Statistical Analysis Plan

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

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STATISTICAL ANALYSIS PLAN

HYQVIA/HyQvia
PHASE 1

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

PROTOCOL IDENTIFIER: TAK-771-1001

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	Original Version	
2.0	22APR2022	• Section 7: Tolerability Analysis Definitions of tolerability analysis clarified. • Section 8.1 Adverse Events: Text added to define local versus systemic adverse events; definition of subject-years updated. • Section 9: Pharmacokinetic Analysis Clarification on required tables and figures; clarification of handling of baseline-corrected concentrations <0; another PK parameter ($AUC_{0\text{-}D8}$) added.

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ABBREVIATIONS

λ_z	terminal disposition elimination rate constant
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	area under the concentration-time curve
$AUC_{0\text{-}D8}$	area under the concentration-time curve from time zero to Day 8
$AUC_{0\text{-}last}$	area under the concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0\text{-}\infty}$	area under the concentration-time curve from time zero extrapolated to infinity
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count;
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
C_{max}	maximum observed concentration
CL/F	apparent total clearance after extravascular administration
CRU	clinical research unit
DL	dose level
DMC	Data monitoring committee
eCRF	electronic case report form
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
IgG	Immunoglobulin G
IGI	Immune Globulin Infusion
INR	International normalized ratio
IP	investigational product
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
N	number of subjects
nADA	neutralizing anti-drug antibody
PCI	potentially clinically important
PK	pharmacokinetic(s)
p.p	percentage points
PT	preferred term
RBC	red blood cells
RDW	Red Cell Distribution Width
rHuPH20	recombinant human hyaluronidase PH20
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
t½	terminal disposition phase half-life
TDL	target (full) dose level
TEAE	treatment-emergent adverse event
t_{max}	time of maximum observed concentration
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration
WBC	white blood cells

1. INTRODUCTION

Dose ramp up has been considered necessary for HYQVIA in the Phase 3 Study (Study 161403) because the majority of chronic inflammatory demyelinating polyradiculoneuropathy (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 primary immunodeficiency disease 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 pharmacokinetics (PK) of total Immunoglobulin G (IgG) and IgG subclasses in serum after SC administration of HYQVIA in healthy adult subjects.

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of safety and tolerability data as well as PK analyses, as described in the amended protocol (amendment 1) dated 30 Jun 2020. Specifications for tables, figures, and listings are contained in a separate document.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

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

2.2 Endpoints

2.2.1 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.
Note: For definitions related to tolerability of infusions refer to section 7.1.

2.2.2 Safety and Immunogenicity Endpoints

- Occurrence of treatment-emergent adverse events (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 (AR) plus AR of interest.
- Clinical laboratory parameters
- Vital signs
- Immunogenicity: occurrence of binding and neutralizing antibodies (anti-drug antibodies [ADA]) to recombinant human hyaluronidase PH20 (rHuPH20)

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

2.2.3 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 not limited to maximum observed concentration (C_{max}), time of maximum observed concentration (t_{max}), the area under the concentration-time curve, from time zero to the last quantifiable concentration, as calculated by the linear-log trapezoidal method (AUC_{last}), area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), terminal disposition phase half-life ($t_{1/2}$), apparent total clearance after extravascular administration (CL/F, only for total IgG) and apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F, only for total IgG).

3. STUDY DESIGN

3.1 General Description

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.

The investigational product is subcutaneous Immune Globulin Infusion 10% (Human) (IGI 10%) with Recombinant Human Hyaluronidase (rHuPH20) (also referred to as IGI 10% with rHuPH20, or HYQVIA); infusion of IGI 10% will be followed by an infusion of rHuPH20.

This study is comprised of two parts, Study Parts 1 & 2. The IGI 10% target dose level (TDL) of either 0.4 g/kg (Part 1) or 1.0 g/kg (Part 2) will be achieved through dose ramp-up or no ramp up (i.e., immediate 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.

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

Subjects meeting all eligibility criteria will be assigned to one of the 3 treatment arms in a Study Part at a randomization ratio of 1:1:1, and a minimum of 3 subjects in each of the body mass index (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).

After all subjects in Treatment Arms 1-3 have completed Week 9 treatment in Study Part 1, their tolerability, safety and immunogenicity data through Week 9 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. Proceeding to Study Part 2 dosing may only occur following this review.

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 IGI 10%

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	0.50
DL3	3/4 of TDL	0.3	0.75
DL4	TDL	0.4	1.0

Each study part 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 or early termination (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.

Figure 1: 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.

3.2 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.

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).

3.3 Blinding

Blinding is not applicable for this open-label study.

3.4 Sample Size and Power Considerations

Assessment of tolerability is the primary objective of this study. This study was 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.

4. STATISTICAL ANALYSIS SETS

4.1 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, unless otherwise specified in this SAP.

4.2 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.

4.3 Pharmacokinetic 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.

The protocol deviation log will be reviewed on a case-by-case basis. Exclusion of any subject from the PK Set will be determined at the discretion of the Sponsor's Pharmacokineticist.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

Subject disposition summaries and listings will be based on the Enrolled Set, and the summaries will be presented by dosing group (Ramp-Up , No Ramp-Up, and Overall) and treatment arms within dosing group, following the format in Table 2 below.

Table 2 General Display of Subject Disposition and Subject Characteristics Summary Data

Ramp-Up (N=32)					No Ramp-Up (N=16)			Overall Total (n=48)
Schedule A		Schedule B		Total	Schedule C		Total	
Low TDL	High TDL	Low TDL	High TDL		Low TDL	High TDL		
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.								

Note: Sample sizes (n) shows planned sample size; n for Ramp-Up Total (n=32) results from pooling of Treatment Arms 1, 2, 4, and 5, with 8 subjects each; n for No Ramp-Up Total (n=16) results from pooling Treatment Arms 3 and 6, with 8 subjects each; n for Overall Total (n=48) results from pooling across Ramp-Up and No Ramp-Up.

Subject disposition will be summarized once for the whole population and additionally once by BMI group.

The number and percentage of subjects included in each analysis set (Enrolled, Safety and PK) will be summarized. The reasons for exclusion from the PK set will be included in the same summary.

The number and percentage of subjects who completed the study or prematurely discontinued will be presented, along with primary reasons for discontinuation, as recorded on the study completion page of the eCRF.

All enrolled subjects who prematurely discontinued the study will be listed in the subject disposition listing along with reasons for discontinuation.

5.2 Demographic and Other Baseline Characteristics

The following demographic characteristics will be summarized in the following order in the tables: age (years), sex, ethnicity, race. Other baseline characteristics include weight (kg), height (cm), BMI (kg/m^2), and BMI group (18 to <25 kg/m^2 and ≥25 to 30 kg/m^2).

Age will be calculated as the integer part of (date of informed consent is signed – date of birth + 1)/365.25. BMI from the screening visit eCRF will be used; if BMI from screening visit is missing, height and weight from the screening visit will be used to calculate BMI as: weight (kg) / (height [m])^2.

Continuous variables, such as age, weight, height, and BMI will be summarized using descriptive statistics including n, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables such as sex, ethnicity, and race will be summarized by reporting the number and percentage of subjects in each category.

All demographic and other baseline characteristics variables that will be summarized will be taken from the Screening Visit (or the last value measured prior to the first administration of investigational product). Summaries will be based on the Safety Set and PK Set, as appropriate. Demographics and other baseline characteristics data will be listed, and the listing will be based on the Enrolled Set.

5.3 Medical History

At screening, the subject's medical history will be described for the following body systems including severity 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

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0.

Medical history will be listed and summarized by system organ class (SOC) and preferred term (PT) for each dosing group (Ramp-Up, No Ramp-Up) and treatment arms within dosing group for the Safety Set. The summary will include number and percentage of subjects who experienced the event, and number of events experienced. System organ class will be sorted alphabetically, and PT will be sorted within each SOC in descending overall frequency of no-ramp-up group.

5.4 Prior Therapies, Procedures, and Medication

Prior treatments, medications, or procedures are defined as any treatment, medication, or procedure received within 60 days prior to the date of first dose of HYQVIA.

Prior medications will be coded using the World Health Organization (WHO) Drug Dictionary version Global B3 March 2020. Prior therapies and procedures will not be coded.

The number and proportion of subjects receiving each prior medication will be summarized by therapeutic class and preferred name for each dosing group (Ramp-Up, No Ramp-Up) and treatment arms within dosing schedule for the Safety Set. Therapeutic class will be sorted alphabetically, and preferred name within each therapeutic class will be sorted in descending overall frequency of the no-ramp up group. Multiple medication usage by a subject in the same category will be counted only once.

No summaries will be provided for prior therapies and prior procedures.

All prior therapies, procedures, and medications will be listed.

5.5 Concomitant Therapies, Procedures, and Medications

Concomitant therapies, medications, or procedures are defined as any therapy, medication, or procedure with start date on or after first date of HYQVIA administration, or with start date prior to HYQVIA administration but continuing at or after HYQVIA administration. Any therapy, medication, or procedure with a start date after the end of the follow-up period (Weeks 24 (± 1) (Treatment Arms 1 and 4) or 25 (± 1) (Treatment Arms 2, 3, 5, and 6)) will be considered post-treatment and not concomitant.

Concomitant medications will be coded using the WHO Drug Dictionary version Global B3 March 2020. Concomitant therapies and procedures will not be coded.

The number and proportion of subjects receiving each concomitant medication will be summarized by therapeutic class and preferred name for each dosing group (Ramp-Up, No Ramp-Up) and treatment arms within dosing schedule for the Safety Set. Therapeutic class will be sorted alphabetically, preferred name within each therapeutic class will be sorted by descending overall frequency of the no ramp-up group. Multiple medication usage by a subject in the same category will be counted only once.

No summaries will be provided for concomitant therapies and concomitant procedures.

All concomitant therapies, procedures, and medication will be listed.

5.6 Exposure to Investigational Product

An exposure data listing, based on the Safety Set, will be provided and include start and end date and time of dose administration, and other exposure data, e.g. planned dose/volume.

5.7 Measurements of Treatment Compliance

Treatment compliance will be summarized by means of number of infusions completed, number of infusions with change of infusion rate (flow), number of infusions interrupted, number of infusions stopped (discontinued), and the percentage of total volume administrated relative to the planned volume; all based on the number of initiated infusions. All compliance-related data will be included in the exposure data listing.

To determine whether the infusion rate is changed, the Study Drug Administration CRF form will be used. If “Was the infusion rate reduced?” = “Yes” or “Infusion Rate Changed” is checked, then the infusion rate will be considered to have been changed.

5.8 Protocol Deviations

Protocol deviations will be recorded separately from the clinical database using a Protocol Deviation tracker. Protocol deviations will be classified as major or minor per the agreed protocol deviation management plan and will be documented in the Protocol Deviation tracker. The Sponsor study team will review the protocol deviations and their classification throughout the study and before database lock.

Protocol deviations will be summarized by category (major/minor) for each dosing group (Ramp-Up, No Ramp-Up) and treatment arms within dosing group, based on the Safety Set. All protocol deviations will be listed based on the Safety Set.

6. EFFICACY ANALYSES

There is no efficacy endpoint in this study; therefore, no efficacy analyses are planned for this study.

7. TOLERABILITY ANALYSIS

For the purpose of the tolerability analysis, the term "tolerability" refers to tolerability of the infusion ("infusion tolerability"). An infusion is considered tolerable if the infusion rate was not reduced and the infusion was neither interrupted nor stopped due to a HYQVIA-related AE with onset during the infusion. This definition is an interpretation/clarification of the original definition written in the protocol.

7.1 Definitions

An infusion is considered *not tolerated* (*intolerable)*, if the infusion rate was reduced or the infusion was interrupted or stopped, due to a HYQVIA-related AE with onset during the infusion. Otherwise, the infusion is considered tolerable.

The complete HYQVIA infusion will be considered *not tolerated (intolerable)* if either of the component infusions (rHuPH20 or IGI 10%) was not tolerated.

A component infusion (rHuPH20 or IGI 10%) will be considered *not tolerated (intolerable)* if both of the following are true:

1. The infusion rate was reduced, the infusion was interrupted, or the infusion was stopped prior to completion.
2. The reason for the rate reduction, interruption, or stoppage was a HYQVIA-related AE with onset during the infusion.

The following algorithm will be used to connect the above logic to the eCRF and thus determine if a component infusion was not tolerated.

1. Did a HYQVIA-related AE occur during the infusion?
    a. "HYQVIA related" means that at least one of the following two items is true
        i. On the AE form: "Relationship to investigational product" = "Possibly related" or "Probably related"
        ii. On the AE form: "Relationship to IP administration process" = "Possibly related" or "Probably related"
    b. "occur during infusion" means that start time of the AE (from the AE form) was between start and end time of the infusion (from the infusion form).
    c. If the answer to this question is no, stop here: the infusion will be considered tolerated.
    d. If the answer to this question is yes, proceed to the next question.
2. Are any of the following true? If yes, the infusion was *not* tolerated; otherwise, it was tolerated.
    a. Dose was reduced and interrupted, which is determined by either of the following:
        i. On the AE form, "Action taken with study procedure" = "Procedure interrupted" or "Procedure stopped"
        ii. On the AE form, "Action taken with study drug" = "Dose reduced" or "Drug interrupted" or "Drug withdrawn"
        iii. On the infusion form, "Was the infusion rate reduced" = "Yes"
    b. Dose was not completed, which is determined by either of the following:
        i. On the infusion form, "Was the drug administration complete" = "No"
        ii. On the infusion form, "Total Volume Administered" < "Planned Volume"

7.2 Summaries of Infusion Tolerability

All tolerability summaries will be presented by dosing group (Ramp-Up, No Ramp-Up), treatment arm within dosing group, and stratified by BMI group. For subjects who dropped out early (before the last infusion as per protocol), planned infusions for the treatment arm that were not initiated for the subject are not considered for those summaries.

All tolerability summaries will also be performed for the complete HYQVIA infusion, and broken down by the two component infusions, rHuPH20 and IGI 10%.

The number and percentage of subjects who tolerated all actual, defined as infusions that were initiated, infusions will be summarized for the complete HYQVIA infusion, and broken down by the two component infusions, rHuPH20 and IGI 10%. A similar summary will be provided for the IGI 10% infusions broken down by dose level (¼ TDL, ½ TDL, 3/4TDL, TDL, as applicable).

Further summary tables (for HYQVIA overall and for each component rHuPH20 and IGI 10%) will be done showing the number of planned infusions for each subject and descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum) for the number actual (initiated) infusions, the number of tolerated infusions and the percentage of tolerated infusions (relative to the number of initiated infusions).

Finally, the number and percentage of tolerated infusions (HYQVIA overall, rHuPH20, IGI 10%) across all subjects within a treatment arm will be summarized. The percentage will be calculated as total number of tolerated infusions of all subjects within the treatment arm divided by total number of infusions initiated for all subjects within the treatment arm.

Infusion tolerability data, including the percentage of tolerated infusions for each subject, will be presented in a data listing.

8. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Set. Details for reporting AEs are described in section 8.1; details reporting of laboratory data and vital signs are described in section 8.2 and 8.3, respectively; ECG data will be provided in the subject data listing(s) only (see section 8.4); for details on reporting immunogenicity refer to section 8.5.1.

For each safety variable, unless otherwise specified, the last non-missing value before the administration of IP will be used as baseline for all analyses of that safety endpoint.

All safety data, including derived data, will be presented in subject data listings, and all listings will include subject's sex, age, and race. Immunogenicity data will be listed accordingly.

8.1 Adverse Events

Adverse events will be coded using MedDRA version 24.0.

8.1.1 Definitions

Treatment-emergent AEs (TEAEs) are defined as any events 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.

HYQVIA-related AEs:
To determine whether an AE is related to HYQVIA, two items on the AE CRF form will be used: "Relationship to investigational product" and "Relationship to IP administration process".

If either of these items is marked as "Possibly related" or "Probably related", then the AE is related to HYQVIA. Otherwise, the AE is not related.

Local vs systemic TEAEs will be classified using the AE term. If the reported term includes "infusion site" or "injection site", it will be classified as a local AE; all other AEs will be classified as a systemic TEAE. In the case of the following terms: "EDEMA", "PRURITUS", "ERYTHEMA" without also including "at infusion/injection site", these will be queried to determine local or systemic TEAE. In addition, prior to final analysis the medical director will review all AEs reported terms to verify if local or systemic TEAE. Following all queries and medical director review, the reported terms will be updated as appropriate to include "infusion site" or "injection site".

Infusion-associated TEAEs will be defined as any TEAE that begins during the infusion or within 24 hours following.

Temporally-associated TEAEs will be defined as TAEs which begin during the infusion or within 72 hours following the end of IP infusion.

Adverse reaction (AR) plus suspected adverse reaction is any AE that meets any of the following criteria:

- the AE is considered a local (infusion site) AE;
- the AE is considered by either the investigator and/or the sponsor to be HYQVIA related;
- the AE is a temporally associated TEAE;
- the AE's causality assessment is missing or indeterminate.

8.1.2 AE Data Summaries

All TEAE summaries will be provided by dosing group (Ramp-Up, No Ramp Up, and Overall) and treatment arms within dosing schedule, similarly as shown in Table 2 in section 5.1.

An overall TEAE summary will be presented, showing the number and percent of subjects (and number of events) with/of any TEAEs, severe TEAEs, serious and nonserious TEAEs, HYQVIA-related and non-related TEAEs, HYQVIA-related SAEs, local and systemic TEAEs, TEAEs leading to premature discontinuation from the study, infusion-associated TEAEs, temporally associated TEAEs, and AR plus suspected AR of interest.

Further summaries will be provided for

- Number and percentage of subjects with TEAEs, as well as the number of TEAEs, summarized by SOC and PT
- Number and percentage of subjects with TEAEs, as well as the number of TEAEs, summarized by PT (descending frequency in no-ramp up group)
- TEAE rates (per infusion, per subject, annual rate) by SOC and PT
- Number and percentage of subjects with TEAEs (and number of TEAEs) by PT and severity
- Percent of subjects with AR and suspected AR of interest by dosing schedule (ramp-up, no ramp-up, overall) and dose level (high vs low dose, and difference high-dose) by PT; see further details below
- Number and percentage of subjects with TEAEs, as well as the number of TEAEs, leading to discontinuation summarized by SOC and PT
- Number and percentage of subjects with serious TEAEs, as well as the number of TEAEs, leading to discontinuation summarized by SOC and PT
- Number and percentage of subjects with HYQVIA-related TEAEs, as well as the number of TEAEs, summarized by SOC and PT
- Number and percentage of subjects with HYQVIA-related TEAEs (and number of TEAEs) by PT and severity
- Number and percentage of subjects with serious HYQVIA-related TEAEs, as well as the number of TEAEs, leading to discontinuation summarized by SOC and PT
- Number and percentage of subjects (and number of events) of local versus systemic AEs by PT and relationship
- Number and percentage of subjects with TEAEs, as well as the number of TEAEs, leading to death summarized by SOC and PT

For the above summaries the following rules shall be applied. If more than 1 AE occurs with the same PT for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to HYQVIA. For example, if a subject experienced a mild headache not related to HYQVIA, and a moderate headache related to HYQVIA, then the subject will be counted once for headache using the moderate headache related to HYQVIA. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC sorted by descending overall frequency of no ramp-up group. The TEAEs, and TEAEs related to HYQVIA, will be summarized by PT, sorted by descending frequency of no-ramp up group.

For the summary of subjects with AR and suspected AR of interest it is planned to display only AEs with an absolute difference of ≥ 5 percentage points (p.p.) in the incidence rate between the high and low dose arm overall, as illustrated below in an example, using dummy (not real) data; "XX" represents data.

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

The rate of each TEAE, HYQVIA-related and HYQVIA-unrelated TEAEs, local/systemic TEAEs, expressed as number of events per infusion, per subject, and per subject-year will be derived as described below:

- The number of events per infusion will be calculated as total number of AEs divided by total number of infusion performed for each treatment arm.
- The number of events per subject will be calculated as total number of AEs divided by total number of subjects for each treatment arm.
- The number of events per subject-year will be calculated as total number of AEs divided by total subject-year by treatment arm. Total subject-years for a treatment arm will be calculated as the sum of the individual subject-years, which will be calculated as the time (in years) from first treatment initiation until 72 hours after the last treatment, and will be calculated as following:

$$Subject - Years = \frac{(Date\ of\ Last\ Treatment + 72) - (Date\ of\ First\ Treatment) + 1}{365.25}$$

All AEs (TEAEs and non-TEAEs) will be provided in the AE subject listings.

8.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values and changes from baseline at each assessment time point as well shift tables from baseline to each visit for quantitative variables (based on the respective normal ranges) will be presented by dosing group (Ramp-Up, No Ramp-Up) and treatment arms within dosing schedule, for the following clinical laboratory variables:

Biochemistry	Blood urea nitrogen (BUN), bilirubin (total and direct), ALP, AST, triglycerides, cholesterol, ALT, lactate dehydrogenase (LDH), urine acid, albumin, sodium, potassium, chloride, glucose, creatinine (At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula), low-density lipoprotein, high-density lipoprotein, magnesium, calcium
Hematology	Hemoglobin, red cell distribution width (RDW), 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, red blood cell count, platelet count
Hemolytic Panel	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, urine hemosiderin.
Urinalysis	pH, specific gravity, protein, glucose, ketones, color, bilirubin, blood, nitrites, urobilinogen, leukocyte esterase. 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.
Coagulation	Activated partial thromboplastin time (aPTT), and international normalized ratio (INR).

Clinical significance of abnormal laboratory values was to be assessed by the investigator; this assessment of clinical significance is not captured in the study database. Clinically significant laboratory values were to be reported as AE and therefore are summarized in context with the AE data summaries described in section AE Data Summaries.

Selected clinical laboratory parameters will be graded as the toxicity grading criteria listed in Appendix 17.2, Table 7. When the units in this table are specified as "ULN", the grades will be derived by using the ULN values given in each grade column, i.e. for ALP, Grade 1 = ULN to 2.5*ULN. Else, they will be derived by comparing the laboratory values to the ones in the tables. If a lab parameter doesn't show a value for a particular grade, that grade won't be assessed. For example, Bilirubin will not have a grade 1; consequently, bilirubin will have a Grade 0 and Grade 2 will be calculated as ULN – ULN*1.4.

For each parameter for that toxicity grading is applied, the number and percentage of subjects by toxicity grade will be summarized for baseline and for the maximum post-baseline toxicity grade (by dosing schedule and treatment arm). The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 post-baseline grade value.

All laboratory data will be listed, all abnormal laboratory data will be identified.

8.3 Vital Signs

Descriptive statistics for vital signs (e.g. weight, heart rate, respiratory rate, systolic and diastolic blood pressure) and their changes from baseline at each post-baseline visit will be presented by dosing group (Ramp-Up, No Ramp-Up) and treatment arms within dosing schedule.

Vital sign values will be considered potentially clinically important (PCI) if they meet both the observed value criteria and the change from baseline criteria listed in Table 3 below.

The number and percentage of subjects with PCI post-baseline values will be tabulated by treatment arm. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline vital sign value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, baseline, and post-baseline PCI values.

Table 3 Criteria for Potentially Clinically Important (PCI) Vital Signs

Parameter	Classification	Criteria
Systolic blood pressure (mm Hg)	HIGH and INCREASE	≥ 140 and increase of ≥ 20 from baseline value
	LOW and DECREASE	≤ 90 and decrease of ≥ 20 from baseline value
Diastolic blood pressure (mm Hg)	HIGH and INCREASE	≥ 90 and increase of ≥ 15 from baseline value
	LOW and DECREASE	≤ 50 and decrease of ≥ 15 from baseline value
Heart rate (bpm)	HIGH and INCREASE	≥ 100 and increase of > 15 from baseline value
	LOW and DECREASE	≤ 45 and decrease of > 15 from baseline value
Weight	HIGH	Increase of ≥ 5% from baseline value
	LOW	Decrease of ≥ 5% from baseline value

All vital signs data (including height and weight) will be listed.

8.4 Electrocardiogram

Electrocardiogram (ECG) data will be provided in the subject data listing(s) only.

8.5 Other Safety Data

8.5.1 Immunogenicity Testing for Anti-Drug Antibodies

The number and percentage of subjects who have developed binding and neutralizing antibodies to rHuPH20, along with the number and percentage of subjects who have binding titers ≥ 160, will be summarized by visit/time and by treatment arm.. The ADA results will also be included in a listing.

8.5.2 COVID-19

All COVID-19 data collected in the eCRF will be presented in a data listing.

8.5.3 Physical Examination

All physical examination data will be presented in a data listing.

8.5.4 Pregnancy

All pregnancy data will be presented in a data listing.

9. PHARMACOKINETIC ANALYSIS

All summaries and analyses of the PK data will be based on the PK Set defined in Section 4.3.

9.1 Drug Concentration

Blood samples will be drawn from each subject during this study for the determination of serum concentrations of total IgG and IgG subclasses (IgG1, IgG2, IgG3, and IgG4). Serial blood samples will be collected on Day 1 (pre-dose), and Days 2, 4, 6, 8, (all Treatment Arms 1 to 6), 15 (Treatment Arms 2, 3, 5, and 6 only), and 29 (Treatment Arms 3 and 6 only) after administration of the investigational product. The Day 1 pre-dose concentration will be considered as baseline. Serum concentrations of total IgG and IgG subclasses will be measured using validated analytical methods.

Individual total IgG and IgG subclasses serum concentrations (uncorrected and baseline-corrected) will be listed by treatment arm, subject, and time (showing scheduled and actual time).

Individual total IgG and IgG subclasses serum concentrations (uncorrected and baseline-corrected) will be summarized by treatment arm and scheduled time by means of descriptive statistics (including number of subjects (N), number of observations (n), arithmetic mean, SD, percent coefficient of variation (%CV), median, minimum, maximum, and geometric mean, geometric mean %CV and 95% confidence interval of geometric mean).

Individual and mean total IgG and IgG subclasses serum concentrations (uncorrected and baseline-corrected) will be presented in figures listed below on both linear and semi-logarithmic scales:

- Individual uncorrected concentration-time profiles by treatment arm
  (all subjects of a treatment arm within 1 figure, using actual time)
- Individual baseline-corrected concentration-time profiles by treatment arm
  (all subjects of a treatment arm within 1 figure, using actual time)
- Mean uncorrected concentration -time profile
  (all treatment arms within 1 figure, using scheduled time)
- Mean baseline-corrected concentration -time profile
  (all treatment arms within 1 figure, using scheduled time)

9.2 Handling Below Limit of Quantitation Values

The following procedures will be used for total IgG and IgG subclasses serum PK concentrations below the lower limit of quantification (LLOQ):

- Samples that are below limit of quantification (BLQ) will be reported as <LLOQ in the data listings, where LLOQ is replaced by the actual value for LLOQ for the specific PK assay. Baseline-corrected concentrations < 0, will be reported as 0 (in listings those values will be specially marked as set to 0).

- Samples that are BLQ are treated as zero in the calculation of summary statistics (e.g. mean, SD, etc.) for the serum PK concentrations at individual time points; similarly, baseline-corrected concentrations < 0 will be set to zero for calculation of the summary statistics. Geometric mean will be set to missing where zero values exist.

- Mean concentrations (uncorrected and baseline-corrected) are reported as zero if all values are BLQ or zero, and no other descriptive statistics are reported. If the calculated mean (±SD) concentration is less than the LLOQ, the value will be reported as calculated. The mean values derived using these concentrations will be used to create the mean serum concentration versus time plots.

- For calculation of area under the serum concentration curve (AUC), BLQ values are set equal to zero in the dataset loaded into Phoenix® WinNonlin® (Certara USA, Inc,

Princeton, NJ) for PK analysis. WinNonlin® uses the zero values that occur before the first time point with a concentration greater than LLOQ. Values that are BLQ after the first measurable concentration will be set to "missing" in the dataset loaded into WinNonlin®.

- Missing values will not be imputed.

9.3 Pharmacokinetic Parameters

The PK analysis will be conducted using Phoenix® WinNonlin® (Certara USA, Inc, Princeton, NJ) Version 8.0 or higher. Pharmacokinetic parameters will be determined from the IgG (total and subclasses) uncorrected and baseline-corrected serum concentration-time data using non-compartmental analysis based on actual sampling times. No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with measurable concentrations.

The PK parameters for IgG (total and subclasses) will include, but may not be limited to:

C_{max}	Maximum observed concentration
t_{max}	Time of maximum observed concentration
AUC_{last}	Area under the concentration-time curve from time zero to the last quantifiable concentration, calculated using the linear-up/log-down trapezoidal rule. In this method, the linear trapezoidal method of calculation is used for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero extrapolated to infinity
AUC_{0-D8}	Area under the concentration-time curve from time zero (Day 1) to Day 8.
λ_z	Terminal disposition elimination rate constant
$t_{½}$	Terminal disposition phase half-life
CL/F	Apparent total clearance after extravascular administration (only for total IgG)
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration (only for total IgG)

9.4 Statistical Analysis of Pharmacokinetic Data

Descriptive statistical analysis of PK parameters will be based on the PK Set. The uncorrected and baseline-corrected serum PK parameters of total IgG and IgG subclasses (listed in section 9.3) will be summarized by treatment arm. Summaries will include; N, n, arithmetic mean, SD, %CV, median, minimum, maximum, geometric mean, %CV of geometric mean and 95%

confidence intervals (CIs) for geometric mean. For t_{max} summaries will include only N, n, median, minimum, and maximum.

Uncorrected and baseline-corrected serum PK parameters AUC_{last}, $AUC_{0-\infty}$, AUC_{0-D8} and C_{max} of total IgG and IgG subclasses will be illustrated graphically (by treatment arm) as listed below

- Scatter plot of individual with mean uncorrected PK parameter
- Scatter plot of Individual with mean baseline-corrected PK parameter
- Boxplot of uncorrected PK parameters
- Boxplot of baseline-corrected PK parameters

Individual uncorrected and baseline-corrected serum PK parameters of total IgG and IgG subclasses will be listed.

10. PHARMACODYNAMIC ANALYSIS

Not applicable.

11. OTHER ANALYSES

Not applicable.

12. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

No planned interim analysis, or data monitoring committee are planned for this study.

13. DATA HANDLING CONVENTIONS

13.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: number of subjects (n), mean, median, SD, minimum, maximum. Unless specified otherwise, summary statistics will be presented to 1 more significant digit than the raw data. The minimum and maximum values will be presented to the same number of decimal places as the raw data; the mean and median will be presented to 1 more decimal place than the raw data; and the SD and standard error will be presented to 2 more decimal places than the raw data. BMI, averaged laboratory results e.g. diastolic/systolic blood pressure and pulse (when taken in triplicate), and derived questionnaire scores will be rounded to 1 decimal place for reporting.

Categorical and count variables will be summarized by the number of subjects and the percent of subjects in each category, as appropriate. Percentages will be presented as whole numbers.

13.2 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated or unscheduled assessments before the start of IP, then the results from the most recent assessment made prior to the start of IP will be used as baseline.

If post-baseline assessments are repeated, these will be captured as unscheduled visits, and the value recorded at the scheduled visit will be used for generating descriptive statistics.

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

13.3 Handling of Missing, Unused, and Spurious Data

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

For prior or concomitant medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

13.3.1.1 Incomplete Start Date

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

13.3.1.1.1 Missing Day and Month

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

13.3.1.1.2 Missing Month Only

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

13.3.1.1.3 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the dose date of IP, then the day of the dose date of IP will be assigned to the missing day

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

13.3.1.2 Incomplete Stop Date

The following rules will be applied to impute the missing stop dates. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

13.3.1.2.1 Missing Day and Month

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

13.3.1.2.2 Missing Month Only

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

13.3.1.2.3 Missing Day Only

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

13.3.2 Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, e.g. AE start year and month are the same as the year and month of the dose date of IP, then the AE will be classified as

treatment-emergent.

To facilitate categorization of AEs as treatment emergent, imputation of dates can be used. For AEs, incomplete (i.e., partially missing) start dates start dates will be imputed and will follow the same rules as in Section 13.3.1.1. Incomplete stop dates will not be imputed.

13.3.2.1 Incomplete Start Date

Follow the same rules as in Section 13.3.1.1.

13.3.2.2 Incomplete Stop Date

Incomplete stop dates will not be imputed.

13.3.3 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the dose date of IP, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the dose date of IP, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while both the actual and the imputed values will be used in data listings.

13.3.4 Missing Relationship to IP for Adverse Events

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

13.3.5 Character Values of Clinical Laboratory Variables

The actual values of clinical laboratory variables as reported in the database will be presented in data listings. No coded values (e.g., when a character string is reported for a numerical variable) are necessary.

14. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

PK analyses will be performed using Phoenix WinNonlin (Certara USA, Inc., Princeton, NJ) Version 8.0 or higher.

15. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Not applicable.

16. REFERENCES

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/GuidanceComplianceRegulatory yInformation/Guidances/Blood/ucm078526.pdf

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

17. APPENDICES

17.1 Schedule of Activities

The below tables are from the amended protocol (amendment 1) dated 30 Jun 2020. Sections referenced in the footnotes are protocol sections.

Table 4 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.

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.

Table 5 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.

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.

Table 6 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.

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.

17.2 Grading of Laboratory Parameters

Table 7 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.