

No multiplicity adjustment for the control of type 1 error (risk of false positive conclusion) will be made in the final (end-of-study) analysis, considering that the interim analysis was descriptive, with no statistical hypothesis testing.

The final analysis covers additional outcome measures and analyses beyond those covered by the interim analysis and is planned to include the following:

- Efficacy
- Adverse events
- Infections
- Mode of product administration (infusion data)
- Health-related Quality of Life data
- Treatment Preference and Satisfaction data
- Healthcare Resource Utilization data
- Safety-supporting data as specified

Specifications for corresponding tables, figures, and listings (TFLs) will be provided separately, in the final analysis TFL shells document.

In the event of any inconsistency between the statistical content provided in this SAP and the TFL specifications provided separately in the final analysis TFL shells document, this SAP will not be amended as a result of the inconsistency. Inconsistencies, if any, will be documented appropriately in the Clinical Study Report for this study.

1.4 Investigational Products

The investigational products (IP) in this study are:

- HyQvia, Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase PH20 (IGI, 10% with rHuPH20). IP in Epoch 1 and Epoch 2.
- KIOVIG 100 mg/mL solution for infusion. IP in Epoch 3.
- Cuvitru 200 mg/mL solution for subcutaneous injection. IP in Epoch 3.

2. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is to assess the safety of HyQvia treatment in pediatric subjects with PIDD who received immunoglobulin therapy *prior* to study enrollment.

2.1.2 Secondary Objectives

Secondary objectives of this study are further assessments (e.g. immunogenicity), tolerability, characteristics of product administration, and efficacy (IgG trough levels).

2.1.3 Tertiary Objectives

Tertiary objectives of the study are further safety and efficacy assessments, including assessments of the following:

- Treatment Preference via Treatment Preference Questionnaire
- Treatment Satisfaction via Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- Health-related Quality of Life (HRQoL) via HRQoL Questionnaire
- Other Safety not part of the study primary objective or secondary objectives

2.2 Estimands

The Estimand framework is not applicable to this study. According to ICH E9(R1) "Estimands should be defined and explicitly specified in the clinical trial protocol". ICH

E9(R1) came into effect on 30th July 2020 (step 5 of the ICH process) whereas the original protocol was finalized prior to this date (July 2016).

2.3 Endpoints

2.3.1 Primary Endpoints

Assessment of safety (not efficacy) of HyQvia is the primary objective of this study. The dual primary endpoints/outcome measures corresponding to the study primary objective, as defined in the study protocol and with clarification, are:

1. Number and rate per infusion (excluding infections) of all **severe related** AEs in Epoch 1 and in Epoch 2
2. Number and rate per infusion (excluding infections) of **related** SAEs in Epoch 1 and in Epoch 2

2.3.2 Secondary Endpoints

The secondary endpoints/outcome measures corresponding to the study secondary objectives, as defined in the study protocol, cover efficacy (IgG trough levels), safety/tolerability, mode of product administration, and health-related quality of life.

Note that the study protocol defined some adverse events outcome measures/endpoints in terms of "number", rather than, for example, "occurrence."

2.3.2.1 Efficacy Endpoint

Trough levels of IgG (Epoch 1 and Epoch 2):

- IgG total trough levels
- IgG subclass trough levels
- Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae, and Hepatitis B Virus ([HBV])

2.3.2.2 Safety/Tolerability Endpoints

1. Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
2. Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months
3. Number and rate per infusion (excluding infections) of local AEs and Adverse Reactions (ARs)
4. Number and rate per infusion (excluding infections) of systemic AEs and ARs
5. Number and rate per infusion (excluding infections) of all AEs and all ARs
6. Number and rate per infusion (excluding infections) of all temporally associated AEs

7. Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
8. Number and rate per infusion (excluding infections) of all SAEs
9. Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20
10. Additional safety outcome measures include clinical laboratory outcomes: raw (actual) values and change from baseline, and vital signs: raw (actual) values and change from baseline

2.3.2.3 Mode of Product Administration Endpoints

1. Infusions
   - Number of infusions
   - Number of infusions per month
   - Number of infusion sites (needle sticks) per infusion; number of infusion sites (needle sticks) per month
   - Duration of infusion (defined as time from the start of rHuPH20 infusion until the stop time of immunoglobulin infusion). "Time" implies date and time.
   - Maximum infusion rate/site
   - Infusion volume/site
   - Number/proportion of infusions that are discontinued, slowed, or interrupted due to an AE
2. Number of weeks to reach final dose interval (three weeks or four weeks)
   - Number of weeks to reach final dose interval (three weeks or four weeks) (Epoch 1)
   - Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
   - Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months

2.3.2.4 Health-related Quality of Life Endpoints

Assessment of Health-related Quality of Life (HRQoL) Questionnaires:

- HRQoL Questionnaire: Peds-QL, EQ-5D
  - Pediatric Quality of Life Inventory (Peds-QL)
  - EuroQol five dimensions questionnaire (EQ-5D)

2.3.2.5 Treatment Preference and Satisfaction Endpoints

- Treatment Satisfaction Questionnaire and Medication (TSQM-9)
- Treatment Preference Questionnaire

2.3.3 Tertiary Endpoints

Infections Endpoints

1. Acute serious bacterial infections:
    - Number and proportion of subjects with any acute serious bacterial infection
    - Number of acute serious bacterial infections
    - Acute serious bacterial infections per infusion
    - Acute serious bacterial infections per subject-year
2. All infections:
    - Number and proportion of subjects with any acute serious bacterial infection
    - Number of all infections
    - Infections per infusion
    - Infections per subject-year

Healthcare Resource Utilization Endpoints

3. Days not able to go to school/work or to perform normal daily activities due to infection or other illness: *raw values (actual), per subject, and per subject-year*
4. Days on antibiotics: *raw values (actual), per subject, and per subject-year.*
5. Number of hospitalizations, indication for the hospitalization (infection or non-infection) and days hospitalized: *raw values (actual), per subject, and per subject-year*
6. Number of acute physician visits (office and emergency room) due to infection or other illnesses: *raw values (actual), per subject, and per subject-year*

Calculating per subject and per subject-year, refer to Section 8.2.3 and adapt AEs per subject and per subject-year calculations.

3. STUDY DESIGN

3.1 General Description

Study 161504 is a Phase 4, open-label non-randomized, non-controlled, multicenter, safety, tolerability and immunogenicity evaluation of HyQvia in pediatric subjects with PIDD who have received immunoglobulin therapy *before* enrollment into this study.

Approximately 40 pediatric subjects with PIDD who have received prior immunoglobulin therapy are planned to be enrolled in this study.

Of the 40 subjects planned to be enrolled, approximately 6 subjects are expected to be ages 2 to <6 years, 12 subjects ages 6 to <12 years, and 22 subjects ages 12 to <18 years. The study will be conducted only in the European Economic Area.

All subjects will have regular anti-rHuPH20 antibody testing (binding and neutralizing anti-rHuPH20 antibody) throughout the study (approximately every 3 months).

The overall study design is illustrated in the Study Flow Chart (Appendices). Details on the procedures to be performed at each study visit, including screening, can be found in the Schedule of Study Procedures and Assessments (Appendices).

This study comprises 3 epochs (parts):

Epoch 1: Treatment with HYQVIA, Ramp-up

Pediatric subjects with PIDD who are on **non-HyQvia** IV or SC treatment with immunoglobulin (IV-pretreated, SC-pretreated) at time of enrollment will be treated with HyQvia subcutaneously with a dose or interval ramp-up period of up to 6 weeks.

Subjects who were already treated with HyQvia (HyQvia-pretreated) by time of enrollment will be enrolled directly into Epoch 2, followed by Epoch 3 if needed.

Epoch 1 subjects can be viewed as the HyQvia-treated ramp-up subjects.

Epoch 2: Treatment with HYQVIA, No Ramp-up

The ramp-up (Epoch 1) is followed by Epoch 2. Subjects in Epoch 2 will be treated with HyQvia, with no ramp-up, at the following intervals:

- For IV-pretreated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule.
- For SC-pretreated subjects: every three or four weeks, at the discretion of investigator and subject.
- For HyQvia pre-treated subjects: No change in frequency of administration.

Alternative treatment intervals, for example infusion every 2 weeks, may be considered

for tolerability reasons at the discretion of the investigator, after informing the sponsor. After 1 year in Epoch 2, the anti-rHuPH20 binding antibody assay results during that year will be used to decide the next steps in the study (see Study Flow Chart in Appendices):

- Subjects with anti-rHuPH20 antibody titer <160 at all time-points during the study will complete the study termination/completion visit at the next possible occasion.
- Subjects with anti-rHuPH20 antibody titer ≥160 during the study and/or at the last measurement will continue in Epoch 2 for an additional two years of HyQvia treatment and observation.

The first two or three infusions during Epoch 2 will be administered at the study site.

Epoch 2 subjects can be viewed as the HyQvia-treated no ramp-up subjects.

Epoch 3: Treatment with KIOVIG or Cuvitru

Epoch 3 is approximately a one-year safety follow-up, if needed. Only subjects whose antirHuPH20 antibody titer was ≥160 during Epoch 1 or Epoch 2 and who experience either a related SAE or a related severe AE will be enrolled.

Subjects in Epoch 3 will be treated with KIOVIG (IGI, 10%) intravenously or Cuvitru subcutaneously, at the discretion of the investigator and the subject.

In the event that a subject in Epoch 1 or in Epoch 2 experiences a related SAE or severe AE without anti-rHuPH20 antibody titer ≥160 , the subject can (at the discretion of the investigator and subject): 1) be terminated from the study; or, 2) change directly to Epoch 3; or, 3) continue in Epoch 1 or 2 with appropriate medical intervention such as decreasing the HyQvia infusion rate and/or premedication.

Subjects with antibody titer of ≥160 when entering Epoch 3 continue regular anti-rHuPH20 antibody testing (approximately every 3 months) for approximately 1 year. These subjects complete the study termination/completion visit when the AE/SAE resolves or the anti-rHuPH20 titer is <2560.

Epoch 3 subjects can be viewed as the Epoch 1 subjects (HyQvia ramp-up subjects) and Epoch 2 subjects (HyQvia no ramp-up subjects) who met the Epoch 3 entry criteria.

3.2 Duration of Study Period and Study Participation

The planned overall duration of the study is approximately 7 years, from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The planned maximum subject participation period is approximately 4 years, partitioned as follows:

- Epoch 1 (Ramp-up): Up to 6 weeks for HyQvia-naïve subjects
- Epoch 2 (Final dosing): Up to 3 years

- Epoch 3 (Safety Follow-up): Up to 1 year

3.3 Schedule of Study Assessments

This study has 3 main assessment periods: Epoch 1, Epoch 2, and, if needed, Epoch 3. The Appendices contain the schedules of study procedures and assessments separately for Epoch 1 (HyQvia, ramp-up), Epoch 2 (HyQvia, no ramp-up), Epoch 3 (KIOVIG or Cuvitru).

3.4 Randomization

Not applicable. This study is non-randomized.

3.5 Blinding and Unblinding

3.5.1 Blinding

Not applicable. This study is open-label.

3.5.2 Unblinding

Not applicable. This study is open-label.

3.6 Sample Size and Power Considerations

The planned sample size is 40 subjects enrolled.

This study was not designed for statistical hypothesis testing. The sample size selected for the study is primarily determined by the objective to collect safety data on HyQvia in a sufficient number (about 40) of pediatric (age 2 to <18 years) subjects with PIDD who have received prior immunoglobulin therapy before enrollment into this study. In addition, the guideline of the CHMP on the clinical investigation of human normal immunoglobulin for SC and/or intramuscular administration indicates that at least 40 patients should be included to evaluate replacement therapy in primary immunodeficiency syndromes.

4. STATISTICAL ANALYSIS SETS

Prior to statistical analysis, subjects will be classified into the analysis sets defined below.

4.1 Screened Set

All subjects who have signed informed consent. This set includes screen successes and screen failures. No statistical analysis will be based on the Screened Set.

4.2 Enrolled Set

All subjects who provide informed consent (i.e., sign and date the ICF, if applicable), and meet enrollment eligibility (i.e., meets all inclusion criteria and do not meet any exclusion criteria) will be included in the Enrolled Set.

4.3 Full Analysis Set

In this study, the Full Analysis Set and the Enrolled Set are identical. Both are provided n this SAP for completeness and for consistency with other SAPs focused on HyQvia. The Full Analysis Set is applicable to efficacy analysis only.

4.4 Safety Analysis Set

The safety analysis set will contain all subjects in the Full Analysis Set (Enrolled Set) who receive at least one dose of HyQvia. Safety analysis and corresponding subject-level listings will be based on this set.

4.5 Treatment Groups and Cohorts

For purposes of data analysis and presentation of data in statistical outputs (TFLs), treatment groups and treatment cohorts are defined in the table below.

Epoch 1 (table below) comprises subjects who were treated with non-HyQvia treatment by time of enrollment and then treated with HyQvia.

Epoch 2 (table below) comprises subjects already treated with HyQvia by time of enrollment (HyQvia pretreated) and then treated with HyQvia.

Epoch 1 and Epoch 2 can be viewed as 2 parallel treatment groups, and therefore will be summarized accordingly.

Epoch 3 is Part 3 of the study. Only subjects whose anti-rHuPH20 antibody titer was ≥160 during *either* Epoch 1 or Epoch 2 and who experience either a study drug-related serious adverse event (SAE) or a related severe adverse event (AE) will be enrolled in Epoch 3 and followed for safety purposes for approximately 1 year.

Any Epoch 3 data available at time of study database lock for final analysis will be provided in subject-level data listings only.

	Treatment Group/Cohort Labels in Statistical Outputs
Epoch 1:	HyQvia New Starters
Epoch 2:	HyQvia Pre-treated
Overall (Total)	All HyQvia
Epoch 3 Treatment Cohort:	KIOVIG or Cuvitru

5. STATISTICAL ANALYSIS OVERVIEW

No statistical hypothesis testing will be performed.

Statistical analysis will be descriptive.

Continuous data (e.g., change from baseline) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation (SD), minimum value, maximum value; for trough level summaries, geometric mean will be provided also. Categorical data (e.g., occurrence of adverse events) will be summarized in terms of number and percent of subjects and number of occurrences in each category, as appropriate.

Baseline is defined as the last non-missing value before the initial dose of HyQvia. Change from baseline will be calculated as post-baseline minus baseline, percentage change from baseline, if any, will be calculated as 100 x (change / baseline).

Subject-level data will be provided in subject listings.

Table 1 provides an overview of study subject data that will be included in the final analysis, the statistical analysis that is planned to be performed, and the statistical output that is planned to be produced (similarly for the interim analysis). For example, an "X" indicates that the corresponding data will be analyzed as part of the final analysis.

Table 1 applies to Epoch 1 and/or Epoch 2 data. Any Epoch 3 data will be listed in the listings.

Table 1. Study Data for Final Analysis

Outcome Measure Category	Data Description	Data for Interim Analysis (X = Yes)	Data for Final Analysis (X = Yes)	Final Analysis Method	Statistical Output
Background	Disposition	X	X	DA	TL
	Demographics and Other Baseline Characteristics	X	X	DA	TL
	Medical History (also includes PIDD history)		X	DA	TL
	Prior Medications		X	DA	TL
	Concomitant Medications		X	DA	TL
	Exposure to IP (IP is defined in Section 1.4)		X	DA	TL
	Treatment Compliance		X	DA	TL
	Protocol Deviations		X	NA	L
Primary (Safety)	Number and rate per infusion of severe related AEs and related SAEs (primary safety endpoints), and proportion of subjects with **severe related**	X	X	DA and Wilson [b]	TL

	AEs and with **related** SAEs				
	Additional: Severe related AEs and related SAEs by age group and gender		X	DA and Wilson [b]	T
Secondary	Adverse /Events	X	X	DA	TL
	Laboratory Parameters		X	DA	TL
	Vital Signs		X	DA	TL
	Physical Examinations		X	NA	L
	Efficacy: IgG Trough Levels	X	X	DA [a]	TL
	Mode of Product Administration (incl. dosing)	X	X	DA	TL
	HRQoL		X	DA	TL
	Treatment Preference and Satisfaction Endpoints	X	X	DA	TL
Tertiary	Infections	X	X	DA and Wilson [b]	TL
	Healthcare Resource Utilization	X	X	DA	TL

Refer to the Interim Analysis SAP (dated 31 Jan 2020) for the planned IA methods and statistical outputs.
[a] An addition to endpoints listed in the Data for Interim Analysis section of the study protocol. Additional analysis may be performed and will be documented appropriately outside the scope of this SAP.
[b] Wilson = 95% CI for proportion using Wilson score method, in addition to descriptive analysis. Refer to the corresponding the "Analysis" section for additional information.
DA = Descriptive analysis is planned to be performed. No statistical hypothesis testing is planned, unless otherwise specified.
NA = Not applicable. No summary is planned.
TL = Table and listing are planned to be produced.
L = Only listing is planned to be produced.

6. STUDY SUBJECTS

6.1 Overview of Study Subjects Data

Subject disposition, and demographic and other baseline characteristics will be summarized. Summaries will be presented as described in Section 5.

Disposition summaries and listings will be based on all subjects, and demographics and other baseline characteristics summaries will be based on the Safety Set.

6.2 Disposition of Subjects

Disposition summaries (based on all subjects) will include, but are not limited to, number and percentage of subjects in the following category, where applicable.

- Screened (Screened Set)
- Screened failed
- Enrolled (Enrolled Set)

- Dosed (Safety Set)
- Completed study
- Discontinued study prematurely
- Primary reason for premature discontinuation
- By Epoch for the following, if applicable
    - Completed
    - Discontinued study prematurely
    - Primary reason for premature discontinuation

6.3 Demographic and Other Baseline Characteristics

Summaries of demographic and other baseline characteristics will include, but are not limited to: age (years), age group (2 to <6 years, 6 to <12 years, 12 to <18 years), gender, race, ethnicity, height (cm), weight (kg), and body mass index (BMI, kg/m^2).

6.4 Medical History and Prior Procedures

Table 1 contains an overview of the planned summaries of medical history and prior procedures (hereafter simply referred to as medical history).

Subject medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.1 or higher) and then summarized by system organ class (SOC) and preferred term (PT). Summaries will include, but are not limited to: number and percentage of subjects with the medical history. System organ class (SOC) will be sorted alphabetically, and preferred term (PT) will be sorted within each SOC in descending frequency in the table Total column (i.e., the Total column will be sorted in descending order after sorting by SOC and PT).

A table summarizing the diagnosis of PIDD will be provided.

6.5 Prior Medications, Non-Drug Therapies and Procedures

Table 1 contains an overview of the planned summary of prior medications, non-drug therapies and procedures, hereafter simply referred to as prior medications. Prior medications will also include pre-IgG treatment.

Prior medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Version March 2017 or newer and then summarized.

Summaries will include the number and percentage of subjects who reported using any prior medication within an therapeutic class of medications, and the number and percentage who reported using a specific prior medication based on the PT. Therapeutic class will be sorted alphabetically, and PT will be sorted within each therapeutic class in descending frequency in the table Total column (i.e., the Total column will be sorted in

descending order after sorting by therapeutic class and PT). Medications can be counted both as prior and concomitant medications if the medication meets the definition of prior medication as well as the definition of concomitant. Each subject will be counted only once per therapeutic class and once per PT within the therapeutic class; ie, multiple medication usage by a subject in the same category will be counted only once.

Definitions

For statistical analysis purposes, prior and concomitant medications are defined as follow ("time" implies date and time):

- **Prior medication:** Any medication with start time **prior to** time of Epoch 1 IP. Prior non-drug therapies and procedures are defined similarly.
- **Concomitant medication**: Any medication with start time **at or after** time of IP administration, OR medications with start time **prior to** IP administration but continuing at or after IP administration. Concomitant non-drug therapies and procedures are defined similarly.

Note that medications with start time prior to time of Epoch 1 IP administration and stop time after time of IP administration will be counted as both prior and concomitant medications.

For medications with partial onset times, non-missing date parts will be used to determine if the medication is concomitant or prior medication. If a determination cannot be made using the non-missing date parts as to when the medication occurred relative to the date of IP administration, then the medication will be classified as concomitant medication.

6.6 Concomitant Medications, Non-Drug Therapies, and Procedures

Table 1 includes an overview of the planned summary of concomitant medications, non-drug therapies and procedures (simply referred to as concomitant medications).

Concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Version March 2017 or never, and then summarized and listed in a similar manner as planned for prior medications.

6.7 Exposure to Investigational Product

Table 1 includes an overview of the planned summary of exposure to IP.

In addition, a summary table grouped by treatment groups will present the number of infusions and the total dose per kg body weight (g/kg) administered for individual subjects.

A summary table grouped by treatment group will present the mean, standard deviation, median, min and max value of the total dose per kg body weight per week overall

(g/kg/week) and by age group (subjects aged 2 to < 6 years, 6 to <12 years and 12 to <18 years, respectively). The planned duration of study period and study participation is indicated in Section 3.2.

For analysis purposes, exposure will be summarized in terms of each subject's total duration of treatment with IP (in days), calculated as: the minimum of (date of last dose of IP + the last assigned treatment interval (3 or 4 weeks) and date of study completion/termination) – date of initial dose of IP + 1, and then converted into months, for consistency with the study Schedule of Study Procedures and Assessments (Appendices).

For statistical summary purposes, 1 month = 30 days, 3 months = 91 days, 6 months = 183 days.Treatment duration will be summarized in 2 ways:

- As a continuous variable, in terms of mean and other descriptive statistics.
- As a categorical variable, in terms of number and percentage of subjects in each of the following duration categories (exposure groups):

  ≤6 weeks
  >6 weeks - <12 months
  12 - <24 months
  24 - <36 months
  ≥36 months

Note that the planned maximum duration of subject participation in Epoch 1 is 6 weeks and in Epoch 2 is 3 years (36 months).

6.8 Measurementsof Infusion Completion

Subjects are to receive infusion of IP (including home infusion) in accordance with the applicable Schedule of Study Procedures and Assessments (Appendices).

The measures of infusion completion will include:

- Number (%) of infusions completed, of the number of infusions started
- Number (%) of infusions completed without interruption or discontinuation.

Completion of an infusion in a time period means that the full planned dose of IP was administered within the planned time period; otherwise, the infusion was not completed.

Treatment infusion summaries will be based on the Safety Analysis Set. Subject data listings will be based on the Safety Set.

6.9 Protocol Deviations

Protocol deviations will be recorded by the study site, outside of the study clinical database. Protocol deviations will be classified as major or minor in accordance with applicable legacy Shire standard operating procedure(s).

Protocol deviations will be classified, and classification will be finalized and documented, per Shire applicable process (Shire is now part of Takeda).

Examples (not exhaustive) of protocol deviations include:

- Missing informed consent
- Did not meet eligibility (inclusion/exclusion) criteria
- Off-schedule infusion
- Missed infusion
- Infusion administration error
- Prohibited concomitant medication
- Prohibited non-drug therapy
- Missed procedure or assessment
- Off-schedule visit
- Missed visit

Protocol deviations data will be provided in a subject data listing only and based on the Safety Analysis Set. In addition, protocol deviations that relate to COVID-19 will be flagged in the listing.

No statistical summaries are planned.

7. EFFICACY ANALYSIS

7.1 Analysis of Primary Efficacy Endpoint

Not applicable. Safety, not efficacy, is the primary endpoint in this study.

7.2 Analysis of Secondary Efficacy Endpoint

7.2.1 Trough Levels of IgG

IgG trough levels (Epoch 1 and Epoch 2) will be determined at several time points, specified in the Clinical Laboratory Assessments (Appendices).

The secondary efficacy endpoints pertaining to trough levels of IgG (IgG total and IgG subclass trough levels and trough levels of specific antibodies) will be analyzed using descriptive statistics, including geometric mean, as indicated in Section 5. The above analysis will also be done by each age group, in years (2 to < 6, 6 to < 12, 12 to < 18). Figures of individual and mean (± SD) concentration-time profiles will be produced. Tabular and graphical summaries will be presented, *as appropriate*, by Epoch, visit and timepoint. No statistical hypothesis testing will be performed.

The analysis of IgG trough level will be done using the Full analysis set.

Additional analysis/analyses may be performed and, if performed, will be documented appropriately outside the scope of this SAP.

7.3 Multiplicity Adjustment

Not applicable.

7.4 Subgroup Analysis of Primary Endpoints

For exploratory purposes, age and gender subgroup analysis is planned.

The study primary endpoints (safety) will be summarized by age group to assess differences (if any) between age groups, and similarly by gender, as follows:

- By Age Group: Descriptive summary of number and rate per infusion (excluding infections) of all **severe related** AEs in Epoch 1 and in Epoch 2, by age group
- By Age Group: Descriptive summary of number and rate per infusion (excluding infections) of **related** SAEs in Epoch 1 and in Epoch 2, by age group
- By Gender: Descriptive summary of number and rate per infusion (excluding infections) of all **severe related** AEs in Epoch 1 and in Epoch 2, by gender
- By Gender: Descriptive summary of number and rate per infusion (excluding infections) of **related** SAEs in Epoch 1 and in Epoch 2, by gender

The summaries should be interpreted cautiously, given the study small total sample size.

7.4.1 Sensitivity Analysis of Primary Endpoint

Not applicable.

8. SAFETY ANALYSIS

8.1 Analysis of Primary Safety Endpoints

Assessment of safety, not efficacy, is the primary objective of this study.

Table 1 contains an overview of the planned analysis of the primary endpoints/outcome measures. The primary endpoints/outcome measures (number and rate per infusion [excluding infections] of all **severe related** AEs, and number and rate per infusion [excluding infections] of **related** SAEs), will be analyzed using descriptive statistics.

In addition, the following outcomes will be summarized for severe related AEs and related SAEs.

1. Number and proportions of subjects of severe related AEs, excluding infections.
2. Number and proportions of subjects of related SAEs, excluding infections.

In addition, the following analysis will be performed:

- Proportions: For each endpoint of incidence calculated as a proportion, a point estimate and corresponding 95% confidence interval (CI) will be provided. The 95% CI will be based on the Wilson score method, with continuity correction, using the SAS procedure PROC FREQ with the binomial option CL=WILSON(CORRECT) to obtain the Wilson confidence limits that include a continuity correction. The Wilson method is an improvement over the normal approximation to the binomial distribution in estimating CI around the proportion, meaning the actual coverage is closer to the nominal value of 95% for the 95% CI. Note that CIs are for descriptive purposes, as this study is not designed for hypothesis testing.

  In addition, incidences and corresponding CIs will be provided by time interval (intervals are aligned with the IP exposure time intervals provided in Section 6.7), to assess changes in incidences over time, as follows:

  ≤6 weeks
  >6 weeks - <12 months
  12 - <24 months
  24 - <36 months
  ≥36 months

  Note that the planned maximum duration of subject participation in Epoch 1 is 6 weeks and in Epoch 2 is 3 years (36 months).

- Rates: For each endpoint of incidence calculated as a rate, the rates will be displayed also by the time interval, in the manner planned for proportions, to assess changes in rates over time.

For exploratory analysis purposes, the primary outcome measure will also be summarized by clinically meaningful subgroups: sex and age groups as specified in *Section 7.4.1*. No statistical hypothesis testing will be performed.

8.2 Adverse Events

8.2.1 Definitions

TEAEs: AEs with onset after date-time of first dose of IP in Epoch 1, or medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP in Epoch 1.

In this study, date-time will be recorded, not only date.

All TEAEs that occurred before first dose of IP in Epoch 2 will be considered Epoch 1 TEAEs, and therefore assigned to Epoch 1. All TEAEs that occurred after first dose of IP in Epoch 2 will be considered Epoch 2 TEAEs, and therefore assigned to Epoch 2.

Non-TEAEs: AEs with onset before date-time of first dose of IP in Epoch 1, or medical conditions present prior to the start of IP but did not increase in severity or relationship after date-time of first dose of IP in Epoch 1.

Temporally-associated TEAEs: TEAEs which begin during infusion of IP or within 72 hours following the end of IP infusion.)

8.2.2 Handling of Recurrent AEs and Other AE Situations

Multiple Severities and Relationships: Subject with multiple severities of the same AE, the maximum severity (most serious severity) will be used in analysis, and similarly with multiple relationships of the same AE, the worst relationship will be used. If a subject experiences multiple severities of the same AEs (eg, 3 occurrences: 1 mild, 1 moderate, 1 severe) all categorized under the same causality assessment (eg, all related to IP), the AE with the maximum severity (AE that is severe) will be used in analysis.

Related AEs: An AE that is recorded as “possibly related” or “probably related” to IP will be considered “related AE”, or called Adverse reaction (AR), and AE recorded as “unlikely related” or “not related” will be considered “unrelated” AE.

Recurrent AEs: If more than 1 AE occurs within the same PT for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to IP. For example, if a subject experienced a mild headache not related to the IP, and a moderate headache related to IP, then the subject will be counted once for headache using the moderate headache related to IP.

Section 11 provides additional information on data handling conventions.

8.2.3 Analysis of AEs

Section 2.3 outlines the adverse events endpoints/outcome measures for analysis.

All AEs will be coded using the MedDRA, version 23.1 or higher and then reported by MedDRA SOC and PT, and overall. Codes for uncoded terms for AEs, if any, will be assigned by the study Global Safety Lead, and the codes will be applied via statistical programming.

Only TEAEs will be analyzed. Non-TEAEs will be listed only.

The following approaches will be used, where applicable:

- Overall summary: Overall summary will include, but not limited to: Any TEAE, any AR, any severe related TEAE, any serious TEAE, any serious related TEAE , any local TEAE, any local AR, any systemic TEAE, any systemic AR, any temporally-accosiated TEAE, any related and/or temporally-associated TEAE, any local related and/or temporally-associated TEAE, any systemic related and/or temporally-associated TEAE.
- Summaries by SOC and PT: In the summaries, SOC will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency in the Total column (i.e., the Total column will be sorted in descending order after the sorting by SOC and PT).
- Summaries by PT only: In the summaries, PT will be sorted in decreasing frequency in the table Total column.
- In AE incidence summaries, subjects with multiple events in the same category will be counted only once in the AE category. Subjects with events in more than one category will be counted once in each of the categories.
- In AE count summaries, multiple occurrences of the same AE will be counted multiple times.

Analysis of AEs per Infusion, per Subject, per Subject-Year:

- AEs per subject-year summary adjusts for differences in subjects' durations in the study and differential dropout rates between treatment groups.
- For number-of-AE summaries, multiple occurrences of the same AE in the same subject will be counted multiple times.
- Number of AEs and AEs per subject-year will be provided for all AEs (if analyzable), by primary SOC and PT for each treatment group and overall,

The following calculations will be applied as necessary:

- AEs per infusion = number of AEs / number of infusions administered (started) to subjects in the analysis set.
- AE per subject = number of AEs / number of subjects in the analysis set.
- AEs per subject-year = number of AEs / number of years of exposure, i.e., the sum of duration of treatment for all subjects in the analysis set, expressed in years.

Note for the AE analysis:

- For each outcome measures of incidence summarized by number and proportion of subjects, the number of such incidence will also be provided.
- For each outcome measures of incidence summarized as a rate per infusion, the rate per subject and rate per subject-year will also be provided.

In additional to the analysis on the primary safety endpoints specified in Section 8.1, the following AE endpoints/outcomes will be summarized:

1. Overall summary. Excluding infections.
2. Overall summary. Including infections.
3. Overall summary, Epoch 1. Excluding infections.
4. Overall summary, Epoch 1. Including infections.
5. Overall summary, Epoch 2. Excluding infections.
6. Overall summary, Epoch 2. Including infections.
7. AE leading to discontinuation.
8. AE summary by preferred terms, localization, relationship, and severity. Excluding infections.
    - All subjects, Epoch 1 and 2
    - For HyQvia New Starters
    - For HyQvia Pre-treated
    - Epoch 1: for HyQvia New Starters
    - Epoch 2: All
    - Epoch 2: for HyQvia New Starters
9. TEAE, overall summary by maximum severity, by SOC and PT. Including infections.

The following endpoints/outcomes will be presented for both types of summaries: by number and proportion of subjects and by rate per infusions.

10. TEAE, by SOC and PT. Excluding infections.
11. AR, by SOC and PT. Excluding infections.

12. Mild AR, by SOC and PT. Excluding infections.
13. Moderate AR, by SOC and PT. Excluding infections.
14. Severe related TEAE, by SOC and PT. Excluding infections.
15. Serious TEAE, by SOC and PT. Excluding infections.
16. Serious TEAE, by SOC and PT. Including infections.
17. Serious related TEAE, by SOC and PT. Excluding infections.
18. Serious related TEAE, by SOC and PT. Including infections.
19. Local TEAE, by SOC and PT. Excluding infections.
20. Local AR, by SOC and PT. Excluding infections.
21. Systemic TEAE, by SOC and PT. Excluding infections.
22. Systemic AR, by SOC and PT. Excluding infections.
23. Temporally-Associated TEAE, by SOC and PT. Excluding infections.
24. Related and/or Temporally-Associated TEAE, by SOC and PT. Excluding infections.
25. Local Related and/or Temporally-Associated TEAE, by SOC and PT. Excluding infections.
26. Systemic Related and/or Temporally-Associated TEAE, by SOC and PT. Excluding infections.
27. Treatment emergent infections, by PTs.

8.2.4 Signal Detection

No analysis/summary is planned purposely for signal detection in AEs. The safety of subjects in this study is monitored by an independent ISMC, who, as part of their review of safety TFLs (unblinded), may detect potential safety signals.

8.2.5 Clinical Laboratory Data

Clinical laboratory schedules of assessment are provided in the Appendices. Raw (actual) values, changes from baseline at each scheduled time point, and shifts from baseline (categorical change from baseline) at each scheduled time point in clinical laboratory parameters will be summarized via descriptive statistics defined in Section 5.

8.2.6 Vital Signs

Vital signs schedules of assessment are provided in the Appendices. Raw (actual) values and changes from baseline at each scheduled time point in vital signs parameters will be analyzed using descriptive statistics defined in Section 5.

8.2.7 Physical Examinations

Physical examination (PE) data will be provided in a subject data listing only. No PE summaries are planned.

9. OTHER ANALYSIS

The other analysis, which is neither efficacy nor safety, encompasses analysis of the other secondary endpoint data: infections, mode of product administration, and HRQoL.

9.1 Analysis of Infections

Section 2.3.3 outlines the infection endpoints/outcome measures that will be analyzed using descriptive statistics, as indicated in Section 5.

In addition, the following analysis will be performed:

- Proportions: For each endpoint of incidence calculated as a proportion, a point estimate and corresponding 95% confidence interval (CI) will be provided, using the Wilson score method described for AE incidence in Section 8.1. CIs will be provided for descriptive purposes only. No incidence-based analysis will be performed by time interval.
- Rates: For each endpoint of incidence **calculated as a rate**, the rates will be displayed overall. No rate-based summary will be performed by time interval.

9.2 Analysis of Mode of Product Administration

Section 2.3.2.3 outlines the mode of product administration endpoints/outcome measures that will be analyzed descriptively as indicated in Section 5.

9.3 Analysis of Health-related Quality of Life

Section 2.3.2.4 outlines the HRQoL endpoints/outcome measures. Total and domain scores on each of the HRQoL measures will be calculated for each subject, at each data assessment time point. Assessment time points are indicated in the Schedule of Study Procedures and Assessments (Appendices). Raw (actual) and change from in baseline in the endpoints will be analyzed descriptively as indicated in Section 5.

9.3.1 Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (Peds-QL) is a is a validated questionnaire designed to measure generic HRQoL among a pediatric population. Both patient and proxy versions of the questionnaire are available. This questionnaire measures four domains, including; Physical functioning, Emotional functioning, Social functioning and school functioning. A total score and domain scores can be calculated. **Higher scores** indicate better health status.

Quality of life (QoL) will be assessed separately for the age groups two to four years, and five to seven years, eight to 12 years (PEDS-QL, observer: parent), and 13 to <18 years

(PEDS-QL, observer: subject). The same observer should be employed for the duration of subject participation.

Age will be defined as the age at screening, in order to determine which age-specific assessment is to be used. The same age-specific assessment is to be used for the duration of the study. In the event that the language or age group is not available, the assessment in the closest age group will be used. In the event that the appropriate language is not available, the questionnaire will not be administered for that subject.

9.3.2 EuroQol Five Dimensions Questionnaire (EQ-5D)

The EuroQol five dimensions questionnaire (EQ-5D) is a validated, self-administered assessment of overall health. It is a descriptive system of HRQoL states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Subjects are asked to describe their health state that day by choosing 1 of 3 responses that reflect the levels of severity for each of the 5 dimensions: no problems, some or moderate problems, or extreme problems. The EQ-5D also includes a standard vertical 20-cm visual analogue scale (similar to a thermometer) for recording a subject's rating of their current HRQoL state.

The EQ-5D will be administered at the study site using a validated translated version, as applicable. It is recommended that the subject complete the assessment using the same translated version throughout the course of the study. For subjects aged 13 to <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). In the event that the appropriate language is not available, the questionnaire will not be administered for that subject.

9.4 Analysis of Treatment Preference and Satisfaction

Total scores and domain scores will be calculated, if applicable, for each subject at each data collection time point, and analyzed using descriptive statistics defined in Section 5. In addition to the descriptive statistics at each time point, change from baseline in each domain will be provided. Note that in the case that the Month 36 visit is not applicable for most patients, the End of Epoch 2 visit will be presented.

9.4.1 Treatment Satisfaction Questionnaire for Medication

The Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) is a 9-item, validated, self-administered instrument to assess subjects' satisfaction with

medication. The 3 domains assessed are effectiveness, convenience, and global satisfaction.

The TSQM-9 will be administered at the study site using a validated translated version, as applicable. It is recommended that the subject complete the assessment using the same translated version throughout the course of the study. For subjects aged 13 to <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). The same observer should be employed for the duration of subject participation.

9.4.2 Treatment Preference Questionnaire

The treatment preference questionnaire, internally developed at Baxalta*, is a self-administered, non-validated scale assessing patient preference for various attributes of IgG therapy, such as ease of administration, frequency and duration of administration, and convenience. *Baxalta is now part of Shire, and Shire is now part of Takeda.

The treatment preference questionnaire will be administered at the study site using a translated version, as applicable. It is recommended that the subject complete the assessment using the same translated version throughout the course of the study. For subjects aged 13 to <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). The same observer should be employed for the duration of subject participation.

9.5 Analysis of Healthcare Resource Utilization

Section 2.3.3 lists the HRU endpoints/outcome measures.

All outcomes will be analyzed using summary statistics, along with corresponding 95% CI for the mean. In additional, all outcomes will be presented by the uses per subject and the uses per subject-year.

10. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

10.1 Study Stopping Rules

There are no specific stopping rules established for this study as the pediatric subjects will be treated with a licensed human normal immunoglobulin, according to the routine standard at the study site for the duration of the study. There are no statistical stopping criteria (go/no-go decision criteria) for this study. However, the study may be terminated by the sponsor at any time. Additionally, an independent ISMC, established to monitor

the study for any safety or medical concerns, may recommend stopping the study (details are provided in the ISMC Charter).

10.2 Data Monitoring Committee

Not applicable. Instead of a DMC, an independent ISMC was established to monitor the study for any safety or medical concerns (additional information is provided in the ISMC Charter).

10.3 Interim Analysis

10.3.1 Overview of Interim Analysis

Additional information is provided in the interim analysis SAP.

A single IA was planned. The *purpose of the IA* is to update the scientific community, via publications and presentations, on the interim safety, tolerability and immunogenicity of HyQvia in pediatric subjects with PIDD.

All of the following applied to the IA, or applied as a result of the IA:

- Analysis included, but not limited to: safety/tolerability, infusion data, infections, and Healthcare Resource Utilization data.
- Analysis was planned to be performed when 75% of all subjects enrolled have completed 12 months of participation (1-year observation period) in Epoch 2.
- Definition of completed 12 months of participation: Any subject who completes 12 months in Epoch 2, or discontinues prematurely from Epoch 2, irrespective of reason for withdrawal, is considered as having completed 12 months of participation in Epoch 2.
- No statistical hypothesis testing was performed.
- No early stopping of study (the interim analysis is not planned with the intention of deciding whether or not to terminate the study).
- No modifications to the study design, study conduct, or final analysis was made during or after the interim analysis.
- No interim clinical study report was planned.

11. DATA HANDLING CONVENTIONS

In the event of any inconsistency between the data handling conventions specified in this section and the conventions specified separately in the final analysis TFL shells document, this SAP will not be amended as a result of the inconsistency. Inconsistencies, if any, will be documented appropriately in the Clinical Study Report for this study.

11.1 General Data Reporting Conventions

Study datasets, analyses, and TFLs will be produced using SAS version 9.4 or higher. Datasets will be constructed using the IQVIA (CRO) implementation of CDISC standards, based on the SDTM IG v3.2 and the ADaM IG v1.1.

TFLs will follow Shire standards, where applicable. IQVIA SOPs and work instructions will apply to all statistical programming, unless otherwise specified in this SAP or the corresponding TFL shells document. Listings will be sorted by country, study site, and subject identification number, unless otherwise specified. Both derived and non-derived data, if available, will be displayed in listings.

11.1.1 Continuous Data Reporting

Summaries of continuous variables (eg, change from baseline) will display the following descriptive statistics: number of subjects (n), mean, median, SD, minimum, maximum. Standard error of mean (SEM) will be displayed in all summaries that display statistical analysis results from between-group comparisons, as well as the corresponding 95% CIs, where applicable. Unless specified otherwise, summary statistics will be presented to 1 more significant digit than the raw (actual) data. The minimum and maximum values will be presented to the same number of decimal places as the raw data; the mean and median will be presented to 1 more decimal place than the raw data; and the SD and SEM will be presented to 2 more decimal places than the raw data. BMI, averaged laboratory results (eg, diastolic/systolic blood pressure) and pulse (when taken in triplicate), and derived scores will be rounded to 1 decimal place for reporting.

11.1.2 Categorical Data Reporting

Summaries of categorical and count variables (eg, adverse events) will display the following: number of subjects (n), percentage (%) of subjects in the category, and number of outcomes/events/occurrences. Each summary containing a percentage will include a footnote stating the denominator that was used in calculating the percentage, unless the percentage is self-explanatory. Percentages and confidence intervals will be presented to 1 more significant digit than the raw (actual) data. No percentages will be displayed if the number of subjects is 0.

11.1.3 P-Value and Confidence Interval Reporting

No p-values will be provided, considering that this study was not designed for statistical hypothesis testing. CIs, if any are provided, are for descriptive purposes, and therefore caution should be exhibited in their interpretation.

11.2 Definition of Baseline

For statistical analysis purposes and in general, Baseline is defined as the last non-missing value before the initial dose of IP. Determination of "last" is based on date or date-time. Change from baseline will be calculated as post-baseline minus baseline, and percent change from baseline as 100 x (change/baseline).

This definition applies to all safety, efficacy and patient-reported outcomes analyses in each of the 5 analysis categories, unless otherwise specified.

11.3 Definition of Visit Windows

Not applicable. There are no general or endpoint-specific visit widows in this study. Visit windows for analysis visits does not differ from study visit schedule. For example, the dual primary endpoints/outcome measures (defined in the Primary Endpoints section) is not specific to a time point (study visit).

11.4 Derived Efficacy Endpoints

Not applicable.

11.5 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated before initial dose of IP, then the most recent assessment value will be used as baseline in analysis/summaries involving baseline.

If a subject has repeated assessments after initial dose of IP (repeated post-baseline assessments), then the most recent assessment value will be used in analysis/summaries involving post-baseline.

Unscheduled assessments (i.e., assessments not done at a planned visit) will used only in summaries of abnormalities or toxicities (not otherwise).

All assessments, including repeated and unscheduled assessments, will be presented in the subject data listings.

11.6 Handling of Missing, Unused, and Spurious Data

This section provides a general plan for handling of missing data, unused and spurious data. Specifics regarding handling are addressed in the specific endpoint analysis section.

Data that appear to be spurious (e.g., outliers, incompatible with life) will be queried by Clinical Data Management and then either corrected, or explained in the CSR if not correctable. Outliers will not be excluded from analysis unless otherwise specified. Any exclusion of data from analysis will be appropriately footnoted in the relevant TFLs.

11.6.1 Missing Date of Investigational Product

If the date of the last dose of IP is missing for a subject in the Safety Set, then all efforts will be made by the study sponsor, or on behalf of the sponsor, to obtain the date from the study investigator. If the date cannot be obtained despite all efforts, then the last visit date when IP was dispensed will be used in the calculation of treatment duration.

That is, if last dose date is missing, then last visit date will be used.

11.6.2 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications (and/or therapies/procedures), incomplete (fully or partially missing) start date and/or stop date of mediation will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first using the imputation approach described in the subsequent sections.

11.6.2.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

11.6.2.1.1 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of IP, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of IP, then 01 January will be assigned to the missing fields.

11.6.2.1.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

11.6.2.1.3 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of IP, then the day of the date of the first dose of IP will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of IP, or if both years are the same but the month is before the month of the date of the first dose of IP, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of IP, or if both years

are the same but the month is after the month of the date of the first dose of IP, then the first day of the month will be assigned to the missing day.

11.6.2.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of IP is missing, then replace it with the last visit date. If the imputed stop date is before the (imputed or non-imputed) start date, then the imputed stop date will be equal to the start date.

If imputation of an incomplete stop date is required for calculating duration, and both the start date and the stop date are incomplete for a subject, then the start date will be imputed first.

A completely missing stop date will be interpreted as ongoing.

11.6.2.2.1 Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of IP, then the day and month of the date of the last dose of IP will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of IP, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of IP, then 01 January will be assigned to the missing fields.

11.6.2.2.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

11.6.2.2.3 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of IP, then the day of the date of the last dose of IP will be assigned to the missing day.
- If the year is before the year of the date of the last dose of IP, or if both years are the same but the month is before the month of the date of the last dose of IP, then the last day of the month will be assigned to the missing day.
- If the year is after the year of the last dose of IP, or if both years are the same but the month is after the month of the date of the last dose of IP, then the first day of the month will be assigned to the missing day.

11.6.3 Missing Date Information for Adverse Events

The following approaches will be applied:

- To facilitate categorization of AEs as treatment emergent, imputation of dates can

be used.

- If an AE start date is completely missing, then the AE will be considered treatment-emergent in Epoch 1.
- For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to IP (eg, AE start year and month are the same as the year and month of the first dose of IP), then the AE will be classified as treatment-emergent.
- For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol.
- If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

11.6.3.1 Incomplete Start Date

Rules in Section 11.6.2.1 apply.

11.6.3.2 Incomplete Stop Date

Rules in Section 11.6.2.2 apply.

11.6.4 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of IP, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of IP, then a severity of "Severe" will be assigned.

If a subject experiences more than one AE categorized under the same preferred term, where one of them is categorized as "severe" and one of them is categorized as "unknown", then the severity of this AE will be counted as "severe".

If a subject experiences more than one AE categorized under the same preferred term, where one of them is categorized as "mild" or "moderate" and one of them is categorized as "unknown", then the severity of this AE will be counted as "unknown".

The imputed values for severity assessment will be used for summaries, while both the actual and the imputed values will be used in subject data listings.

11.6.5 Missing Seriousness of Adverse Events

AEs of unknown seriousness will be tabulated as SAEs in summaries; however, every effort will be made to avoid study data lock with AEs for which a determination of seriousness is missing.

11.6.6 Missing Relationship to Investigational Product for Adverse Events

If the relationship to IP is missing for an AE starting on or after the date of the first dose of IP, then a causality of "related" will be assigned. The imputed values for relationship to IP will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

11.6.7 Character Values of Clinical Laboratory Variables

Laboratory measurements will be presented in SI units, unless otherwise specified for an analysis. If a laboratory result is expected to have a numeric value, but the data which are received include a special character such as ">" or "<", then the result will be assumed to lie outside the range of quantitation.

Tables based on a dichotomous or categorical grouping, including but not limited to shift tables, will place such data appropriately prior to removal of the special character, so that particularly low or high values remain recognized as such. For quantitative summaries by time-point or visit, the numeric part of such a result will be used, unless the table is designed to include explicit tabulation of results that are outside the range of quantitation.

12. ANALYSIS SOFTWARE

All statistical analyses will be performed using SAS®, Version 9.4 or higher.

13. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

1. Given the primary objective of the study is to acquire additional data on safety of HyQvia treatment in pediatric subjects with PIDD who have received prior immunoglobulin therapy before enrollment into the study, the per-protocol set (PPS) is not used in this study. Therefore, the PPS definition is not provided in the SAP. The analysis based on the PPS is not provided in this TFL.

2. Clarification on the protocol endpoint "Number of infusion sites (needle sticks) per infusion/month" is made in the final SAP. This endpoint is equivalent to "Number of infusion sites (needle sticks) per infusion" and "Number of infusion sites (needle sticks) per month".

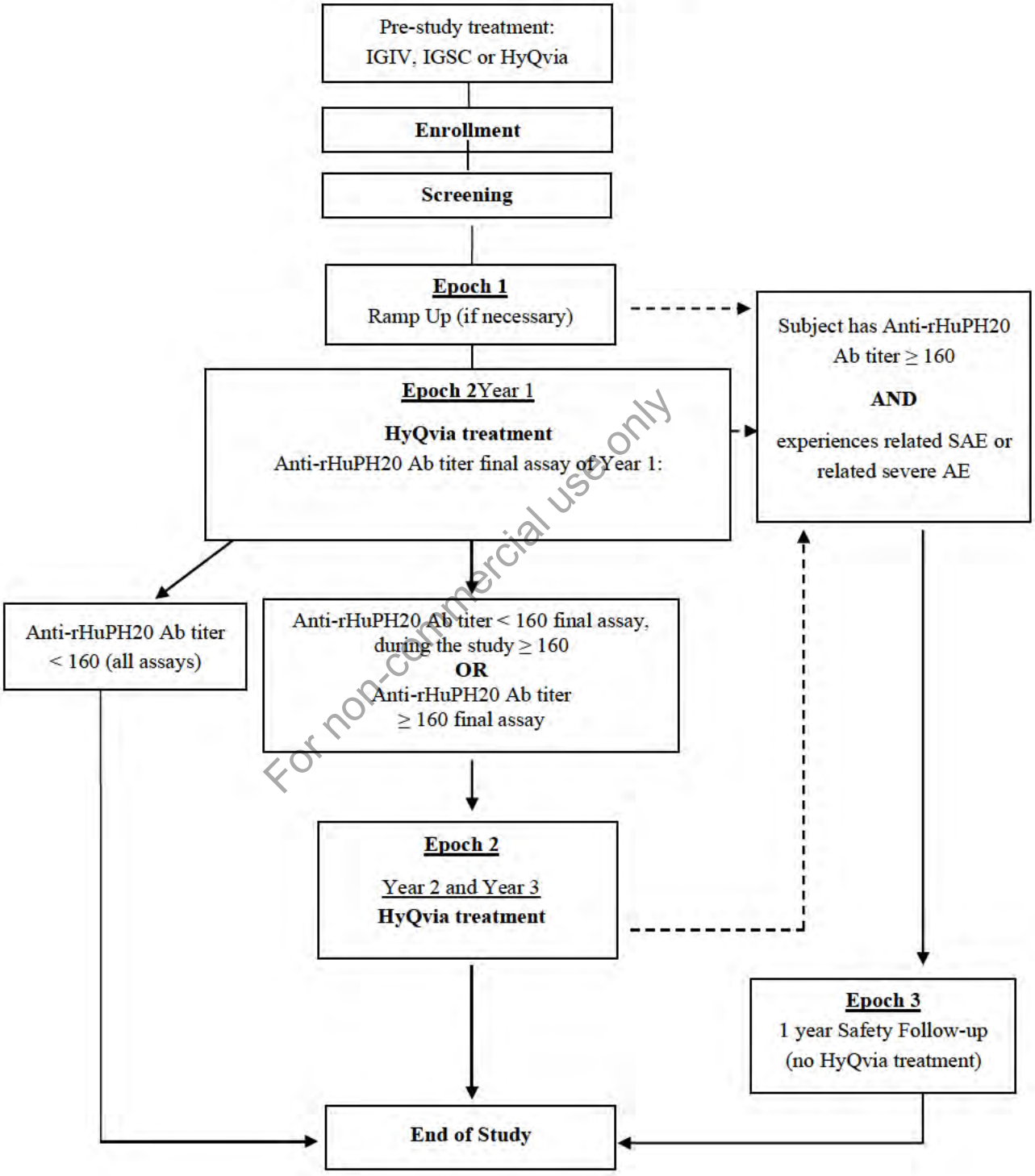
Additional endpoints and outcome measures for analysis were added for a more complete and robust analysis and for alignment with Study 161503, where applicable.

14. APPENDICES

14.1 Study Flow Chart

The Study Flow Chart was copied from the study protocol. In case of a discrepancy between this section and the protocol, the flow chart in the protocol will be used instead.

Figure 1
Study Design for Clinical Study 161504



14.2 Schedule of Study Procedures and Assessments

The Schedule of Study Procedures and Assessments was copied from the study protocol. In case of a discrepancy between this section and the protocol, the version in the protocol will be used instead.

Table 2. STUDY EPOCH 1 – Ramp Up
Schedule of Study Procedures and Assessments

Procedures/Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Enrollment / Screening		Treatment Visit in Study Epoch 1 (Visit +/- 1 Day)	
		First Infusion: Baseline	2nd Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for 3-Week Treatment Intervals)	3rd Infusion: Week 3 (Only for Subjects Planning to Ramp Up to 4-Week Treatment Intervals)
Location	Site	Site	Site	Site
Informed Consent[a]	x			
Eligibility Criteria	x			
Infusion		x	x	x
Medical History	x			
Concomitant Medications	x	x	x	x
Non-drug Therapies	x	x	x	x
Physical Exam	x	x	x	x
Adverse Events		x	x	x
Laboratories[b]	x	x		
Vital Signs	x	x	x	x
HRQoL (PedsQL, EQ-5D)/, TSQM-9 Assessment		x		

[a] Occurs prior to any study-specific procedure.
[b] For laboratory assessments, see Section 20.3 of the study protocol.

Table 3. STUDY EPOCH 2 – Year 1
Schedule of Study Procedures and Assessments

Procedures/ Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise		Visit in Study Epoch 2 (Visit +/- 2 weeks)				
	Month 0	Month 3	Month 6	Month 9	Month 12[a]	Study Completion/ Termination Visit (at Next Infusion), if Applicable
Location	Site	Site	Site	Site	Site	Site
Informed Consent						
Infusion[e]	x	x	x	x	x	
Concomitant Medications	x	x	x	x	x	x
Non-drug Therapies	x	x	x	x	x	x
Physical Exam	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x
Laboratories[d]	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x
HRQoL (PedsQL, EQ-5D), Treatment Preference Questionnaire, TSQM-9	(x) [b]				x	(x) [c]

[a] Further (additional) infusions may be administered after the 12 months visit until anti-rHuPH20-antibody results become available to determine the subject´s continuation in the study. AEs, concomitant medications, and non-drug therapies will continue to be recorded until EOS or continuation of Epoch 2 dependent on antibody assay result.

[b] Only subjects who did not perform Epoch 1 will take these assessments in Epoch 2 at Month 0.

[c] All subjects will complete assessments at the month 12 visit. Only subjects who prematurely exit the study will complete the questionnaires at the study termination visit.

[d] For laboratory assessments, see Section 20.3 of the study protocol.

[e] Infusions (including home infusions) administered between scheduled site visits/site infusions may deviate up to +/- 3 days from original schedule

Table 4. STUDY EPOCH 2 – Year 2 and Year 3
Schedule of Study Procedures and Assessments

Procedures/ Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Visit in Study Epoch 2 (Visit +/- 2 Weeks)							
	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	Month 36/ Study Completion/ Termination Visit, if Applicable[a]
Location	Site	Site	Site	Site	Site	Site	Site	Site
Infusion[c]	x	x	x	x	x	x	x	
Concomitant Medications	x	x	x	x	x	x	x	x
Non-drug Therapies	x	x	x	x	x	x	x	x
Physical Exam	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x
Laboratories[b]	x	x	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x	x	x
HRQoL (PedsQL, EQ-5D), Treatment Preference Questionnaire, TSQM-9				x				x

[a] In case a subject moves to Study Epoch 3, he/she will have the Study Completion/Termination Visit at the end of Epoch 3.
[b] For laboratory assessments, see Section 20.3 of the study protocol.
[c] Infusions (including home infusions) administered between scheduled site visits/site infusions may deviate up to +/- 3 days from original schedule.

Table 5. STUDY EPOCH 3
Schedule of Study Procedures and Assessments

Procedures/Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Visit in Study Epoch 3(Visit +/- 2 Weeks)				
	Month 0	Month 3	Month 6	Months 9	Month 12/ Study Completion/ Termination Visit[a]
Location	Site	Site	Site	Site	Site
Infusion[d]	x	x	x	x	
Concomitant Medications	x	x	x	x	x
Non-drug Therapies	x	x	x	x	x
Physical Exam[b]	x	x	x	x	x
Adverse Events	x	x	x	x	x
Laboratories[c]	x	x	x	x	x
Vital Signs	x	x	x	x	x
HRQoL (PedsQL, EQ-5D), Treatment Preference questionnaire, TSQM-9 Assessment	x				x

[a] Includes for cases of withdrawal or discontinuation.
[b] Occurs prior to any study-specific procedure.
[c] For laboratory assessments, see Section 20.3 of the study protocol.
[d] Infusions (including home infusions) administered between scheduled site visits/site infusions may deviate up to +/- 3 days from original schedule.

Table 6. STUDY EPOCH 1 – Ramp Up
Clinical Laboratory Assessments

Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Enrollment / Screening		Treatment Visit in Study Epoch 1 (Visit +/- 1 Day)	
		First Infusion: Baseline	Second Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for 3-Week Treatment Intervals)	Third Infusion: Week 3 (Only for Subjects Planning to Ramp Up to 4-Week Treatment Intervals)
Location	Site	Site	Site	Site
Hematology	x			
Clinical Chemistry	x			
Urinalysis	x			
Pregnancy Test in females of childbearing potential – Urine	x			
Viral Pathogen Serology	x			
Hemolysis Test				
Specific Antibody Tests		x		
IgG Trough Levels and IgG Subclasses	x			
Antibodies to rHuPH20		x		

Table 7. STUDY EPOCH 2 – Year 1
Clinical Laboratory Assessments

Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise		Visit in Study Epoch 2 (Visit +/- 2 Weeks)				
	Month 0[c]	Month 3	Month 6	Month 9	Month 12	Study Completion/ Termination Visit (at Next Infusion), if Applicable
Location	Site	Site	Site	Site	Site	Site
Hematology	x		x		x	
Clinical Chemistry	x		x		x	
Urinalysis	x		x		x	
Pregnancy Test in females of childbearing potential– Urine						x
Viral Pathogen Serology						x
Hemolysis Test	x[a]					
Specific Antibody Tests	(x)[b]					**x**
IgG Trough Levels and IgG Subclasses	X		x		x	
Antibodies to rHuPH20	X	x	x	x	x	

[a] If there is a reduction in Hgb of two g/dL or more compared to baseline Hgb, every effort is to be made to perform a repeat test consisting of the hemolysis tests described in the study protocol section 12.7.4 within 72 hours in addition to the prescribed tests.
[b] Only for subjects who did not perform Epoch 1.
[c] Month 0 will be considered to be the "Baseline" visit for subjects who do not participate in Epoch 1.

Table 8. STUDY EPOCH 2 – Year 2 and Year 3
Clinical Laboratory Assessments

Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Visit in Study Epoch 2(Visit +/- 2 Weeks)							
	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	Month 36/ Study Completion/ Termination Visit, if Applicable[a]
Location	Site	Site	Site	Site	Site	Site	Site	Site
Hematology		x		x		x		x
Clinical Chemistry		x		x		x		x
Urinalysis		x		x		x		x
Pregnancy Test in females of childbearing potential – Urine								x
Viral Pathogen Serology								x
Hemolysis Tests[b]				x				
Specific Antibody Tests								x
IgG Trough Levels and IgG Subclasses		x		x		x		x
Antibodies to rHuPH20	x	x	x	x	x	x	x	x

[a] In case a subject moves to Study Epoch 3, he/she will have the Study Completion/Termination Visit at the end of Epoch 3.
[b] If there is a reduction in Hgb of two g/dL or more compared to baseline Hgb, every effort is to be made to perform a repeat test consisting of the hemolysis tests described in the study protocol section 12.7.4 within 72 hours

Table 9. STUDY EPOCH 3
Clinical Laboratory Assessments

Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Visit in Study Epoch 3 (Visit +/- 2 Weeks)				
	Month 0	Month 3	Month 6	Months 9	Month 12/ Study Completion/ Termination Visit
Location	Site	Site	Site	Site	Site
Hematology	x		x		x
Clinical Chemistry	x		x		x
Urinalysis	x		x		x
Pregnancy Test in females of childbearing potential – Urine					x
Viral Pathogen Serology					x
Hemolysis Test			x		
Specific Antibody Tests					x
IgG Trough Levels and IgG Subclasses	x		x		x
Antibodies to rHuPH20	x	x	x	x	x

14.3 Toxicity Grading Scale for Laboratory Values

Table 10. Grading of Laboratory Parameters

Analyte	Direction	WNL is Grade 0	No Grade 1	Units	Grade 0[a]		Grade 1[a]		Grade 2[a]		Grade 3[a]		Grade 4[a]		Source
					Low	High	Low	High	Low	High	Low	High	Low	High	
ALP	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
ALT	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
AST	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
LDH	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	N/A
BUN	Increase	NO	NO	ULN	0.0	1.4	1.5	2.5	2.6	5.0	5.1	10	10.1	.	ECOG
Hemoglobin	Decrease	YES	NO	g/dL	.	.	10.0	Normal	8.0	9.9	6.5	7.9	0.0	6.4	ECOG
Lymphocytes	Decrease	NO	NO	x10^3/uL	2.0	.	1.5	1.9	1.0	1.4	0.5	0.9	0.0	0.4	ECOG
Neutrophils	Decrease	NO	NO	x10^3/uL	2.0	.	1.5	1.9	1.0	1.4	0.5	0.9	0.0	0.4	ECOG
Platelet Count	Decrease	YES	NO	x10^3/uL	.	.	75.0	Normal	50.0	74.9	25	49.9	0.0	24.9	ECOG
Potassium	Decrease	NO	NO	mmol/L	3.5	.	3.0	3.4	2.5	2.9	2.0	2.4	0.0	1.9	WHO
Potassium	Increase	NO	NO	mmol/L	0.0	5.5	5.6	6.0	6.1	6.5	6.6	7.0	7.1	.	WHO
Serum Creatinine	Increase	YES	NO	ULN	.	.	.	1.4	1.5	3.0	3.1	6.0	6.1	.	ECOG
Sodium	Decrease	NO	NO	mmol/L	136	.	130	135	123	129	116	122	0.0	115	WHO
Sodium	Increase	NO	NO	mmol/L	0.0	145	146	150	151	157	158	165	166	.	WHO
Serum Total Bilirubin	Increase	YES	YES	ULN	.	.	.	.	.	1.4	1.5	3.0	3.1	.	ECOG
WBC	Decrease	NO	NO	x10^3/uL	4.0	.	3.0	3.9	2.0	2.9	1.0	1.9	0.0	0.9	ECOG

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; N/A=not applicable; ULN=upper limit of normal; WBC=white blood cell; WHO=World Health Organization; WNL=within normal limits.

[a] Grade refers to severity: 1=mild, 2=moderate, 3=severe, 4=life-threatening or disabling, 5 (not shown in the table)=death. Grading scale criteria taken from ECOG (Oken et al., 1982) and WHO (World Health Organization, 2003) guidelines, with the exception of LDH that uses the same thresholds as defined for ALT and AST

15. REFERENCES

None