Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

HYQVIA
PHASE 3

Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases

PROTOCOL IDENTIFIER: 161503

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

Version	Issue Date	Summary of Changes
1.0 Draft	08 Mar 2020	N/A (New document)
2.0 Draft (Stable Draft)	13 Mar2020	Editorial adjustments. Also, incorporated additional endpoints/outcome measures for a more complete and robust analysis
2.1 Draft	05 Oct 2020	Updated the author of the SAP. Updated and clarified the scope of analysis in adverse events, mode of administration, treatment compliance, PK analysis, HRU. Clarification made on the analysis sets. Editorial adjustments to match the protocol order.
1.0 Final	04 Nov 2020	

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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
FDA	Food and Drug Administration
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
LQI	Life Quality Index
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

Abbreviations	Descriptions
WHO	World Health Organization

1. INTRODUCTION

1.1 Study 161503

Study 161503 (SHP671-PIDD-161503) is a Phase 3, open-label, non-randomized, non-controlled, multicenter, efficacy, safety, tolerability, immunogenicity, and pharmacokinetic 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.

HYQVIA was approved in Europe in 2013 for treatment of PIDD in adults (ages ≥18 years) and approved in the U.S. in 2014 for PIDD in adults (ages ≥16 years).

The purpose of U.S. Study 161503 is to acquire additional data on efficacy, safety, tolerability, immunogenicity, pharmacokinetics and other parameters of HYQVIA in pediatric (age ≥ 2 to < 16 years) subjects with PIDD.

Hereafter, "HYQVIA" is referred to as "HyQvia."

This study comprises 3 epochs (parts):

Epoch 1 is Part 1 of the study.

Pediatric subjects with PIDD who are on non-HYQVIA IV or SC treatment with immunoglobulin (IV-pre-treated, SC pre-treated) will be enrolled and treated with HYQVIA subcutaneously with a dose or interval ramp-up period of up to six weeks.

Epoch 2 is Part 2 of the study.

Subjects who completed Epoch 1 will be followed by Epoch 2 with HYQVIA treatments. After one 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:

- Subjects with anti-rHuPH20 antibody titer < 160 at all time-points during the study will complete the study completion visit at the next possible occasion following the 12-months visit.
- 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, and complete the study completion visits at the next possible occasion following the 36-months visit.

Epoch 3 is Part 3 of the study.

Epoch 3 is approximately one year safety follow-up, if needed: subjects whose anti-rHuPH20 antibody titer was ≥ 160 during 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 followed accordingly. Only subjects whose anti-rHuPH20 antibody titer was ≥160 during *either* Epoch 1 or Epoch 2 and who experienced 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 GAMMAGARD LIQUID intravenously (IV) or subcutaneously (SC).

The safety of subjects in Study 161503 and in a similar Study 161504 which is focused exclusively on subjects with PIDD in the European Economic Area, 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 161503:

- Periodic ISMC Subject-Level Listings *
- Interim Analysis (IA)
- Final Analysis (end-of-study analysis)

* Out of scope of this SAP and are documented in the study ISMC Charter, dated 20 July 2020, version 7.0 or most recent version.

1.3 Statistical Analysis Plan Overview

Note: The purpose of Study 161503 is to acquire additional data on efficacy, safety, tolerability, immunogenicity, pharmacokinetic (PK) and other parameters of HyQvia in pediatric PIDD subjects.

This document is the statistical analysis plan (SAP) for the study and is planned to be approved *before* study database lock for interim analysis, also in accordance with the Shire Statistical Analysis Plan Work Instruction (RD JBA-0348). This SAP is for both interim analysis and final analysis.

This SAP provides a technical and detailed elaboration of the statistical analysis described in the approved study Protocol Amendment 2, dated 25 Mar 2019. All analyses

planned, unless otherwise specified, will be performed externally by the sponsor-designated contract research organization (CRO), using SAS®, Version 9.4 or higher.

The analysis is planned to cover the following:

- Efficacy
- Pharmacokinetics
- 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 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 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.
- GAMMAGARD LIQUID, Immune Globulin Infusion (Human), 10% Solution for intravenous (IV) and subcutaneous (SC) administration. 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 efficacy of HyQvia treatment in pediatric subjects with PIDD who received prior IV or SC immunoglobulin therapy before enrollment into the study.

2.1.2 Secondary Objectives

Secondary objectives of the study:

- Further efficacy assessments (assessments that are not part of the primary objective)
- Safety assessments, also including immunogenicity
- Tolerability
- Mode of product administration (infusion data)
- 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
- PK parameters

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 efficacy of HyQvia is the primary objective of this study. The primary endpoint/outcome measure corresponding to the study primary objective is the rate of acute serious bacterial infections, defined as the mean number of acute serious bacterial infections per subject per year.

Acute serious bacterial infections include:

- Bacteremia/sepsis
- Bacterial meningitis
- Osteomyelitis/septic arthritis
- Bacterial pneumonia
- Visceral abscess

2.3.2 Secondary Endpoints

The following are the secondary endpoints/outcome measures corresponding to the study secondary objectives.

2.3.2.1 Efficacy Endpoints

1. Number of all infections per subject-year
2. Trough levels of IgG and IgG subclasses for Study Epoch 2
3. Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae, and Hepatitis B Virus [HBV]) for Study Epoch 2

2.3.2.2 Safety/Tolerability Endpoints

1. Number and rate per infusion (excluding infections) of SAEs, related and not related
2. Number and rate per infusion (excluding infections) of all AEs, related and not related
3. Number and rate per infusion (excluding infections) of local AEs, related and not related
4. Number and rate per infusion (excluding infections) of systemic AEs, related and not related
5. Number and rate per infusion (excluding infections) of all temporally associated AEs (begin during or within 72 hours of completion of infusion)
6. Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
7. Rates of all AEs (excluding infections) defined as number of AEs categorized by MedDRA preferred terms, seriousness, and severity, divided by the number of infusions
8. Number and proportion of subjects who develop positive titer ($\geqslant$ 160) of binding or neutralizing antibodies to rHuPH20

2.3.2.3 Pharmacokinetics Endpoints

For the PK assessment in Epoch 2 the following PK parameters will be determined:

- Area under the curve (AUC)
- Clearance (CL)
- Maximum concentration (Cmax)
- Minimum concentration (Cmin)
- Time to maximum concentration (Tmax)
- Terminal half-life

2.3.2.4 Mode of Product Administration Endpoints

1. Infusions (Epoch 2)
   a. Number of infusions per month
   b. Number of infusion sites (needle sticks) per infusion/month
   c. Duration of infusion (defined as time from the start of rHuPH20 infusion until the stop time of immunoglobulin infusion). "Time" implies date and time.
   d. Maximum infusion rate/site
   e. Infusion volume/site
   f. 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) (Epoch 1)
3. Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
4. Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months

2.3.2.5 Health-related Quality of Life Endpoints

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

1. Pediatric Quality of Life Inventory (Peds-QL)
2. EuroQol five dimensions questionnaire (EQ-5D)

2.3.2.6 Treatment Preference and Satisfaction Endpoints

1. Assessment of Life Quality Index (LQI)
2. Assessment of Treatment Satisfaction Questionnaire and Medication (TSQM-9)
3. Assessment of Treatment Preference Questionnaire

2.3.2.7 Healthcare Resource Utilization Endpoints

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

3. STUDY DESIGN

3.1 General Description

Study 161503 is a Phase 3, open-label, non-randomized, non-controlled, multicenter, efficacy, safety, tolerability, immunogenicity, and PK 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, will be enrolled in this study.

Of the 40 subjects planned to be enrolled, at least 6 subjects are expected in each of the three age groups: 2 to <6 years, 6 to <12 years, and 12 to <16 years. The study will be conducted only in the United States.

This study comprises 3 epochs (parts):

Epoch 1: Treatment with HYQVIA

Additional information is provided in Section 1.1.

Pediatric subjects with PIDD who are on IV or non-HyQvia SC treatment with immunoglobulin (IV-pre-treated, SC-pre-treated) will be enrolled and treated with HyQvia subcutaneously with a dose or interval ramp-up period of up to six weeks.

Epoch 2: Treatment with HYQVIA

Additional information is provided in Section 1.1.

The ramp-up (Epoch 1) is followed by Epoch 2 with HyQvia treatment at the following intervals:

- For IV-pre-treated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule.
- For SC-pre-treated subjects: every three or four weeks, at the discretion of investigator and subject.

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 one 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 completion visit at the next possible occasion following the 12-months visit.
- 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, and complete the study completion visits at the next possible occasion following the 36-months visit.

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

At the six-month infusion visit, a PK assessment should be performed. If the PK assessment cannot be done at the six-month visit for any reason, it may alternatively be performed at the infusion before or after the six-month visit.

Epoch 3: Treatment with GAMMAGARD LIQUID

Subjects in Epoch 3 will be treated with GAMMAGARD LIQUID intravenously or subcutaneously, at the discretion of the investigator and the subject.

Epoch 3 is approximately one-year safety follow-up, if needed. Only subjects whose anti-rHuPH20 antibody titer was ≥160 during *either* Epoch 1 or Epoch 2 and who experienced either a study drug-related SAE or a related severe AE will be followed accordingly. Enrolled subjects in Epoch 3 will be followed for safety purposes for approximately 1 year.

Subjects with antibody titer of ≥160 when entering Epoch 3 continue regular anti-rHuPH20 antibody testing (approximately every 3 months) for approximately 1 year.

In the event that a subject in Epoch 1 or in Epoch 2 experiences a study drug-related SAE or related 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.

Epoch 3 infusions will be administered at home or at the study site.

3.2 Duration of Study Period and Study Participation

The planned overall duration of the study is approximately 6 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
- 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 the following assessment periods: Screening, Baseline, Epoch 1, Epoch 2, and, if needed, Epoch 3. The Appendices contain the schedules of study procedures and assessments separately for Epoch 1, Epoch 2, Epoch 3.

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.

The primary objective of this study is to evaluate the efficacy of HyQvia in terms of the rate of acute serious bacterial infections, defined as the mean number of acute serious bacterial infections per subject per year. A sample size of 35 provides 83% power to reject the null hypothesis (H_0) of an acute serious bacterial infection rate greater or equal 1.0 ($H_0 \geq 1.0$), by means of a 1-sided test and a significance level of 0.01, versus the alternative hypothesis (H_1) of less than 1.0 ($H_1 < 1.0$), assuming a true rate of 0.5/year. Based on previous clinical experience, a dropout rate of 12% is assumed. Allowing for 12% dropouts, approximately 40 subjects will be enrolled in the study. Subjects who prematurely discontinued the study will not be replaced.

The sample size (40), power (at least 80%) and hypothesis testing (significance level of 0.01, 1-sided) are consistent with the FDA's guidance ("Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency").

Summarized below are sample size and power estimates under 2 scenarios of the rate of acute serious bacterial infections: 0.5/year and 0.4/year, which are in line with the FDA guidance, which indicates that IGIV administration to individuals with primary immunodeficiency has observed acute serious bacterial infection rates of 0.5/year. The sample size and power estimates were derived using nQuery software (Version 4.0), with the following specifications: One Poisson Mean, $\alpha = 0.01$ (type 1 error), 1-sided.

	Rate under H_0	Rate under H_1	Sample Size [a]		Power [b]
			Subjects Enroll	Subjects Complete	
ASBI	1.0/year	0.5/year	34	30	75%
			36	32	81%
			40	35	83%
		0.4/year	34	30	94%
			36	32	96%
			40	35	97%

ASBI = Acute serious bacterial infections.
[a] Subjects Enroll = Number of Subjects Complete after adjusting for the assumed 12% dropout rate.
[b] Power is study power based on Subjects Complete.

3.6.1 Evaluation of Safety

For evaluation of AEs (treatment-emergent AEs), the FDA's guidance ("Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency") recommends a minimum sample size of 30 subjects for evaluation of safety. The planned sample size for this study is 40 subjects. For AEs that occur with a frequency of 10% ($\theta = 10\%$), the probability of observing at least 1 AE in this sample size is 98.5%. Displayed below are probabilities of observing at least 1 AE in this sample size under varying scenarios of θ, the frequency is AEs.

Sample Size	$\theta = 1\%$	$\theta = 5\%$	$\theta = 10\%$
34	28.9%	82.5%	97.2%
36	30.4%	84.2%	97.7%
40	33.1%	87.1%	98.5%

4. STATISTICAL ANALYSIS SETS

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. Subject disposition 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 (FAS) and the Enrolled Set are identical. All efficacy analyses will be based on the FAS.

4.4 Per-Protocol Analysis Set

All subjects in the FAS who have no major protocol deviations will be included in the Per-protocol Analysis Set (PPS). The PPS is applicable to efficacy analysis only, specifically sensitivity analysis of efficacy.

Protocol deviations will be classified as major or minor in accordance with applicable study sponsor's standard operating procedure(s) and prior to statistical analysis in which the PPS will be used. For the interim and final analysis, major protocol deviations will be determined before study clinical database lock.

4.4.1 Safety Analysis Set

All subjects who receive at least one dose of HyQvia. All safety analyses will be based on the Safety Analysis Set.

4.4.2 Pharmacokinetic Analysis Set

All subjects in the Safety Analysis Set who have at least 1 evaluable post-dose concentration data for PK assessments without major protocol deviations or events affecting the PK results. All PK summaries will be based on the Pharmacokinetic Analysis Set (PKAS).

4.5 Treatment Groups and Cohorts

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

Epoch 2 comprises subjects who complete Epoch 1 and enter Epoch 2 with HyQvia treatment.

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 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 GAMMAGARD LIQUID intravenously or subcutaneously, at the discretion of the investigator and the subject.

Any Epoch 3 data available at time of study database lock for interim or/ and final analysis will be provided in subject-level data listings only, or summarized in addition to listings if summarizing is expected to be clinically meaningful; for example, if the total number of subjects with data in Epoch 3 is greater than 2, the Epoch 3 data may be summarized.

5. STATISTICAL ANALYSIS OVERVIEW

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 PK 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.

In the event of any inconsistency between the statistical analysis content provided in this SAP and the TFL specifications provided separately in the 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.

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 available at database lock will be summarized also if the total number of subjects in Epoch 3 is greater than 2.

Note on the Interim Analysis column in Table 1:

- Only subjects whose anti-rHuPH20 antibody titer was ≥160 during *either* Epoch 1 or Epoch 2 and who experienced 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.

- As indicated in Section 3.2, duration of Epoch 2 is up to 3 years. If no subject continues into Year 2 and Year 3 of Epoch 2, and no subject continues into Epoch 3, meaning the study is expected to end with a final analysis; if otherwise, the interim analysis is planned, followed by the final analysis.

	Table 1. Study Data for Interim and Final Analysis					
Outcome Measure Category	**Data Description**	**Analysis Set**	**Data for Interim Analysis (X = Yes)**	**Data for Final Analysis (X = Yes)**	**Analysis Method (Interim and Final)**	**Statistical Output (Interim and Final)**
Background	Disposition	Screened Set	X	X	DA	TL
	Demographics and Other Baseline Characteristics	FAS	X	X	DA	TL
	Medical History (also includes PIDD history)	FAS	X	X	DA	TL
	Prior Medications	FAS	X	X	DA	TL
	Concomitant Medications	FAS	X	X	DA	TL
	Exposure to IP (IP is defined in Section 1.4)	Safety Set	X	X	DA	TL
	Treatment Compliance	Safety Set	X	X	DA	TL
	Protocol Deviations	FAS	X	X	NA	L
Primary (Efficacy)	Acute serious bacterial infections (primary efficacy endpoint)	FAS, PPS	X	X	DA and Poisson [a]	TL
Secondary	Adverse Events	Safety Set	X	X	DA and Wilson [d] (selected endpoints)	TL
	Laboratory Parameters	Safety Set	X	X	DA	TL
	Vital Signs	Safety Set	X	X	DA	TL
	Physical Examinations	Safety Set	X	X	NA	L
	Additional Efficacy: IgG Trough Levels	FAS	X	X	DA [b]	TFL
	Pharmacokinetics	PK Set	X	X	DA [b]	TFL
	Mode of Product Administration	Safety Set	X	X	DA	TL
	HRQoL	Safety Set	X	X	DA	TL
	Treatment Preference and Satisfaction Endpoints	Safety Set	X	X	DA and Wilcoxon [c]	TL
	Infections	Safety Set	X	X	DA and Wilson [d]	TL

	Table 1. Study Data for Interim and Final Analysis					
Outcome Measure Category	**Data Description**	**Analysis Set**	**Data for Interim Analysis (X = Yes)**	**Data for Final Analysis (X = Yes)**	**Analysis Method (Interim and Final)**	**Statistical Output (Interim and Final)**
	Healthcare Resource Utilization	Safety Set	X	X	DA and CI	TL
	[a] Poisson regression via PROC GENMOD, in addition to descriptive analysis. [b] Additional analysis may be performed and will be documented appropriately outside the scope of this SAP. [c] Change from baseline will be analyzed using Wilcoxon signed rank test, in addition to descriptive analysis. [d] Wilson = 95% CI for proportion using Wilson score method, in addition to descriptive analysis. Refer to the corresponding "Analysis" section for additional information. DA = Descriptive analysis is planned to be performed. No statistical hypothesis testing is planned, unless otherwise specified. CI = 95% Confidence interval (refer to the corresponding "Analysis" section for additional information. NA = Not applicable. No summary is planned. TFL = Table, figure and listing TL = Table and listing L = Lisitng FAS: Full Analysis Set PPS: Per Protocol Set					

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, using screened set. Demographics and other baseline characteristics summaries will be based on the Full Analysis Set.

A summary of number and proportion of subjects in different population sets will be provided.

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)

- By Epoch for the following, if applicable
  - Completed
  - Ongoing (apply to the interim analysis only)
  - 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, and 12 to <16 years), gender, race, ethnicity, height , weight. Height and weight will be presented in both metric and imperial units.

6.4 Medical History and Prior Procedures

Table 1 contains an overview of the planned summaries of medical history, PID diagnosis, 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 20.0 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 team (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).

Medical history listing will also include disease (PIDD) diagnosis history: date of first PIDD symptoms, date of PIDD diagnosis, and type of PIDD. Note: this is presented in the demographics and baseline characteristics listing.

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 All Subjects column (i.e., the All Subjects 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.

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: date of last dose of IP – date of

initial dose of IP + 1, and then converted into months, for consistency with the study Schedule of Study Procedures and Assessments (Appendices).

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

For statistical summary purposes, exposure in days / 30.4 days per month, 6 weeks = 42 days, 12 months = 365 days, 24 months = 730 days, and 36 months = 1095 days.

6.8 Measurements of Treatment Compliance

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

HyQvia treatment completion status will include:

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

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.

Hyqvia treatment completion status summaries will be based on the Safety Set. Subject data listings will be based on the Safety Set.

6.9 Protocol Deviations and Subject Exclusions

Protocol deviations will be classified as major or minor in accordance with applicable legacy Shire standard operating procedure(s).

The following definitions will apply:

- Major protocol deviation is a subset of protocol deviations that may significantly impact subject's rights, safety or well-being, the statistical analysis, and/or the interpretation of product safety/efficacy.
- Minor protocol deviation is a subset of protocol deviations, which include changes or alterations in the conduct of the study that do not have a significant impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

Protocol deviations will be classified, and classification will be finalized and documented, per Shire applicable process (Shire is now part of Takeda). Subjects with major protocol deviations will not be included in any PP Set-based analysis.

Categories of protocol deviations that lead to exclusion from the PP Set include but are not limited to:

- Violations of inclusion and/or exclusion criteria
- Non-compliance with IP
- Incorrect timing of assessments
- Prohibited concomitant medications

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 Full Analysis Set. In addition, protocol deviations that relate to COVID-19 will be flagged in the listing.

No summary tables are planned.

7. EFFICACY ANALYSIS

7.1 Analysis of Primary Efficacy Endpoint

Assessment of efficacy of HyQvia is the primary objective of this study. The primary endpoint/outcome measure corresponding to the study primary objective is the rate of acute serious bacterial infections, defined as the mean number of acute serious bacterial infections per subject per year.

Number of infections will be counted from start of initial dose of HyQvia (start of Epoch 1) through end of Epoch 2. HYQVIA is administered in Epoch 1 and Epoch 2, and GAMMAGARD LIQUID only in Epoch 3.

The primary analysis of the primary endpoint will be based on a Poisson model (details below), accounting for the length of the observation periods per subject. No imputation will be made for missing data, if any. The Full Analysis Set will be used. The null hypothesis of an acute serious bacterial infection rate greater or equal 1.0 ($H_0 \geq 1.0$) will be tested against the alternative hypothesis of less than 1.0 ($H_1 < 1.0$) at the 0.01 significance level (1-sided). The mean number of acute serious bacterial infections per subject per year and the corresponding 99% upper confidence limit will be provided. This approach is consistent with the **FDA guidance**, which states that a statistical demonstration of an acute serious bacterial infection rate per subject-year **less than 1.0** is adequate to provide substantial evidence of efficacy. The null hypothesis is: the infection rate is greater than or equal to 1.0 per subject-year at the 0.01 level of significance or, equivalently, the upper 1-sided 99% confidence limit is less than 1.0.

A generalized linear model assuming the Poisson distribution for the number of acute serious bacterial infections, with the logarithm as link function, will be used via the SAS procedure PROC GENMOD. The Poisson model will include the natural logarithm of the length of the observation period in years as an offset to account for the (possibly) different lengths of the observation periods per subject. To handle over-dispersion, the exponential distribution dispersion parameter will be assumed to be given by the deviance divided by the degrees of freedom and all statistics will be adjusted accordingly. In case of over-dispersion, a SCALE=DEVIANCE option in the MODEL statement in PROC GENMOD will be specified.

The null hypothesis will be rejected in favor of the alternative hypothesis if the resulting p-value is less than 0.01; equivalently, if the upper bound of the 99% confidence limit is less than 1. Efficacy of HYQVIA will be claimed if the null hypothesis is rejected.

7.1.1 Subgroup Analysis of Primary Endpoint

For exploratory analysis purposes, the primary outcome measure will be summarized by clinically meaningful subgroups: sex and age groups, in years at screening (2 to <6, 6 to <12, 12 to <16). No statistical hypothesis testing will be performed.

7.1.2 Sensitivity Analysis of Primary Endpoint

The primary analysis of the primary outcome measure will be based on a Poisson model and the FAS. To assess robustness of inference from the primary analysis, the following sensitivity analyses will be performed by repeating the primary analysis as follows:

- Replacing FAS with PPS and re-run the primary analysis. This is, only subjects with no major protocol deviations will be included in this sensitivity analysis of the primary endpoint. In other words, exclude all subjects with major protocol deviation, and then re-run the primary analysis.
- Excluding Epoch 1 from analysis and re-run the primary analysis. That is, number of infections will be counted from start of Epoch 2 through end of Epoch 2.

7.2 Analysis of Secondary Endpoints

7.2.1 Efficacy

7.2.1.1 Number of all infections per subject-year

The annual rate of infection under HyQvia treatment will be computed using a Poisson model and presented as point estimate and 95% CI. The Poisson model will include the natural logarithm of the length of the observation period in years as an offset to account for the different lengths of the observation periods per subject and handle over-dispersion by the deviance method (as for the primary endpoint).

A descriptive statistics of number of all infections, number of subjects with an event, rate of infections per subject-year by age group in years at screening (2 to < 6 years, 6 to < 12 years, 12 to < 16 years) will also be presented.

7.2.1.2 Trough Levels of Total IgG, IgG subclasses and specific antibodies

Total IgG trough levels, IgG subclass trough levels, and trough levels of specific antibodies will be analyzed via descriptive statistics defined in Section 5. The above will also be done by each age group, in years (2 to <6, 6 to <12, 12 to <16).
The following figures will be presented:

- Box plot for Ctrough at Month 0, Month 6 and Month 12 in Epoch 2 by Analyte (total IgG, IgG subclasses and specific antibodies) for each age group, in years (2 to <6, 6 to <12, 12 to <16).

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

7.3 Additional efficacy analysis

Descriptive statistics will be provided for the following additional efficacy outcome meansures:

Acute serious bacterial infections:

- Number and proportion of subjects with any acute serious bacterial infection
- Number of acute serious bacterial infections

All infections:

- Number of all infections

8. SAFETY ANALYSIS

8.1 Analysis of Safety Endpoint

In general, safety endpoints will be summarized descriptively in this study using Safety Analysis Set.

Table 1 contains an overview of the planned analysis of the safety endpoints/outcome measures.

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.

Related AEs: An AE that is recorded as "possibly related" or "probably related" to IP will be considered "related AE", and AE recorded as "unlikely related" or "not related" will be considered "unrelated" AE.

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

Maximum severity: In addition, subjects with multiple severities of the same AE, an AE summary table by maximum severity (most serious severity) will also be presented in a separated table.

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 20.0 or higher and then reported by MedDRA SOC and PT, and overall. TEAEs are defined in Section 8.1. 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.

All the AEs, SAEs provided in the analsyis are treatment emergent adverse event, unless otherwise specified. All the AEs, SAEs will be summarized by epoch.

The following safety outcomes will be summarized:

1. Number and proportions of subjects of AEs, overall summary. Excluding infections.
2. Number and proportions of subjects of AEs, overall summary. Including infections.
3. Number and proportion of subjects of SAEs. Excluding infections.

4. Number and rate per infusion of SAEs. Excluding infections.
5. Number and proportion of subjects of related SAEs. Excluding infections.
6. Number and rate per infusion of related SAEs. Excluding infections.
7. Number and proportion of subjects of unrelated SAEs. Excluding infections.
8. Number and rate per infusion of unrelated SAEs. Excluding infections.
9. Number and proportion of subjects of related SAEs, by time interval. Excluding infections.
10. Number and rate per infusion of related SAEs, by time interval. Excluding infections.
11. Number and rate per infusion of SAEs. Including infections.
12. Number and proportion of subjects of SAEs. Including infections.
13. Number and rate per infusion of related SAEs. Including infections.
14. Number and proportion of subjects of related SAEs. Including infections.
15. Number and proportion of subjects of AEs. Excluding infections.
16. Number and rate per infusion of AEs. Excluding infections.
17. Number and proportion of subjects of related AEs. Excluding infections.
18. Number and rate per infusion of related AEs. Excluding infections.
19. Number and proportion of subjects of unrelated AEs. Excluding infections.
20. Number and rate per infusion of unrelated AEs. Excluding infections.
21. Number and proportion of subjects with related AEs that were mild, moderate, or severe in severity, and number of events in each category. Excluding infections.
22. Number and rate per infusion with related AEs that were mild, moderate, or severe in severity, and number of events in each category. Excluding infections.
23. Number and proportion of subjects of related severe AEs, by time interval. Excluding infections.
24. Number and rate per infusion of subjects of related severe AEs, by time interval. Excluding infections.
25. Number and proportion of subjects with local AEs. Excluding infections.
26. Number and rate per infusion of local AEs. Excluding infections.
27. Number and proportion of subjects with local AEs, related. Excluding infections.
28. Number and rate per infusion of local AEs, related. Excluding infections.
29. Number and proportion of subjects with local AEs, unrelated. Excluding infections.
30. Number and rate per infusion of local AEs, unrelated. Excluding infections.
31. Number and proportion of subjects with related local AEs that were mild, moderate, or severe in severity, and number of events in each category. Excluding infections.
32. Number and proportion of subjects with systemic AEs. Excluding infections.
33. Number and rate per infusion of systemic AEs. Excluding infections.
34. Number and proportion of subjects with systemic AEs, related. Excluding infections.
35. Number and rate per infusion of systemic AEs, related. Excluding infections.
36. Number and proportion of subjects with systemic AEs, unrelated. Excluding infections.
37. Number and rate per infusion of systemic AEs, unrelated. Excluding infections.

38. Number and proportion of subjects with related systemic AEs that were mild, moderate, or severe in severity, and number of events in each category. Excluding infections.
39. Number and proportion of subjects with temporally-associated AEs. Excluding infections.
40. Number and rate per infusion with temporally-associated AEs. Excluding infections.
41. Number and proportion of subjects with related and or temporally-associated AEs. Excluding infections.
42. Number and rate per infusion with related and or temporally-associated AEs. Excluding infections.
43. AE leading to discontinuation.
44. All infections.
45. Summary of preferred terms.

Subgroup analysis:

Subgroup analysis will be provided for the following AEs outcomes:

1. Related SAEs,
    a. summary of rate per infusion. Excluding infections.
    b. summary of number and proportion of subjects. Excluding infections.
2. Related severe AEs,
    a. summary of rate per infusion. Excluding infections.
    b. summary of number and proportion of subjects. Excluding infections.

The outcome measures will be summarized by clinically meaningful subgroups: sex and age groups, in years at screening (2 to <6, 6 to <12, 12 to <16).

In addition, the following analysis will be performed for the outcome measures

1. Severe related AEs (number and proportion of subjects. Excluding infections) by subgroup analysis and by time interval.
2. Related SAEs (number and proportion of subjects. Excluding infections) by subgroup analysis and by time interval.
    - 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.

For the by time interval summary, incidences and corresponding CIs will be provided to "Epoch 1 and Epoch 2" column (intervals are aligned with the IP exposure time intervals provided in Section 6.7).

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.

The following approaches will be used, where applicable:

- Overall summary: Overall summary will include the following categories by epoch summary and "epoch 1 and epoch 2" (where applicable), but not limited to:
  - Any AE, severe AE, SAE, local AE, systemic AE. For these AEs, the summary for related, unrelated, and all will be provided.
  - In addition, temporally-associated AE, related and /or temporally associated AE, AE leading to discontinuation, and any AE leading to death.
- 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 will be presented by "Epoch 1 and Epoch 2" column. It will be sorted in descending order after the sorting by SOC and PT).
- Maximum severity summary: 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.
- 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.
- Rate of AEs per infusion, per subject, and 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 days of exposure, i.e., the sum of duration of treatment for all subjects in the analysis set, converted into years.

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, 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. An abnormal lab listing will be provided.

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. PHARMACOKINETIC ANALYSIS

PK analysis will use the actual observed sample drawing times, not the nominal times specified in the protocol. A deviation from the protocol-specified drawing time window will not be a reason for exclusion of an observation. However, samples with unknown drawing time and/or where the concentration could not be determined will be excluded from the analysis.

For the serum levels of total IgG, , tabular summeries will be presented by visit and nominal timepoints at the 6-month visit. For these summaries, actual value and beaseline-corrected value will be presented. The above will be repeated by age group, in years (2 to <6, 6 to <12, 12 to <16).

For total IgG, the following figures will be provided:

- Individual subject level concentration-time line plots at 6 month time points.
- Mean concentration-time plot of all subjects at the 6 month time points.

Mean concentration-time plot for each age group, in years (2 to <6, 6 to <12, 12 to <16) at the 6 month time points

- Box plot for each PK parameters for each age group, in years (2 to <6, 6 to <12, 12 to <16) at the 6 month time point
- Box plot for Ctrough at the 6 month visit for each age group, in years (2 to <6, 6 to <12, 12 to <16).

For the PK assessment in Epoch 2, analysis of PK will be based on the PKAS, unless otherwise specified in this SAP. PK parameters (see Sec 2.3.2.3) will be determined for total IgG on individual subject level on actual concentrations and baseline-corrected concentrations, and tabular summeries with appropriate descriptive statistics (defined in Section 5) will be presented at the 6 month visit. The above will be repeated by gender and by age group, in years (2 to <6, 6 to <12, 12 to <16).

A listing of PK blood sample collection times(nominal and actual) and derived sampling time deviations will be provided. The listng will also present serum levels of total IgG and PK parameters.

To facilitate comparisons of exposure parameters across different dosing intervals (three and four weeks), the AUC over the dosing interval ($AUC_{0-\tau}$) for total IgG will be normalized by week.

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

10. 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.

10.1 Analysis of Infections

Section 2.3.2.1 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. 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.

10.2 Analysis of Mode of Product Administration

Section 2.3.2.4 lists the mode of production administration endpoints/outcome measures. All outcomes will be analyzed using descriptive statistics defined in Section 5. In addition, the following outcome mesures in Epoch 2 will be summarized:

- Number of infusions
- Number of infusion sites per month
- Number of subjects with infusions that are stopped, slowed, or interrupted due to an AE
- Number of infusions per subject-year that are stopped, slowed, or interrupted due to an AE

All endpoints/outcome measures will be summarized by age group, in years (2 to < 6, 6

to < 12, 12 to < 16).

10.2.1 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.

10.2.2 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 <16 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.

10.2.3 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 <16 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.

10.3 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 descriptive statistics at each time point, statistical hypothesis testing will be performed, limited to 4 domains: Treatment Interferences and Therapy Setting (a Life Quality Index domain), and Convenience and Global Satisfaction (a Treatment Satisfaction and Medication Questionnaire domain). Change from baseline in each domain score at end of Epoch 2 will be analyzed using Wilcoxon signed rank test at significance level of 0.05, 2-sided.

10.3.1 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 <16 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.

10.3.2 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 <16 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.

10.3.3 Life Quality Index

The Life Quality Index (LQI) is validated questionnaire assessing patient perceptions of their HRQoL and their treatment specifically among patients who use immunoglobulin therapy. This questionnaire covers 4 domains: Treatment Interferences, Therapy-related Problems, Therapy Setting, and Treatment Costs. A score can be calculated for each domain, with higher scores indicating higher satisfaction. 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/age group is not available, the assessment in the closest language/ age group will be used. For the age group 2 to 12 years the observer will be a parent, for the age group 13 years and older the observer will be the subject. The same observer should be employed for the duration of subject participation.

10.4 Analysis of Healthcare Resource Utilization

Section 2.3.2.7 lists the HRU endpoints/outcome measures.

All outcomes will be analyzed using summary statistics defined in Section 5, along with corresponding 95% CI for the mean.

In additional to summarize the endpoints in subject-year, the endpoints will also be summarized per subject during the trial duration.

11. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

11.1 Study Stopping Rules

There are no statistical stopping 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).

11.2 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).

11.3 Interim Analysis

The primary objective of this study is to evaluate the efficacy of HyQvia. HyQvia is administered in Epoch 1 (ramp-up period of up to 6 weeks) and Epoch 2 (final dosing period of up to 3 years), and GAMMAGARD LIQUID is administered only in Epoch 3 (safety follow-up period of approximately 1 year).

A single, formal IA will be performed, for planned submission to regulatory authorities in support of HYQVIA label expansion to pediatric population. All of the following will apply to the IA:

- Analysis will include all efficacy, safety and other study outcome measures.
- Analysis will be performed when all subjects 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 early stopping of study for efficacy or futility is planned.
- Multiplicity will be adjusted.

  For the primary analysis of the primary outcome measure, the null hypothesis of an acute serious bacterial infection rate greater than or equal to 1.0 ($H_0 \geq 1.0$) will be tested against the alternative hypothesis of less than 1.0 ($H_1 < 1.0$), at the interim analysis and at the final analysis. While no early stopping of study is planned, the Lan-DeMets alpha spending function approach will be used to preserve the overall type 1 error.

  O'Brien-Flening boundary will be used to adjust the alpha level at each look.

  The information fraction at the interim analysis will be estimated by: observed patient years at the interim / expected total patient years at the final.

  - If the test statistic at the interim analysis is greater than the pre-specified boundary at the interim, the analysis for the primary endpoint at the final will be administrative purpose.

- If the test statistic at the interim analysis is less or equal to the pre-specified boundary at the interim, the final analysis will be planned in the statistical inferential manner. The alpha level at the final may be adjusted based on the actual total information at the final.

- Analysis results will be reported in an interim clinical study report.

The final analysis of all study data will be performed after study database lock.

In addition to the IA, the safety of HyQvia in study subjects is monitored by an ISMC comprising of individuals who have product experience and substantial expertise in the review and evaluation of safety data generated from study participants within Immunology and in the monitoring subject safety during study. Safety and safety-supported data will be provided in the ISMC for review. Details and procedural information is provided in the ISMC Charter.

12. DATA HANDLING CONVENTIONS

In the event of any inconsistency between the data handling conventions specified in this section and the conventions specified separately in 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.

12.1 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 implementation of CDISC standards, based on the SDTM IG v3.2 and the ADaM IG v1.1.

TFLs will follow Shire standards, where applicable, except that footnotes will be printed at the bottom of every output page. 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.

12.1.1 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.

12.1.2 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.

12.1.3 P-Value and Confidence Interval Reporting

P-value and confidence interval will be provided in the analysis of the primary endpoint. CIs, if any are provided other than the analysis of primary endpoint, are for descriptive purposes, and therefore caution should be exhibited in their interpretation.

12.2 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.

12.3 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 primary endpoint is the rate of acute serious bacterial infections, defined as the mean number of acute serious bacterial infections per subject per year, which is not specific to a time point (study visit).

12.4 Derived Efficacy Endpoints

Incorporated in the efficacy endpoints and analysis sections.

12.5 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments 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.

12.6 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.

12.6.1 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.

12.6.2 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.

12.6.2.1 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.

12.6.2.1.1 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.

12.6.2.1.2 Missing Month Only

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

12.6.2.1.3 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.

12.6.2.2 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.

12.6.2.2.1 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.

12.6.2.2.2 Missing Month Only

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

12.6.2.2.3 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.

12.6.3 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.

12.6.3.1 Incomplete Start Date

Rules in Section 12.6.2.1 apply.

12.6.3.2 Incomplete Stop Date

Rules in Section 12.6.2.2 apply.

12.6.4 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.

12.6.5 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.

12.6.6 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.

12.6.7 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.

13. ANALYSIS SOFTWARE

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

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

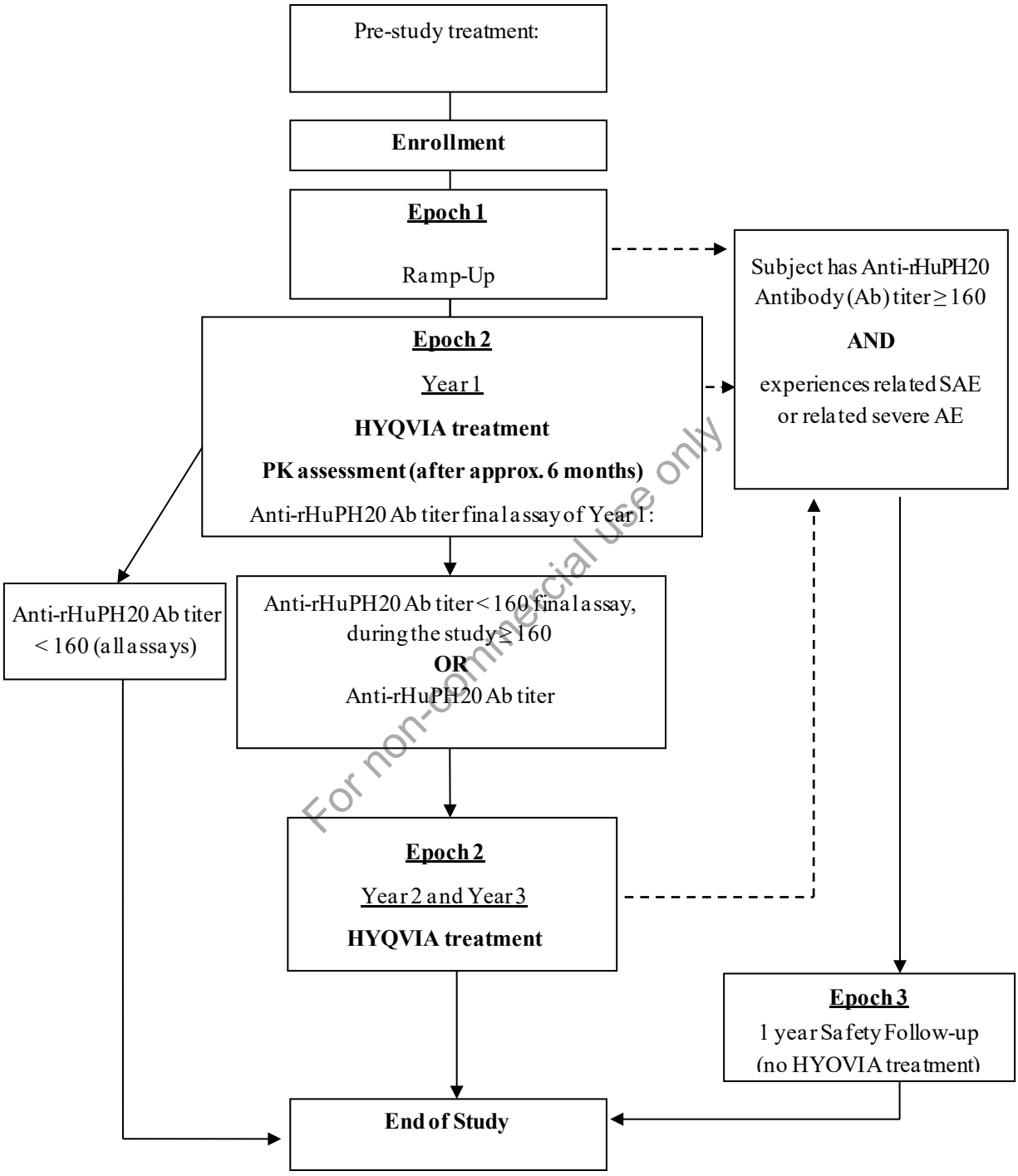
Additional endpoints and outcome measures for analysis were added for a more complete and robust analysis, where applicable.

15. APPENDICES

15.1 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 161503



15.2 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	Screening/ Enrollment	First Infusion: Baseline	Treatment Visit in Study Epoch 1 (Visit +/- 1 Day)	
			Second Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for three-Week Treatment Intervals) [c]	Third Infusion: Week 3 (Only for Subjects Planning to Ramp Up to four-Week Treatment Intervals) [d]
Location	Site	Site	Site	Site
Informed Consent [a]	x			
Eligibility Criteria	x			
Infusion		x	x	x
Follow-up call after infusion [e]		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 – see Lab Table [b]	x	x		
Vital Signs	x	x	x	x
HRQoL (PedsQL, EQ-5D)		x		
Treatment Preference and Satisfaction Questionnaires: LQI and TSQM-9 only		x [f]		

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Continued

[a] Occurs prior to any study-specific procedure.

[b] For laboratory assessments, see Supplement 20.3 of the study protocol.

[c] For subjects planning for three-week intervals: The first infusion in Epoch 2 will be given two weeks after the second infusion (Week 1) in Epoch 1. See also Section 8.7.2.1 of the study protocol.

[d] For subjects planning for four-week intervals: The first infusion in Epoch 2 will be given three weeks after the third infusion (Week 3) in Epoch 1. See also Section 8.7.2.1 of the study protocol.

[e] The investigator/designee will contact the subject 3-5 days after completion of each HYQVIA infusion (including home infusions) during Epoch 1 and 2 (see Section 8.2 of the study protocol).

[f] At baseline, only LQI and TSQM-9 will be done. Treatment Preference Questionnaire will not be administered.

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

Procedures/ Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Month 0[g]	Visit in Study Epoch 2[g] - (Visit +/- 2 Weeks)				
		Month 3	Month 6	Month 9	Month 12[a]	Study Completion/ Termination Visit (at Next Infusion), if Applicable[h]
Location	Site	Site	Site	Site	Site	Site
Informed Consent						
Infusion [f]	x	x	x	x	x	
Follow-up call after infusion [b]	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 [i]	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x
HRQoL (PedsQL, EQ-5D)					x	(x)[d]
Treatment Preference and Satisfaction Questionnaires [c] (LQI, TSQM-9, Treatment Preference Questionnaire)					x	(x)[d]
PK assessment [e]			x			

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Continued

[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 End of Study or continuation of Epoch 2 dependent on antibody assay result.

[b] The investigator/designee will contact the subject 3-5 days after completion of each HYQVIA infusion (including home infusions) during Epoch 1 and 2 (see Section 8.2 of the study protocol)

[c] All Treatment Preference and Satisfaction Questionnaires, including LQI, TSQM-9 and Treatment Preference Questionnaire as described in Section 10.3.1 and Section 11.3 of the study protocol will be applied.

[d] 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. Refer to Section 10.3.1 of the study protocol.

[e] For details of PK assessments refer to Section 8.2.2.2 and Section 10.3.2 of the study protocol.

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

[g] Site Visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)

[h] In case a subject moves to Study Epoch 3, he/she will have the Study Completion/Termination Visit at the end of Epoch 3.

[i] For laboratory assessments, see Supplement 20.3 of the study protocol

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[e] - (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 [d]	x	x	x	x	x	x	x	
Follow-up call after infusion [b]	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 [f]	x	x	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x	x	x
HRQoL (PedsQL, EQ-5D) [c]				x				x
Treatment Preference and Satisfaction Questionnaires[c] (LQI, TSQM-9, Treatment Preference Questionnaire)				x				x

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Continued

[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] The investigator/designee will contact the subject 3-5 days after completion of each HYQVIA infusion (including home infusions) during Epoch 1 and 2 (see Section 8.2 of the study protocol).
[c] Refer to Section 10.3.2 and Section 11.3 of the study protocol. Subjects who prematurely exit the study will complete assessments at the Study Termination Visit.
[d] Infusions (including home infusions) administered between scheduled site visits/site infusions may deviate up to +/- 3 days from original schedule.
[e] Site visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)
[f] For laboratory assessments, see Supplement 20.3 of the study protocol

Table 5
STUDY EPOCH 3
Schedule of Study Procedures and Assessments

Procedures/Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Month 0	Visit in Study Epoch 3[f] (Visit +/- 2 Weeks)			
		Month 3	Month 6	Months 9	Month 12/ Study Completion/ Termination Visit[a]
Location	Site	Site	Site	Site	Site
Infusion [b, e]	x	X	x	x	
Concomitant Medications	x	x	x	x	x
Non-drug Therapies	x	x	x	x	x
Physical Exam	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 questionnaires (PedsQL, EQ-5D) [d]	x				x

[a] Includes cases of withdrawal or discontinuation.
[b] Follow-up calls by the investigator/designee will not be required following infusion with GAMMAGARD LIQUID
[c] For laboratory assessments, see Supplement 20.3 of the study protocol.
[d] Treatment Satisfaction Questionnaires (Treatment Preference Questionnaire, TSQM 9 Assessment) will not be done in Epoch 3.
[e] Infusions (including home infusions) administered between scheduled site visits/site infusions may deviate up to +/- 3 days from original schedule
[f] Site visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)

Table 6
STUDY EPOCH 1 – Ramp Up
Clinical Laboratory Assessments

Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Screening/ Enrollment	First Infusion: Baseline [a]	Treatment Visit in Study Epoch 1 (Visit +/- 1 Day)	
			Second Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for three-Week Treatment Intervals)	Third Infusion: Week 3 (Only for Subjects Planning to Ramp Up to four-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		
Retention Samples [b]		x		

[a] See Section 12.7 of the study protocol.

[b] Approximately 1 mL serum will be taken and stored frozen at -70°C or below at the central laboratory in the event further safety testing is needed.

Table 7
STUDY EPOCH 2 – Year 1
Clinical Laboratory Assessments

Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Month 0	Visit in Study Epoch 2[c] (Visit +/- 2 Weeks)				
		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[b]	x				x	
Specific Antibody Tests						x
IgG Trough Levels and IgG Subclasses	x		x		x	
Antibodies to rHuPH20	x	x	x	x	x	
PK assessment[a]			x			

[a] For details of PK assessments refer to Section 8.2.2.2 and Section 10.3.2 of the study protocol.

[b] If there is a reduction in Hgb of 2 g/dL or more compared to baseline Hgb, hemolysis tests should be repeated within 72 hours. Also, an unscheduled hemolytic panel may be performed if hemolytic anemia is suspected. If clinical hematology/chemistry testing coincides with hemolysis tests, overlapping tests need to be performed only once. For details see Section 12.7.4 of the study protocol.

[c] Site visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)

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[c] (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 Test [b]				x				
Specific Antibody Tests				x				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 2 g/dL or more compared to baseline Hgb, hemolysis tests should be repeated within 72 hours. Also, an unscheduled hemolytic panel may be performed if hemolytic anemia is suspected. If clinical hematology/chemistry testing coincides with hemolysis tests, overlapping tests need to be performed only once. For details see Section 12.7.4 of the study protocol.

[c] Site Visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)

Table 9
STUDY EPOCH 3
Clinical Laboratory Assessments

Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Month 0	Visit in Study Epoch 3[b] (Visit +/- 2 Weeks)			
		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[a]			x		
Specific Antibody Tests					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 2 g/dL or more compared to baseline Hgb, hemolysis tests should be repeated within 72 hours. Also, an unscheduled hemolytic panel may be performed if hemolytic anemia is suspected. If clinical hematology/chemistry testing coincides with hemolysis tests, overlapping tests need to be performed only once. For details see Section 12.7.4 of the study protocol.

[b] Site visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)

15.3 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

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	
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: one = mild, two = moderate, three = severe, four = life-threatening or disabling, and five (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.

16. REFERENCES

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