Clinical Study Protocol

NCT Number: NCT04578535

Title: A Phase 1, Open-Label, Randomized Study to Assess the Tolerability, Safety, and Pharmacokinetics of Subcutaneous Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) with Ramp-Up and No Ramp-Up Dosing in Healthy Adult Subjects

Study Number: TAK-771-1001

Document Version and Date: Protocol Amendment #1, 30-JUN-2020

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL: TAK-771-1001

Title:	A Phase 1, Open-Label, Randomized Study to Assess the Tolerability, Safety, and Pharmacokinetics of Subcutaneous Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) with Ramp-Up and No Ramp-Up Dosing in Healthy Adult Subjects
Drug:	HYQVIA/HyQvia
IND:	014381
EUDRACT No.:	Non-EUDRACT
Sponsor:	Baxalta US Inc.* 300 Shire Way, Lexington, MA 02421 AND Baxalta Innovations GmbH* Industriestrasse 67, A-1221 Vienna *Baxalta is now part of Shire
Principal/ Coordinating Investigator:	[redacted], MD, JD, CPI, FCLM
Protocol History:	**Amendment 1.0: 30 JUN 2020** **Replaces: Original Protocol: 04 FEB 2020**

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: *Date:*

[redacted], **PhD**
[redacted] Clinical Pharmacology & Pharmacokinetics

Signature: *Date:*

[redacted], **MD**
[redacted] Clinical Medicine

Investigator's Acknowledgement

I have read this protocol for Study TAK-771-1001.

Title: A Phase 1, Open-Label, Randomized Study to Assess the Tolerability, Safety, and Pharmacokinetics of Subcutaneous Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) with Ramp-Up and No Ramp-Up Dosing in Healthy Adult Subjects.

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: *(please hand print or type)*	_____
	_____
	_____

Signature: _____ *Date:* _____

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

Protocol Amendment 1.0		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **1.0**	**Amendment Date** **30 JUN 2020**	**Country Specific** **Global**
Protocol Amendment Summary and Rationale: Some updates were made, in particular regarding sample volumes for PK and ADA assays; minor clarifications were also made.		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Changes were made for more consistent terms, improved grammar and syntax throughout document.	Clarification	Throughout document.
The study conduct period was updated to reflect a delay in study start due to COVID-19 and manufacture's infusion pump (for IP administration) recall.	Update	Synopsis
To exclusion criterion #11, "or D-1" was added for consistency and clarification.	Update	Synopsis; Section 5.2
Clarification to exclusion criterion #9 about live attenuated vaccines was added.	Update	Synopsis; Section 5.2
Clarification/re-wording to exclusion criterion #12 regarding the virology tests was made.	Clarification	Synopsis; Section 5.2
Additional time points were added for HIV, HBV, HCV testing added during follow-up period for safety reasons.	Update	Section 1.3.1, Section 1.3.2, Section 1.3.3
The wording regarding immunogenicity testing timing and glucose testing were slightly amended for clarity.	Clarification	Section 1.3.1, Section 1.3.2, Section 1.3.3, Section 8.2.3.4.1
The wording regarding vials' contents and preparation of doses was clarified.	Clarification	Section 7.1, Section 7.3.1
The description of how the IP will be supplied to the investigational site was clarified.	Clarification	Section 7.1
The disposal of partially or unused vials was clarified.	Clarification	Section 7.4
The procedure for storing of screening data was clarified.	Clarification	Section 8.1.1
Test location for hemolytic tests (local, (and not central laboratories) was updated.	Update	Section 8.2.3, Section 8.2.4
The pregnancy test procedures were clarified.	Clarification	Section 8.2.3.5
The procedures for sample collection and testing of PK, plasma ADA and nADA samples were clarified.	Clarification	Section 8.2.4
Blood volumes to be drawn were amended.	Update	Section 8.2.5

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the "Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by the Protocol" within 24 hours to the Shire Global Drug Safety Department (**Fax: +1-484-595-8155; E-mail: drugsafety@shire.com**). The fax number and e-mail address are also provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Shire Medical Monitor using the details below.

For protocol- or safety-related questions or concerns during or outside normal business hours, the investigator must contact the Medical Monitor:

[redacted]**, MD**
[redacted], Clinical Medicine
Global R&D, Plasma Derived Therapies
Takeda Pharmaceutical Company Limited

Mobile: [redacted]
E-mail: [redacted]

ADDITIONAL CONTACT INFORMATION

In case of any other issues, including non-safety-related issues or if the medical monitor is unable to be reached, the investigator must contact the Shire Study Manager.

[redacted]**, RN**
E-mail: [redacted]
Mobile: [redacted]

If unavailable, please contact:

[redacted]
E-mail: [redacted]
Mobile: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Shire within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Shire licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that the product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	• Bottle/vial fill shortage or overage • Syringe/vial cracked/broken	• Syringe leakage • Missing components • Product discoloration • Device malfunction
Labeling	• Label missing • Leaflet or Instructions For Use (IFU) missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing
Packaging	• Damaged packaging (e.g., secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottles/vials • Particulate in packaging	

Please report the product quality complaint using the "Product Quality Complaint Data Collection Form" via the email address:

PQC@shire.com

Telephone number (provided for reference if needed):
Shire, Lexington, MA (USA)
1-800-828-2088

For instructions on reporting AEs related to product complaints, see Section 9.5.2.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AR	Adverse reaction
AST	Aspartate aminotransferase
AUC_{last}	The area under the concentration-time curve, from time 0 to the last quantifiable concentration, as calculated by the linear-log trapezoidal method.
BMI	Body mass index
BP	Blood pressure
BUN	blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CL/F	Apparent total plasma clearance after extravascular administration
C_{max}	Maximum observed concentration
CRF	Case report form
CRO	Contract research organization
CRU	Clinical Research Unit
CTA	Clinical Trial Agreement
D	Day
DL	Dose level
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
EOS	End of study
ET	Early termination
EU	European Union
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
h	Hour(s)
Hb	Hemoglobin

Abbreviation	Definition
Hct	Hematocrit
HbsAG	Hepatitis B surface antigen
HbsAb	Hepatitis B surface Antibody
HbcAb	Hepatitis B core Antibody
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IGI	Immune Globulin Infusion
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional Review Board
IP	Investigational product
Kg	Kilogram
LDH	lactate dehydrogenase
M	Molar
m^2	Meters squared
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
Min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
mOsmol	Milliosmolar
msec	Millisecond
nADA	Neutralizing anti-drug antibody
NCA	Noncompartmental analysis

Abbreviation	Definition
PE	Full physical examination
PID	Primary immune deficiency
P-gp	P-glycoprotein
PGx	Pharmacogenomics
PI	Principal investigator
PK	Pharmacokinetic(s)
PT	Prothrombin time
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cells
RDW	Red Cell Distribution Width
RNA	Ribonucleic acid
rHuPH20	Recombinant human hyaluronidase PH20
RR	Respiratory rate
Sch	Schedule
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SIC	Subject identification code
$t_{½}$	Terminal disposition phase half-life
TDL	Target (full) dose level
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
UPCR	urine protein to creatinine ratio
US	United States
USA	United States of America
V_z/F	Volume of distribution during the terminal disposition phase after extravascular administration
W	Week
WBC	White blood cells

1. PROTOCOL SUMMARY

1.1 Study Synopsis

<table>
<tr><td colspan="2">Protocol number: TAK-771-1001</td><td>Drug: Subcutaneous Immune Globulin Infusion 10% (Human, abbreviated as IGI, 10%) with Recombinant Human Hyaluronidase (abbreviated as rHuPH20) (referred to as HYQVIA or HyQvia)</td></tr>
<tr><td colspan="3">Title of the study: A Phase 1, Open-Label, Randomized Study to Assess the Tolerability, Safety, and Pharmacokinetics of Subcutaneous Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) with Ramp-Up and No Ramp-Up Dosing in Healthy Adult Subjects</td></tr>
<tr><td colspan="3">Number of subjects (total and for each treatment arm):
The planned total sample size for this study is 48 randomized subjects with 8 subjects enrolled in each of the 6 treatment arms.</td></tr>
<tr><td colspan="3">Site(s) and Region(s):
Single site, USA</td></tr>
<tr><td>Study period (planned):
Initiation: approximately Q3 2020
Completion: approximately Q3 2021</td><td>Clinical phase:</td><td>1</td></tr>
<tr><td colspan="3">Study Subject Population: Healthy male and female subjects aged 19 – 50 years inclusive, at screening and Body Mass Index (BMI) between 18 and 30 kg/m^2, inclusive at screening. This study plans to enroll 8 subjects in each of the 6 treatment arms, and a minimum of 3 subjects in each of the 2 BMI groups (18 to <25 kg/m^2, ≥25 to 30 kg/m^2) in each treatment arm, achievable using stratified randomization (BMI as the stratification factor).</td></tr>
<tr><td colspan="3">Objectives:
Primary:
To assess the tolerability of HYQVIA with and without ramp-up dosing in healthy adult subjects.

Secondary:
• To assess the safety and immunogenicity of HYQVIA with and without ramp-up dosing in healthy adult subjects.
• To characterize the pharmacokinetics (PK) of total IgG and IgG subclasses after subcutaneous administration of HYQVIA in healthy adult subjects.</td></tr>
<tr><td colspan="3">Rationale:
Dose ramp up has been considered necessary for HYQVIA in the Phase 3 Study (Study 161403) because the majority of CIDP patient population are naïve to subcutaneous (SC) infusions, or inexperienced with SC infusions at large volumes (>60 mL per infusion site; infusion volume maximum per day: up to 600 mL (1 site) or 1200 mL (2 sites)). As a result, a dose ramp-up schedule has been included in Study 161403, which involves stepwise gradual increase until the subject's full dose is reached to improve tolerability. Dose ramp up is currently in the approved prescribing information for primary immune deficiency. Despite the current use of ramp up dosing in PID and CIDP patients, the tolerability and safety of HYQVIA without ramp-up has not been evaluated in clinical studies. This Phase 1 study is planned to assess the tolerability, safety and immunogenicity profiles of HYQVIA with and without ramp-up dosing and to characterize the PK of total IgG and IgG subclasses after Sc administration of HYQVIA in healthy adult subjects.</td></tr>
</table>

Investigational product, dose, and mode of administration:

Subcutaneous Immune Globulin Infusion 10% (Human, abbreviated as IGI, 10%) with Recombinant Human Hyaluronidase (abbreviated as rHuPH20) (referred to as HYQVIA or HyQvia).

The target dose level (TDL) for IGI, 10% will be 0.4 g/kg (Part 1) and 1.0 g/kg (Part 2).

Dose Level 1 (DL1) =1/4 of TDL;

Dose Level 2 (DL2) =1/2 of TDL;

Dose Level 3 (DL3) =3/4 of TDL;

Dose Level 4 (DL4) =TDL.

The dose for rHuPH20 is 80 U/g IgG.

Methodology:

This study is a phase 1, open-label, randomized, single-center study to evaluate the tolerability, safety and immunogenicity of HYQVIA with and without ramp-up dosing and to characterize the PK of total IgG and IgG subclasses after SC administration of HYQVIA in healthy adult subjects.

Study Parts:

This study is comprised of two parts, Study Parts 1 & 2. The target dose level (TDL) of either 0.4g/kg (Part 1) or 1.0 g/kg (Part 2) will be achieved through dose ramp-up or no ramp up (i.e. direct administration of the TDL). Each study part consists of three Treatment Arms (Part 1: Treatment Arms 1-3 and Part 2: Treatment Arms 4-6):

- Treatment Arms 1 and 4 will follow ramp up Schedule-A (Sch-A), in which subjects will receive HYQVIA from ¼ of the TDL at Week 1 to the full TDL at Week 8.
- Treatments Arms 2 and 5 will follow ramp up Schedule-B (Sch-B), in which subjects will receive HYQVIA from ½ of the TDL at Week 1 to the full TDL at Week 5.
- Treatment Arms 3 and 6 will follow ramp up Schedule-C (Sch-C), in which subjects will directly receive the full TDL at Week 1 without ramp-up dosing.

A total of 48 subjects are planned and will be randomized to 6 parallel treatment arms (8 subjects per treatment arm, equal randomization ratio): 24 subjects in total to Part 1 and 24 subjects in total to Part 2. Treatment arms will be initiated in parallel within each study part. Each subject will participate in only one treatment arm.

After subjects in Treatment Arms 1-3 have completed Week 9 treatment in Study Part 1, and the tolerability, safety and immunogenicity data through Week 9 for the subjects has been reviewed by a safety review team consisting of the Investigator, the Sponsor's Medical Monitor, and the Sponsor’s Global Drug Safety Physician, Treatment Arms 4-6 in Study Part 2 will begin.

Study Periods

The study consists of 3 periods:

- Screening period: up to 21 days prior to first dosing.
- Study treatment period: 8 weeks for Treatment Arms 1 and 4; 9 weeks for Treatment Arms 2, 3, 5, and 6.

- Follow up period: 16 (± 1) weeks after receiving the last infusion of HYQVIA with the end of study (EOS) being in Weeks 24 (± 1) (Treatment Arms 1 and 4) or 25 (± 1) (Treatment Arms 2, 3, 5, and 6). All subjects who received at least one dose of HYQVIA (including subjects who terminate the study early) will return to the Clinical Research Unit (CRU) 16 (± 1) weeks after the last infusion of HYQVIA for follow-up procedures.

Tolerability, safety and immunogenicity will be assessed throughout the treatment period for all treatment arms.

The PK of immunoglobin G (IgG) and IgG subclasses will be characterized based on their serum concentration-time profiles post the first infusion.

All subjects will be monitored for the formation of binding anti-rHuPH20 antibodies (binding ADA). Samples with antibody titers ≥1:160 (ADA positive) will be analyzed for the presence of neutralizing antibodies. At any time over the course of the study, subjects who have (a) 2 consecutive anti-rHuPH20 antibody titers of ≥1:160 that are elevated from the subject's baseline titers, and (b) a moderate or severe AE that may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other concomitant medications will be asked to return to the CRU as soon as possible to undergo an additional panel of immunogenicity testing.

After the EOS visit has been completed, no further visits are planned, unless determined necessary by the investigator. Positive binding antibody titers associated with serious or severe AEs may require additional follow-up assessments.

Eligibility criteria:

The subject will not be considered eligible for the study without meeting all the criteria below. Subjects cannot be randomized or enrolled before all inclusion and exclusion criteria (including laboratory test results) are within acceptable ranges as per protocol.

Inclusion Criteria:

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent as applicable to participate in the study.
3. Age 19-50 years inclusive at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
4. Male, or non-pregnant, non-breastfeeding female who agrees to comply with any applicable contraceptive requirements of the protocol, or females of non-childbearing potential.
5. Must be considered "healthy". Healthy as determined by the investigator on the basis of screening evaluations and healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.
6. Body mass index (BMI) between 18.0 and 30.0 kg/m² inclusive.

Exclusion Criteria:

1. Any current or relevant history of medical (e.g. any hematological, hepatic, respiratory, cardiovascular, renal or neurological) or psychiatric conditions, which by judgment of the investigator might compromise the safety of the subject or integrity of the study, interfere with the subject's participations in the trial and compromise the trial objectives or any condition that presents undue risk from the investigational product or procedures.

   Note: Subjects on stable dose of hormone replacements (i.e. thyroid hormone replacement) or oral contraceptives are permitted.
2. Clinically significant cardiac conditions including but not limited to uncontrolled hypertension, myocardial infarction, unstable coronary artery disease and clinically significant arrythmias and conduction disorders.
3. Known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients (e.g. human IG, hyaluronidase, albumin).
4. Known history of hypersensitivity or severe allergic reactions (e.g. urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following administration of blood or blood components.
5. Significant illness, as judged by the investigator, within 30 days of the first dose of investigational product.
6. Known history of alcohol or other substance abuse within the last year.
7. Donation of blood within 60 days, or blood products (e.g., plasma or platelets) within 2 weeks prior receiving the first dose of investigational product.
8. Subjects will be excluded if any of the following laboratory parameters meet the criteria below:
   - Hemoglobin < 11 g/dL
   - Absolute neutrophil count ≤1500/mm and platelet count ≤100,000/mm^3
   - Liver function: alanine aminotransferase (ALT) ≥2.5 × upper limit normal (ULN), aspartate aminotransferase (AST) ≥2.5 × upper limit normal (ULN), alkaline phosphatase ≥1.5 × ULN or total bilirubin ≥1.5 mg/dL
   - Renal function: creatinine clearance ≤60 mL/min based on Cockcroft-Gault equation
   - Coagulation tests: aPTT >1.2 X ULN; INR >1.2

   Subjects will be excluded if any other laboratory values are outside the reference range and are clinically significant per investigator's judgment.
9. Within 30 days prior to the first dose of investigational product:
   - Has participated in another clinical study involving immunoglobulin products within 12 months of screening.
   - Have used an investigational product (or 5 half-lives, whichever is longer).
   - Have been enrolled in a clinical study (including vaccine studies or has been vaccinated with approved product) that, in the investigator's opinion, may impact this study. Subjects who have received any vaccine (including live attenuated vaccines) during the last 30 days before dosing will be excluded. No live attenuated virus vaccines are allowed during the study until the end of the follow up period.
   - Have had any substantial changes in eating habits, as assessed by the investigator.

10. Confirmed systolic blood pressure >139 mmHg or <89 mmHg and diastolic blood pressure >89 mmHg or <49 mmHg.
11. A positive screen for alcohol or drugs of abuse at screening or D-1.
12. A positive HIV, HCV, or ongoing/active hepatitis B infection at screening. Subjects with immunity to hepatitis B from either active vaccination or from previous natural infection are eligible to participate in the study.
13. Smoking more than 5 cigarettes or equivalent per day, unable to stop smoking during confinement in the CRU.
14. Severe dermatitis or anatomical abnormality that would interfere with HYQVIA administration or endpoint assessments. Note: the skin at the administration site should not be covered by tattoos.
15. Current use of any herbal, or homeopathic preparations are not permitted.
16. Unable or unwilling to discontinue antihistamines or medications with antihistamine properties, sedatives, anxiolytics, systemic steroids, or topical steroids or antibiotics on any area below the chest for a minimum of 48 hours prior to each infusion visit and through 72 hours post last infusion.
17. Current or relevant history of hypercoagulable conditions (e.g. Protein C, Protein S, and antithrombin III deficiency), thrombotic/thromboembolic events or venous thrombosis.

Maximum duration of subject involvement in the study:

Planned Study Duration: Up to 28 weeks from screening to EOS

Duration of Treatment: Up to 9 weeks

Endpoints and statistical analysis:

Primary Endpoints:

The primary endpoint corresponding to the primary objective of the study is the occurrence of tolerability events related to the infusion of HYQVIA.

Definition: An infusion is considered tolerable if the infusion rate was not reduced or the infusion was not interrupted or stopped, due to HYQVIA infusion.

A tolerability event is considered to have occurred if an infusion was tolerable. Tolerability events will be measured in terms of the number and percentage of subjects for which the infusion was tolerable.

Secondary Endpoints:

Safety and Immunogenicity endpoints:

- Occurrence of TEAEs, including but not limited to: HYQVIA-related and non-related *, serious, nonserious, severe, local and systemic TEAEs, TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs, as well as number and percentage of subjects and infusions with suspected adverse reactions plus adverse reactions of interest (additional information is provided in Section 10.10).

  * Any TEAE that is recorded by the investigator as "possibly related" or "probably related" to HYQVIA will be considered HYQVIA-related AE, and any AE recorded as "unlikely related" or "not related" will be considered unrelated AE.

- Clinical laboratory parameters
- Vital signs

- Immunogenicity: occurrence of binding and neutralizing antibodies to rHuPH20

Note that clinically significant treatment-emergent changes in clinical laboratory measurements and vital signs will be recorded in the study database as TEAEs.

PK endpoints:

- PK parameters for serum total IgG and IgG subclasses after a single dose of HYQVIA (i.e. after Week 1 dosing), including but are not limited to C_{max}, T_{max}, AUC_{last}, $t_{1/2}$, CL/F and V_z/F.

Statistical Considerations:

No interim analysis is planned for this study.

No statistical hypothesis testing will be performed.

Tolerability, safety and immunogenicity endpoint data will be analyzed using descriptive statistics. Continuous endpoints (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. Baseline is defined as the last non-missing value before the initial dose of HYQVIA. Categorical endpoints (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.

Summaries of AEs, labs, vital signs, and immunogenicity will be presented, as appropriate, by dosing group (Ramp-Up, No Ramp-Up) and treatment arms within dosing schedule, as displayed with the planned total sample size and sample size for each treatment arm:

Ramp-Up (N=32)					**No Ramp-Up (N=16)**		
Schedule A		**Schedule B**		**Total**	**Schedule C**		**Total**
Low	**High**	**Low**	**High**		**Low**	**High**	
Treatment 1 (n=8)	Treatment 4 (n=8)	Treatment 2 (n=8)	Treatment 5 (n=8)	All (n=32)	Treatment 3 (n=8)	Treatment 6 (n=8)	All (n=16)
Low=0.4 g/kg, High=1.0 g/kg.							

Additional summaries will be presented by visit/time point (e.g., laboratory parameters).

The overall summary, based on descriptive statistics, is the summary of the overall tolerability/safety/immunogenicity profile in the Ramp-Up dosing group (all treatments pooled) versus the overall profile in the No Ramp-Up group (all treatments pooled).

Claim of tolerability/safety/immunogenicity of HYQVIA will be based on clinical judgment on the totality of evidence, to be derived from the overall summary, with no predefined tolerability/safety/immunogenicity statistical margin or criteria.

Note: AEs below refer to TEAEs.

The following will be displayed in statistical outputs, including but not limited to:

- Number (percentage) of subjects with HYQVIA-related AEs (causally related AEs), and HYQVIA-related SAEs, and number of such events
  - AEs recorded in the study database as "possibly related" or "probably related" to HYQVIA will be considered HYQVIA-related AEs
- Number (percentage) of subjects with HYQVIA-related AEs that were mild, moderate, or severe in severity, and number of events in each category
- Number (percentage) of subjects with any AEs, any serious and/or nonserious AEs, and any local and systemic AEs/SAEs, regardless of causality
- Number (percentage) of infusions for which the infusion rate was reduced, and/or the infusion was interrupted or stopped due to intolerability and/or AEs.
- Number (percentage) subjects who completed infusions without requiring any adjustment due to intolerability and/AEs
- Number (percentage) of subjects who prematurely discontinued study due to AEs
- Rate of AEs, expressed as number of events per infusion, per subject, and per subject-year
- Raw (actual) values and change from baseline in clinical laboratory parameters
- Raw (actual) values and change from baseline in vital signs
- Number (percentage) of subjects who have developed binding and neutralizing antibodies to rHuPH20.

Subject-level tolerability and safety data, including derived data, will be presented in subject data listings.

The PK parameters including but not limited to the following, will be calculated for total IgG and IgG subclasses in serum, as appropriate, using noncompartmental analysis (NCA):

- AUC_{last}, C_{max}, t_{max}, $t_{½}$, CL/F, and V_z/F.

Sample Size Justification:

Assessment of tolerability to HYQVIA SC administration is the primary objective of this study.

This study is not designed for statistical hypothesis testing, and therefore the sample size was not based on statistical considerations. The planned total sample size for this study is 48 randomized subjects (8 subjects per treatment arm and 6 treatment arms, equal randomization ratio).

Of the 48 subjects to be randomized, a minimum of 36 subjects are expected to complete the study, assuming a conservative overall dropout rate of 25% in this healthy subject study (overall dropout rates assumed for HYQVIA patient studies are generally 10%-15%). The number of subjects expected to complete the study (36) is considered adequate for providing statistically reliable assessment of tolerability, safety, immunogenicity, and PK.

1.2 Study Schematic

Study Part 1: Treatment Arms 1, 2 and 3 (TDL=0.4 g/kg)

Treatment Arm	Screening	Study Week										
	Within 21 days	W1D1	W1	W2	W3		W5		W8	W9*		W24	W25
1 Sch-A	SCREEN	RANDO	DL1	DL1	DL2		DL3		DL4			FU/EOS	
2 Sch-B			DL2		DL2		DL4			DL4			FU/EOS
3 Sch-C			DL4				DL4			DL4			FU/EOS

Abbreviations:
Screen = Screening; Rando = Randomization to a Schedule; Sch = Schedule;
DL = Dose Level; TDL = Target Dose Level; DL1 = ¼ TDL; DL2 -= ½ TDL; DL3 = ¾ TDL; DL4 = TDL; FU/EOS = Follow up/End Of Study.
* Safety Data Review after all subjects in Study Part 1 complete Week 9 dosing.

After all subjects in Study Part 1 complete Week 9, a safety data review of the data collected through Week 9 will be conducted before the first dosing is initiated in Study Part 2.

Study Part 2: Treatment Arms 4, 5 and 6 (TDL=1.0 g/kg)

Treatment Arm	Screening	Study Week										
	Within 21 days	W1D1	W1	W2	W3		W5		W8	W9		W24	W25
4 Sch-A	SCREEN	RANDO	DL1	DL1	DL2		DL3		DL4			FU/EOS	
5 Sch-B			DL2		DL2		DL4			DL4			FU/EOS
6 Sch-C			DL4				DL4			DL4			FU/EOS

Abbreviations:
Screen = Screening; Rando = Randomization to a Schedule; Sch = Schedule;
DL = Dose Level; TDL = Target Dose Level; DL1 = ¼ TDL; DL2 -= ½ TDL; DL3 = ¾ TDL; DL4 = TDL;
FU/EOS = Follow up/End Of Study.

1.3 Study Schedules

1.3.1 Schedule of Study Procedures: Treatment Arms 1 and 4

Visit/Assessment	Screening Period		Treatment Period								Follow-up Period (EOS/ET)
Study Week/Day	Within 21 Days prior to dosing	D-1	W1				W2	W3	W5	W8	W24 (+/- 1 week)
			D1	D2	D4	D6	D8	D15 ±2	D29 ±2	D50 ±3	
Informed Consent[1]	X										
Demographics[2]	X										
Visit at Clinical Site	X	X[6]	X[6]	X	X	X	X[6]	X[6]	X[6]	X[6]	X
Inclusion/Exclusion Criteria	X	X									
Medical History[3]	X	X									
Concomitant Medications	◄----------										----------►
Randomization			X								
Physical Examination [4]	X	X					X	X	X	X	X
Height &BMI calculation (screening only), Weight Measurements[5]	X	X					X	X	X	X	X
Study Treatment Administration [7]			DL1				DL1	DL2	DL3	DL4	
Drugs of Abuse/Alcohol Screen[8]	X	X									
Infusion Site Evaluation[9]			X	X	X	X	X	X	X	X	
HIV, HBV, HCV[10]	X										X
Pregnancy (all females) & FSH (postmenopausal females only)[11]	X	X					X	X	X	X	X
Adverse Events/Serious Adverse Events	◄----------										----------►
Vital Signs [12]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[13]	X										X
Serum Chemistry, Hematology, and Urinalysis [14]	X	X						X	X	X	X
Hemolytic Panel[15]		X	◄----------				X (as applicable)				----------►
Coagulation Tests[16]	X										X

Visit/Assessment	Screening Period		Treatment Period								Follow-up Period (EOS/ET)
Study Week/Day	Within 21 Days prior to dosing	D-1	W1				W2	W3	W5	W8	W24 (+/- 1 week)
			D1	D2	D4	D6	D8	D15 ±2	D29 ±2	D50 ±3	
rHuPH20 Immunogenicity: ADA and nADA Blood Collection			X						X	X	X
PK Blood Sample Collection[17]			X	X	X	X	X				
Immunogenicity Panel[18]			X	← X (as applicable) →							

Abbreviations: ADA=anti-drug antibody; BMI=body mass index; BP= blood pressure; BUN= blood urea nitrogen; CBC= complete blood count; CRU= Clinical Research Unit; D=Day; DL=dose level; ECG=electrocardiogram; EOS=end of study; ET=early termination; FSH=follicle stimulating hormone; Hb=Hemoglobin, Hct=Hematocrit; HBsAG=hepatitis B surface antigen; HBsAb= Hepatitis B surface Antibody; HBcAb= hepatitis B core Antibody; HBV= hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR= heart rate; LDH= lactate dehydrogenase; MCH= Mean Corpuscular Hemoglobin; MCHC= Mean Corpuscular Hemoglobin Concentration; MCV= Mean Corpuscular Volume; nADA=neutralizing anti-drug antibody; PI= Principal Investigator; PK=pharmacokinetic; RBC= red blood cell; RDW= Red Cell Distribution Width; RR= respiratory rate; TDL= Target dose level; UPCR= urine protein to creatinine ratio; W=week; WBC= white blood cells.

1. Written consent must be obtained prior to performing any protocol specific procedure.
2. Age, gender, ethnicity, and race.
3. Medical History: includes any significant or relevant diseases, surgeries, or other medical events and medication/treatment history if applicable.
4. Physical Examination: Full physical examination will be performed at screening and EOS/ET visit, and partial physical examination can be done at the rest of the visits to assess any new abnormalities or changes from baseline.
   Full physical examination will include general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological.
   Partial physical examination will include: general appearance, head and neck, assessment of injection sites, and skin. Other organ systems will be assessed per PI's judgment (Section 8.2.3.1).
5. **Height and BMI will be assessed at the first physical examination only.**
   Weight: Body weight will be measured on the day of each dosing specified in **Section 1.3.1**. The dose should be recalculated if the body weight differs more than 10% from the previous dosing day body weight.
6. Overnight stay at the CRU. Subjects will check in on D -1 and will stay for 2 overnights for the first visit (D-1 and D1). For rest of the visits subjects will be confined to the CRU for 24 hours from the start of the infusion. During confinement period, standard meals and snacks will be provided at appropriate times. Subjects must be well hydrated prior to drug administration.
7. The TDL is 0.4 and 1.0 g/kg with rHuPH20 80U/g IgG for Study Parts 1 and 2, respectively. Each DL is calculated as the following: DL1=1/4 of TDL; DL2=1/2 of TDL; DL3 =3/4 of TDL; and DL4=TDL. See also footnote 5.
8. Drug screen will include: opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone), amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, phencyclidine. See Section 8.2.3.6.

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9. Infusion sites will be evaluated for any potential local or systemic effects such as infusion site (local) events (e.g. erythema, pain, oedema and leaking). Subjects will also be evaluated/observed for acute or delayed allergic reactions, change in vital signs, pyrexia, upper abdominal pain, nausea, vomiting, diarrhea, and/ or pain in extremities. Please refer also to Section 9.7 and Table 8 in Section 8.2.4.2 for more information about infusion related AEs.
10. Testing will be performed by the local laboratory at Screening, during the follow up period and at EOS/ET. Include HCV antibody, HBsAg, HBsAb, HBcAb and HIV 1/2 antibodies. Subjects who are HIV, HBsAg or HCV antibody positive at screening will not be enrolled.
11. Pregnancy test will be done only in women of childbearing potential. Serum pregnancy test will be obtained at screening and subjects must have a negative serum pregnancy test (within 7 days prior to inclusion). For subsequent dosing days, a urine pregnancy test prior to dosing will be acceptable. Follicle stimulating hormone (FSH) levels may be done once at screening on menopausal or peri-menopausal women, or as judged by investigator
12. Vital signs, RR, HR, BP and body temperature will be measured at screening. Only BP, HR and RR will be measured every 30 minutes from starting the infusion until the end of infusion, and every 1-2 hours after the infusion for 8 hours, at discharge and as needed per investigator's judgment until discharged.
13. ECGs (12-lead) will be collected at prespecified time points in the **Section 1.3.1** and **as clinically indicated**.
14. **Hematology includes** CBC (Hct, Hg, RBC, RDW, MCV, MCH, MCHC, platelets, WBC with absolute differential counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils). See Section 8.2.3.4.2.
    Serum Chemistry ALT, AST, ALP, K+, Na+, Cl-, Ca^{2+}+Mg^{2+}, Bilirubin (total and direct), LDH, BUN, creatinine, uric acid, glucose , albumin, lipid profile. See Section 8.2.3.4.1.
    Urine Test. Urinalysis will include color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase.
    Dipstick urine test is acceptable. Microscopic analyses will be done if clinically indicated. If ≥ 2+ protein on urine dipstick, then collect spot urine sample to calculate UPCR or collect 24h urine. Tests will be performed at prespecified time points in the **Section 1.3.1** and as **clinically indicated**. No need to repeat before first dose if screening test is done within 7 days. See Section 8.2.3.4.4.
15. The hemolytic anemia panel will consist of Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive), reticulocyte count, as well as urine hemosiderin. The lab results obtained from the D-1 and will serve as the baseline values. In case of absence of D-1 result for any reason screening Hgb result serve as the baseline Hgb value. Hgb and LDH values can be taken from the hematology and clinical chemistry panels, if conducted on the same day as the hemolytic panel. For subsequent tests, if there is a reduction in Hgb of 1 g/dL or more compared to baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 h; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible, but at the next scheduled visit, at the latest. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia. Any LDH test result of 2× ULN or greater will trigger analysis of the sample for LDH isoenzymes (see Section 8.2.3.4.3).
16. aPTT and INR: assessments will be performed at specified time points in the **Section 1.3.1** and **as clinically indicated. See Section 8.2.3.4.5**.
17. PK samples will be obtained at specified time points in the **Section 1.3.1** and on the subsequent days approximately the same time as the start of Day 1 dosing.
18. The immunogenicity panel outlined in Section 8.2.4.2 will be collected at baseline (D1) and any time deemed necessary during the course of the study. Subjects, who have (a) two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers, and (b) a moderate or severe AE which may be a result of immune-mediated response to either immunoglobulin, rHuPH20 (see Table 8), or other concomitant medications , will be asked to return to the CRU as soon as possible to undergo an additional panel of immunogenicity testing outlined in Table 9.

Note: Multiple activities scheduled on the same day or at the same time will be conducted in the following order, when applicable: ECG, vital signs, blood sampling and study drug administration.

1.3.2 Schedule of Study Procedures: Treatment Arms 2 and 5

Visit/Assessment	Screening Period		Treatment Period								Follow-up Period (EOS/ET)	
Study Week/Day	Within 21 Days prior to dosing	D-1	W1				W2	W3	W5	W9	W25 (+/- 1 week) [6]	
			D1	D2	D4	D6	D8	D15 ±2	D29 ±2	D57 ±3		
Informed Consent[1]	X											
Demographics[2]	X											
Visit at Clinical Site	X	X[6]	X[6]	X	X	X	X	X[6]	X[6]	X[6]	X	
Inclusion/Exclusion Criteria	X	X										
Medical History[3]	X	X										
Concomitant Medications	◄----------										----------►	
Randomization			X									
Physical Examination [4]	X	X						X	X	X	X	
Height &BMI Calculation (screening only) & Weight Measurements[5]	X	X						X	X	X	X	
Study Treatment Administration [7]			DL2					DL2	DL4	DL4		
Drugs of Abuse/Alcohol Screen[8]	X	X										
Infusion Site Evaluation [9]			X	X	X	X	X	X	X	X		
HIV, HBV, HCV[10]	X										X	
Pregnancy (all females) & FSH (postmenopausal females only)[11]	X	X						X	X	X	X	
Adverse Events/Serious Adverse Events	◄----------										----------►	
Vital Signs [12]	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[13]	X										X	
Serum Chemistry, Hematology, and Urinalysis [14]	X	X						X	X	X	X	
Hemolytic Panel[15]		X	◄----------					X (as applicable)			----------►	
Coagulation Tests[16]	X										X	
rHuPH20 Immunogenicity: ADA and nADA Blood Collection			X						X	X	X	

Visit/Assessment	Screening Period		Treatment Period								Follow-up Period (EOS/ET)	
Study Week/Day	Within 21 Days prior to dosing	D-1	W1				W2	W3	W5	W9	W25 (+/- 1 week) [6]	
			D1	D2	D4	D6	D8	D15 ±2	D29 ±2	D57 ±3		
PK Blood Sample Collection[17]			X	X	X	X	X	X				
Immunogenicity Panel[18]			X	← X (as applicable) →								

Abbreviations: ADA=anti-drug antibody; BMI=body mass index; BP= blood pressure; BUN= blood urea nitrogen; CBC= complete blood count; CRU= Clinical Research Unit; D=Day; DL=dose level; ECG=electrocardiogram; EOS=end of study; ET=early termination; FSH=follicle stimulating hormone; Hb=Hemoglobin, Hct=Hematocrit; HBsAG=hepatitis B surface antigen; HBsAb= Hepatitis B surface Antibody; HBcAb= hepatitis B core Antibody; HBV= hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR= heart rate; LDH= lactate dehydrogenase; MCH= Mean Corpuscular Hemoglobin; MCHC= Mean Corpuscular Hemoglobin Concentration; MCV= Mean Corpuscular Volume; nADA=neutralizing anti-drug antibody; PI= Principal Investigator; PK=pharmacokinetic; RBC= red blood cell; RDW= Red Cell Distribution Width; RR= respiratory rate; TDL= Target dose level; UPCR= urine protein to creatinine ratio; W=week; WBC= white blood cells.

1. Written consent must be obtained prior to performing any protocol specific procedure.
2. Age, gender, ethnicity, and race.
3. Medical History: includes any significant or relevant diseases, surgeries, or other medical events and medication/treatment history if applicable.
4. Physical Examination: Full physical examination will be performed at screening and EOS/ET visit, and partial physical examination can be done at the rest of the visits to assess any new abnormalities or changes from baseline.
   Full physical examination will include general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological.
   Partial physical examination will include: general appearance, head and neck, assessment of injection sites, skin. Other organ systems will be assessed per PI's judgment (Section 8.2.3.1).
5. **Height and BMI will be assessed at the first physical examination only.**
   Weight: Body weight will be measured on the day of each dosing specified in **Section 1.3.2.** The dose should be recalculated if the body weight differs more than 10% from the previous dosing day body weight.
6. Overnight stay at the CRU. Subjects will check in on D -1 and will stay for 2 overnights for the first visit (D-1 and D1). For rest of the visits subjects will be confined to the CRU for 24 hours from the start of the infusion. During confinement period, standard meals and snacks will be provided at appropriate times. Subjects must be well hydrated prior to drug administration.
7. The TDL is 0.4 and 1.0 g/kg with rHuPH20 80U/g IgG for Study Parts 1 and 2, respectively. Each DL is calculated as the following: DL1=1/4 of TDL; DL2=1/2 of TDL; DL3 =3/4 of TDL; and DL4=TDL**.** See also footnote 5.
8. Drug screen will include: opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone), amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, phencyclidine. See Section 8.2.3.6.
9. Infusion sites will be evaluated for any potential local or systemic effects such as infusion site (local) events (e.g. erythema, pain, oedema and leaking). Subjects will also be evaluated/observed for acute or delayed allergic reactions, change in vital signs, pyrexia, upper abdominal pain, nausea, vomiting, diarrhea, and/ or pain in extremities. Please refer also to Section 9.7 and Table 8 in Section 8.2.4.2 for more information about infusion related AEs.

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10. Testing will be performed by the local laboratory at Screening, during the follow up period and at EOS/ET. Include HCV antibody, HBsAg, HBsAb, HBcAb and HIV 1/2 antibodies. Subjects who are HIV, HBsAg or HCV antibody positive at screening will not be enrolled.
11. Pregnancy test will be done only in women of childbearing potential. Serum pregnancy test will be obtained at screening and subjects must have a negative serum pregnancy test (within 7 days prior to inclusion). For subsequent dosing days, a urine pregnancy test prior to dosing will be acceptable. Follicle stimulating hormone (FSH) levels may be done once at screening on menopausal or peri-menopausal women, or as judged by investigator
12. Vital signs, RR, HR, BP and body temperature will be measured at screening. Only BP, HR and RR will be measured every 30 minutes from starting the infusion until the end of infusion, and every 1-2 hours after the infusion for 8 hours, at discharge and as needed per investigator's judgment until discharged.
13. ECGs (12-lead) will be collected at prespecified time points in the **Section 1.3.2** and **as clinically indicated**.
14. **Hematology includes** CBC (Hct, Hg, RBC, RDW, MCV, MCH, MCHC, platelets, WBC with absolute differential counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils). See Section 8.2.3.4.2.
    Serum Chemistry ALT, AST, ALP, K+, Na+, Cl-, Ca^{2}+Mg^{2+}, Bilirubin (total and direct)LDH, BUN, creatinine, uric acid, glucose, albumin, lipid profile. See Section 8.2.3.4.1.
    Urine Test. Urinalysis will include color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase. **Dipstick urine test is acceptable**. Microscopic analyses will be done if clinically indicated. If ≥ 2+ protein on urine dipstick, then collect spot urine sample to calculate UPCR or collect 24h urine. Tests will be performed at prespecified time points in the **Section 1.3.2** and **as clinically indicated**. No need to repeat before first dose if screening test is done within 7 days. See Section 8.2.3.4.4.
15. The hemolytic anemia panel will consist of Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive), reticulocyte count, as well as urine hemosiderin. The lab results obtained from the D-1 and will serve as the baseline values. In case of absence of D-1 result for any reason screening Hgb result serve as the baseline Hgb value. Hgb and LDH values can be taken from the hematology and clinical chemistry panels, if conducted on the same day as the hemolytic panel. For subsequent tests, if there is a reduction in Hgb of 1 g/dL or more compared to baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 h; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible, but at the next scheduled visit, at the latest. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia Any LDH test result of 2× ULN or greater will trigger analysis of the sample for LDH isoenzymes (see Section 8.2.3.4.3).
16. aPTT and INR: assessments will be performed at specified time points in the **Section 1.3.2** and **as clinically indicated. See Section 8.2.3.4.5.**
17. PK samples will be obtained at specified time points in the **Section 1.3.2** and on the subsequent days approximately the same time as the start of Day 1 dosing.
18. The immunogenicity panel outlined in Section 8.2.4.2 will be collected at baseline (D1) and any time deemed necessary during the course of the study. Subjects who have (a) two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers, and (b) a moderate or severe AE which may be a result of immune-mediated response to either immunoglobulin, rHuPH20 (see Table 8), or other concomitant medications, will be asked to return to the CRU as soon as possible to undergo an additional panel of immunogenicity testing outlined in Table 9.

Note: Multiple activities scheduled on the same day or at the same time will be conducted in the following order, when applicable: ECG, vital signs, blood sampling and study drug administration.

1.3.3 Schedule of Study Procedures: Treatment Arms 3 and 6

Visit/Assessment	**Screening Period**		**Treatment Period**								**Follow-up Period (EOS/ET)**
Study Week/Day	**Within 21 D prior to dosing**	**D-1**	**W1**				**W2**	**W3**	**W5**	**W9**	**W25 (+/- 1 week)[6]**
			D1	**D2**	**D4**	**D6**	**D8**	**D15 ±2**	**D29 ±2**	**D57 ±3**	
Informed Consent[1]	X										
Demographics[2]	X										
Visit at Clinical Site	X	X[6]	X[6]	X	X	X	X	X	X[6]	X[6]	X
Inclusion/Exclusion Criteria	X	X									
Medical History[3]	X	X									
Concomitant Medications	◄----------										----------►
Randomization			X								
Physical Examination [4]	X	X							X	X	X
Height & BMI Calculation (screening only), Weight Measurements[5]	X	X							X	X	X
Study Treatment Administration [7]			DL4						DL4	DL4	
Drugs of Abuse/Alcohol Screen[8]	X	X									
Infusion Site Evaluation [9]			X	X	X	X	X	X	X	X	
HIV, HBV, HCV[10]	X										X
Pregnancy (all females) & FSH (postmenopausal females only)[11]	X	X							X	X	X
Adverse Events/Serious Adverse Events	◄----------										----------►
Vital Signs [12]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[13]	X										X
Serum Chemistry, Hematology, and Urinalysis [14]	X	X						X	X	X	X
Hemolytic Panel[15]		X	◄----------				X (as applicable)			----------►	
Coagulation Tests[16]	X										X

Visit/Assessment	Screening Period		Treatment Period								Follow-up Period (EOS/ET)
Study Week/Day	Within 21 D prior to dosing	D-1	W1				W2	W3	W5	W9	W25 (+/- 1 week)[6]
			D1	D2	D4	D6	D8	D15 ±2	D29 ±2	D57 ±3	
rHuPH20 Immunogenicity: ADA and nADA Blood Collection			X						X	X	X
PK Blood Sample Collection[17]			X	X	X	X	X	X	X		
Immunogenicity Panel[18]			X	← X (as applicable) →							

Abbreviations: ADA=anti-drug antibody; BMI=body mass index; BP= blood pressure; BUN= blood urea nitrogen; CBC= complete blood count; CRU= Clinical Research Unit; D=Day; DL=dose level; ECG=electrocardiogram; EOS=end of study; ET=early termination; FSH=follicle stimulating hormone; Hb=Hemoglobin, Hct=Hematocrit; HBsAG=hepatitis B surface antigen; HBsAb= Hepatitis B surface Antibody; HBcAb= hepatitis B core Antibody; HBV= hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR= heart rate; LDH= lactate dehydrogenase; MCH= Mean Corpuscular Hemoglobin; MCHC= Mean Corpuscular Hemoglobin Concentration; MCV= Mean Corpuscular Volume; nADA=neutralizing anti-drug antibody; PI= Principal Investigator; PK=pharmacokinetic; RBC= red blood cell; RDW= Red Cell Distribution Width; RR= respiratory rate; TDL= Target dose level; UPCR= urine protein to creatinine ratio; W=week; WBC= white blood cells.

1. Written consent must be obtained prior to performing any protocol specific procedure.
2. Age, gender, ethnicity, and race.
3. Medical History: includes any significant or relevant diseases, surgeries, or other medical events and medication/treatment history if applicable.
4. Physical Examination: Full physical examination will be performed at screening and EOS/ET visit, and partial physical examination can be done at the rest of the visits to assess any new abnormalities or changes from baseline.
   Full physical examination will include general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological.
   Partial physical examination will include: general appearance, head and neck, assessment of injection sites, skin. Other organ systems will be assessed per PI's judgment (Section 8.2.3.1).
5. **Height and BMI will be assessed at the first physical examination only.**
   Weight: Body weight will be measured on the day of each dosing specified in **Section 1.3.3.** The dose should be recalculated if the body weight differs more than 10% from the previous dosing day body weight.
6. Overnight stay at the CRU. Subjects will check in on D -1 and will stay for 2 overnights for the first visit (D-1 and D1). For rest of the visits subjects will be confined to the CRU for 24 hours from the start of the infusion. During confinement period, standard meals and snacks will be provided at appropriate times. Subjects must be well hydrated prior to drug administration.
7. The TDL is 0.4 and 1.0 g/kg with rHuPH20 80U/g IgG for Study Parts 1 and 2, respectively. Each DL is calculated as the following: DL1=1/4 of TDL; DL2=1/2 of TDL; DL3 =3/4 of TDL; and DL4=TDL**.** See also footnote 5.
8. Drug screen will include: opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone), amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, phencyclidine. See Section 8.2.3.6.

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9. Infusion sites will be evaluated for any potential local or systemic effects such as infusion site (local) events (e.g. erythema, pain, oedema and leaking). Subjects will also be evaluated/observed for acute or delayed allergic reactions, change in vital signs, pyrexia, upper abdominal pain, nausea, vomiting, diarrhea, and/ or pain in extremities. Please refer also to Section 9.7 and Table 8 in Section 8.2.4.2 for more information about infusion related AEs.
10. Testing will be performed by the local laboratory at Screening, during the follow up period and at EOS/ET. Include HCV antibody, HBsAg, HBsAb, HBcAb and HIV 1/2 antibodies. Subjects who are HIV, HBsAg or HCV antibody positive at screening will not be enrolled.
11. Pregnancy test will be done only in women of childbearing potential. Serum pregnancy test will be obtained at screening and subjects must have a negative serum pregnancy test (within 7 days prior to inclusion). For subsequent dosing days, a urine pregnancy test prior to dosing will be acceptable. Follicle stimulating hormone (FSH) levels may be done once at screening on menopausal or peri-menopausal women, or as judged by investigator
12. Vital signs, RR, HR, BP and body temperature will be measured at screening. Only BP, HR and RR will be measured every 30 minutes from starting the infusion until the end of infusion, and every 1-2 hours after the infusion for 8 hours, at discharge and as needed per investigator's judgment until discharged.
13. ECGs (12-lead) will be collected at prespecified time points in the **Section 1.3.3** and **as clinically indicated**.
14. **Hematology includes** CBC (Hct, Hg, RBC, RDW, MCV, MCH, MCHC, platelets, WBC with absolute differential counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils). See Section 8.2.3.4.2.
    Serum Chemistry ALT, AST, ALP, K+, Na+, Cl-, Ca^{2+}+Mg^{2+}, Bilirubin (total and direct), LDH, BUN, creatinine, uric acid, glucose, albumin, lipid profile. See Section 8.2.3.4.1.
    Urine Test. Urinalysis will include color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase. **Dipstick urine test is acceptable**. Microscopic analyses will be done if clinically indicated. If ≥ 2+ protein on urine dipstick, then collect spot urine sample to calculate UPCR or collect 24h urine. Tests will be performed at prespecified time points in the **Section 1.3.3** and **as clinically indicated**. No need to repeat before first dose if screening test is done within 7 days. See Section 8.2.3.4.4.
15. The hemolytic anemia panel will consist of Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive), reticulocyte count, as well as urine hemosiderin. The lab results obtained from the D-1 and will serve as the baseline values. In case of absence of D-1 result for any reason screening Hgb result serve as the baseline Hgb value. Hgb and LDH values can be taken from the hematology and clinical chemistry panels, if conducted on the same day as the hemolytic panel. For subsequent tests, if there is a reduction in Hgb of 1 g/dL or more compared to baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 h; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible, but at the next scheduled visit, at the latest. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia. Any LDH test result of 2× ULN or greater will trigger analysis of the sample for LDH isoenzymes (see Section 8.2.3.4.3).
16. aPTT and INR: assessments will be performed at specified time points in the **Section 1.3.3** and **as clinically indicated. See Section 8.2.3.4.5.**
17. PK samples will be obtained at specified time points in the **Section 1.3.3** and on the subsequent days approximately the same time as the start of Day 1 dosing.
18. The immunogenicity panel outlined in Section 8.2.4.2 will be collected at baseline (D1) and any time deemed necessary during the course of the study. Subjects who have (a) two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers, and (b) a moderate or severe AE which may be a result of immune-mediated response to either immunoglobulin, rHuPH20 (see Table 8), or other concomitant medications will be asked to return to the CRU as soon as possible to undergo an additional panel of immunogenicity testing outlined in Table 9).

Note: Multiple activities scheduled on the same day or at the same time will be conducted in the following order, when applicable: ECG, vital signs, blood sampling and study drug administration.

2. BACKGROUND INFORMATION

HYQVIA (also known as TAK-771) is an immune globulin infusion (IGI) (Human) 10% with a recombinant human hyaluronidase (rHuPH20) indicated for the treatment of Primary Immunodeficiency in adults. This includes, but is not limited to, common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (Baxalta US Inc., 2019). HYQVIA is administered subcutaneously and has 2 components, Human IGI, 10% which provides the therapeutic effect, and rHuPH20 which enhances the absorption and dispersion of the volume when using a subcutaneous administration.

The IGI, 10% (Human) of HYQVIA supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The IGI, 10% (Human) also contains a spectrum of antibodies capable of interacting with and altering the activity of cells of the immune system as well as antibodies capable of reacting with cells such as erythrocytes. The role of these antibodies and the mechanisms of action of IgG in the IGI, 10% (Human) of HYQVIA have not been fully elucidated (Baxalta US Inc., 2019).

Hyaluronan is a polysaccharide found in the extracellular matrix of the connective tissue. It is depolymerized by naturally occurring enzymes in the hyaluronidase family. Unlike the stable structural components of the interstitial matrix, hyaluronan has a very fast turnover with a half-life of approximately 0.5 days. The rHuPH20 component of HYQVIA increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan. In the doses administered, rHuPH20 of HYQVIA acts locally. The effects of the hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours (Baxalta US Inc., 2019).

HYQVIA has been approved for primary immune deficiency and is being studied in Study 161403, a Phase 3 double blind randomized placebo-controlled study to evaluate the efficacy, and safety and tolerability of HYQVIA as a maintenance therapy for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Majority of CIDP patient population are naïve to subcutaneous infusions, or inexperienced with subcutaneous infusions of large volumes (>60 mL per infusion site). There have been concerns for potential dropout in the Phase 3 study of CIDP due to intolerability of HYQVIA, and measures have been taken to improve tolerability and mitigate dropout, including infusing over multiple concurrent infusion sites (1-2) to allow smaller volume at each site, splitting the dose into divided doses to be given over more than 1 day, and utilizing a dose ramp-up schedule which involves stepwise gradual increase until the subject's full dose is reached, as well as an infusion rate ramp-up regimen that is in place and will not exceed 300 mL/hr/site. However, the safety and tolerability of HYQVIA without utilizing dose or infusion rate ramp-up has not been evaluated.

2.1 Indications for HYQVIA/HyQvia

IGI, 10% with rHuPH20 is licensed as HyQvia® in the EU (as of May 2013) and as HYQVIA® in the US (as of Sep 2014). Licensed indications vary by country/region. Indications may include replacement therapy in adults for primary immunodeficiency disease (PIDD) (in EU and US) and replacement therapy in patients with multiple myeloma, chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections, and hypogammaglobulinaemia in patients pre- or post-allogenic hematopoietic stem cell transplantation (HSCT) (in EU).

2.2 Product Background

2.2.1 Preclinical Information

Findings from nonclinical studies for HYQVIA are detailed in the investigator's brochure (IB) for IGI, 10% with rHuPH20.

Development and reproductive toxicology studies have been conducted with recombinant human hyaluronidase in mice and rabbits. No adverse effects on pregnancy were associated with anti-rHuPH20 antibodies (Baxalta US Inc., 2019).

An *in vitro* mutagenicity test was performed for IGI, 10% (Human) and there was no evidence of mutagenicity observed. No long-term carcinogenicity tests were performed (Baxalta US Inc., 2019).

2.2.2 Clinical Information

The clinical development program for HYQVIA/HyQvia has demonstrated that IGI, 10% administered via SC treatment with rHuPH20 is safe in healthy subjects and patient populations, which are detailed in the IB for IGI, 10% with rHuPH20.

Common adverse reactions observed in clinical trials in >5% of subjects were: local infusion site reactions, headache, antibody formation against rHuPH20, fatigue, nausea, pyrexia, and vomiting (Baxalta US Inc., 2019).

Study 160603 compared the efficacy, PK, safety and tolerability of IGIV, 10% and IGI, 10% administered subcutaneously following rHuPH20 solution. Study 160902, an extension to study 160603, assessed the long-term tolerability and safety of IGI, 10% following administration of rHuPH20 solution. Eighteen percent (15 of 83) of subjects of patients with PID receiving IGI, 10% with rHuPH20 in Baxter Study 160603 and Study 160902 developed non-neutralizing antibodies to rHuPH20. The clinical significance of these antibodies is not known. The clinical data from Study 160603 and Study 160902 have shown no temporal association between ARs and the presence of anti-rHuPH20 antibodies, and there was no increase in incidence or severity of ARs in subjects who developed anti-rHuPH20 antibodies.

In all subjects, antibody titers decreased despite continued treatment. There is a theoretical potential risk for such antibodies to cross-react with human hyaluronidase which is known to be expressed in the adult male testes, epididymis, and sperm. It is unknown whether these antibodies may interfere with fertilization and fetal development in humans. Treatment-emergent antibodies against rHuPH20 (binding and neutralizing antibodies) will be monitored during this clinical study (See Section 8.2.4.2 for details).

No clinical studies have been conducted with HYQVIA in pregnant women. HYQVIA should not be used by women who are pregnant or are planning to become pregnant and an alternate treatment should be considered. It is recommended that women of childbearing potential take appropriate measures to prevent pregnancy during HYQVIA treatment (see Section 5.3.1 for a list of highly effective contraceptive measures). If a woman becomes pregnant, treatment with HYQVIA should be stopped.

IGI, 10%, the therapeutically active component of HYQVIA/HyQvia, is identical to that in GAMMAGARD LIQUID/KIOVIG. IGI, 10% administered via IV treatment (GAMMAGARD LIQUID/KIOVIG) is efficacious and safe in the particular fields of therapeutic use and approved indications, i.e., PID, ITP and MMN, as demonstrated in the clinical development program for GAMMAGARD LIQUID/KIOVIG. Please see the IB for Immune Globulin Infusion (Human), 10% Solution (IGI, 10%) for further information, as well as the Prescribing Information for GAMMAGARD LIQUID and the SmPC for KIOVIG.

Serious ARs (defined as SAEs occurring during or within 72 hours (h) of infusion or any casually related SAE occurring within the study period) which occurred in the clinical trials of GAMMAGARD LIQUID/KIOVIG were aseptic meningitis, pulmonary embolism, and blurred vision. The most common ARs observed in ≥5% of patients were:

- PID, IV administration: headache, fatigue, pyrexia, nausea, chills, rigors, pain in extremity, diarrhea, migraine, dizziness, vomiting, cough, urticaria, asthma, laryngeal pain, rash, arthralgia, myalgia, oedema peripheral, pruritus, and cardiac murmur.
- PID, SC administration: infusion site (local) event, headache, fatigue, heart rate increased, pyrexia, abdominal pain upper, nausea, vomiting, asthma, blood pressure systolic increased, diarrhea, ear pain, aphthous stomatitis, migraine, oropharyngeal pain, and pain in extremity.
- MMN, IV administration: headache, chest discomfort, muscle spasms, muscular weakness, nausea, oropharyngeal pain, and pain in extremity.

Rare but serious events may occur with IGI products, including hypersensitivity, thrombosis, renal dysfunction/failure, hyperproteinemia, increased serum viscosity, and hyponatremia hemolysis, hemolysis, transfusion related acute lung injury (TRALI), and aseptic meningitis syndrome.

Thrombosis may occur following treatment with immune globulin products, including HYQVIA. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors (Baxalta US Inc., 2019).

IgG products, including HYQVIA, contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells (RBC) with IgG. These antibodies may cause a positive direct antiglobulin reaction and hemolysis. Acute intravascular hemolysis has been reported following intravenously administered IgG, including IGI, 10% (Human), and delayed hemolytic anemia can develop due to enhanced RBC sequestration (Baxalta US Inc., 2019).

In patients who are at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs), renal function should be monitored and lower, more frequent dosing can be considered (Baxalta US Inc., 2019).

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk for developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen and serum creatinine, before the initial infusion of HYQVIA and again at appropriate intervals thereafter. If renal function deteriorates, consider discontinuation of HYQVIA (Baxalta US Inc., 2019).

Always refer to the latest version of the IB for HYQVIA for the overall risk/benefit assessment and the most accurate and current information regarding the metabolism, pharmacokinetics, efficacy, and safety of HYQVIA.

2.3 Risk/Benefit and Ethical Assessment

There will be no direct health benefit for healthy participants in this study from receipt of HYQVIA. An indirect health benefit to the subjects enrolled in this study is the free medical tests received at screening and during the study.

The risks associated with dosing HYQVIA are anticipated to be similar to those previously documented in the product label for HYQVIA, please refer to the safety information in Section 2.2.2 as the dose provided in the study are within the dosing recommendation of the product label (Baxalta US Inc., 2019). The risk of HYQVIA in healthy subjects in this study is anticipated to be similar to those previously reported studies found in the HYQVIA IB (IB 2019).

The inclusion and exclusion criteria, screening, and safety monitoring practices employed in this protocol (i.e., 12-lead ECG, vital signs, clinical laboratory tests, AE monitoring, and physical examination) are adequate to protect the subject's safety.

2.4 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; ICH E6 R2, 2016), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

The responsibilities of the study sponsor and investigator(s) are described fully in Section 11 and Section 13.

3. STUDY RATIONALE, OBJECTIVES AND ENDPOINTS

3.1 Rationale for the Study

Dose ramp up has been considered necessary for HYQVIA in the Phase 3 Study (Study 161403) because the majority of CIDP patient population are naïve to subcutaneous (SC) infusions, or inexperienced with SC infusions at large volumes (>60 mL per infusion site; infusion volume maximum per day: up to 600 mL (1 site) or 1200 mL (2 sites)). As a result, a dose ramp-up schedule was included in Study 161403 which involves a stepwise gradual increase until the subject's full dose is reached to improve tolerability. Dose ramp-up is currently in the approved prescribing information for primary immune deficiency. Despite the current use of ramp up dosing in PID and CIDP patients, the tolerability and safety of HYQVIA without ramp-up has not been evaluated in clinical settings. This Phase 1 study is planned to assess the tolerability, safety and immunogenicity profile of HYQVIA with and without ramp-up dosing in healthy adult subjects and to characterize the PK of total IgG and IgG subclasses in serum after SC administration of HYQVIA in healthy adult subjects.

3.2 Study Objectives

3.2.1 Primary Objectives

To assess the tolerability of HYQVIA with and without ramp-up dosing in healthy adult subjects.

3.2.2 Secondary Objectives

- To assess the safety and immunogenicity of HYQVIA with and without ramp-up dosing in healthy adult subject
- To characterize the pharmacokinetics (PK) of total IgG and IgG subclasses in serum after subcutaneous administration of HYQVIA in healthy adult subjects.

3.3 Study Endpoints

3.3.1 Primary Endpoints

The primary endpoint corresponding to the primary objective of the study is the occurrence of tolerability events related to the infusion of HYQVIA.

Definition: An infusion is considered tolerable if the infusion rate was not reduced, or the infusion was not interrupted or stopped, due to HYQVIA infusion.

A tolerability event is considered to have occurred if an infusion was tolerable. Tolerability events will be measured in terms of the number and percentage of subjects for which the infusion was tolerable).

3.3.2 Secondary Endpoints

3.3.2.1 Safety and Immunogenicity Endpoints

- Occurrence of TEAEs, including but not limited to: HYQVIA-related and non-related *, serious, nonserious, severe, local and systemic TEAEs, TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs, as well as number and percentage of subjects and infusions with suspected adverse reactions plus adverse reactions of interest (additional information is provided in Section 10.10).

  *Any TEAE that is recorded by the investigator as "possibly related" or "probably related" to HYQVIA will be considered HYQVIA-related AE, and any AE recorded as "unlikely related" or "not related" (defined in Section 9.1.2.2) will be considered unrelated AE.

- Clinical laboratory parameters
- Vital signs
- Immunogenicity: occurrence of binding and neutralizing antibodies to rHuPH20

Note that clinically significant treatment-emergent changes in clinical laboratory measurements and vital signs will be recorded in the study database as TEAEs.

3.3.2.2 PK Endpoints

- PK parameters for serum total IgG and IgG subclasses after a single dose of HYQVIA (i.e. after Week 1 dosing), including but are not limited to C_{max}, T_{max}, AUC_{last}, $t_{1/2}$, CL/F and Vz/F.

4. STUDY DESIGN

4.1 Study Design

This study is a Phase 1, open-label, randomized, single-center study to evaluate the tolerability, safety and immunogenicity of HYQVIA with and without ramp-up dosing and to characterize the PK of total IgG and IgG subclasses in serum after SC administration of HYQVIA in healthy adult subjects.

Section 1.2 provides a schematic of the study design.

Study Parts:

This study is comprised of two parts, Study Parts 1 & 2. The target dose level (TDL) of either 0.4g/kg (Part 1) or 1.0 g/kg (Part 2) will be achieved through dose ramp-up or no ramp up (i.e. direct administration of the TDL). Each study part consists of three Treatment Arms (Part 1: Treatment Arms 1-3 and Part 2: Treatment Arms 4-6):

- Treatment Arms 1 and 4 will follow ramp up Schedule-A (Sch-A), in which subjects will receive HYQVIA from ¼ of the TDL at Week 1 to the full TDL at Week 8.
- Treatments Arms 2 and 5 will follow ramp up Schedule-B (Sch-B), in which subjects will receive HYQVIA from ½ of the TDL at Week 1 to the full TDL at Week 5.
- Treatment Arms 3 and 6 will follow ramp up Schedule-C (Sch-C), in which subjects will directly receive the full TDL at Week 1 without ramp-up dosing.

Each subject meeting all eligibility criteria will be randomized to 1 of the 3 treatment arms in each Study Part. Additional information regarding randomization is provided in Section 8.1.2.

Subjects meeting all eligibility criteria will be assigned to the 3 treatment arms in each Study Part at a randomization ratio of 1:1:1, and a minimum of 3 subjects in each of the 2 BMI groups (18 to <25 kg/m2, >25 to 30 kg/m2) in each treatment arm, achievable using stratified randomization (BMI as the stratification factor).

After all subjects in Treatment Arms 1-3 have completed Week 9 treatment in Study Part 1, and their tolerability, safety and immunogenicity data through Week 9 have been reviewed by a safety review team consisting of the Investigator, the Sponsor's Medical Monitor, and the Sponsor's Global Drug Safety Physician. Proceeding to Study Part 2 dosing may only occur following this review.

Treatment arms will be initiated in parallel in each study part. Each subject will participate in only one treatment arm.

The planned dose levels including ramp-up dose levels of IGI, 10% to be evaluated are outlined in Table 1.

Table 1. Planned Dose Levels

DL	Fraction of TDL	Part 1 (g/kg)	Part 2 (g/kg)
DL1	1/4 of TDL	0.1	0.25
DL2	1/2 of TDL	0.2	0.5
DL3	3/4 of TDL	0.3	0.75
DL4	TDL	0.4	1.0

Study Periods

The study consists of 3 periods:

- Screening period: up to 21 days prior to first dosing.
- Study treatment period: 8 weeks for Treatment Arms 1 and 4; 9 weeks for Treatment Arms 2, 3, 5, and 6.
- Follow up period: 16 (± 1) weeks after receiving the last infusion of HYQVIA with the end of study (EOS/ET) being in Weeks 24 (± 1) (Treatment arms 1 and 4) or 25 (± 1) (Treatment arms 2, 3, 5, and 6).

All subjects who received at least one dose of HYQVIA (including subjects who terminate the study early) will return to the Clinical Research Unit (CRU) 16 (± 1) weeks after the last infusion of HYQVIA for follow-up procedures.

Tolerability, safety and immunogenicity will be assessed throughout the study treatment period for all treatment arms.

The PK of total IgG and IgG subclasses in serum will be characterized based on their serum concentration-time profiles post the first infusion (i.e. Week 1 dosing).

All subjects will be monitored for the formation of binding anti-rHuPH20 antibodies (binding ADA). Samples with antibody titers ≥1:160 (ADA positive) will be analyzed for the presence of neutralizing antibodies. At any time during the course, subjects who have (a) 2 consecutive anti-rHuPH20 antibody titers of ≥1:160 that are elevated from the subject's baseline titers, and (b) a moderate or severe AE that may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other concomitant medications will be asked to return to the CRU as soon as possible to undergo an additional panel of immunogenicity testing.

After the EOS visit has been completed, no further visits are planned, unless determined necessary by the investigator. Positive binding antibody titers associated with serious or severe AEs may require additional follow-up assessments.

4.2 Duration and Study Completion Definition

The approximate overall duration of the study is 27 to 28 weeks from screening to EOS.

The study completion date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s). Please note that this includes the follow-up visit or contact, whichever is later (refer to Section 8.1.4 for the defined follow-up period for this protocol).

4.3 Study Continuation from Study Part 1 to Study Part 2

After all study subjects in Study Part 1 complete the treatment period (Week 9), a safety data review of the data collected through Week 9 for all subjects in Study Part 1 (including but not limited to AEs, vital signs, clinical laboratory data) will be conducted. This safety data review will be conducted by a safety review team consisting of the Investigator, the Sponsor's Medical Monitor, and the Sponsor's Global Drug Safety Physician before the first dosing in Study Part 2 is initiated. Ad hoc study team members may be included in the safety data review as needed. This safety data review will be based on unmonitored and unverified data at the time that the review takes place.

Safety data listing (including AEs, vital signs, and clinical laboratory data) from Study Part 1 will be prepared by the designated CRO. Proceeding to Study Part 2 may only occur following a review of the safety data. The safety review team consisting of the investigator, the Sponsor's Medical Monitor and the Sponsor's Global Drug Safety Physician may consider potential changes in Study Part 2 based on the overall tolerability and safety data from Study Part 1. The changes to Study Part 2 may include, but are not limited to:

- Administration of an intermediate dose between the current dose for Study Part 1 and the planned dose for Study Part 2.
- Not proceeding to Study Part 2 and terminating the study.

All data provided for the safety review meeting will be based on unmonitored/unverified data. The decision from the safety review meeting will be documented to include, at a minimum:

- A list of meeting participants
- A summary of the data considered during the meeting
- A summary of the decision, including any concerns which were raised

- The final decision, stating that the decision is agreed by the Investigator, the Sponsor's Medical Monitor(s) and the Sponsor's Global Drug Safety Physician.

The final decision to proceed to Study Part 2 must be confirmed in writing (scanned copy or fax is acceptable) by the Sponsor's Medical Monitor prior to dosing any subjects in Study Part 2.

In the absence of the Investigator, the decision to proceed to Study Part 2 may be delegated in writing to a medically qualified Sub-investigator, on the provision that this delegation is in agreement with the Sponsor.

5. STUDY POPULATION

The subject will not be considered eligible for the study without meeting all of the criteria below. Subjects cannot be randomized or enrolled before all inclusion and exclusion criteria (including laboratory test results) are within acceptable ranges as per protocol.

5.1 Inclusion Criteria

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent to participate in the study.
3. Age 19-50 years inclusive at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
4. Male, or non-pregnant, non-breastfeeding female who agrees to comply with any applicable contraceptive requirements of the protocol, or females of non-childbearing potential.
5. Must be considered "healthy". Healthy as determined by the investigator on the basis of screening evaluations and healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.
6. Body mass index (BMI) between 18.0 and 30.0 kg/m² inclusive.

5.2 Exclusion Criteria

1. Any current or relevant history of medical (e.g. any hematological, hepatic, respiratory, cardiovascular, renal or neurological) or psychiatric conditions, which by judgment of the investigator might compromise the safety of the subject or integrity of the study, interfere with the subject's participations in the trial and compromise the trial objectives or any condition that presents undue risk from the investigational product or procedures.

   Note: Subjects on stable dose of hormone replacements (i.e. thyroid hormone replacement) or oral contraceptives are permitted.

2. Clinically significant cardiac conditions including but not limited to uncontrolled hypertension, myocardial infarction, unstable coronary artery disease and clinically significant arrythmias and conduction disorders.

3. Known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients (e.g. human IG, hyaluronidase, albumin).
4. Known history of hypersensitivity or severe allergic reactions (e.g. urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following administration of blood or blood components.
5. Significant illness, as judged by the investigator, within 30 days of the first dose of investigational product.
6. Known history of alcohol or other substance abuse within the last year.
7. Donation of blood within 60 days, or blood products (e.g., plasma or platelets) within 2 weeks prior receiving the first dose of investigational product.
8. Subjects will be excluded if any of the following laboratory parameters meet the criteria below:
   - Hemoglobin < 11 g/dL
   - Absolute neutrophil count ≤1500/mm3 and platelet count ≤100,000/mm3
   - Liver function: alanine aminotransferase (ALT) ≥2.5 × upper limit normal (ULN), aspartate aminotransferase (AST) ≥2.5 × upper limit normal (ULN), alkaline phosphatase ≥1.5 × ULN or total bilirubin ≥1.5 mg/dL
   - Renal function: creatinine clearance ≤60 mL/min based on Cockcroft-Gault equation
   - Coagulation tests: aPTT >1.2 X ULN; INR >1.2

   Subjects will be excluded if any other laboratory values are outside the reference range and are clinically significant per investigator's judgment.
9. Within 30 days prior to the first dose of investigational product:
   - Has participated in another clinical study involving immunoglobulin products within 12 months of screening.
   - Have used an investigational product (or 5 half-lives, whichever is longer).
   - Have been enrolled in a clinical study (including vaccine studies or has been vaccinated with approved product) that, in the investigator's opinion, may impact this study. Subjects who received any vaccine (including live attenuated vaccines) in the 30 days before dosing will be excluded. No live attenuated virus vaccines are allowed during in the study until the end of the follow up period.
   - Have had any substantial changes in eating habits, as assessed by the investigator.

10. Confirmed systolic blood pressure >139 mmHg or <89 mmHg and diastolic blood pressure >89 mmHg or <49 mmHg.
11. A positive screen for alcohol or drugs of abuse at screening.
12. A positive HIV HCV, or ongoing/active hepatitis B infection at screening. Subjects with immunity to hepatitis B from either active vaccination or from previous natural infection are eligible to participate in the study.
13. Smoking more than 5 cigarettes or equivalent per day, unable to stop smoking during confinement in the CRU.
14. Severe dermatitis or anatomical abnormality that would interfere with HYQVIA administration or endpoint assessments. Note: the skin at the administration site should not be covered by tattoos.
15. Current use of any herbal, or homeopathic preparations are not permitted.
16. Unable or unwilling to discontinue antihistamines or medications with antihistamine properties, sedatives, anxiolytics, systemic steroids, or topical steroids or antibiotics on any area below the chest for a minimum of 48 hours prior to each infusion visit and through 72 hours post last infusion.
17. Current or relevant history of hypercoagulable conditions (e.g. Protein C, Protein S, and antithrombin III deficiency), thrombotic/thromboembolic events or venous thrombosis.

5.3 Reproductive Potential

No clinical studies have been conducted with GAMMAGARD LIQUID/KIOVIG or HYQVIA in pregnant women.

Animal reproduction studies have not been conducted with GAMMAGARD LIQUID/KIOVIG (IGI, 10%) and IGI, 10% component of HYQVIA. It is also not known whether IGI, 10% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, clinical experience with immunoglobulins suggests that no harmful effects of IGI, 10% on fertility are to be expected.

Development and reproductive toxicology studies have been conducted with recombinant human hyaluronidase in mice and rabbits. No adverse effects on pregnancy were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to recombinant human hyaluronidase were transferred to offspring in utero. The effects of antibodies to the rHuPH20 component of HYQVIA on the human embryo or on human fetal development are unknown.

5.3.1 Female Contraception

Sexually active females of child-bearing potential should be using an acceptable form of contraception. Females of child-bearing potential must be advised to use acceptable contraceptives throughout the study period and for 90 days following the last dose of IP. If hormonal contraceptives are used, they should be administered according to the package insert. Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 90 days following the last dose of IP.

Female subjects should be either:

1. Postmenopausal (12 consecutive months of spontaneous amenorrhea and ≥age 51 years)
2. Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
3. Of child-bearing potential with a negative urine and/or serum β-hCG pregnancy test at screening and prior to randomization. Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception listed below:
    i. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
        - oral
        - intravaginal
        - transdermal
    ii. Progestogen-only hormonal contraception associated with inhibition of ovulation:
        - oral
        - injectable
        - implantable*
    iii. Intrauterine device (IUD)*
        - Intrauterine hormone-releasing system (IUS) *
        - Bilateral tubal occlusion*
        - Vasectomised partner(s) *
        - Sexual abstinence during the entire study period

* Contraception methods that are considered to have low user dependency.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

5.3.2 Male Contraception

From signing of informed consent, throughout the duration of the study, and for 90 days after last dose of HYQVIA, nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use barrier contraception (e.g., condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

5.4 Discontinuation of Study and Subjects

5.4.1 Stopping Criteria for Individual Subjects

Individual subjects may be discontinued from study if any of the following criteria are met:

- Subject experiences:
  - thrombotic/thromboembolic event
  - acute intravascular hemolysis
  - anaphylactic / anaphylactoid reaction
  - acute renal failure
  - aseptic meningitis or
  - any HYQVIA-related toxicity deemed to pose an unacceptable risk to the subject, as determined by the study investigator.
- If there is a persistent HYQVIA-related AE that does not recover to baseline within 30 days, unless otherwise agreed by medical monitor and the study investigator, based on the type and severity of AE.
- Any other AE, laboratory abnormality, or intercurrent illness, which in the opinion of the study investigator presents a substantial clinical risk to the subject, with continued dosing with the investigational drug (IP).

5.4.2 Subject Withdrawal Criteria

The participation in this trial is completely voluntary. Subjects are free to withdraw anytime from the study by informing the investigator. If a subject, for whatever reason is no longer appropriate to continue receiving study drug, they will be notified and withdrawn from the study. Prior to removal from the study all efforts must be made to have all subjects' complete safety assessment as completely as possible, as defined in Section 1.3 for early termination.

The reason for discontinuation, date of discontinuation of the IP, and the total amount of IP administered must be recorded in the source documents and the case report form (CRF). Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. If a subject discontinued for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be indicated.

Reasons for discontinuation include but are not limited to:

- Completion of the protocol
- Protocol violation
- Voluntary withdrawal: the subject wishes to withdraw from the study.
  Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).
- Study termination: the sponsor, IRB, IEC, or regulatory agency terminates the study.
- Screen failure
- investigator's discretion
- Lost to follow-up.
- A positive pregnancy test for females.
- Adverse event
- Other

Subjects who withdraw or are discontinued early may be replaced at the discretion of the Sponsor. Replacement of discontinued or withdrawn subjects due to any reason will be assessed on a case by case basis.

For subjects "Lost to Follow-up" Prior to Last Scheduled Visit, a minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations.

5.4.3 Criteria for Premature Termination or Suspension of the Study

The sponsor reserves the right to terminate this study at any time. The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- The safety data review team (the Investigator, the Sponsor's Medical Monitor, and the Sponsor's Global Drug Safety Physician) recommends discontinuation of the study based on review of the data as described in Section 4.3.
- New information or other evaluation regarding the safety or efficacy of the IP that indicates a change in the known risk/benefit profile of this product and the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject's safety.

6. PRIOR AND CONCOMITANT TREATMENT

6.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments) received within 60 days from the date of first dose of IP. Prior treatment information must be recorded on the appropriate CRF page.

6.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of IP and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate CRF page.

6.2.1 Permitted Treatment

Subjects should refrain from taking any medications (excluding those medications listed below) during the course of the study. Any medication which is considered necessary for the subject's safety and well-being may be given at the discretion of the investigator. The administration of all medications (including IPs) must be listed on the appropriate CRF page.

Medications permitted during the study are listed below:

- Hormonal contraceptives for females of childbearing potential administered according to the package insert.
- Hormone replacement therapy
- Over the counter (OTC) medications (e.g. NSAIDs, Tylenol, vitamins) if needed per discretion of investigator.

6.2.2 Prohibited Treatment

No concomitant medications or treatments allowed except those mentioned in Section 6.2.1 or necessary for SAE or AE treatments as SOC.

7. INVESTIGATIONAL PRODUCT

7.1 Identity of Investigational Product

Subcutaneous Immune Globulin Infusion 10% (Human) (IGI, 10%) with Recombinant Human Hyaluronidase (rHuPH20) (also referred to as IGI, 10% with rHuPH20, or HYQVIA). IGI, 10% (Human) will be supplied in 5 g/50 mL and 20 g/200mL vials with rHuPH20 160U/mL supplied separately in 15 mL vials.

The IGI, 10% (Human) is a ready-for-use, sterile, liquid preparation of highly purified and concentrated IgG antibodies. The distribution of the IgG subclasses is similar to that of normal plasma. The fragment crystallizable region (Fc) and the antigen-binding fragment (Fab) functions are maintained in the primary component. Pre-kallikrein activator activity is not detectable. The IGI, 10% (Human) contains 100 mg/mL protein. At least 98% of the protein is IgG, average immunoglobulin A (IgA) concentration is low (not more than 140 ug/mL), and immunoglobulin M (IgM) is present in trace amounts. The IGI, 10% (Human) contains a broad spectrum of IgG antibodies against bacterial and viral agents. Glycine (0.25 M) serves as a stabilizing and buffering agent. There is no added sugar, sodium, or preservatives. The pH is 4.6 to 5.1. The osmolality is 240 to 300 mOsmol/kg. The IGI, 10% (Human) is manufactured from large pools of human plasma. IgG preparations are purified from plasma pools using a modified Cohn Oncley cold ethanol fractionation process, as well as cation and anion exchange chromatography.

7.1.1 Blinding the Treatment Assignment

Not applicable.

7.2 Administration of Investigational Product(s)

Prior to receiving the first dose of HYQVIA, subjects are to be randomized to a treatment arm as shown in Section 1.3 and Section 1.2.

Subjects will receive IGI, 10% either from a partial TDL dose to a full TDL dose with a ramp-up dosing scheme or directly at the full TDL dose without ramp-up. The TDLs are 0.4 g/kg and 1.0 g/kg for Study Part 1 and Study Part 2, respectively. Each study part consists of three treatment arms with different ramp up schedules.

rHuPH20 is administered prior to the infusion of IGI, 10%. The dose for rHuPH20 is 80 U/g IG. Please refer to the infusion manual/pharmacy manual for detailed instructions on the administration of the investigational product.

7.2.1 Allocation of Subjects to Treatment

Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number at the time of the first dosing, different from the screening number, and will receive the corresponding HYQVIA dose, according to a randomization scheme.

Each subject will participate in only one Study part and will receive only one of the three treatment arms: Treatment Arms 1, 2, or 3 (Part 1) or Treatment Arms 4, 5, or 6 (Part 2).

If replacement subjects are used, the replacement subject number will be 100 more than the original (e.g., Subject No. 101 will replace Subject No. 1).

7.2.2 Dosing

Infusion sites:

Please refer to the infusion manual/Pharmacy manual for complete dosing instruction of the investigational product.
One (1) or 2 infusion sites per infusion day will be used. If two sites are to be used, they must be on the opposite sides of the body. Infusion sites will be rotated if the infusion occurs on consecutive days due to dose is greater than 120 grams per day. The infusion site will be either:

- Right upper quadrant (RUQ) or left upper quadrant (LUQ) (please avoid 2 inches away from the umbilicus) and/or
- Upper 2/3rds of the medial or lateral thigh.

Infusion volume maximum per day:

- Up to 600 mL (1 site) or 1200 mL (2 sites). For infusions greater than 600 mL, a bifurcated needle will be used. Volumes will be evenly infused over two sites (e.g. 1000mLs will be infused in 2 sites at 500 mL each.) [rHuPH20 volume is not counted in the total dose of 600 mL/site]

Infusion rate:

- rHuPH20: Infuse the two components (rHuPH20 and IGI, 10%) sequentially, beginning with rHuPH20 solution administered subcutaneously, at a dose of 80 U/g IgG, to be followed by subcutaneous infusion of IGI, 10% solution within 10 minutes of completion of the infusion of rHuPH20 solution. The rHuPH20 should be administered at an initial rate per site of approximately 1 to 2 mL per minute (60 to 120 mL/h/site), or a total of 120 to 240 mL/h, over 2 sites), or as tolerated. For subsequent administrations, rHuPH20 solution infusion rate may be increased as tolerated by the subject and at the discretion of the investigator, but is not to exceed 300 mL/h/site or not to exceed a total of 600 mL/h over 2 sites.

- IGI, 10%: The maximum infusion rate should be 240 mL/h/site for the first infusion and then maximum infusion rate of up to 300 mL/h/site. Stepwise increase in subcutaneous infusion rate will be used according to Table 2.

Sequential administration:

- rHuPH20 will be infused first by the pump; within 10 minutes, IGI, 10% will be administered using the same infusion site(s).

Table 2: Subcutaneous Infusion Rates for IGI, 10%

	Infusion Rate Per Infusion Site (mL/h)	
	1st infusion	Remaining infusions
First 15 min	10	10
Next 15 min	30	30
Next 15 min	60	120
Next 15 min	120	240
Remainder of infusion	240	300

7.3 Labeling, Packaging, Storage, and Handling

7.3.1 Labeling

Study drug containers will be affixed with a clinical label in accordance with local regulatory requirements.

The pharmacy at the CRU will provide each dose of the IGI, (Human) 10% in a pooling bag and a bag tag label for each subject based on the randomized ramp up schedules. The pharmacy will prepare and dispense the rHuPH20 to be administered prior to IGI, (Human) 10% per the instructions in the Pharmacy Manual.

7.3.2 Packaging

Each labeled carton of IGI, 10% (Human) will contain either one labeled vial of IGI, 10% (Human) 5 gram, 5g/50 mL or one labeled vial of 20 gram, 20g/200mL.

Each labeled carton of rHuPH20 will contain one labeled 15 mL vial of rHuPH20 160U/mL.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

7.3.3 Storage

The Sponsor will supply sufficient quantities of HYQVIA products to allow completion of this study.

The lot numbers and expiration dates of HYQVIA supplied will be recorded in the final report. HYQVIA will be stored according to the product labels provided with the product.

Records will be made of the receipt, preparation, dispensing, and final disposition of HYQVIA supplied.

7.4 Drug Accountability

The investigator will be provided with sufficient amounts of IGI, 10% (Human) and rHuPH20 to carry out this protocol for the agreed-upon number of subjects. The investigator or designee will acknowledge receipt of the products, documenting shipment content (quantities, lot numbers and condition. Accurate records of all IP dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing and administering IP. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense and administer IGI, 10% and rHuPH20 only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only IGI, 10% and rHuPH20 for his/her treatment assignment. All dispensed and administered medication will be documented on the CRFs and/or other IP records (including all lot numbers and expiration dates). The pharmacy will retain all empty, partially used and unused vials of IGI 10% and rHUPH20 for drug accountability. Due to health and safety concerns, the IP pooling bags, needle sets and other disposable ancillary supplies used for infusion will be disposed of as per protocol and local health waste regulations.

No IP, stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, empty/partially used cartons and vials of IGI, 10% and rHuPH20 will be destroyed by the site according to their procedures and/or SOPs. There will be a well-documented site procedure and/or SOP for destruction of the study drug. Prior to the destruction of IGI 10% and rHuPH20 vials, drug accountability must be performed. Vials will be counted and verified by clinical site personnel and the sponsor (or designated CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. The following information will be documented on the destruction certificate or documented in conjunction with the destruction certificate and verified at time of destruction: date of destruction, method of destruction, number of units destroyed, including lot numbers, and, if applicable, the name of the company contracted by the pharmacy who performed the destruction (if not directly performed by the pharmacy). Destruction of all IGI, 10% and rHuPH20 must comply with the site SOPs, and local, state, and national laws.

Please refer to the current version of the pharmacy manual that has been provided for any other instructions or updates to this procedure.

Based on entries in the site drug accountability forms, it must be possible to reconcile IGI, 10% and rHuPH20 delivered with those used and returned. All IGI, 10% and rHuPH20 must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

7.5 Subject Compliance

Compliance must be assessed by observation of dosing by the investigator or designee. The investigator/nominated person will record details on the drug accountability log(s) and/or source documents. In addition, details of the dosing time (time, date, dose level) will be captured in the appropriate CRF.

Drug accountability must be assessed at the container/packaging level for unused IP that is contained within the original tamper-evident sealed container (e.g., bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

8. STUDY PROCEDURES

8.1 Study Schedule

See Section 1.3 for study procedures.

8.1.1 Screening Period

Screening procedures must be completed within 21 days prior to receiving the first dose of IP. The CRU is responsible for maintaining an enrollment/screening log that includes all subjects who provided informed consent. The log will also serve to document the reason for screening failure. All screening data for enrolled/randomized subjects will be collected and reported in CRFs. Screen failures will be reviewed according to the monitoring plan, but will not be entered in the EDC. All screening assessments and procedures are to be performed by the principal investigator or a qualified designee. See Section 1.3 for a complete list of screening procedures to be performed.

Written, signed, and dated informed consent prior to the performance of any study-related procedures must be obtained by the principal investigator or a designee. A copy of the signed informed consent must be given to the subject or legally-authorized representative for their records.

8.1.1.1 Screening Failure

A screen failure is a subject who has given informed consent and fail to meet all inclusion/exclusion criteria and has not been administered IP.

For purposes of data collection, all subjects who give consent to the study but are not dosed will be reported as screen failures even if they were otherwise fully eligible for the study (for example, alternates/reserve subjects).

8.1.1.2 Rescreening of Subjects

Subjects who fail to meet all inclusion/exclusion criteria will not be permitted to be rescreened for the study at any point.

Eligible subjects who meet all inclusion/exclusion criteria but are unable to participate in the study due to scheduling conflicts/timing may be rescreened based on investigator's discretion and sponsor's approval. In these cases, a new screening number must be assigned for each subject who is rescreened and a new informed consent form must be signed.

8.1.2 Randomization

Prior to receiving the first infusion of HYQVIA, screened subjects who are qualified to enroll in this study are to be randomized to a treatment arm as depicted in the Study Schematic (Section 1.2).

This study comprises of two parts, Study Parts 1 & 2. Each study part consists of 3 Treatment Arms, and each subject will participate in only one Treatment Arm:

- Part 1 (TDL 0.4 g/kg): Treatment Arms 1-3
- Part 2 (TDL 1.0 g/kg): Treatment Arms 4-6

A total of 48 subjects will be randomized to 6 parallel treatment arms (8 subjects per treatment arm, equal randomization ratio): 24 subjects in total to Part 1 and 24 subjects in total to Part 2. Randomization will be stratified by BMI group (18 to <25 kg/m^2 and ≥25 to 30 kg/m^2) in order to ensure a minimum of 3 subjects are randomized to each of the 2 BMI groups in each treatment arm in each part (BMI as the stratification factor).

Example

It is worthwhile to provide an example to illustrate the planned stratified randomization, using dummy (not real) data. The example below shows a balance between the treatment arms in each Part (8 subjects in total per Treatment Arm) while ensuring that each Treatment Arm has a minimum of 3 subjects in each stratum (BMI group). Note that the stratified randomization is not to ensure an equal number of subjects for each stratum, but instead it is to ensure a minimum of 3 subjects are randomized to each Treatment Arm in each Study Part, as displayed in the example.

BMI group (kg/m^2)	Study Part 1			Study Part 2			Total
	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6	
18 to <25	3	4	3	5	4	4	23
≥25 to ≤30	5	4	5	3	4	4	25
Total	8	8	8	8	8	8	48

8.1.3 Day Prior Treatment (D-1)/Treatment Period

8.1.3.1 Day -1 (For all Treatment Arms)

Subjects will check into the CRU and undergo the assessments as described in Schedule of Study Procedures (Section 1.3).

NOTE: When confined, standard meals and snacks will be provided at appropriate times. Subjects must be well hydrated prior to drug administration.

8.1.3.2 Week 1 (For all Treatment Arms)

Study drug will be administered on Day 1 at the clinical research center and assessments specified in Schedule of Study Procedures (Section 1.3) will be completed.

8.1.3.3 Weeks 2-9

All subjects in Treatment Arms 1 and 4 will be dosed on D8, D15, D29 and D50.

All subjects in Treatment Arms 2 and 5 will be dosed on D15, D29 and D57.

All subjects in Treatment Arms 3 and 6 will be dosed on D29 and D57.

Procedures and laboratory test performed are assessed as described in Schedule of Study Procedures (Section 1.3).

8.1.4 Week 24/25 Follow-up Period (EOS/ET Visit)

The follow-up period for this study is 16 (± 1) weeks after receiving the last infusion of HYQVIA with the end of study being in Weeks 24 (Treatments 1 and 4) or 25 (Treatments 2, 3, 5, and 6).

At the end of the study follow up period visit (EOS/ET), final inquiries for SAEs, AEs, and concomitant treatments will be made.

Procedures and laboratory tests performed are assessed as described in Schedule of Study Procedures (Section 1.3).

8.2 Study Evaluations and Procedures

The Schedule of Study Procedures (Section 1.3) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the investigator or designee and/or the Sponsor for reasons related to subject safety.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

8.2.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign, and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

8.2.2 Demographic and Other Baseline Characteristics

Baseline is defined as the last non-missing value before the initial dose of HYQVIA.

Demographic data, including patient number, gender, age, race and ethnicity will be recorded.

Body height (cm) and weight (kg) will be measured and reported as outlined in the Schedule of Study Procedures (Section 1.3).

BMI will be calculated based on the height and weight measured at screening. The weight should be measured on the same scale throughout the course of the study. If applicable, BMI will be recalculated with the subsequent measures of weight from screening.

Abnormalities identified at the screening visit will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit will be captured as AEs on the AE CRF page, as deemed by the investigator.

8.2.3 Safety

8.2.3.1 Physical Examinations

At screening and subsequent study visits (as described in Section 1.3) a complete physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to error, due to a preexisting not clinically significant disease, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

A partial physical exam will be done at the times specified in Section 1.3. A partial physical exam will include: general appearance, head and neck, assessment of injection sites, and skin. Other organ systems will be assessed per the PI's judgement.

8.2.3.2 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate, will be measured as outlined in the Schedule of Study Procedures (Section 1.3). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and heart rate measurements will be performed with subjects in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the investigator or designee.

At the predose time points, blood pressure and heart rate will be performed within 2 hours prior to dosing. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

Only BP, HR and RR will be measured every 30 minutes from starting the infusion until the end of infusion, and every 1-2 hours after the infusion for 8 hours, at discharge and as needed per investigator's judgement until discharged.

8.2.3.3 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at screening for the determination of eligibility (e.g., exclusion of clinically significant cardiac abnormalities, such as unstable cardiac arrhythmias, and detection of other clinically significant cardiac abnormalities that may indicate an underlying condition that may impede the subject's participation in the study, pose increased risk to the subject, or confound the results of the study). ECG will be reviewed by the investigator or a designee. ECG will be performed at EOS/ET.

8.2.3.4 Clinical Laboratory Tests

All clinical laboratory tests will be performed according to the laboratory's standard procedures. Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 1.3). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the investigator or designee.

Samples for hematology and clinical chemistry assessments will be collected in the appropriate matrix as specified in the laboratory manual. With the exception of screening and early termination visits, samples for hematology and clinical chemistry collected during the treatment period must be collected prior to IP administration. At any time during the study, unscheduled hematology and/or clinical chemistry test(s) may be performed as part of AE/safety investigation or may be repeated once in the event of abnormalities in test results due to errors.

Hematology and clinical chemistry assessments will be performed at the local laboratory following standardized assay procedures.

Some of the parameters will be evaluated according toxicity grading scale provided in Section 9.5.4.1.

8.2.3.4.1 Biochemistry

Blood samples for serum biochemistry will be collected according to the timepoints provided in Section 1.3. Sample collection details are provided in the Laboratory Manuals.

Serum chemistry tests will be performed after at least an 8-hour fast (on the screening day only); however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken.

Chemistry evaluations will consist of the following standard chemistry panel (Table 3):

Table 3. Chemistry Panel

Blood Urea Nitrogen	Albumin
Bilirubin (total and direct)	Sodium
ALP	Potassium
AST	Chloride
Triglycerides	Glucose
Cholesterol	Creatinine *
ALT	Low-density lipoprotein
LDH	High-density lipoprotein
Uric acid	Magnesium
	Calcium

* At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

8.2.3.4.2 Hematology

Blood samples for hematology will be collected according to the timepoints provided in Section 1.3. Sample collection details are provided in the Laboratory Manuals. The following parameters will be assessed:

Hematology will consist of the following tests (Table 4):

Table 4. Hematology Panel

Hemoglobin	Red blood cell count
Red Cell Distribution Width (RDW)	Platelet count
Mean Corpuscular Volume (MCV)	
Mean Corpuscular Hemoglobin (MCH)	
Mean Corpuscular Hemoglobin Concentration (MCHC)	
Hematocrit	
White blood cells (WBC) with absolute differential counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils	

8.2.3.4.3 Hemolytic Panel

The first hemolytic panel will be measured at D-1. The Hgb result obtained from the D-1 will serve as the baseline Hgb value for the duration of the study. In case of absence of D-1 results for any reason, screening Hgb result serve as the baseline Hgb value. Hemoglobin and LDH values can be taken from the hematology and clinical chemistry panels, if conducted on the same day as the hemolytic panel. For subsequent tests, if there is a reduction in Hgb of ≥1 g/dL compared to baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 hours. If it is not feasible to do so, the hemolytic panel must be performed as soon as possible but at the next scheduled visit, at latest. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia. Any LDH test result of 2 x ULN or greater will trigger analysis of the sample for LDH isoenzymes.

It is not necessary to repeat the hemolytic panel if the drop of ≥ 1 g/dL Hgb remains constant 72 hours after the first full dose of the IP or after an unscheduled visit blood draw, unless it drops further. It is recommended that the investigator uses good medical judgement in assessing subjects with an unexplained decrease in serum Hgb as other medical conditions beside hemolysis can cause this, and therefore may require additional investigations.

The hemolytic anemia panel will consist of Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive), reticulocyte count, as well as urine hemosiderin.

Hemolytic tests will be performed at the local laboratory or other laboratories as appropriate (e.g., antibody elution in the event of positive direct Coombs test). Complete hematology and clinical chemistry assessments may be performed in order to obtain laboratory results required for a hemolytic panel.

8.2.3.4.4 Urinalysis

A urine sample for urinalysis will be collected according to the timepoints provided in Section 1.3. Sample collection details are provided in the Laboratory Manuals.

Urinalysis will consist of the following tests (Table 5).

Table 5. Urinalysis Panel

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *
Color	

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

Microscopic examination will be conducted if protein and/or blood is/are detected during urinalysis. At a minimum the microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

8.2.3.4.5 Coagulation

Samples will be collected according to the timepoints provided in Section 1.3. Sample collection details are provided in the Laboratory Manual.

Coagulation will consist of the following tests (Table 6).

Table 6: Coagulation Panel

aPTT
INR

8.2.3.5 Pregnancy Screen

Subjects must have a negative serum pregnancy test at screening and a negative serum pregnancy test within 7 days before the first IP administration If the serum pregnancy test at screening is older than 7 days., a serum pregnancy test is required on D-1. For the rest of the visits, a urine pregnancy test prior to dosing will be acceptable. Pregnancy tests are to be performed on all females of child-bearing potential at the screening visit, D-1, or if pregnancy is suspected, prior to each dosing and at EOS/ET visits.

Follicle stimulating hormone (FSH) levels may be done once at screening on menopausal or peri-menopausal women, or as judged by investigator.

8.2.3.6 Drug and Alcohol Screen

A urine screen for drugs of abuse and alcohol will be performed at the time points described in Section 1.3. Additional drug and alcohol screens may be performed at the investigator's discretion.

Urine samples are to be tested for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone), and phencyclidine. Results of urine drug and alcohol screens will be reviewed and verified by the study monitor but will not be collected in the CRF database.

Any positive result for drugs of abuse or alcohol at screening or on Day -1 will exclude the subject from further participation in the study.

8.2.3.7 Virology Screen

Blood samples will be drawn at timepoints listed in Section 1.3. Sample collection details are provided in the Laboratory Manual. The following parameters will be drawn for the virology screen: HIV 1/2 antibodies, HBsAg, HBsAb, HBcAb and HCV antibody.

The test results must be confirmed negative prior to enrollment in the study. If a test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor but will not be collected in the CRF database.

8.2.4 Pharmacokinetic and Immunogenicity Sample Collection and Handling Procedures

8.2.4.1 Blood Sample Collection and Handling Procedures

Blood samples will be collected at the time specified in Section 1.3 to measure serum concentrations of total IgG and IgG subclasses, and anti-rHuPH20 antibodies (ADA and nADA).

Blood samples will be drawn according to the time points specified in Section 1.3 and processed as described in the Laboratory Manual. The actual time that the sample was obtained will be recorded in the subject's source document and on the appropriate CRF page. In instances where more than 1 blood collection tube is used, the time of the initial blood draw will be recorded for all tubes collected at that time point on the appropriate CRF page. After applying a tourniquet, venous blood will be drawn with a disposable needle. If a catheter is used, the first milliliter of blood on each sampling occasion will be discarded. Saline can be used to keep catheters patent.

Serum or plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the specialty laboratory. The labels will contain the following information:

- Study number
- Subject identifier
- Treatment
- Period
- Nominal day
- Nominal time
- Matrix identifier (plasma)
- Split (primary or backup)

Primary specimen collection parameters are provided in Table 7.

Table 7. Primary Specimen Collections

Specimen Name	Primary Specimen	Description of Intended Use	Sample Collection
Serum sample for PK	Serum	Serum sample for PK analysis	Mandatory
rHuPH20 Immunogenicity ADA and nADA sample	Plasma	Plasma sample for Immunogenicity analyses	Mandatory

ADA=anti-drug antibody; nADA=neutralizing anti-drug antibody

Serum PK samples and plasma ADA and nADA samples will be collected and processed according to the instructions provided in the Laboratory Manual.

All subjects will be monitored for the formation of anti-rHuPH20 antibodies using validated anti-rHuPH20 antibody detection assay (ADA) (also known as the Screening and Confirmatory Binding Assay). Samples with antibody titers ≥1:160 will be analyzed for the presence of neutralizing antibodies (nADA) using a validated assay based on neutralization of rHuPH20 activity.

8.2.4.2 Immunogenicity Panel

At baseline (D1 predose), samples are to be collected for the following tests to be conducted: 50% hemolytic complement activity of serum (CH50), serum complement component 3 (C3), serum complement component 4 (C4), C1q binding assay, and circulating immune complex (CIC) Raji cell assay.

At any time during the course, subjects who have (a) 2 consecutive anti-rHuPH20 antibody titers of ≥1:160 that are elevated from the subject's baseline titers, and (b) a moderate or severe AE that may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other concomitant medications (Table 8) will be asked to return to the CRU as soon as possible to undergo an additional panel of testing outlined in Table 9.

Table 8. List of Conditions/Symptoms That May be a Result of Immune-Mediated Response to Either Immunoglobulin, rHuPH20, or Other Factors

Allergic reactions ➢ Urticaria ➢ New-onset bronchospasm ➢ Oedema of tongue, lips, face (angioedema) ➢ Anaphylaxis ➢ Stevens-Johnson syndrome ➢ Erythema multiforme ➢ Toxic epidermal necrolysis
Immune complex mediated reactions – Local ➢ Induration/nodule at the site of administration that persists for more than 48 hours ➢ Excessive inflammation at the site of administration - severe redness, heat, swelling, and/or pain ➢ Tissue necrosis/ulceration at the site of administration ➢ Dystrophic or fibrotic changes at the site of administration ➢ Pigmented skin changes at the site of drug administration
Immune complex mediated reactions – Systemic ➢ Arthritis ➢ Vasculitis (purpuric rash) ➢ Glomerulonephritis - hematuria, red cell casts in urine, progressive renal dysfunction

Table 9. Immunogenicity Panel

1. Repeat test for anti-rHuPH20 binding antibody titers ≥1:160
2. Hematology panel with manual differential
3. Clinical chemistry panel
4. CH50
5. Serum C3
6. Serum C4
7. C1q binding assay
8. CIC Raji cell assay
9. Blood draw for additional testing as necessary

Blood samples are to be collected and processed according to the directions provided in the laboratory manual. The tests should be performed at the central laboratory and/or specialty laboratories as appropriate.

8.2.5 Volume of Blood to be Drawn from Each Subject

Table 10. Estimated Volume of Blood to be Drawn from Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
PK Samples	15	5 (Treatment Arms 1 and 4) 6 (Treatment Arms 2 and 5) 7 (Treatment Arms 3 and 6)	Up to 105 mL
ADA and nADA samples	10	4	40mL
Hemolytic Anemia Panel	17	1	17
Serology test	5	2	10
Serum chemistry (male and female subjects) and β-hCG (female subjects only per Section 1.3)	5	6	30
Hematology	4	6	24
Total			**Up to 226 mL**

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 226 mL. When more than 1 blood assessment is to be done at the same time point/period and if they require the same type of tube, the assessments may be combined. Additional samples may be collected as required per protocol.

8.3 Backup Samples and Biobanking

Backup samples from PK and immunogenicity testing should be taken and stored appropriately for repeat or additional analysis, if necessary. These samples may also be used short-term for further evaluation of an AE, or follow-up of other test results. The following back up samples are planned:

- Serum IgG samples (back-up aliquots)
- Anti-rHuPH20 binding antibody samples (back-up aliquots)
- Anti-rHuPH20 neutralizing antibody samples (back-up aliquots)

By signing the informed consent form (ICF), subjects agree to the possible future analysis of these samples. At any time, the subjects can contact the CRU staff to request destruction of the residual samples once PK and immunogenicity assessments required to meet the secondary objective of the study are completed. Any additional research on these samples unspecified by this protocol and ICF will require approval from the subjects.

Samples will be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

9. SAFETY ASSESSMENT

9.1 Adverse Events

9.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

9.1.1.1 Serious Adverse Event

A **serious** adverse event (SAE) is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

1. Outcome is fatal/results in death (including fetal death)
2. Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
4. Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
5. Is a congenital anomaly/birth defect
6. Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
    - Reviewed and confirmed seroconversion for HIV, HAV, HBV, HCV, HEV, or B19V

- Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular events [e.g., stroke, transient ischemic attack])
- Hemolytic anemia

Uncomplicated pregnancies, following maternal exposure to IP are not considered as an (S)AE. Any pregnancy that occurs after maternal administration of medicinal product will be reported on a Pregnancy Report Form and 1 year postdelivery, if feasible. Any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

9.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, a SAE should be submitted to regulatory agencies expeditiously.

The sponsor will ensure that all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening, as well as all other serious unexpected ARs, are reported to regulatory authorities within the timeframes mandated by the applicable regulations (e.g. ICH Guideline E2A and the European Clinical Trial Directive (2001/20/EC). The sponsor will comply with applicable laws/requirements for reporting SUSARs and all other SAEs to the ECs and investigators.

9.1.1.3 Nonserious Adverse Event

A nonserious AE is an AE that does not meet the criteria of an SAE.

9.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB and/or prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the product but are not specifically mentioned as occurring with the particular product under investigation. The expectedness of AEs will be determined by the sponsor using the IB and prescribing information as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

9.1.1.5 Adverse Reactions Plus Suspected Adverse Reactions

An AR plus suspected AR is any AE that meets any of the following criteria:

- An AE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or
- An AE that begins during infusion of IP or within 72 h following the end of IP infusion, or
- An AE for which causality assessment is missing or indeterminate.

9.1.1.6 Preexisting Diseases

Preexisting diseases that are present before entry into the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

9.1.2 Assessment of Adverse Events

All other AE from the first IP exposure until study completion/discontinuation date will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 9.1). Each AE will be evaluated by the investigator for:

1. Seriousness as defined in Section 9.1.1.1
2. Severity as defined in Section 9.1.2.1.
3. Causal relationship to IP exposure or study procedure as defined in Section 9.1.2.2.

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first. Follow-up information will be recorded in the appropriate CRF(s) as applicable, unless the database has already locked. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including overdosing, underdosing, and withdrawal) that result in adverse events meeting criteria for SAEs, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after maternal administration of IP will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year postdelivery, if feasible. Any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

If an investigator becomes aware of an SAE occurring in a subject within 30 days after study completion, the SAE must be reported on the provided SAE Report Form within 24 h after awareness; no additional reporting on CRFs is necessary. Thereafter, AEs of any nature are to be reported using standard forms such as the Council for International Organizations of Medical Sciences (CIOMS) form or MedWatch form, etc.

9.1.2.1 Severity

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity is captured as a new event. Worsening medical conditions, signs or symptoms present prior to initiation of IP, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the IP, and the dyspepsia becomes severe and more frequent after first dose of a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source.

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

1. Mild
    - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
    - The AE resolves spontaneously or may require minimal therapeutic intervention.
2. Moderate
    - The AE produces limited impairment of function and may require therapeutic intervention.
    - The AE produces no sequela/sequelae.
3. Severe
    - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
    - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

9.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

1. Not related (both circumstances must be met)
    - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
    - Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).

2. Unlikely related (either 1 or both circumstances are met)
    - Has little or no temporal relationship to the IP
    - A more likely alternative etiology exists
3. Possibly related (both circumstances must be met)
    - Follows a reasonable temporal relationship to the administration of IP
    - An alternative etiology is equally or less likely compared to the potential relationship to the IP
4. Probably related (both circumstances must be met)
    - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
        - Reappearance of a similar reaction upon re-administration (positive rechallenge)
        - Positive results in a drug sensitivity test (skin test, etc.)
        - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
    - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 72 h after completion of IP administration, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

Note: all local infusion site adverse events will be considered adverse reactions irrespective of investigator/sponsor opinions of causality.

9.2 Outcome Categorization

The outcome of AEs must be recorded in the source during the course of the study. Outcomes are as follows:

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining “recovering/resolving.”

- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

If applicable, action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF.

9.3 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

1. Immediate change in study design or study procedures
2. Temporary or permanent halt of a given clinical trial or trials
3. Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees and relevant competent authorities are notified of the urgent safety measures taken in such cases according to local regulations.

9.4 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 9.1). However, each serious untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF and on the SAE Report Form. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, each nonserious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) before the first IP exposure will be recorded on the AE CRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

9.5 Reporting Procedures

9.5.1 Reporting AEs

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE prior to the first exposure to IP must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin prior to the first exposure to IP, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event (systemic/local):

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (investigator's opinion of the causal relationship between the event and administration of HYQVIA).

- Action taken with HYQVIA.
- Outcome of event.
- Seriousness.

9.5.2 Reporting SAEs

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the CRO/Shire Medical Monitor within 24 hours of becoming aware of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless they result in an SAE.

The investigator must complete, sign, and date the Shire "Clinical Study Serious Adverse Event for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested), and fax or e-mail the form to the Shire Global Drug Safety Department.

Fax: +1-484-595-8155
E-mail: drugsafety@shire.com

A copy of the Shire Clinical Study Serious Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO/Shire Medical Monitor using the details specified in the emergency contact information section of the protocol.

A Takeda SAE form must be completed, in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the Sponsor if considered related to study participation.

Reporting of SAEs that begin before first administration of IP will follow the same procedure for SAEs occurring on treatment.

9.5.3 SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to IP) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.1.4, and must be reported to the Shire Global Drug Safety Department and the CRO/Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the IP and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first becoming aware of the event.

9.5.4 Assessment of Laboratory Values

9.5.4.1 Toxicity Grading Scale

The Common Toxicity Criteria of the Eastern Cooperative Oncology Group, 2006, published by Oken et al., 1982, will be used to grade the following laboratory values:

- ALP, ALT, AST, BUN, Hgb, lymphocytes, neutrophils, platelet count, serum creatinine, serum total bilirubin, and WBC.
  Grading for LDH will use the same thresholds as defined for ALT and AST.
- Sodium and potassium will be graded using the thresholds taken from the World Health Organization (WHO) toxicity grading system (World Health Organization, 2003).

The laboratory parameters and the corresponding grading scale are provided below.
The toxicity scale is defined as: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening (Food and Drug Administration, 2008).

Laboratory parameters not listed Table 11 will not be graded. However, clinical significance of those abnormal laboratory values will be assessed as described in Section 9.1.2.

Table 11. 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	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	50.0	74.9	25	49.9	0.0	24.9	ECOG
Potassium	Decrease	NO	NO	mmol/L	3.5	.	3.0	3.4	2.5	2.9	2.0	2.4	0.0	1.9	WHO
Potassium	Increase	NO	NO	mmol/L	0.0	5.5	5.6	6.0	6.1	6.5	6.6	7.0	7.1	.	WHO
Serum Creatinine	Increase	YES	NO	ULN	.	.	.	1.4	1.5	3.0	3.1	6.0	6.1	.	ECOG
Sodium	Decrease	NO	NO	mmol/L	136	.	130	135	123	129	116	122	0.0	115	WHO
Sodium	Increase	NO	NO	mmol/L	0.0	145	146	150	151	157	158	165	166	.	WHO
Serum Total Bilirubin	Increase	YES	YES	ULN	.	.	.	.	.	1.4	1.5	3.0	3.1	.	ECOG
WBC	Decrease	NO	NO	x10^3/uL	4.0	.	3.0	3.9	2.0	2.9	1.0	1.9	0.0	0.9	ECOG

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; BUN = blood urea nitrogen; ULN = upper limit of normal; ECOG = Eastern Cooperative Oncology Group; WHO = World Health Organization; WNL = within normal limits.

[a] The toxicity scale is defined as: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening (Food and Drug Administration, 2008). Grading scale criteria taken from ECOG (Eastern Cooperative Oncology Group, 2006) and WHO (World Health Organization, 2003) guidelines, with the exception of LDH that use the same thresholds as defined for ALT and AST.

9.6 Precautions and Warnings

Please see Section 2.2.2 for clinical information.

9.7 Management of Infusion-Related AEs

It is the investigator's responsibility to monitor the safety and well-being of the subject and to assure that all post-randomization infusions are conducted in the prescribed and timely manner throughout the study, regardless of the location of administration. Subjects will be provided with information about the typical signs and symptoms of possible AEs, and when the subject should immediately call the investigator or go to the emergency room/department for immediate treatment.

The occurrence of certain AEs, such as headache, chills, or body aches, may be reduced by slowing the infusion rate.

Any suspicion of allergic, hypersensitivity, or anaphylactic reaction(s) requires immediate discontinuation of the infusion and administration of appropriate medical treatment in accordance with the local standard of care.

Any rate reductions, interruptions or discontinuation of an infusion and, if applicable, any medications and/or non-drug therapies used to treat AE(s), must be recorded in the appropriate CRF(s). The use of any pre-medication(s) must be recorded in the appropriate CRF(s).

9.8 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE**. NMCs include but are not limited to the following:

1. A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
2. Missing components
3. Damage to the product or unit carton
4. A mislabeled product (e.g., potential counterfeiting/tampering)
5. A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

9.9 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 9.1.2.1.) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All other medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

9.10 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The investigator is responsible for notifying the local IRB/EC of SAEs or significant safety findings, or the relevant local regulatory authority of all SAEs that occur at his or her site as required by IRB/EC procedures.

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions **(SUSARs)** and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the Study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

In addition, the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the TAK-771 program.

10. DATA MANAGEMENT AND STATISTICAL METHODS

10.1 Data Collection

The investigators' authorized site personnel must enter the information required by the study CRF Completion Guidelines or similar for all data requiring transcription of the source. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

10.1.1 CRFs (Electronic and Paper)

Completed CRFs are required for each subject who signs an informed consent.

The Sponsor or its designee will supply investigative site with access to CRFs. The Sponsor will make arrangements to train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto CRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs should be made by the investigator with use of change and modification records of the CRFs. The principal investigator must review the data change for completeness and accuracy and must sign and date.

CRFs will be reviewed for completeness and acceptability at the CRU during periodic visits by study monitors. The Sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the CRFs.

The completed CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

10.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

10.3 Data Handling

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

10.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The study SAP will provide the statistical methods and definitions for the analysis of the study data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, IP exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

To preserve the scientific integrity and regulatory utility of the statistical analysis and study conclusions, the SAP will be finalized prior to the study database lock.

All statistical analyses will be performed externally by the sponsor-designated contract research organization (CRO), using SAS® (SAS Institute, Cary, NC 27513), Version 9.4 or higher.

10.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis or adaptive design in this study. There is no DMC planned for this study.

The tolerability and safety date up to Week 9 in Study Part 1 will be reviewed by a safety review team consisting of the Investigator, the Sponsor's Medical Monitor, and the Sponsor's Global Drug Safety Physician before the first dosing in Study Part 2 is initiated (Section 4.1).

10.6 Sample Size Calculation and Power Considerations

Assessment of tolerability is the primary objective of this study.

This study is not designed for statistical hypothesis testing, and therefore the sample size was not based on statistical considerations.

The planned total sample size for this study is 48 randomized subjects (8 subjects per treatment arm and 6 treatments arms, equal randomization ratio).

Of the 48 subjects to be randomized and enrolled, a minimum of 36 subjects are expected to complete the study, assuming a conservative dropout rate of 25% in this healthy subject study (overall dropout rates assumed for HYQVIA patient studies are generally 10%-15%). The number of subjects expected complete the study (36) is considered also adequate for providing reliable estimates of tolerability, safety, and PK for those using ramp up and no ramp up dosing.

10.7 Study Population

Analysis of tolerability, safety, immunogenicity and PK data will be based on the following analysis sets (analysis populations):

Enrolled Set:

All screened subjects for whom a randomization number has been assigned. Background summaries (e.g., subject disposition) will be based on the Enrolled Set.

Safety Set:

All enrolled subjects who received at least one dose of HYQVIA will be included in the safety evaluations. Analysis of tolerability, safety, and immunogenicity data will be based on the Safety Set.

PK Set:

All enrolled subjects who received at least one dose of HYQVIA and have at least one evaluable post-dose serum concentration for total IgG or IgG subclasses. Analysis of PK data will be based on the PK Set.

10.8 Pharmacokinetic and Pharmacodynamic Analyses

10.8.1 Pharmacokinetic Analysis

Serum levels of total IgG and IgG subclasses with and without baseline corrections will be summarized. Serum concentrations of total IgG and IgG subclasses at each nominal sampling time will also be summarized by dosing group and visit/timepoint using descriptive statistics. Individual PK parameters derived using NCA based on baseline-corrected total serum IgG or IgG subclasses levels will also be summarized. Summary statistics (number of subjects in the dosing group, number of subjects in the dosing group with evaluable PK parameter values, arithmetic mean, and SD, coefficient of variation, median, maximum, minimum, and geometric mean) will be provided for all PK parameters. In addition, 95% confidence intervals for geometric mean for the PK parameters will be provided for descriptive purposes only. Figures of individual and mean (± SD) concentration-time profiles will be produced. No statistical hypothesis testing will be performed. Tabular and graphical summaries will be presented, *as appropriate*, by Treatments (or Schedules), visit and timepoint.

PK parameters that may be calculated from concentration-time profiles of total serum IgG and IgG subclasses using non-compartmental analysis (NCA), may include and not be limited to the following.

Table 12. PK Parameters

Pharmacokinetic Parameter	Definition
C_{max}	Maximum concentration occurring at t_{max}
t_{max}	Time of maximum observed concentration sampled during a dosing interval
AUC_{last}	Area under the curve from the time of dosing to the last time point with measurable concentration
$t_{½}$	Terminal half-life
CL/F	Apparent total clearance after extravascular administration
V_z/F	Apparent volume of distribution associated with the terminal slope following extravascular administration

No value for V_z/F, or $t_{½}$ will be reported for cases that do not exhibit a terminal log linear phase in the concentration time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

Individual and mean serum concentration time curves (both linear and log linear) will be included in the final report.

10.8.2 Pharmacodynamic Analysis

Not applicable.

10.9 Safety and Immunogenicity Analyses

The study will assess the tolerability, safety, and immunogenicity of HYQVIA in terms of the occurrence of HYQVIA-related AEs (primary endpoint), the occurrence of other AEs, anti-rHuPH20 antibody formation during treatment with HYQVIA (immunogenicity), as well as changes in clinical laboratory parameters and vital signs.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Number and percentage of subjects with TEAEs, number of TEAEs, and other outcomes will be calculated overall, by SOC and by preferred term. TEAEs will be further summarized by severity and relationship to IP. TEAEs related to IP, TEAEs leading to withdrawal, SAEs, and deaths will be similarly summarized.

Tolerability, safety and immunogenicity endpoint data will be analyzed using descriptive statistics. Continuous endpoints (e.g., change from baseline) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, SD, minimum value, maximum value. Baseline is defined as the last non-missing value before the initial dose of HYQVIA. Categorical endpoints (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.

Summaries of AEs, clinical laboratory parameters, vital signs, and immunogenicity will be presented, as appropriate, by dosing group (Ramp-Up, No Ramp Up) and treatment arms within dosing schedule, as displayed in the table below with the planned total sample size and sample size for each treatment arm. In addition, labs, vital signs, and immunogenicity data will be summarized by dosing group and visit. Potentially clinically important findings will also be summarized. ECGs data will be provided in the subject data listing(s) only. No statistical summary is planned.

Note that in the display above, Ramp-Up dosing group (32 subjects in total) resulted from pooling of Treatment Arms 1, 2, 4, and 5, with 8 subjects each, and No Ramp-Up (16 subjects in total) resulted from pooling Treatment Arms 3 and 6, with 8 subjects each.

Table 13. Summary of Ramp-Up and No Ramp-Up Dosing Groups

Ramp-Up (N=32)					No Ramp-Up (N=16)		
Schedule A		Schedule B		Total	Schedule C		Total
Low	High	Low	High		Low	High	
Treatment 1 (n=8)	Treatment 4 (n=8)	Treatment 2 (n=8)	Treatment 5 (n=8)	All (n=32)	Treatment 3 (n=8)	Treatment 6 (n=8)	All (n=16)
Low = 0.4 g/kg, High = 1.0 g/kg.							

The overall summary, based on descriptive statistics, is the summary of the overall tolerability/safety/immunogenicity profile in the Ramp-Up dosing group (all treatments pooled) versus the overall profile in the No Ramp-Up group (all treatments pooled).

Claim of tolerability/safety/immunogenicity of HYQVIA will be based on clinical judgment on the totality of evidence, to be derived from the overall summary, with no predefined tolerability/safety/immunogenicity statistical margin or criteria.

Note: AEs below refer to TEAEs.

The following will be displayed in statistical outputs, including but not limited to:

- Number (percentage) of subjects with HYQVIA-related AEs (causally related AEs), and HYQVIA-related SAEs, and number of such events
  - AEs recorded in the study database as "possibly related" or "probably related" to HYQVIA will be considered HYQVIA-related AEs
- Number (percentage) of subjects with HYQVIA-related AEs that were mild, moderate, or severe in severity, and number of events in each category
- Number (percentage) of subjects with any AEs, any serious and/or nonserious AEs, and any local and systemic AEs/SAEs, regardless of causality
- Number (percentage) of infusions for which the infusion rate was reduced, and/or the infusion was interrupted or stopped due to intolerability and/or AEs.
- Number (percentage) subjects who completed infusions without requiring any adjustment due to intolerability and/AEs
- Number (percentage) of subjects who prematurely discontinued study due to AEs
- Rate of AEs, expressed as number of events per infusion, per subject, and per subject-year

- Raw (actual) values and change from baseline in clinical laboratory parameters
- Raw (actual) values and change from baseline in vital signs
- Number (percentage) of subjects who have developed binding and neutralizing antibodies to rHuPH20.

Subject-level tolerability and safety data, including derived data, will be presented in subject data listings.

Refer to Section 9.1 for AE definitions and details of procedures for recording, evaluating, and Reporting of AEs.

10.10 Additional Analysis of AEs

Specified in Section 3.3 is the safety endpoint, the number (percentage) of subjects and infusions with adverse reactions (AR) plus suspected AR of interest. This additional safety endpoint will be analyzed using descriptive statistics.

Separate AE summaries will be produced for each criterion listed below.

Definition: An AR plus suspected AR of interest is defined all AEs that meet one or more of the following criteria:

a. The AE is a local infusion site AE.

   Note: All local infusion site AEs will be considered AR irrespective of investigator/sponsor opinions of causality.

b. The AE began during infusion of HYQVIA or within 72 hours of the last infusion.

c. The AE was considered at least possibly related to HYQVIA infusion by the investigator and/or the sponsor.

d. The AE's causality assessment was missing or indeterminate.

e. The incidence of the AE preferred term among subjects in the **combined high** target level dose (1.0 g/kg) groups exceeded that among subjects in the **combined low** target level dose (0.4 g/kg) groups by 5% (absolute) or more.

The summary is planned to display only AEs with Overall absolute difference of ≥5%, as illustrated below in *an example, using dummy* (not real) data; "XX" represents data.

AE Preferred Term	Ramp-Up			No Ramp-Up			Overall		
	High Dose (N=16)	Low Dose (N=16)	Difference (absolute)	High Dose (N=8)	Low Dose (N=8)	Difference (absolute)	High Dose (N=24)	Low Dose (N=24)	Difference (absolute)
Term 1	XX	XX	XX	XX	XX	XX	20%	15%	5%
Term 2	XX	XX	XX	XX	XX	XX	12%	6%	6%
Term 3	XX	XX	XX	XX	XX	XX	3%	11%	8%

10.11 Other Analyses

10.11.1 Analysis of Demography and Other Baseline Characteristics

Demographic and other baseline characteristics data (including but not limited to baseline age, gender, weight, height, and BMI) will be summarized. Continuous data (e.g., age) and categorical data (e.g., gender) will be summarized using descriptive statistics.

All subject-level data, including derived data, will be displayed in subject data listings.

11. ETHICS

11.1 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the IRB and regulatory authority(ies), where applicable, (see Section 11.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, that have been approved by the applicable IRB and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the Sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally-authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

11.2 Institutional Review Board or Ethics Committee

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (i.e., before shipment of the Sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date. The Sponsor will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the Study. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the Sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and Sponsor.

Responsibility for coordinating with IRBs/ECs is defined in the clinical trial agreement.

IP supplied will not be released until the sponsor has received written IRB/EC approval.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue. If required by local law, substantial amendments to the protocol must also be approved by the appropriate regulatory agency prior to implementation.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC appraised of the progress of the study and of any changes made to the protocol, at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. This can be the responsibility of the sponsor or investigator for sites within the EU; or for multicenter studies, the coordinating principal investigator, according to national provisions.

The investigator must also keep the local IRB/EC informed of any serious and significant AEs as required by IRB/EC procedures.

11.3 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

12. DATA HANDLING AND RECORD KEEPING

12.1 Privacy and Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 11.1).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's CRF).

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives' reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market Subcutaneous Immune Globulin Infusion 10% (Human)(HYQVIA/HyQvia) with Recombinant Human Hyaluronidase (rHuPH20); national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies-containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

12.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data", records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the IRB and the study monitor/sponsor, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized CRU personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the CRU in accordance with the data retention policy (see Section 12.2).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

12.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the IRB), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the CRU and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Subinvestigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

13.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

13.2 Training

The study monitor will ensure that the investigator and CRU personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the CRU, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the CRU and the sponsor.

13.3 Monitoring

The study monitor is responsible for ensuring and verifying that each CRU conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the CRU at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

13.4 Auditing

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the CRU, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

13.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC/IRB and relevant competent authority is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC/IRB and applicable regulatory authorities of any investigator termination.

14. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

15. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

16. REFERENCES

Baxalta US Inc. 2019. HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] - Prescribing Information.Web Link: https://www.shirecontent.com/PI/PDFs/HYQVIA_USA_ENG.pdf

Eastern Cooperative Oncology Group 2006. Common toxicity criteria of the Eastern Cooperative Oncology Group.Web Link: http://www.ecog.org/general/ctc.pdf

Food and Drug Administration 2008. U.S.Department of Health and Human Services, Center for Biologics Evaluation and Research, Guidance for industry: Safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency.Web Link: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm078526.pdf

Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T. & Carbone, P. P. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol,* 5**,** 649-655.

World Health Organization 2003. Toxicity grading scale for determining the severity of adverse events.Web Link: http://www.icssc.org/Documents/Resources/AEManual2003AppendicesFebruary_06_2003%20final.pdf

Investigator's Brochure, IGI, 10% with rHuPH20, Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase. Edition 6.0: Approval Date: 05 Mar 2019

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Protocol Amendment 1.0	30 JUN 2020	Global
Original Protocol	04 FEB 2020	Global