Clinical Study Protocol

NCT Number: NCT05059977

Title: A Phase 1, Single-Dose, Single-Center, Open-Label, Three-Arm Study to Assess the Tolerability and Safety of Immune Globulin Subcutaneous (Human), 20% Solution with Recombinant Human Hyaluronidase (TAK-881) at Various Infusion Rates in Healthy Adult Subjects

Study Number: TAK-881-1001

Document Version and Date: Protocol Amendment #1, 09-JUL-2021

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-881-1001

Title:	A Phase 1, Single-Dose, Single-Center, Open-Label, Three-Arm Study to Assess the Tolerability and Safety of Immune Globulin Subcutaneous (Human), 20% Solution with Recombinant Human Hyaluronidase (TAK-881) at Various Infusion Rates in Healthy Adult Subjects
Drug:	Immune Globulin Subcutaneous (Human), 20% Solution (abbreviated as IGSC, 20%) with Recombinant Human Hyaluronidase (abbreviated as rHuPH20) (referred to as TAK-881)
IND:	27372
EUDRACT No.:	Non-EUDRACT
Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Ave, Lexington, MA 02421 AND Baxalta Innovations GmbH* Industriestrasse 67, A-1221 Vienna *Baxalta is now part of Shire, a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited.
Principal Investigator:	[redacted]
Protocol History:	**Amendment 1: 09 JUL 2021** **Original Protocol: 08 MAR 2021**

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

[redacted]

12July2021

Signature: *Date:*

[redacted] **PhD**
Phase 1 Clinical [redacted],
[redacted] Clinical Pharmacology & Pharmacokinetics

[redacted]

12 July 2021

Signature: *Date:*

[redacted], **MD**
Study Medical Monitor,
[redacted] Clinical Medicine

Investigator's Acknowledgement

I have read this protocol for Study TAK-881-1001.

Title: A Phase 1, Single-Dose, Single-Center, Open-Label, Three-Arm Study to Assess the Tolerability and Safety of Immune Globulin Subcutaneous (Human), 20% Solution with Recombinant Human Hyaluronidase (TAK-881) at Various Infusion Rates 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 VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **09 Jul 2021**	**Global/Country/Site Specific** **Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Additional treatment arm (Treatment Arm 3, 1.0 g/kg, un-warmed) was added to the study design with assessments and safety reviews similar to Treatment Arm 1 and 2, to explore impact of administering un-warmed immune globulin subcutaneous (human), 20% solution (IGSC, 20%)		Study Title, Synopsis, Section 1.2.2, Section 1.3, Section 4.1, Section 7.2.1, Section 7.2.2, Section 8.1.2, Section 9.5
Name of Principal Investigator was added		Title Page, Synopsis
Contact information for Takeda PV Operations Department was updated		Emergency Contact Information, Appendix 3.4
Details for planned study period were added		Synopsis
Study schedule for Day 3 and Day 4; and the footnotes for Table 1 (Schedule of Assessments) in Section 1.3 were clarified for consistency		Synopsis, Section 1.2.1, Section 1.3, Section 7.2.2, Section 8.1.2.2, Section 8.1.2.3, Section 9.5, Appendix 3.3
Additional subgroup was added to allow a 72-hour waiting period between first 2 subjects in each treatment arm of the study based on the US FDA recommendation		Synopsis, Section 1.2.2, Section 4.1, Section 7.2.2
Categorization of intensity of AEs was changed to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 based on the US FDA recommendation		Synopsis, Section 1.3, Section 4.1, Section 5.5.1, Section 8.2.4.2, Appendix 3.3
Definition of tolerability event and related text for primary endpoint were updated for clarification		Synopsis, Section 3.3.1, Section 9.8.1
SC administration endpoints and related text were updated for clarification		Synopsis, Section 3.3.2.2, Section 9.8.2
Sponsor's Study Medical Monitor was specified as the lead of safety review team for process clarification		Synopsis, Section 4.1, Section 5.5.5, Section 7.2.2, Section 9.5
Duration of treatment period and related description was updated for clarification		Synopsis, Section 4.1, Section 8.1.2.2, Section 8.1.2.3
Planned total sample size increased to 24 subjects considering the addition of new arm (Treatment Arm 3)		Synopsis, Section 4.1, Section 9.6
Exclusion Criteria #9 was revised based on the US FDA recommendation		Synopsis, Section 5.2
Type of infusion pump; infusion rate ramp-up schedule and evaluation were clarified based on operational clarification and infusion rates for Treatment Arm 3 were added.		Synopsis, Section 7.2.2
The infusion site(s) recommended for the study were specified per the US FDA recommendation		Synopsis, Section 7.2.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **09 Jul 2021**	**Global/Country/Site Specific** **Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Hgb assessment was added for Day 3 to evaluate the need for hemolytic panel		Section 1.3, Section 8.1.2.2
Physical examination requirement and schedule for infusion site evaluation were updated for clarification		Section 1.3, Section 8.1.2.3, Section 8.1.3.1
Evaluation of infusion related AEs was revised to align with CTCAE categories		Section 1.3, Appendix 3.3
Text relating to collection of photographs of infusion site(s) was clarified for timing and to specify that it is optional.		Section 1.3, Appendix 3.3
Pregnancy testing requirements were changed based on operational clarity		Section 1.3, Section 8.2.3.6
Stopping criteria for IP administration were revised based on the US FDA recommendation		Section 5.5.1
New section describing the stopping criteria for study was added based on the US FDA recommendation		Section 5.5.4
Definition for concomitant treatment was updated based on operational clarity		Section 6.2
Allocation of subject numbers based on BMI group was specified based on operational clarity		Section 7.2.1
Updates to IP storage for clarification		Section 7.3.3
Temperature of the warmer system for infusion of IGSC 20% (Treatment Arms 1 and 2 only) was specified per the US FDA recommendation		Section 7.3.4
Additional clarification regarding rescreening process		Section 8.1.1.2
Calculation of the volume of recombinant human hyaluronidase (rHuPH20) was added per the US FDA recommendation		Section 8.1.2.1
Protocol deviation consideration pertaining to scheduled assessment time set forth in the protocol for safety assessments was removed		Section 8.2.3
Updated AE collection language for clarification on process and timing		Section 8.2.3.3
Text relating to the timing of laboratory sample collection prior to IP administration was removed as it is not applicable		Section 8.2.3.5
Process for repeat test with regard to immunogenicity panel was specified for clarity		Section 8.2.4.2
Volume of blood to be drawn from each subject was revised based on operational clarity		Section 8.2.5
Data handling for concurrent conditions was removed as they would be captured under “Medical History”		Section 9.3
Terms for AESIs were updated for clarification		Appendix 3.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **09 Jul 2021**	**Global/Country/Site Specific** **Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Catheter leakage scoring system was added to the protocol for clarity on assessment		Appendix 3.3
Minor grammatical, editorial, and/or administrative changes have been made to improve the readability and/or clarity of the protocol		Throughout document

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a Serious Adverse Event (SAE), the investigator must fax or e-mail the " Takeda Safety Report Form" within 24 hours to the Takeda PV Operations 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)/Takeda 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**

Study Medical Monitor
[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 Takeda Study Manager.

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

If unavailable, please contact:

[redacted] **PharmD, MSc, PMP**
E-mail: [redacted]
Mobile: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product (IP) quality complaints or non-medical complaints to Takeda 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 Takeda licensed or IPs, 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 IP 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 (eg, secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottle/vial • Particulate in packaging	

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

ctmcomplaint@Takeda.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 Appendix 3.4.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
CCGs	case report form completion guidelines
CFR	Code of Federal Regulations
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
CRA	clinical research associate
CRC	clinical research center
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CUVITRU	immune globulin subcutaneous 20% (human)
D	day
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture system
EOS	end of study
ET	early termination
EU	European Union
Fab	antigen-binding fragment
Fc	fragment crystallizable region
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus

Abbreviation	Definition
Hgb	hemoglobin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IG	immune globulin
IGI	immune Globulin Infusion
IgG	immunoglobulin G
IGSC	immune globulin subcutaneous
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
K_3EDTA	ethylenediamine tetraacetic acid tripotassium
LDH	lactate dehydrogenase
MedDRA®	Medical Dictionary for Regulatory Activities®
nADA	neutralizing anti-drug antibody
NCI	National Cancer Institute
PI	Principal Investigator
PIDD	primary immunodeficiency disease
PK	pharmacokinetics
PT	preferred term
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TQ	targeted questionnaires
U	unit
ULN	upper limit of normal
US	United States
USA	United States of America
WBC	white blood cells

1. PROTOCOL SUMMARY

1.1 Study Synopsis

Protocol number: TAK-881-1001	**Drug:** TAK-881 - Immune Globulin Subcutaneous (Human), 20% Solution (abbreviated as IGSC, 20%) with Recombinant Human Hyaluronidase (abbreviated as rHuPH20)	
Title of the study: A Phase 1, Single-Dose, Single-Center, Open-Label, Three-Arm Study to Assess the Tolerability and Safety of Immune Globulin Subcutaneous (Human), 20% Solution with Recombinant Human Hyaluronidase (TAK-881) at Various Infusion Rates in Healthy Adult Subjects		
Number of subjects (total and for each treatment arm): The planned total sample size for this study is 24 subjects with 8 subjects enrolled/treated in each of the 3 treatment arms.		
Investigator(s): [redacted]		
Site(s) and Region(s): Single site, USA		
Study period (planned): Initiation: approximately September 2021 Completion: approximately March 2022	**Clinical phase:**	1
Study Subject Population: Healthy male and female subjects aged 19 to 50 years (inclusive) at the time of consent and body mass index (BMI) between 18.0 and 30.0 kg/m^2 (inclusive) at screening. This study plans to enroll 8 subjects in each of the 3 treatment arms, and a minimum of 3 subjects in each of the 2 BMI groups (18.0 to <25.0 kg/m^2, ≥25.0 to 30.0 kg/m^2) in each treatment arm.		
Objectives: **Primary:** To assess the tolerability of TAK-881 at various subcutaneous (SC) infusion rates in healthy adult subjects. **Secondary:** To assess the safety of TAK-881 at various SC infusion rates and immunogenicity of TAK-881 in healthy adult subjects. **Exploratory:** To assess serum total immunoglobulin G (IgG) levels.		
Rationale: TAK-881 (IGSC, 20% solution with rHuPH20) is a facilitated immune globulin subcutaneous (IGSC) infusion evolved from HYQVIA (IGSC 10%) and CUVITRU (IGSC 20%). Both HYQVIA and CUVITRU have very well-established efficacy and safety data. The higher concentration of TAK-881 (IGSC 20%) in comparison with HYQVIA (IGSC 10%) has the potential of reducing infusion volumes by 50%, decreasing infusion time, and potentially leading to improved tolerability. This Phase 1 study is being conducted to assess the tolerability, safety, and immunogenicity of TAK-881 at various SC infusion rates in healthy adult subjects with a focus on evaluating key dosing and administration parameters to support further clinical development.		

Investigational product, dose, and mode of administration:

TAK-881: Immune Globulin Subcutaneous (Human), 20% Solution (abbreviated as IGSC, 20%) with Recombinant Human Hyaluronidase (abbreviated as rHuPH20).

The dose levels for IGSC, 20% will be 0.4 g/kg (in-line warmed) for Treatment Arm 1, 1.0 g/kg (in-line warmed) for Treatment Arm 2, and 1.0 g/kg (un-warmed) for Treatment Arm 3.

The dose for rHuPH20 is 80 U/g IgG. The rHuPH20 units will be calculated as per the following:

- The dose of rHuPH20 is 80 Units × planned IGSC 20% dose in grams = total units to be infused (eg, 80 U × 40 g = 3200 U).
- Then, to calculate the volume required, divide the prescribed units by 160 as each vial has a concentration of 160 U/mL, (eg, 3200 U ÷ 160 U/mL = 20 mL).

Methodology:

This study is a Phase 1, single-dose, single-center, open-label, three-arm study to evaluate the tolerability, safety, and immunogenicity of TAK-881 at various infusion rates in healthy adult subjects.

This study comprises 3 treatment arms:

- Treatment Arm 1 - Subjects will receive a single dose of TAK-881 comprising of 0.4 g/kg (in-line warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.
- Treatment Arm 2 - Subjects will receive a single dose of TAK-881 comprising of 1.0 g/kg (in-line warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.
- Treatment Arm 3 - Subjects will receive a single dose of TAK-881 comprising of 1.0 g/kg (un-warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.

Mode of Administration:

The TAK-881-1001 investigational product (IP) will be administered via a SC route of administration using a 22 to 24-gauge SC needle set. The rHuPH20 solution will be administered first followed by IGSC 20% using the same needle set.

The rHuPH20 solution will be administered subcutaneously via a peristaltic infusion pump at a rate of 120 mL/hour/site (2 mL/minute/site) and infusion volumes of up to 30 mL/site.

The infusion site(s) can be either the abdomen (middle to upper abdomen) or the thighs (left or right).

The SC infusion of the IGSC 20% solution will begin within 10 minutes of completion of the SC infusion of the rHuPH20 solution via a peristaltic infusion pump with programmable infusion rates and infusion volumes of up to 300 mL/site and may require 1 or 2 infusion sites. If 2 infusion sites are required, the doses will be administered sequentially; the infusion of up to 300 mL will be administered first. A flushing step of normal saline will be required to ensure the total dose is administered due to the large priming volumes of the 2 administration systems. Normal saline will not be infused into the subject. For each infusion site, infusion rate ramp-up schedule will be followed as shown below.

If the infusion rate is reduced or interrupted due to an intolerability event, the infusion rate will stay at the maximally tolerable infusion rate (eg, if the maximum infusion rate is 300 mL and it is not tolerable, the infusion rate will be decreased to the previous infusion rate of 180 mL assuming it was well tolerated).

A step-wise infusion rate escalation regimen as shown below will be followed for the study based on tolerability of each incremental infusion rate increase:

Infusion Rates for Treatment Arm 1 (0.4 g/kg, in-line warmed) Using 1 Pump and 1 Single Needle Set

Administration		Rate Per Infusion Site (mL/hour) Single Needle Set	Volume Delivered	Accumulative Volume for IG per Site
rHuPH20	To be infused first	120	TBD	N/A
IGSC 20% (in-line warmed)	First 10 min	30	5 mL	5 mL
	Next 10 min	60	10 mL	15 mL
	Next 10 min	120	20 mL	35 mL
	Next 10 min	180	30 mL	65 mL
	Remainder of infusion	300	TBD	TBD (up to 300 mL)*

Abbreviations: IG=immune globulin; N/A=not applicable; TBD=to be determined
* Total volume of up to 300 mL will not include the volume of the rHuPH20 delivered first

Infusion Rates for Treatment Arm 2 (1.0 g/kg, in-line warmed) Using 2 Pumps and 1 Single Needle Set for Each Pump

Administration		Rate Per Infusion Site (mL/hour) for Each Pump	Volume Delivered for Each Pump	Accumulative Volume Site 1# (Pump A)	Accumulative Volume Site 2# (Pump B)
rHuPH20	To be infused first	120	TBD	TBD	TBD
IGSC 20% (in-line warmed)	First 10 min	30	5 mL	5 mL	5 mL
	Next 10 min	60	10 mL	15 mL	15 mL
	Next 10 min	120	20 mL	35 mL	35 mL
	Next 10 min	180	30 mL	65 mL	65 mL
	Remainder of infusion	300	TBD	TBD (up to 300 mL)*	TBD (remainder)

Abbreviations: TBD=to be determined
Each site will be evaluated separately
* Total volume of up to 300 mL will not include the volume of the rHuPH20 delivered first

Infusion Rates for Treatment Arm 3 (1.0 g/kg, un-warmed) Using 2 Pumps and 1 Single Needle Set for Each Pump

Administration		Rate Per Infusion Site (mL/hour) for Each Pump	Volume Delivered for Each Pump	Accumulative Volume Site 1# (Pump A)	Accumulative Volume Site 2# (Pump B)
rHuPH20	To be infused first	120	TBD	TBD	TBD
IGSC 20% (un-warmed)	First 10 min	30	5 mL	5 mL	5 mL
	Next 10 min	60	10 mL	15 mL	15 mL
	Next 10 min	120	20 mL	35 mL	35 mL
	Next 10 min	180	30 mL	65 mL	65 mL
	Remainder of infusion	300	TBD	TBD (up to 300 mL)*	TBD (remainder)

Abbreviations: TBD=to be determined
Each site will be evaluated separately
* Total volume of up to 300 mL will not include the volume of the rHuPH20 delivered first

A total of 24 subjects are planned with 8 subjects enrolled/treated in each of the 3 treatment arms.

Dosing will be first initiated at the lower dose level (Treatment Arm 1, 0.4 g/kg, in-line warmed) followed by the higher dose level (Treatment Arm 2, 1.0 g/kg, in-line warmed) and then the un-warmed arm (Treatment Arm 3, 1.0 g/kg, un-warmed). Subjects in all 3 treatment arms will be dosed according to a sentinel dosing design with ongoing safety monitoring by the investigator to ensure optimal tolerability and safety. Subjects in each treatment arm will be grouped into 4 subgroups of 1, 1, 2, and 4 subjects, respectively. The subgroups will be dosed sequentially to allow safety and tolerability evaluation prior to initiating dosing of the following subgroup.

Dosing will start with Treatment Arm 1. Initially, 1 subject will be dosed at the lower dose level and the subject will be closely observed by the investigator during the infusion period and for the first 72 hours (or longer, per investigator's discretion) following drug administration. The subject will be discharged from the site after an overall assessment on Day 4. The investigator will evaluate the safety and tolerability for the first subject from infusion start through 72 hours and consult the sponsor as necessary, prior to dosing the next subject from Treatment Arm 1. The next 2 subjects from Treatment Arm 1 (0.4 g/kg) will be dosed at least 3 days (72 hours) after dosing of the second subgroup of 1 subject. The remaining 4 subjects from Treatment Arm 1 (0.4 g/kg) will be dosed at least 3 days (72 hours) after dosing of the third subgroup of 2 subjects.

Dosing for Treatment Arm 2 will begin upon the recommendation of the safety review team after all subjects in Treatment Arm 1 have been dosed, and the tolerability and safety through Day 4 of the last subject in Treatment Arm 1 have been reviewed by the safety review team consisting of the investigator, the Study Clinical Lead, the sponsor's Study Medical Monitor (chair), and the sponsor's Global Drug Safety Physician.

Dosing for Treatment Arm 3 will begin upon the recommendation of the safety review team after all subjects in Treatment Arm 2 have been dosed, and the tolerability and safety through Day 4 of the last subject in Treatment Arm 2 have been reviewed by the safety review team consisting of the investigator, the Study Clinical Lead, the sponsor's Study Medical Monitor (chair), and the sponsor's Global Drug Safety Physician.

Subjects participating at the higher dose levels (Treatment Arm 2, 1.0 g/kg [in-line warmed] and Treatment Arm 3, 1.0 g/kg [un-warmed]) will be dosed following the same sentinel dosing scheme as Treatment Arm 1.

Study Periods

The study consists of 3 periods:

- Screening period: up to 21 days prior to dosing.
- Study treatment period: 4 days.
- Follow-up period: up to 12 (±1) weeks after TAK-881 infusion.

Tolerability and safety including immunogenicity of TAK-881 will be assessed during the treatment and follow-up periods for all 3 treatment arms.

All subjects will be monitored for the formation of binding anti-rHuPH20 antibodies (binding anti-drug antibody [ADA]) at predose (baseline), postdose (Day 30 ±3 days), and at end of study [EOS] (Week 12 ±1 week). Postdose 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 adverse event (AE) (Grade 2 or higher as per Common Terminology Criteria for Adverse Events [CTCAE] v5.0 (U.S. Department of Health and Human Services, 2017)) that may be a result of an immune-mediated response to either IG, rHuPH20, or other concomitant medications will be asked to return to the clinical research center (CRC) 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. The overall study design is presented in Figure 1 and the sentinel dosing design in Figure 2.

Inclusion and exclusion criteria:

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

Enrolled subjects are defined as subjects who have signed informed consent and meet all of the inclusion and none of the exclusion criteria. In this study, enrolled subjects are the same as treated subjects. Screen failures will not be captured in the electronic data capture (EDC) system or counted as "enrolled".

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 female of non-childbearing potential.
5. Must be considered "healthy." Healthy as determined by the investigator on the basis of screening evaluations. 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. BMI between 18.0 and 30.0 kg/m² inclusive.

Exclusion Criteria:

1. Any current or relevant history of medical (eg, 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 participation in the trial and compromise the trial objectives, or any condition that presents an undue risk from the IP or procedures.

   Note: Subjects on stable dose of hormone replacements (eg, 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 arrhythmias and conduction disorders.
3. Known or suspected intolerance or hypersensitivity to the IP(s), closely related compounds, or any of the stated ingredients (eg, human IG, hyaluronidase, albumin).
4. Known history of hypersensitivity or severe allergic reactions (eg, urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following administration of blood or blood components.
5. Known allergy to hyaluronidase of human (including recombinant human hyaluronidase) or animal origin (such as bee or wasp venom).

6. Significant illness, as judged by the investigator, within 30 days of the first dose of IP.
7. Known history of alcohol or other substance abuse within the last year.
8. Donation of blood within 60 days, or blood products (eg, plasma or platelets) within 2 weeks prior receiving the first dose of IP.
9. Subjects will be excluded if abnormal hematology, chemistry, and other laboratory values are >10% above the upper limit of normal (ULN) or >10% below the lower limit of normal (LLN) except for liver function tests and absolute neutrophils. Subjects will be excluded if any of the following laboratory parameters meet the criteria below:
   - Absolute neutrophil count $<1.5 \times 10^9$ cells/liter
   - Liver function: alanine aminotransferase (ALT) ≥1.5 × ULN, aspartate aminotransferase (AST) ≥1.5 × ULN, alkaline phosphatase (ALP) ≥1.5 × ULN, or total bilirubin ≥1.5 mg/dL

   Subjects will be excluded if any other laboratory values are outside the reference range and are clinically significant per investigator's judgment.
10. Subjects who, within 30 days prior to the first dose of IP:
    - Have participated in another clinical study involving immune globulin (IG) products within 12 months of screening.
    - Have used an IP (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 and COVID-19 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.
11. Confirmed systolic blood pressure >139 mmHg or <89 mmHg and diastolic blood pressure >89 mmHg or <49 mmHg.
12. A positive screen for alcohol or drugs of abuse at screening or Day -1 (D-1).
13. A positive human immunodeficiency virus (HIV), hepatitis C virus (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.
14. Smoking more than 5 cigarettes or equivalent per day, unable to stop smoking during confinement in the CRC.
15. Severe dermatitis or anatomical abnormality that would interfere with TAK-881 administration or endpoint assessments. Note: The skin at the administration site should not be covered by tattoos.
16. Current use of any herbal or homeopathic preparations is not permitted.
17. 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 infusion visit and through 72 hours post infusion.
18. Current or relevant history of hypercoagulable conditions (eg, 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: approximate overall duration of the study is 14 to 16 weeks from screening to EOS

Duration of Treatment Period: 4 days

Endpoints and statistical analysis:

Primary Endpoint:

The primary endpoint corresponding to the primary objective of the study is the occurrence of tolerability events related to the infusion of TAK-881 per infusion site.

Definition: A tolerability event is considered to have occurred if an infusion was tolerable. An infusion is considered tolerable if the infusion rate was not reduced or the infusion was not interrupted or stopped, due to any treatment-emergent adverse event (TEAE) related to TAK-881.

Secondary Endpoints:

Safety and Immunogenicity Endpoints:

- Occurrence of TEAEs, including but not limited to: TAK-881-related and non-related TEAEs
- 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.

SC Administration Endpoints:

The following SC administration endpoints represent supportive tolerability and safety measures:

- Maximum tolerable infusion rate achieved per infusion site
- Total volume infused per infusion site
- Time to deliver the total infused volume per infusion site

Exploratory Endpoint:

- Serum total IgG levels at predose and postdose of TAK-881 SC administration

Statistical Considerations:

No interim analysis is planned for this study. However, before the dosing in Treatment Arm 2, the tolerability and safety data through Day 4 of the last subject in Treatment Arm 1 will be reviewed by a safety review team. Similarly, the tolerability and safety data through Day 4 of the last subject in Treatment Arm 2 will be reviewed by a safety review team before the dosing in Treatment Arm 3.

No statistical hypothesis testing will be performed.

Tolerability, safety, and immunogenicity endpoint data as well as serum total IgG levels will be analyzed using descriptive statistics. Continuous endpoints will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation (SD), minimum value, and maximum value. Categorical endpoints will be summarized in terms of number and percent of subjects and number of occurrences in each category, as appropriate. Baseline is defined as the last non-missing value before the dose of TAK-881.

Study endpoints will be summarized, as appropriate, by treatment arm. Additional summaries will be presented by study visit.

Claim of tolerability/safety/immunogenicity of TAK-881 will be based on clinical judgment on the totality of evidence, with no predefined tolerability/safety/immunogenicity statistical margin or criteria.

Sample Size Justification:

Assessment of tolerability to TAK-881 SC administration at various infusion rates is the primary objective of this study.

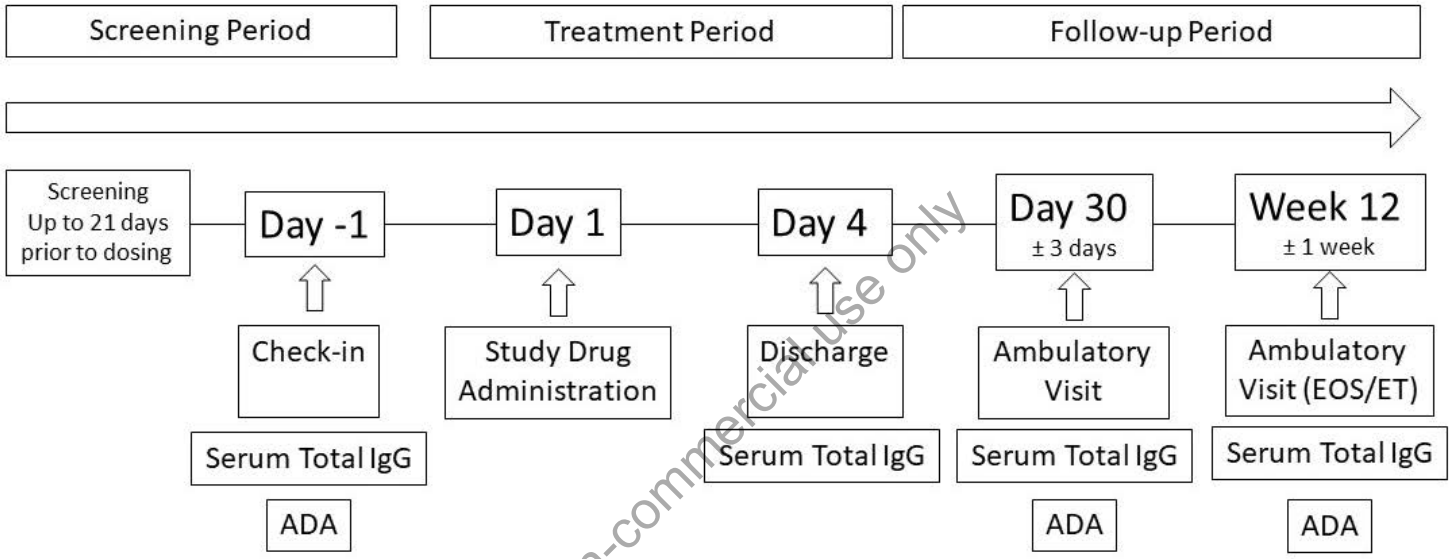
This study is not designed for statistical hypothesis testing; therefore, the sample size was not based on statistical considerations. The planned total sample size for this study is 24 subjects (8 subjects per treatment arm).

Of the 24 subjects to be enrolled, a minimum of 18 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 (≥18) is considered adequate for claiming tolerability and safety of TAK 881 based on clinical judgment.

1.2 Study Schematic

1.2.1 Overall Study Design

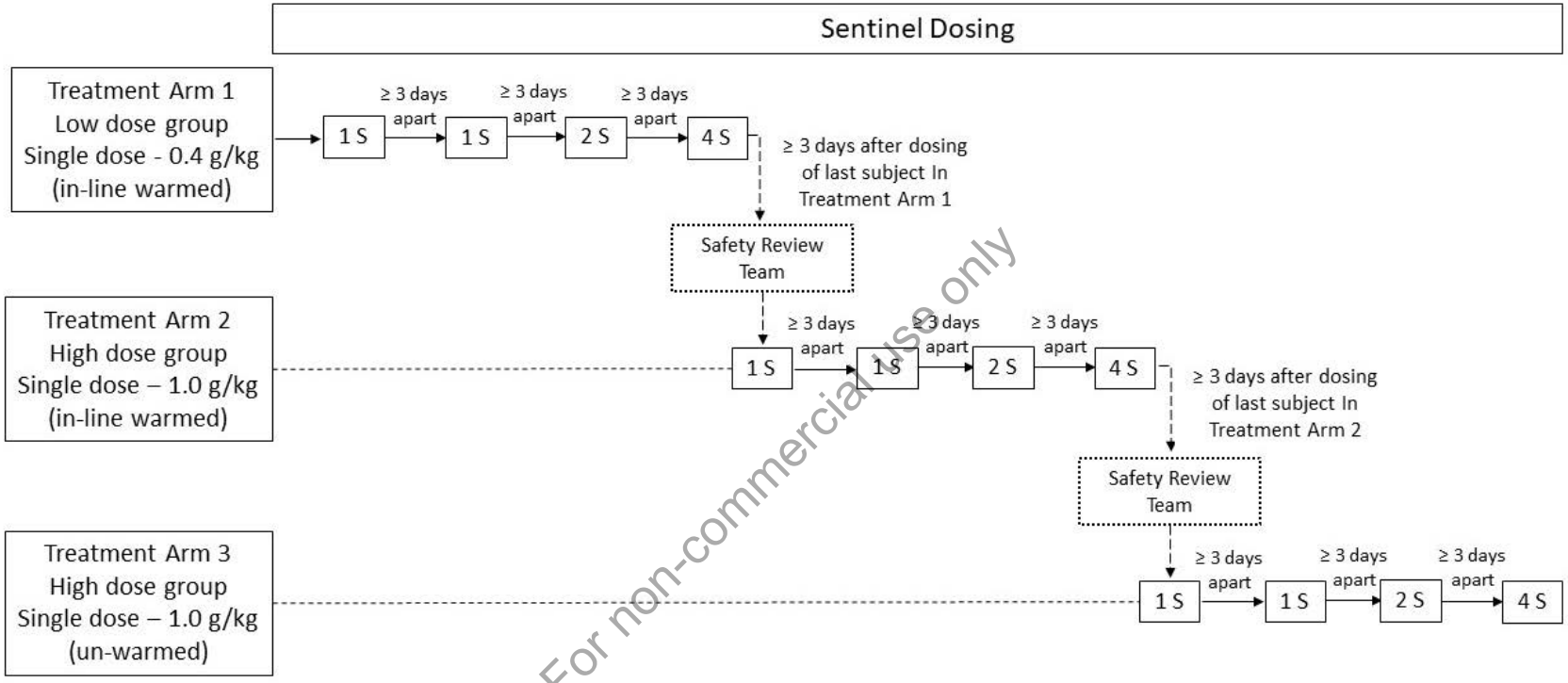
Figure 1. Overall Study Design



Note: All subjects will be admitted to Clinical Research Center on Day -1 prior to dosing and discharged on Day 4.
Abbreviations: ADA=anti-drug antibody; EOS=end of study; ET=early termination; IgG=immunoglobulin G

1.2.2 Sentinel Dosing Design

Figure 2. Sentinel Dosing Design



Abbreviation: S=subject(s)

1.3 Study Schedule(s)

Table 1. Schedule of Assessments

Visit/Assessment	Screening Period		Treatment Period				Follow-up Period	
Study Week/Day	**Within 21 Days prior to dosing**	**D-1**	**D1**	**D2**	**D3**	**D4**	**Day 30 (±3 days)**	**Week 12 (±1 week) EOS/ET**
Informed Consent[1]	X							
Demographics[2]	X							
Ambulatory Visit at CRC[3]	X						X	X
Confinement at CRC[3]		X	X	X	X	X		
Inclusion/Exclusion Criteria	X	X	X					
Medical History[4]	X	X	X					
Prior/Concomitant Medications	←----------							----------→
Physical Examination[5]	X	X						X
Height (screening only), BMI calculation (screening only), Weight Measurements	X	X[6]						
Study Treatment Administration [7]			X[7]					
Drugs of Abuse/Alcohol Screen[8]	X	X					X	X
Infusion Site Evaluation[9]			X	X	X	←X (as clinically indicated)→		
HIV, HBV, HCV[10]	X							X
Pregnancy [11]	X	X						
Adverse Events/Serious Adverse Events	←----------							----------→
Vital Signs [12]	X	X	X			X	X	X
12-Lead ECG	X		X[13]					
Serum Chemistry, Hematology, and Urinalysis [14]	X	X			X (Hgb only)		X	
Hemolytic Panel[15]		X				X		
Coagulation Tests[16]	X	X						
rHuPH20 Immunogenicity: ADA and nADA Blood Collection		X					X	X
Immunogenicity Panel[17]		X	←----------		X (as applicable)		---------→	
Serum Total IgG Levels[18]		X				X	X	X

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Abbreviations: ADA=anti-drug antibody; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BMI=body mass index; BP=blood pressure; BUN=blood urea nitrogen; Ca=calcium; CBC=complete blood count; Cl=chlorine; CRC=Clinical Research Center; CTCAE=Common Terminology Criteria for Adverse Events; D=day; ECG=electrocardiogram; EOS=end of study; ET=early termination; Hgb=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; INR=international normalized ratio; IP=investigational product; K=potassium; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; Mg=magnesium; Na=sodium; nADA=neutralizing anti-drug antibody; PI=principal investigator; RBC=red blood cell; RDW=red cell distribution width; rHuPH20=recombinant human hyaluronidase; RR=respiratory rate; ULN=upper limit of normal; UPCR=urine protein to creatinine ratio; WBC=white blood cells.

1. Written consent must be obtained prior to performing any protocol specific procedure.
2. Age, gender, ethnicity, and race.
3. All subjects will check-in on D-1 and will be discharged after completing scheduled assessments on Day 4, followed by ambulatory visits on Day 30 and EOS/ET. During the confinement period, standard meals and snacks will be provided at appropriate times.
4. Medical history includes any significant or relevant diseases, surgeries, or other medical events and medication/treatment history, if applicable.
5. Physical examination: Complete physical examination will be performed at screening and EOS/ET visit, and a partial physical examination may be done at the PI's discretion to assess any new abnormalities or changes from baseline.
   Complete physical examination will include: general appearance, head and neck, eyes and ears, nose and throat, spine/neck/thyroid, musculoskeletal, respiratory, cardiovascular, abdomen, extremities and joints, lymph nodes, skin, and neurological.
   Partial physical examination will include general appearance, head and neck, assessment of infusion site(s), and skin. Other organ systems will be assessed per investigator's judgment.
6. Weight only (to be measured for dose calculation)
7. Subjects must be well hydrated prior to drug administration.
   The dose levels are 0.4 g/kg (in-line warmed), 1.0 g/kg (in-line warmed), and 1.0 g/kg (un-warmed) with rHuPH20 80 U/g IgG for Treatment Arms 1, 2, and 3, respectively. Subjects will receive a single dose of IP with progressively increased infusion rate per the schedule presented in Section 7.2.2.
8. Drug screen will include opiates (includes morphine, heroin [diacetylmorphine], codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and hydromorphone), amphetamines, barbiturates, benzodiazepines, cocaine, methadone, cannabinoids, and phencyclidine.
9. Infusion related AEs will be evaluated per CTCAE v5.0 for any potential systemic effects such as infusion related reactions or local infusion site events (ie, infusion site extravasation) at 12 hours (Day 1), 24 hours (Day 2), and 48 hours (Day 3) post infusion and **as clinically indicated**. Please also see additional details in Appendix 3.3. Allergic reactions related to infusion, use injury, poisoning, and procedural complications should be reported as infusion related reaction. Do not report both. 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. Photographs of infusions site(s) may be collected (optionally) on Day 1 (prior to start of infusion, 1-hour [±15 minutes] after start of infusion, and within 15 minutes after the end of infusion), Day 2 (24 hours post infusion [±4 hours]), Day 3 (48 hours post infusion [±4 hours]).
10. Testing will be performed by the local laboratory at screening and at EOS/ET. Tests 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.

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11. Pregnancy test will be done for all females. Serum pregnancy test will be obtained at screening and whenever a pregnancy is suspected. If the serum pregnancy test at screening is older than 7 days, a serum pregnancy test is required on D-1; otherwise urine pregnancy test may be performed on D-1. Subjects must have a negative urine and/or serum pregnancy test (within 7 days prior to IP administration).
12. Vital signs, RR, HR, BP, and body temperature will be measured at screening. BP, HR and RR will be measured at predose (within 30 minutes), every 30 minutes post infusion start (±5 minutes) until the end of the infusion, every 1 hour (±15 minutes) post infusion for 4 hours, at discharge (Day 4) and as needed per investigator's judgment. BP, HR, and RR will also be measured at discharge (Day 4), on Day 30, and at EOS or ET.
13. The 12-lead ECG will be collected within 1 hour of dose on Day 1 and **as clinically indicated**.
14. **Hematology** includes CBC (Hct, Hgb, RBC, RDW, MCV, MCH, MCHC, platelet count, WBC with absolute differential counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils).
    Serum Chemistry includes ALT, AST, ALP, K+, Na+, Cl^-, Ca^{2+}, Mg^{2+}, Bilirubin (total and direct), LDH, BUN, creatinine, uric acid, glucose, albumin, and lipid profile.
    Urine Test. Urinalysis will include color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, and 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 24 hour urine. Tests will be performed at prespecified time points and as **clinically indicated**. No need to repeat before first dose if screening test is done within 7 days.
15. The hemolytic 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 laboratory results obtained from D-1 will serve as the baseline values. In case of absence of D-1 result for any reason, screening Hgb result will 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.
16. aPTT and INR: assessments will be performed at screening and D-1 and **as clinically indicated.**
17. The immunogenicity panel will be collected at baseline (D-1) and any time deemed necessary during the course of the study. Subjects, who have (a) 2 consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers, and (b) a moderate or severe AE (Grade 2 or higher as per CTCAE v5.0) which may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other concomitant medications, will be asked to return to the CRC as soon as possible to undergo an additional panel of immunogenicity testing.
18. Serum total IgG samples will be collected on D-1, Day 4 (at discharge), Day 30 (±3 days), and at Week 12 (±1 week)/EOS or ET.

Note: Multiple activities scheduled on the same day or at the same time will be conducted in the following order, when applicable: spontaneous or solicited AE reporting, 12-lead ECG, vital signs, blood sampling for serum total IgG levels, clinical laboratory tests, physical examination, and study drug administration.

2. BACKGROUND INFORMATION

TAK-881, Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) with Recombinant Human Hyaluronidase (rHuPH20) is a facilitated subcutaneous immune globulin (IG) evolved from the currently licensed HYQVIA, Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase, and CUVITRU, Immune Globulin Subcutaneous (Human), 20% Solution. TAK-881 differs from HYQVIA only by the use of warmed IGSC, 20% (CUVITRU) instead of immune globulin infusion (IGI), 10% at room temperature.

TAK-881 is administered by sequential subcutaneous (SC) infusion of rHuPH20 first, followed immediately (within 10 minutes) by warmed IGSC, 20%. The ratio of rHuH20 to IG is the same as for HYQVIA, which is 80 U rHuPH20 per gram of IG.

Given the doubled IG concentration delivered with TAK-881, the required infusion volume would be reduced by 50% at an equivalent dose level as compared to HYQVIA. Reduced volumes potentially lead to improved tolerability due to fewer local site reactions with better patient outcomes.

However, the higher IG concentration, as with CUVITRU, is associated with higher viscosity, increasing in-line pressure, which only allow lower infusion rates in conventional IGSC, 20% therapy.

Dynamic viscosity is inversely proportional to temperature. In liquids, viscous forces are caused by molecules exerting attractive forces on each other and increasing temperature results in a decrease in viscosity as particles gain greater thermal energy and can overcome the attractive forces binding them together.

Therefore, to decrease viscosity, a commercially available in-line warming device is used for TAK-881 (for Treatment Arms 1 & 2 only, in this study) to warm the infusion tubing used to infuse the IGSC, 20% component.

By decreasing viscosity of the IGSC, 20% with warming, TAK-881 may allow for faster infusion time as compared to CUVITRU (currently up to 1 mL/min), and lower SC infusion volume with associated shorter infusion time as compared to HYQVIA.

The IGSC, 20% component of TAK-881 is a liquid immunoglobulin G (IgG) product purified from human plasma marketed as CUVITRU. The IgG subclass distribution for the final product is within the normal range for human serum and comprises antibodies to specific bacterial and viral pathogens. The preparation retains all Fab and Fc mediated functions of the IgG molecule.

The rHuPH20 component of TAK-881 is a highly purified, recombinant human hyaluronidase that de-polymerizes the gel-like hyaluronan in local SC tissue where it is infused. This localized effect results in a transient increase in permeability, allowing IGI to disperse and to reach the systemic circulation more readily than without rHuPH20.

Extensive safety data are available for the individual components of TAK-881, rHuPH20 and IGSC, 20%, based on the safety profiles of the approved products, HYQVIA and CUVITRU. Additionally, it was demonstrated through analytical and preclinical studies that the warming of IGSC, 20% did not influence critical quality parameters and local tolerability and that warming and facilitation of IGSC, 20% allows higher flow rates than currently used for CUVITRU. Finally, the combination of rHuPH20 and warmed IGSC, 20% was well tolerated in preclinical studies, thereby supporting proof of concept clinical trials.

IGSC, 20% with or without rHuPH20 has previously been administered to a limited number of humans without using a warming device (TAK-881 IB).

The clinical development of TAK-881 is based on the development of HYQVIA and CUVITRU. The following sections provide an overview of HYQVIA and CUVITRU along with relevant data summarized from HYQVIA and CUVITRU studies.

2.1 Overview and Relevant Data of HYQVIA/HyQvia

HYQVIA (also known as TAK-771) is an IGI (Human) 10% with a rHuPH20. IGI, 10% with rHuPH20 has been developed to enable the SC administration of large volumes of IgG. IGI, 10% with rHuPH20 is licensed in the European Union (EU) and United States (US) with licensed indications in each country detailed in the corresponding national prescribing information. In the EU, IGI, 10% with rHuPH20 is marketed as HyQvia and in the US, IGI, 10% with rHuPH20 is marketed as HYQVIA. Overall, IGI, 10% with rHuPH20 clinical data and post-marketing data obtained since first licensure are consistent with the known safety profile of IgG preparations and Immune Globulin Infusion (Human), 10% (IGI, 10%) (Baxalta US Inc., 2020).

The rHuPH20 component of IGI, 10% with rHuPH20 is a highly purified, recombinant hyaluronidase that de-polymerizes the gel-like hyaluronan in local SC tissue where it is infused. This localized effect results in a transient increase in permeability, allowing the IGI, 10% component to disperse and to reach the systemic circulation more readily than without rHuPH20.

The IGI, 10% component of IGI, 10% with rHuPH20 is a liquid IgG product purified from human plasma. The IgG subclass distribution for the final product is within the normal range for human serum and comprises antibodies to specific bacterial and viral pathogens. The preparation retains all antigen-binding fragment (Fab) and fragment crystallizable region (Fc) mediated functions of the IgG molecule.

The safety profile of IGI, 10% with rHuPH20 is not considered to be different from the individual components. Since rHuPH20 acts locally with little systemic absorption, no impact on the systemic effects and safety of IGI, 10% is anticipated. Nonclinical studies of IGI, 10% with rHuPH20 showed that rHuPH20 increases the dispersion and absorption of IGI, 10%, while mitigating induration and tissue damage after SC administration of large volumes of IgG. IGI, 10% with rHuPH20 revealed no toxicologically relevant adverse effects on local tolerability. PH20 is a testicular hyaluronidase and nonclinical studies have demonstrated no adverse effects from anti-rHuPH20 antibody exposure from conception through adulthood and no evidence of toxicity during fetal development.

The clinical program for IGI, 10% with rHuPH20 includes 7 completed interventional clinical studies in primary immunodeficiency disease (PIDD) and healthy volunteers, and 1 completed non-interventional registry study in women exposed to treatment before or during pregnancy (pregnancy registry). Together, these studies demonstrate the efficacy, pharmacokinetics (PK), safety and tolerability of IGI, 10% with rHuPH20. rHuPH20 increased the bioavailability of IGI, 10% administered subcutaneously by approximately 20%, thus reducing the clinically effective SC dose. IGI, 10% with rHuPH20 was shown to be effective in preventing infections in patients with PIDD with slightly lower rates of validated serious acute bacterial infections and all infections for IGI, 10% with rHuPH20 compared to IgG administered SC (IGSC), and protection was maintained with long-term treatment. IGI, 10% with rHuPH20 decreased the frequency, severity, and duration of induration at the site of administration compared to controls. During the clinical studies, IGI, 10% with rHuPH20 was well tolerated at large volumes (>600 mL/site) and utilizing maximum flow rates significantly higher than those used for intravenous (IV) infusions. The rate of adverse drug reactions (ADRs) per infusion obtained for IGI, 10% with rHuPH20 compares favorably with published data on IGSC, and the rate of systemic ADRs was lower with IGI, 10% with rHuPH20 than with IgG administered IV treatment, which is in agreement with published data on IGSC treatment. The incidence of treatment-emergent rHuPH20-reactive binding antibodies was low, and neutralizing antibodies have not been observed in any subjects in the completed clinical trials. In addition, no clinical signs or symptoms have been associated with positive rHuPH20-reactive binding antibody titers. In conclusion, the clinical program to date has shown that IGI, 10% with rHuPH20 is safe and infusion of large volumes >600 mL/site are well tolerated, enabling treatment of pediatric and adult patients with PIDD at the same interval used for IGI, 10% administered IV.

Two clinical studies in subjects with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), a Phase 1 dose ramp-up study in healthy adult subjects, 2 post-authorization studies (1 global post-marketing commitment study and 1 post-authorization safety study in the EU), and 2 studies in pediatric populations (a Phase 3 study in the US and 1 post-authorization study in the EU), are ongoing.

Always refer to the latest version of the Investigator's Brochure (IB) for HYQVIA for the overall risk/benefit assessment and the most accurate and current information regarding the metabolism, PK, efficacy, and safety of HYQVIA (HYQVIA IB).

2.2 Overview and Relevant Data of CUVITRU

CUVITRU is an Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) that has been developed with the aim of providing a more concentrated product with a reduced required infusion volume for SC administration. IGSC, 20% is presently approved under the trade name CUVITRU in 17 EU countries and in the US, Switzerland, Canada, Australia, and Brazil.

It was developed based on Baxalta's Immune Globulin Infusion 10% (IGI, 10%). The manufacturing process for IGSC, 20% is essentially the same as for IGI, 10%, with the exception of the final ultra-/diafiltration and formulation steps. IGSC, 20% contains functionally intact IgG. The IgG subclass distribution for the final product is within the normal range for human serum, and comprises antibodies to specific bacterial and viral pathogens. The preparation retains all Fab and Fc mediated functions of the native IgG molecule.

IGSC, 20% is derived from large pools of human plasma. To decrease the potential contamination with blood-borne viruses, each individual plasma donation is tested with approved tests for hepatitis B surface antigen (HBsAg) and antibodies to human immunodeficiency virus (HIV) and hepatitis C virus (HCV). In addition, Baxalta has implemented a donation sample mini-pool strategy to test for the presence of HIV-1, HIV-2, HCV, hepatitis B virus (HBV), hepatitis A virus (HAV), and parvovirus B19 (B19V) nucleic acids. Only donation pools nonreactive in these tests, with the exception of B19V which must not exceed 10000 International Units (IU)/mL, are qualified for manufacture into plasma derivatives.

The modified Cohn-Oncley cold ethanol fractionation process, followed by cation and anion exchange chromatographies, are used for the manufacturing of IGSC, 20%. IGSC, 20% is processed using solvent/detergent (S/D) treatment as a dedicated virus inactivation step. Nanofiltration (35 nm) and low pH incubation with elevated temperature are included in the manufacturing scheme to enhance the virus safety of IGSC, 20%.

Viral safety studies used virus models and target viruses to evaluate the clearance of both lipid-enveloped and non-enveloped deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) viruses by the manufacturing steps specific for viral reduction. These studies demonstrated that the 3 dedicated virus inactivation/removal steps provide effective and robust clearance of HIV, West Nile virus (WNV), HAV, B19V, as well as model viruses for HCV, HBV, HAV, and B19V.

The safety, tolerability, and efficacy of IGSC, 20% in PIDD have been demonstrated in 2 Phase 2/3 studies in Europe (Protocol 170903) and in North America (Protocol 170904).

IGSC, 20% was also administered in a Phase 1 study (Protocol 170901 Part 1) in healthy volunteers designed to investigate the safety and tolerability of IGSC, 20% administered with rHuPH20 as a permeation enhancer and to determine the optimal dose ratio. A total of 14 infusions of IGSC, 20% (12 with and 2 without rHuPH20) were administered in 7 subjects, none of whom experienced serious or severe adverse events (AEs) after administration of IGSC, 20% or withdrew from the study due to AEs.

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

2.3 Risk/Benefit and Ethical Assessment

There will be no direct health benefit for healthy participants in this study from receipt of TAK-881. An indirect health benefit to the subjects screened/enrolled in this study is the free medical tests received at screening and during the study.

The risks associated with dosing TAK-881 are anticipated to be similar to those previously documented in the product labels for HYQVIA and CUVITRU, please refer to the safety information in HYQVIA IB and CUVITRU IB.

The inclusion and exclusion criteria, screening, and safety monitoring practices employed in this protocol (ie, 12-lead electrocardiogram [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, 2018), 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 Appendix 2.

3. STUDY OBJECTIVES AND PURPOSE

3.1 Rationale for the Study

TAK-881 (IGSC, 20% solution with rHuPH20) is a facilitated immune globulin subcutaneous (IGSC) infusion evolved from HYQVIA (IGSC 10%) and CUVITRU (IGSC 20%). Both HYQVIA and CUVITRU have very well-established efficacy and safety data. The higher concentration of TAK-881 (IGSC 20%) in comparison with HYQVIA (IGSC 10%) has the potential of reducing infusion volumes by 50%, decreasing infusion time, and potentially leading to improved tolerability. This Phase 1 study is being conducted to assess the tolerability, safety, and immunogenicity of TAK-881 at various SC infusion rates in healthy adult subjects with a focus on evaluating key dosing and administration parameters to support further clinical development.

3.2 Study Objectives

3.2.1 Primary Objective

To assess the tolerability of TAK-881 at various SC infusion rates in healthy adult subjects.

3.2.2 Secondary Objective

To assess the safety of TAK-881 at various SC infusion rates and immunogenicity of TAK-881 in healthy adult subjects.

3.2.3 Exploratory Objectives

To assess serum total IgG levels.

3.3 Study Endpoints

3.3.1 Primary Endpoint

The primary endpoint corresponding to the primary objective of the study is the occurrence of tolerability events related to the infusion of TAK-881 per infusion site.

Definition: A tolerability event is considered to have occurred if an infusion was tolerable. An infusion is considered tolerable if the infusion rate was not reduced or the infusion was not interrupted or stopped, due to any treatment-emergent adverse event (TEAE) related to TAK-881.

3.3.2 Secondary Endpoints

3.3.2.1 Safety and Immunogenicity Endpoints

- Occurrence of TEAEs, including but not limited to: TAK-881-related and non-related TEAEs
- 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 SC Administration Endpoints:

The following SC administration endpoints represent supportive tolerability and safety measures:

- Maximum tolerable infusion rate achieved per infusion site
- Total volume infused per infusion site
- Time to deliver the total infused volume per infusion site

3.3.3 Exploratory Endpoint

- Serum total IgG levels at predose and postdose of TAK-881 SC administration

4. STUDY DESIGN

4.1 Study Design

This study is a Phase 1, single-dose, single-center, open-label, three-arm study to evaluate the tolerability, safety, and immunogenicity of TAK-881 at various infusion rates in healthy adult subjects.

Section 1.2 provides a schematic of the study design. The overall study design is presented in Figure 1 and the sentinel dosing design in Figure 2.

This study comprises 3 treatment arms:

- Treatment Arm 1 - Subjects will receive a single dose of TAK-881 comprising of 0.4 g/kg (in-line warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.
- Treatment Arm 2 - Subjects will receive a single dose of TAK-881 comprising of 1.0 g/kg (in-line warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.
- Treatment Arm 3 - Subjects will receive a single dose of TAK-881 comprising of 1.0 g/kg (un-warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.

The infusion rates as presented in Section 7.2.2 will be followed for the study.

A total of 24 subjects are planned with 8 subjects enrolled/treated in each of the 3 treatment arms.

Dosing will be first initiated at the lower dose level (Treatment Arm 1, 0.4 g/kg, in-line warmed) followed by the higher dose level (Treatment Arm 2, 1.0 g/kg, in-line warmed) and then the un-warmed arm (Treatment Arm 3, 1.0 g/kg, un-warmed). Subjects in all 3 treatment arms will be dosed according to a sentinel dosing design with ongoing safety monitoring by the investigator to ensure optimal tolerability and safety. Subjects in each treatment arm will be grouped into 4 subgroups of 1, 1, 2, and 4 subjects, respectively. The subgroups will be dosed sequentially to allow safety and tolerability evaluation prior to initiating dosing of the following subgroup.

Dosing will start with Treatment Arm 1. Initially, 1 subject will be dosed at the lower dose level and the subject will be closely observed by the investigator during the infusion period and for the first 72 hours (or longer, per investigator's discretion) following drug administration. The subject will be discharged from the site after an overall assessment on Day 4. The investigator will evaluate the safety and tolerability for the first subject from infusion start through 72 hours and consult the sponsor as necessary, prior to dosing the next subject from Treatment Arm 1.

The next 2 subjects from Treatment Arm 1 (0.4 g/kg) will be dosed at least 3 days (72 hours) after dosing of the second subgroup of 1 subject. The remaining 4 subjects from Treatment Arm 1 (0.4 g/kg) will be dosed at least 3 days (72 hours) after dosing of the third subgroup of 2 subjects.

Dosing for Treatment Arm 2 will begin upon the recommendation of the safety review team after all subjects in Treatment Arm 1 have been dosed, and the tolerability and safety through Day 4 of the last subject in Treatment Arm 1 have been reviewed by the safety review team consisting of the investigator, the Study Clinical Lead, the sponsor's Study Medical Monitor (chair), and the sponsor's Global Drug Safety Physician.

Dosing for Treatment Arm 3 will begin upon the recommendation of the safety review team after all subjects in Treatment Arm 2 have been dosed, and the tolerability and safety through Day 4 of the last subject in Treatment Arm 2 have been reviewed by the safety review team consisting of the investigator, the Study Clinical Lead, the sponsor's Study Medical Monitor (chair), and the sponsor's Global Drug Safety Physician.

Subjects participating at the higher dose levels (Treatment Arm 2, 1.0 g/kg, in-line warmed and Treatment Arm 3, 1.0 g/kg, un-warmed) will be dosed following the same sentinel dosing scheme as Treatment Arm 1.

Study Periods

The study consists of 3 periods:

- Screening period: up to 21 days prior to dosing.
- Study treatment period: 4 days.
- Follow-up period: up to 12 (±1) weeks after TAK-881 infusion.

Tolerability and safety including immunogenicity of TAK-881 will be assessed during the treatment and follow-up periods for all 3 treatment arms.

All subjects will be monitored for the formation of binding anti-rHuPH20 antibodies (binding ADA) at predose (baseline) and postdose (Day 30 ±3 days and end of study [EOS] ±1 week). Postdose 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 (Grade 2 or higher as per Common Terminology Criteria for Adverse Events [CTCAE] v5.0 (U.S. Department of Health and Human Services, 2017)) that may be a result of an immune-mediated response to either IG, rHuPH20, or other concomitant medications will be asked to return to the clinical research center (CRC) 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 (Section 8.1.4).

4.2 Duration and Study Completion Definition

The approximate overall duration of the study is 14 to 16 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 8.1.3 for the defined follow-up period for this protocol).

4.3 Sites and Regions

Single site, USA

5. STUDY POPULATION

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

Enrolled subjects are defined as subjects who have signed informed consent and meet all of the inclusion and none of the exclusion criteria. In this study, enrolled subjects are the same as treated subjects. Screen failures will not be captured in the electronic data capture (EDC) system or counted as "enrolled".

Each subject must participate in the informed consent process and provide written informed consent before any procedures specified in the protocol are performed.

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 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 female of non-childbearing potential.
5. Must be considered "healthy." Healthy as determined by the investigator on the basis of screening evaluations. 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 (eg, 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 participation in the trial and compromise the trial objectives, or any condition that presents an undue risk from the investigational product (IP) or procedures.

   Note: Subjects on stable dose of hormone replacements (eg, 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 arrhythmias and conduction disorders.
3. Known or suspected intolerance or hypersensitivity to the IP(s), closely related compounds, or any of the stated ingredients (eg, human IG, hyaluronidase, albumin).
4. Known history of hypersensitivity or severe allergic reactions (eg, urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following administration of blood or blood components.
5. Known allergy to hyaluronidase of human (including recombinant human hyaluronidase) or animal origin (such as bee or wasp venom).
6. Significant illness, as judged by the investigator, within 30 days of the first dose of IP.
7. Known history of alcohol or other substance abuse within the last year.
8. Donation of blood within 60 days, or blood products (eg, plasma or platelets) within 2 weeks prior receiving the first dose of IP.
9. Subjects will be excluded if abnormal hematology, chemistry, and other laboratory values are >10% above the upper limit of normal (ULN) or >10% below the lower limit of normal (LLN) except for liver function tests and absolute neutrophils. Subjects will be excluded if any of the following laboratory parameters meet the criteria below:
   - Absolute neutrophil count $<1.5 \times 10^9$ cells/liter
   - Liver function: alanine aminotransferase (ALT) $\geq 1.5 \times$ ULN, aspartate aminotransferase (AST) $\geq 1.5 \times$ ULN, alkaline phosphatase (ALP) $\geq 1.5 \times$ ULN, or total bilirubin ≥ 1.5 mg/dL

   Subjects will be excluded if any other laboratory values are outside the reference range and are clinically significant per investigator's judgment.
10. Subjects who, within 30 days prior to the first dose of IP:

- Have participated in another clinical study involving immune globulin (IG) products within 12 months of screening.
- Have used an IP (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 and COVID-19 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.

11. Confirmed systolic blood pressure >139 mmHg or <89 mmHg and diastolic blood pressure >89 mmHg or <49 mmHg.
12. A positive screen for alcohol or drugs of abuse at screening or Day -1 (D-1).
13. 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.
14. Smoking more than 5 cigarettes or equivalent per day, unable to stop smoking during confinement in the CRC.
15. Severe dermatitis or anatomical abnormality that would interfere with TAK-881 administration or endpoint assessments. Note: The skin at the administration site should not be covered by tattoos.
16. Current use of any herbal or homeopathic preparations is not permitted.
17. 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 infusion visit and through 72 hours post infusion.
18. Current or relevant history of hypercoagulable conditions (eg, Protein C, Protein S, and antithrombin III deficiency), thrombotic/thromboembolic events or venous thrombosis.

5.3 Restrictions

1. Subjects should refrain from strenuous physical exercise 48 hours prior to admission to the CRC and during the in-house stay at the CRC.
2. Subjects should refrain from alcohol 48 hours prior to admission to the CRC and during the in-house stay at the CRC.
3. Subjects should be well hydrated on Day 1 prior to IP administration.
4. Subjects will be required to follow standardized meal schedules and eat the meals provided by the site while housed in the CRC.

5.4 Reproductive Potential

No clinical studies have been conducted with TAK-881 or CUVITRU in pregnant women.

Animal reproduction studies have not been conducted with TAK-881 or HYQVIA or CUVITRU. It is also not known whether IGI, 10% or 20% 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% or 20% on fertility are to be expected.

A non-interventional pregnancy registry to collect long-term safety data from women treated with HYQVIA was conducted (Study 161301). None of the AEs reported was assessed as related to previous or current IGI, 10% with rHuPH20 treatment in the mother, or caused treatment changes (ie, dose reduction, interruption, withdrawal). A total of 2 SAEs (thrombocytopenia and pre-eclampsia) were reported in one mother in the IGI, 10% with rHuPH20 arm in the prospective cohort. A total of 2 SAEs (cleft lip without cleft palate and talipes calcaneovalgus) were reported in 2 infants in the IGI, 10% with rHuPH20 arm. None of these events was related to treatment with IGI, 10% with rHuPH20.

No anti-rHuPH20 binding or neutralizing antibodies, or local and immunologic AEs were reported.

Five mothers continued IGI, 10% with rHuPH20 treatment during pregnancy (2 mothers enrolled before delivery and 3 mothers enrolled after delivery with ongoing treatment at the screening visit) and all had live births, with normal APGAR scores. Five mothers in the Retrospective cohort were enrolled after the delivery and therefore no data on anti-rHuPH20 antibodies during the pregnancy was available in those mothers.

IGI, 10% with rHuPH20 given during pregnancy was not associated with labor and delivery complications. Two minor birth defects, ie, cleft lip without cleft palate and talipes calcaneovalgus, were reported in 2 infants in the IGI, 10% with rHuPH20 Arm. These 2 birth defects were not known to be related to one another, they were assessed as unrelated to treatment and, given the small sample size in this study, these events could be attributed to chance. The mothers of these infants did not report any known risk factors associated with cleft lip or talipes, although the mother of the infant with cleft lip, had reported a congenital double kidney abnormality.

Considering the small sample size and limited data collection in this study, the results should be interpreted with caution (HYQVIA IB).

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. In animal studies, exposure to anti rHuPH20 antibodies at every stage of the reproductive and development lifecycle and from conception in one generation through conception in the following generation did not result in adverse effects on the developing fetus, pediatric/juvenile and young adult stages, adult male and female fertility, or after chronic exposure in juvenile and adult animals. Thus, theoretical risks associated with anti rHuPH20 antibodies were extensively evaluated in nonclinical studies, no evidence of a safety signal or increased risk for fertility, embryo fetal development, or pediatric development was observed.

The effects of antibodies to the rHuPH20 component of HYQVIA on the human embryo or on human fetal development are unknown.

5.4.1 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 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:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥ 51 years)

- 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
- Of child-bearing potential with a negative urine and/or serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening and prior to dosing. 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)* plus condom
     - Intrauterine hormone-releasing system (IUS) *
     - Bilateral tubal occlusion*
     - Vasectomized partner(s) *
     - Sexual abstinence during the entire study period
  iv. Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the first dose of IP, plus condoms. NOTE: if subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

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

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

5.4.2 Male Contraception

From signing of informed consent, throughout the duration of the study, and for 90 days after TAK-881 infusion, nonsterilized male subjects who are sexually active with a female partner of child-bearing potential must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

5.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

If IP is discontinued, regardless of the reason, evaluations listed in Section 1.3 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo follow-up evaluations. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for discontinuation, date of discontinuation of the IP, and the total amount of IP administered must be recorded in the source documents.

Subjects who withdraw or are discontinued 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.

5.5.1 Stopping Criteria for IP Administration

Administration of the IP infusion will be stopped, and the subject will be discontinued from the study, if the subject experiences any AE that is Grade 3 or above as rated by CTCAE v5.0 (U.S. Department of Health and Human Services, 2017). Reason for discontinuation should be recorded on the appropriate case report form (CRF).

5.5.2 Reasons for Discontinuation

The reason for discontinuation must be determined by the investigator and recorded in the subject's source document. 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 (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category)
- Study termination: the sponsor, Institutional Review Board (IRB), Independent Ethics Committee (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

5.5.3 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.

5.5.4 Stopping Criteria for the Study

The study will be paused for a safety investigation if any of the following occur:

- Grade 3 and above reported hypersensitivity
- 1 or more Grade 4 or 5 AEs
- 2 or more Grade 3 AEs

5.5.5 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 (ET) of the study:

- The safety review team (the investigator, the Study Clinical Lead, the sponsor's Study Medical Monitor [lead], and the sponsor's Global Drug Safety Physician) recommends discontinuation of the study based on review of the data as described in Section 4.1.

- 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 of receiving 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 start of the IP administration and 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 child-bearing potential administered according to the package insert (see Section 5.4.1)
- Hormone replacement therapy
- Over the counter (OTC) medications (eg, Nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen [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 serious adverse event (SAE) or AE treatments as standard of care.

7. INVESTIGATIONAL PRODUCT

7.1 Identity of Investigational Product(s)

Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) with Recombinant Human Hyaluronidase (rHuPH20) (also referred to as IGSC, 20% with rHuPH20, or TAK-881). IGSC, 20% (human) will be supplied in 8 g/40 mL vials with rHuPH20 160 Units/mL supplied separately in 15 mL vials.

7.1.1 Immune Globulin Subcutaneous 20% (Human) – IGSC, 20%

The IGSC, 20% (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 Fc and the Fab functions are maintained in the primary component. Pre-kallikrein activator activity is not detectable. The IGSC, 20% (Human) contains 200 mg/mL (20%) protein. At least ≥98% of the protein is IgG, contains trace amounts of IgA (average concentration of 80 mcg/mL). The IGSC, 20% (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 280 to 292 milli-osmoles/kg. The IGSC, 20% (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.

To further improve the margin of safety, validated virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely solvent/detergent (S/D) treatment, 35 nm nanofiltration, and a low pH incubation at elevated temperature (30°C to 32°C). The solvent/detergent process includes treatment with an organic mixture of tri-n-butyl phosphate, octoxynol 9 and polysorbate 80 at 18°C to 25°C for a minimum of 60 minutes. Solvent/detergent treatment inactivates the lipid-enveloped viruses investigated to below detection limits within minutes. The ethanol fractionation process provides an additional virus clearance capacity.

7.1.2 Recombinant Human Hyaluronidase – rHuPH20

The rHuPH20 component of TAK-881 is produced from genetically engineered Chinese Hamster Ovary cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase PH20. rHuPH20 is used in HYQVIA. The purified hyaluronidase glycoprotein contains 447 amino acids with an approximate molecular weight of 61,000 Daltons. This component is supplied as a sterile, clear, colorless, ready-for use solution and has approximate pH of 7.4 and an osmolality of 290 to 350 milli-osmoles. Each vial contains 160 U/mL of recombinant human hyaluronidase with the following excipients: sodium chloride, sodium phosphate dibasic dihydrate, human albumin, edentate disodium dihydrate, calcium chloride dihydrate, and sodium hydroxide added for pH adjustment. It does not contain preservatives.

Due to comprehensive virus testing at the master cell bank, working cell bank, and bulk harvest stages, effective virus reduction during the purification process and the use of pharmaceutical grade human albumin as an excipient with no other materials of human or animal origin involved in the manufacturing process, rHuPH20 provides for high margins of safety with respect to viruses.

7.1.3 Blinding the Treatment Assignment

Not applicable.

7.2 Administration of Investigational Product(s)

7.2.1 Allocation of Subjects to Treatment

This is a Phase 1, single-dose, single-center, open-label, three-arm study which plans to enroll 8 subjects in each of the 3 treatment arms, and a minimum of 3 subjects in each of the 2 BMI groups (18.0 to <25.0 kg/m^2, ≥25.0 to 30.0 kg/m^2) in each treatment arm.

A 4-digit subject number will be allocated immediately prior to dosing after eligibility has been determined. Subjects in the 18.0 to <25.0 kg/m^2 BMI group will be assigned numbers starting with 1001, 1002, 1003, etc. Subjects in the ≥25.0 to 30.0 kg/m^2 BMI group will be assigned numbers starting with 2001, 2002, 2003, etc. If a subject number is allocated incorrectly, the study monitor must be notified as soon as the error is discovered. Once a subject number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. For enrolled subjects, the subject number will be the identifying number used throughout the CRF.

7.2.2 Dosing

This study comprises 3 treatment arms:

- Treatment Arm 1 - Subjects will receive a single dose of TAK-881 comprising of 0.4 g/kg (in-line warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.
- Treatment Arm 2 - Subjects will receive a single dose of TAK-881 comprising of 1.0 g/kg (in-line warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.
- Treatment Arm 3 - Subjects will receive a single dose of TAK-881 comprising of 1.0 g/kg (un-warmed) IGSC, 20% at progressively increased infusion rates and rHuPH20 dose of 80 U/g IgG on Day 1 of the study treatment period.

Dosing will be first initiated at the lower dose level (Treatment Arm 1, 0.4 g/kg, in-line warmed) followed by the higher dose level (Treatment Arm 2, 1.0 g/kg, in-line warmed) and then the un-warmed arm (Treatment Arm 3, 1.0 g/kg, un-warmed). Subjects in all 3 treatment arms will be dosed according to a sentinel dosing design with ongoing safety monitoring by the investigator to ensure optimal tolerability and safety. Subjects in each treatment arm will be grouped into 4 subgroups of 1, 1, 2, and 4 subjects, respectively. The subgroups will be dosed sequentially to allow safety and tolerability evaluation prior to initiating dosing of the following subgroup.

Dosing will start with Treatment Arm 1. Initially, 1 subject will be dosed at the lower dose level and the subject will be closely observed by the investigator during the infusion period and for the first 72 hours (or longer, per investigator's discretion) following drug administration. The subject will be discharged from the site after an overall assessment on Day 4. The investigator will evaluate the safety and tolerability for the first subject from infusion start through 72 hours and consult the sponsor as necessary, prior to dosing the next subject from Treatment Arm 1. The next 2 subjects from Treatment Arm 1 (0.4 g/kg) will be dosed at least 3 days (72 hours) after dosing of the second subgroup of 1 subject. The remaining 4 subjects from Treatment Arm 1 (0.4 g/kg) will be dosed at least 3 days (72 hours) after dosing of the third subgroup of 2 subjects.

Dosing for Treatment Arm 2 will begin upon the recommendation of the safety review team after all subjects in Treatment Arm 1 have been dosed, and the tolerability and safety through Day 4 of the last subject in Treatment Arm 1 have been reviewed by the safety review team consisting of the investigator, the Study Clinical Lead, the sponsor's Study Medical Monitor (chair), and the sponsor's Global Drug Safety Physician.

Dosing for Treatment Arm 3 will begin upon the recommendation of the safety review team after all subjects in Treatment Arm 2 have been dosed, and the tolerability and safety through Day 4 of the last subject in Treatment Arm 2 have been reviewed by the safety review team consisting of the investigator, the Study Clinical Lead, the sponsor's Study Medical Monitor (chair), and the sponsor's Global Drug Safety Physician.

Subjects participating at the higher dose levels (Treatment Arm 2, 1.0 g/kg, in-line warmed) and (Treatment Arm 3, 1.0 g/kg, un-warmed) will be dosed following the same sentinel dosing scheme as Treatment Arm 1 (Section 1.2).

Subjects must be well hydrated prior to drug administration.

Mode of Administration:

The TAK-881-1001 IP will be administered via a SC route of administration using a 22 to 24-gauge SC needle set. The rHuPH20 solution will be administered first followed by IGSC 20% using the same needle set.

The rHuPH20 solution will be administered subcutaneously via a peristaltic infusion pump at a rate of 120 mL/hour/site (2 mL/minute/site) and infusion volumes of up to 30 mL/site.

The infusion site(s) can be either the abdomen (middle to upper abdomen) or the thighs (left or right).

The SC infusion of the IGSC 20% solution will begin within 10 minutes of completion of the SC infusion of the rHuPH20 solution via a peristaltic infusion pump with programmable infusion rates and infusion volumes of up to 300 mL/site and may require 1 or 2 infusion sites. If 2 infusion sites are required, the doses will be administered sequentially; the infusion of up to 300 mL will be administered first. A flushing step of normal saline will be required to ensure the total dose is administered due to the large priming volumes of the 2 administration systems. Normal saline will not be infused into the subject. For each infusion site, infusion rate ramp-up schedule will be followed as shown below.

If the infusion rate is reduced or interrupted due to an intolerability event, the infusion rate will stay at the maximally tolerable infusion rate (eg, if the maximum infusion rate is 300 mL and it is not tolerable, the infusion rate will be decreased to the previous infusion rate of 180 mL assuming it was well tolerated).

A step-wise infusion rate escalation regimen as shown below will be followed for the study based on tolerability of each incremental infusion rate increase:

Table 2. Infusion Rates for Treatment Arm 1 (0.4 g/kg, in-line warmed) Using 1 Pump and 1 Single Needle Set

Administration		Rate Per Infusion Site (mL/hour) Single Needle Set	Volume Delivered	Accumulative Volume for IG per Site
rHuPH20	To be infused first	120	TBD	N/A
IGSC 20% (in-line warmed)	First 10 min	30	5 mL	5 mL
	Next 10 min	60	10 mL	15 mL
	Next 10 min	120	20 mL	35 mL
	Next 10 min	180	30 mL	65 mL
	Remainder of infusion	300	TBD	TBD (up to 300 mL)*

Abbreviations: IG=immune globulin; N/A=not applicable; TBD=to be determined
* Total volume of up to 300 mL will not include the volume of the rHuPH20 delivered first

Table 3. Infusion Rates for Treatment Arm 2 (1.0 g/kg, in-line warmed) Using 2 Pumps and 1 Single Needle Set for Each Pump

Administration		Rate Per Infusion Site (mL/hour) for Each Pump	Volume Delivered for Each Pump	Accumulative Volume Site 1# (Pump A)	Accumulative Volume Site 2# (Pump B)
rHuPH20	To be infused first	120	TBD	TBD	TBD
IGSC 20% (in-line warmed)	First 10 min	30	5 mL	5 mL	5 mL
	Next 10 min	60	10 mL	15 mL	15 mL
	Next 10 min	120	20 mL	35 mL	35 mL
	Next 10 min	180	30 mL	65 mL	65 mL
	Remainder of infusion	300	TBD	TBD (up to 300 mL)*	TBD (remainder)

Abbreviations: TBD=to be determined
Each site will be evaluated separately
* Total volume of up to 300 mL will not include the volume of the rHuPH20 delivered first

Table 4. Infusion Rates for Treatment Arm 3 (1.0 g/kg, un-warmed) Using 2 Pumps and 1 Single Needle Set for Each Pump

Administration		Rate Per Infusion Site (mL/hour) for Each Pump	Volume Delivered for Each Pump	Accumulative Volume Site 1# (Pump A)	Accumulative Volume Site 2# (Pump B)
rHuPH20	To be infused first	120	TBD	TBD	TBD
IGSC 20% (un-warmed)	First 10 min	30	5 mL	5 mL	5 mL
	Next 10 min	60	10 mL	15 mL	15 mL
	Next 10 min	120	20 mL	35 mL	35 mL
	Next 10 min	180	30 mL	65 mL	65 mL
	Remainder of infusion	300	TBD	TBD (up to 300 mL)*	TBD (remainder)

Abbreviations: TBD=to be determined
Each site will be evaluated separately
* Total volume of up to 300 mL will not include the volume of the rHuPH20 delivered first

7.2.3 Unblinding the Treatment Assignment

Not applicable.

7.3 Labeling, Packaging, Storage, and Handling

The pharmacy will prepare and dispense the study drugs per the instructions in the Pharmacy Manual.

7.3.1 Labeling

Labels containing study information and pack identification are applied to the IP(s) container.

Additional labels may not be added without the sponsor's prior full agreement.

7.3.2 Packaging

Immune Globulin Subcutaneous (Human), 20% Solution is supplied in single-dose glass vials that nominally contain 8 g of protein per vial.

Recombinant Human Hyaluronidase (rHuPH20) is supplied in single-dose glass vials that nominally contain 160 Units/mL in a 15 mL vial.

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

7.3.3 Storage

The investigator has overall responsibility for ensuring that IP is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. IP is prepared by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the IP preparation as it is prepared prior to administration.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the IP is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (eg, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the IP and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

IGSC 20% solutions for administration have to be prepared as instructed in the Pharmacy Manual. The study drug must only be administered to study subjects at the study site immediately following preparation.

If administration of pooled products will begin more than 3 hours from preparation, they must be kept at 2° to 8°C (36° to 46°F). Pooled products should be taken out of the temperature-controlled storage before administration to allow for equilibration to room temperature. It may take 90 minutes or longer for the pooled products to reach room temperature. The infusion shall be started no later than 3 hours after removal from the temperature-controlled storage.

All solutions for infusion will be labeled according to regulatory requirements for clinical studies.

The sponsor should be notified immediately if there are any changes to the storage area of the IP that could affect the integrity of the product(s), eg, fumigation of a storage room.

7.3.4 Special Handling

The BIEGLER BW 685/BW 685 S is a warming system for infusions and operates on the basis of a continuous flow warmer with a range of +37°C to +41°C, where the heat from the heat exchanger is transferred via the Biegler extension tubing to the liquid flowing within it. The accessory tube warmer Biegler Tubeflow is an active warming system for infusions between BW 685 S and the patient. The warmer system will be set to 39°C for infusion of IGSC 20% (Treatment Arms 1 and 2 only) and temperature of the IGSC 20% liquid will be warmed prior to the infusion delivery into the subcutaneous tissue to decrease IGSC 20% viscosity.

7.4 Drug Accountability

The investigator will be provided with sufficient amounts of IGSC, 20% (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 received. 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 (eg, 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 IGSC, 20% (Human) and rHuPH20 only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only IGSC, 20% (Human) and rHuPH20. All dispensed and administered medication will be documented on the CRFs and/or other IP record (including all lot numbers and expiration dates).

No IP stock or returned inventory from a Takeda-sponsored study may be removed from the site 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.

The disposition of all unused stock, empty/partially used cartons and vials of IGSC, 20% and rHuPH20 will be decided by the sponsor and site at the end of the study.

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 IGSC, 20% and rHuPH20 delivered with those used and returned. All IGSC, 20% 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 (eg, bottles, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

7.6 Retention of Bioavailability and Bioequivalence Testing Samples

Not applicable.

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 as appropriate prior to receiving the dose of IP. The CRC is responsible for maintaining a 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 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 system. All screening assessments and procedures are to be performed by the principal investigator (PI) or a qualified designee. See Section 1.3 for a complete list of screening procedures to be performed.

Written, signed, and dated informed consent must be obtained by the PI or a designee prior to the performance of any study-related procedures. 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 failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria and has not been administered IP(s).

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). Screen failures will not be captured in the EDC system or counted as “enrolled”.

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 discretion and sponsor approval should their availability to participate fall outside the screening window. In these cases, a new screening number must be assigned for each subject who is rescreened, and a new informed consent form (ICF) must be signed.

Subjects who discontinued from screening due to COVID-19 positivity but were otherwise qualified to participate in the trial may be rescreened if they were asymptomatic and recovered with no known clinical sequelae. The final decision about their possible participation will be made after discussion with the sponsor's medical monitor.

8.1.2 Treatment Period

All subjects will be admitted to CRC on Day -1 prior to dosing and discharged on Day 4. See Section 1.3 for Schedule of Study Procedures.

8.1.2.1 Day 1

Subjects will receive a single dose of IGSC, 20% on Day 1 at dose levels 0.4 g/kg (in-line warmed), 1.0 g/kg (in-line warmed), or 1.0 g/kg (un-warmed) with rHuPH20 80 U/g IgG with progressively increased infusion rate per the schedule presented in Section 7.2.2.

The rHuPH20 units will be calculated as per the following:

- The dose of rHuPH20 is 80 Units × planned IGSC 20% dose in grams = total units to be infused (eg, 80 U × 40 g = 3200 U).
- Then, to calculate the volume required, divide the prescribed units by 160 as each vial has a concentration of 160 U/mL, (eg, 3200 U ÷ 160 U/mL = 20 mL).

Subjects must be well hydrated prior to drug administration.

All subjects will undergo safety assessments (infusion site evaluation, vital signs, and ECG) on Day 1, as presented in Section 1.3.

8.1.2.2 Day 2 and Day 3

Infusion site evaluation will be performed for all subjects on Day 2. Infusion site evaluation and Hgb assessment will be performed for all subjects on Day 3.

8.1.2.3 Day 4

All subjects will be discharged from CRC on Day 4 after serum IgG sample collection and safety assessments (vital signs, hemolytic panel, infusion site evaluation [as clinically indicated]).

8.1.3 Follow-up Period

8.1.3.1 Day 30 (±3 days) Ambulatory Visit

All subjects will visit CRC on Day 30 (±3 days) for safety assessments (vital signs, serum chemistry, drugs of abuse/alcohol screen, hematology, urinalysis, infusion site evaluation [as clinically indicated]), serum IgG sample collection, and rHuPH20 immunogenicity assessment (ADA and neutralizing anti-drug antibody [nADA] blood collection).

8.1.4 Week 12 (±1 week) EOS/ET Visit

The follow-up period for this study is up to 12 (±1) weeks after TAK-881 infusion.

At the EOS/ET visit, final inquiries for SAEs, AEs, and concomitant treatments will be made including all the procedures/assessments as presented in Section 1.3. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Appendix 3.2).

8.1.5 Additional Care of Subjects After the Study

No after care is planned for this study.

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 or legally-authorized representative 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 dose of TAK-881.

Demographic data, including subject 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. Body weight will be measured again at Day -1 for dose calculation.

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

The name and address of each third-party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

Actual safety assessment times will be monitored and recorded. The sponsor's expectation is that the investigator will ensure that every effort is made to perform all assessments at the precise protocol-scheduled time.

8.2.3.1 Medical and Medication History

A complete medical and medication history, as well as demographic information, will be performed at the time points described in Section 1.3 by a qualified licensed physician, physician's assistant, or a nurse practitioner. The medical history will be reviewed and recorded, including:

- Date of birth
- Sex
- Race and ethnicity
- Recent ingestion of medication (30 days prior to entering the screening period)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases
- Smoking habits

8.2.3.2 Physical Examination (Including Height and Weight)

A complete physical examination or a partial physical examination will be performed as described in Section 1.3 by a qualified licensed physician, physician's assistant, or nurse practitioner.

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.

8.2.3.3 Adverse Event Collection

At each study visit and during in-house confinement, subjects will be questioned in a general way to ascertain if AEs have occurred. Subjects will be encouraged to report any AEs they may experience during this time. At the follow-up and EOS visits, subjects will again be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed (refer to Appendix 3 for AE definitions, assessment, collection time frame, and reporting procedures).

8.2.3.4 Vital Signs

Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in Section 1.3 of this protocol. Additional blood pressure and pulse rate measurements may be performed, as determined by the investigator, in order to ensure appropriate monitoring of subject safety and accurate recording of vital sign measurements. Any changes from baseline which are deemed clinically significant by the investigator are to be recorded as an AE.

The same method for obtaining blood pressure measurement (auscultatory or oscillometric) should be used throughout the study for all subjects (and documented). In addition, the conditions of vital sign measurements should be controlled and as consistent as possible during the study, in order to minimize external variability of the readings.

It is advised that measurements be collected at a comfortable room temperature with little to no background noise, using the same (appropriately sized) cuff placed at the same location of the same arm during the study. The bladder deflation rate should be deflated (calibrated for oscillometric method or manually by auscultatory method) at a rate of 2-3 mmHg/s (and the first and last audible sounds recorded as systolic and diastolic pressure) after at least 5 minutes of rest in the assumed position.

The cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1).

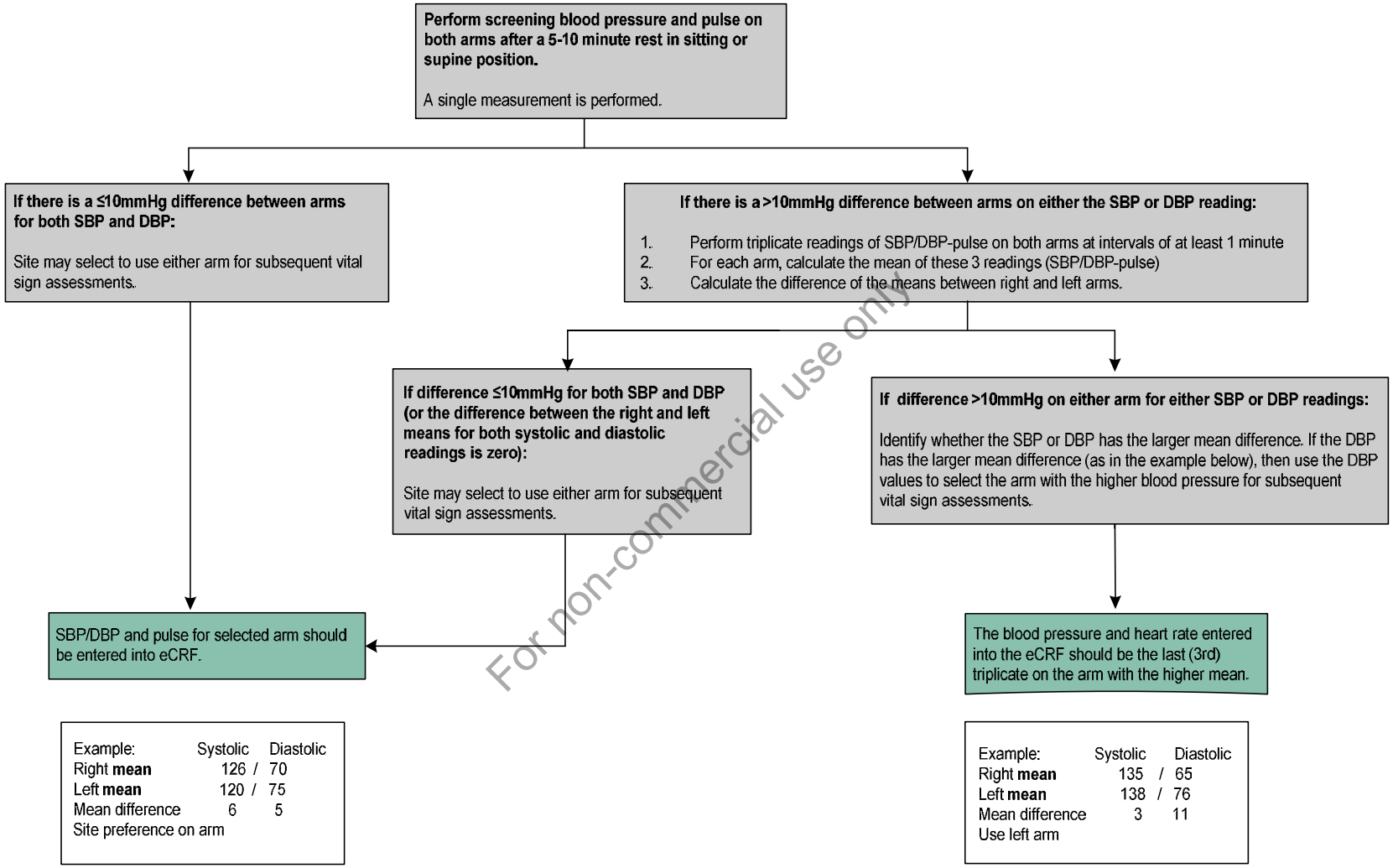
The subject should be asked to remove all clothing that covers the location of cuff placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes of collection. The subject should be instructed to relax as much as possible for at least 5 minutes prior to collection. The subject should remain quiet during this time and through the measurement.

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 (eg, nausea, dizziness) or if deemed necessary by the investigator or designee.

At the screening visit, blood pressure should be compared between both arms. When there is a consistent inter-arm difference confirmed over 3 consecutive measurements (>10 mmHg), the arm with the higher blood pressure should be used for inclusion at screening and the last measurement recorded in the CRF. The same (right or left) arm with the higher blood pressure will be used throughout the study.

For details on blood pressure and pulse procedures for healthy subjects, see Figure 3.

Figure 3. Procedures for Screening Vital Signs (Blood Pressure – Pulse) – Healthy Subjects Only



DBP=diastolic blood pressure; eCRF=electronic case report form; SBP=systolic blood pressure

The use of automated devices for measuring pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

Respiratory Rate

The subject should be in a comfortable position. The observer should hold the extremity of the subject as a distraction for the patient (ie, pretending he/she is taking the subject's radial pulse) and count the respiration for 1 minute.

Body Temperature

Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used.

8.2.3.5 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. 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.

The following clinical laboratory assessments will be performed:

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.

Section 1.3 lists the parameters to be assessed in this study. At screening, creatinine clearance will be calculated using the following Cockcroft-Gault formula (Shrewsberry et al., 2007).

Creatinine clearance = (140 − Age)×mass (kilogram weight)÷72× serum creatinine in (mg/dL) if "female"×85%

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. Section 1.3 lists the parameters to be assessed in this study.

Hemolytic Panel

The first hemolytic panel will be measured at D-1. Refer Section 1.3 for further details on baseline considerations and hemolytic panel parameters.

It is not necessary to repeat the hemolytic panel if the drop of ≥ 1 g/dL Hgb remains constant 72 hours after the 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 judgment 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.

Hemolytic tests will be performed at the local laboratory or other laboratories as appropriate (eg, 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.

Urinalysis

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

Coagulation

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

8.2.3.6 Pregnancy Test

Pregnancy test will be done for all females. Serum pregnancy test will be obtained at screening and whenever a pregnancy is suspected. If the serum pregnancy test at screening is older than 7 days, a serum pregnancy test is required on D-1; otherwise urine pregnancy test may be performed on D-1. Subjects must have a negative urine and/or serum pregnancy test within 7 days prior to IP administration.

8.2.3.7 Drug and Alcohol Screen

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

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.

8.2.3.8 Serology Screen

Blood samples will be drawn at timepoints listed in Section 1.3. Sample collection details are provided in the Laboratory Manual. Section 1.3 lists the parameters to be drawn for the virology screen.

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.

8.2.3.9 Electrocardiogram

A 12-lead ECG will be performed at screening for the determination of eligibility (eg, 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 the time points specified in Section 1.3.

The following parameters will be recorded on the appropriate CRF page: heart rate, PR, RR, QRS, and QT intervals. The QTcB and QTcF will be derived from the data in the database.

The investigator's assessment of the ECG tracing as normal or abnormal must be documented, and if abnormal, his/her determination of whether the abnormality is clinically significant or not will be documented on the tracing and recorded in the CRF.

The subject should be asked to remove all clothing that covers the location of lead placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

8.2.4 Serum Total IgG Levels and Immunogenicity Assessments

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 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 K_3EDTA 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 back-up)

Primary specimen collection parameters are provided in Table 5.

Table 5. Primary Specimen Collections

Specimen Name	Primary Specimen	Description of Intended Use	Sample Collection
Serum sample for total IgG	Serum	Serum sample for total IgG levels	Mandatory
rHuPH20 Immunogenicity ADA and nADA sample	K_3EDTA Plasma	Plasma sample for Immunogenicity analyses	Mandatory

Abbreviations: ADA=anti-drug antibody; IgG=Immunoglobulin G; K_3EDTA=ethylenediamine tetraacetic acid tripotassium; nADA=neutralizing anti-drug antibody

Serum total IgG 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 (also known as the Screening and Confirmatory Binding Assay). Postdose samples with antibody titers ≥1:160 will be analyzed for the presence of nADA using a validated assay based on neutralization of rHuPH20 activity.

8.2.4.2 Immunogenicity Panel

At baseline (D-1), 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 (Grade 2 or higher as per CTCAE v5.0 (U.S. Department of Health and Human Services, 2017)) that may be a result of immune-mediated response to either IG, rHuPH20, or other concomitant medications (Table 6) will be asked to return to the CRC as soon as possible to undergo an additional panel of testing outlined in Table 7.

Table 6. 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 ➢ Edema 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 7. Immunogenicity Panel

1. Repeat test (not an additional blood draw) 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

*Repeat test for anti-rHuPH20 will be run on the additional/back-up sample taken at the same time point that is held at the central laboratory in case repeat test is required.

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 8. Volume of Blood to be Drawn from Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Serum samples for total IgG	7	4	28
ADA and nADA samples	10	3	30
Hemolytic panel	28.5	2	57
Serology test	5	2	10
Serum chemistry (male and female subjects) and β-hCG (female subjects only)	5	3	15
Coagulation	4.5	2	9
Immunogenicity panel	17	1	17
Hematology	3	4	12
Total			**Up to 178 mL**

Abbreviations: β-hCG=beta-human chorionic gonadotropin; ADA=anti-drug antibody; nADA=neutralizing anti-drug antibody

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 178 mL. When more than 1 blood assessment is to be done at the same time point/period, if they require the same type of tube, the assessments may be combined. Additional samples may be collected as required per protocol.

8.3 Back-up Samples and Biobanking

Back-up samples from serum total IgG level assessment 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)

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 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 the study 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 enrolled, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

The study will be monitored in accordance with the current GCP.

9.1.1 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 contract research organization (CRO) 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 PI 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 PI must review the data change for completeness and accuracy and must sign and date.

CRFs will be reviewed for completeness and acceptability at the CRC 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.

9.2 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.

9.3 Data Handling

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

9.4 Statistical Analysis Process

The study will be analyzed by the CRO.

The Statistical Analysis Plan (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 integrity of the statistical analysis and study conclusions, the SAP will be prepared and approved by the sponsor prior to the first study visit of the first subject in this open-label study.

All statistical analyses will be performed using Statistical Analysis Software, SAS® (SAS Institute, Cary, NC 27513), Version 9.4 or higher.

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

There is no planned interim analysis, adaptive design, or Data Monitoring Committee in this study.

However, before the dosing in Treatment Arm 2, the tolerability and safety data through Day 4 of the last subject in Treatment Arm 1 will be reviewed by a safety review team consisting of the investigator, the Study Clinical Lead, the sponsor's Study Medical Monitor (chair), and the sponsor's Global Drug Safety Physician (Section 4.1). Similarly, the tolerability and safety data through Day 4 of the last subject in Treatment Arm 2 will be reviewed by the safety review team before the dosing in Treatment Arm 3.

9.6 Sample Size Calculation and Power Considerations

Assessment of tolerability to TAK-881 SC administration at various SC infusion rates is the primary objective of this study.

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

The planned total sample size for this study is 24 subjects (8 subjects per treatment arm).

Of the 24 subjects to be enrolled, a minimum of 18 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 (≥18) is considered adequate for claiming tolerability and safety of TAK 881 based on clinical judgment.

9.7 Statistical Analysis Sets

Safety Analysis Set:

The Safety Analysis Set will consist of all subjects who received a partial or a full dose of TAK-881. Analysis of tolerability, safety, and immunogenicity data will be based on the Safety Analysis Set.

PK Analysis Set:

The PK Analysis Set will consist of all subjects in the Safety Analysis Set who have at least one evaluable postdose serum concentration for total IgG. Analysis of serum total IgG levels will be based on the PK Analysis Set.

9.8 Methods of Analysis

Statistical analysis for this study will be descriptive in nature; no statistical hypothesis testing will be performed.

Tolerability, safety, and immunogenicity endpoint data as well as serum total IgG levels will be analyzed using descriptive statistics. Continuous endpoints will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation (SD), minimum value, and maximum value. Categorical endpoints will be summarized in terms of number and percent of subjects and number of occurrences in each category, as appropriate. Baseline is defined as the last non-missing value before the dose of TAK-881.

Claim of tolerability/safety/immunogenicity of TAK-881 will be based on clinical judgment on the totality of evidence, with no predefined tolerability/safety/immunogenicity statistical margin or criteria.

9.8.1 Primary Endpoint

The number and percentage of subjects with tolerability events will be summarized per infusion site by treatment arm and overall.

9.8.2 Secondary Endpoints

SC administration endpoints represent supportive tolerability and safety measures and will be summarized per infusion site by treatment arm and overall using descriptive statistics.

The number and percentage of subjects with TEAEs as well as the number of TEAEs will be summarized by treatment arm and overall. TEAEs considered related to TAK-881, serious TEAEs, local TEAEs, systemic TEAEs, temporally associated TEAEs within 72 hours, TEAEs leading to study discontinuation, TEAEs by maximum severity, and TEAEs of special interest will be similarly summarized. Additional TEAEs may be specified in the SAP. In addition, the number and percentage of subjects with TEAEs will be categorized by preferred term (PT) and summarized by treatment arm and overall. The PTs will be grouped by system organ class (SOC). Each TEAE will then be divided into defined severity grades and relationship to TAK-881. Subject identifiers will be included within each PT. If the same subject experiences multiple TEAEs categorized under the same PT and relationship assessment, this TEAE is shown only once at its most serious severity.

Clinical laboratory parameters, vital signs, and immunogenicity assessments will be summarized descriptively by treatment arm and overall as well as by study visit. In addition, shift tables from baseline to each post-infusion study visit will be generated by treatment arm and overall. Note that clinically significant treatment-emergent changes in clinical laboratory measurements and vital signs will be recorded in the study database as TEAEs.

9.8.3 Exploratory Endpoint

Serum levels of total IgG will be summarized descriptively by treatment arm and study visit.

10. REFERENCES

Baxalta US Inc. 2020. *HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] - Prescribing Information.* [Online]. Available: https://www.shirecontent.com/PI/PDFs/HYQVIA_USA_ENG.pdf [Accessed].

Shrewsberry, T. W., Banoub, A., Fleming, K., Snyder, H. & Stehlik, J. 2007. Spreadsheet use to calculate creatinine clearance from serum creatinine. *Journal of extra-corporeal technology,* 39**,** 260-2.

U.S. Department of Health and Human Services 2017. Common terminology criteria for adverse events (CTCAE), Version 5.0, published Nov 27, 2017.Web Link: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

Investigator's Brochure, IGI, 10% with rHuPH20, Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase.

Investigator's Brochure, IGI, 20%, Immune Globulin Subcutaneous (Human) 20% solution.

Investigator's Brochure, IGI, 20% with rHuPH20, Immune Globulin Subcutaneous (Human) 20% solution with Recombinant Human Hyaluronidase.

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	08 MAR 2021	Global
Amendment 1	09 JUL 2021	Global

APPENDIX 2 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Appendix 2.1 Regulatory and Ethical Considerations

This study is conducted in accordance with current applicable regulations including ICH E6, EU Directive 2001/20/EC, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

Appendix 2.2 Sponsor's Responsibilities

Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP guideline E6 (1996), ICH E6 R2 (2018), EU Directive 2001/20/EC Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of IP for shipment to the site.

Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

The timing for study registration and results summary posting must be in accordance with applicable local and national requirements.

Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/IECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

Appendix 2.3 Investigator's Responsibilities

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2018), 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 PI, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The investigator and any sub-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/IEC and provide them with a detailed written explanation. The investigator will also return all IP, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/IEC, and Regulatory Agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/IECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or, for multicenter studies, the coordinating PI, according to national provisions, and will be documented in the investigator agreement.

Documentation and Retention of Records

Case Report Forms

Case report forms are supplied by the CRO and will be completed through their EDC in accordance with the Case Report Form Completion Guidelines (CCGs).

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file or original clinical laboratory reports.

All key data must be recorded in the subject's source documents.

The investigator must permit authorized representatives of the sponsor, the respective national, local, or foreign regulatory authorities, the IRB/IEC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/IEC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/IEC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any Regulatory Agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

Audit/Inspection

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/IEC for the study site.

Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in IP; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

Compliance to all Local, State, and National Controlled-substance Biohazard and Infectious Disease Regulations and Legislation

When using controlled substances, biohazardous material, or substances for infectious diseases, the investigator must at all times comply with all local, state, and national laws pertaining to registration and reporting with the appropriate regulatory body and control and handling of such substances.

Appendix 2.4 Ethical Considerations

Informed Consent

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. 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 subjects must sign an ICF before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the ICF will be reviewed by the sponsor and approved by the IRB and regulatory authority(ies), where applicable. The ICF will include: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities, 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. Subjects will be allowed sufficient time to consider participation in the study. Each subject or the subject's legally-authorized representative, as applicable, is requested to sign and date the subject ICF 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. By signing the ICF, subjects agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason. A copy of the informed consent documentation (ie, 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 PI provides the sponsor with a copy of the consent form which was reviewed by the IRB/IEC and which received their favorable opinion/approval. A copy of the IRB/IEC'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 (ie, sponsor or coordinating PI) is responsible for this action. Additionally, if the IRB/IEC 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.

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. Responsibility for coordinating with IRBs/IECs is defined in the clinical trial agreement. 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. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, will be supplied by sponsor or designee and 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 (ie, 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 (eg, ICF) 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.

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

Prior to implementing changes in the study, the sponsor and the IRB/IEC 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.

The investigator is responsible for keeping the IRB/IEC apprised 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/IEC. The investigator must also keep the local IRB/IEC informed of any serious and significant AEs as required by IRB/IEC procedures.

Privacy and Confidentiality

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 CRO.

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 TAK-881; national or local regulatory authorities; and the IRB/IEC 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.

Study Results / Publication Policy

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form. The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other investigators prior to publication or oral presentations of the study results on an individual basis. The site agrees not to publish or present the site's study results until such time as either the aggregate multi-site study results are published in a cooperative publication or for a period of one (1) year after termination or completion of the study at all participating sites, whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the sponsor by the site for review. Upon the sponsor's request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the sponsor time to file any patent application(s). All publications of the study results shall appropriately reference the multi-site study publication, if any, or the fact that the study results are a subset of data resulting from a larger multi-site study.

Takeda is committed to transparent dissemination of all scientific, technical, and medical manuscripts generated from Takeda-supported research. Therefore, after January 1, 2018, Takeda will require the submission of all Takeda-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an investigator does not confer any rights to authorship of publications.

APPENDIX 3 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Appendix 3.1 Adverse Event Definitions

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this IP or medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an IP or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the IP or medicinal product.

Adverse Event of Special Interest

An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the compound/program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them. Takeda uses Targeted Questionnaires (TQs) to collect additional data on specific safety concerns. Takeda PV Operations team will send the appropriate TQ to the reporter based on the list of PTs or a Standard MedDRA Query (SMQ) associated with certain Takeda compound/program.
The following AESIs apply to this compound/program;

- Allergy
- Catheter leakage
- Thromboembolic events

Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence (whether considered to be related to IP or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term ‘life-threatening’ in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe

- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, that are the result of elective or previously scheduled investigations procedures or surgery for pre-existing conditions and have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s)
- Results in persistent or significant disability/incapacity
- Results in a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include bronchospasm associated with anaphylaxis requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse

Unexpected Adverse Event

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 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 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.

Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (ie, 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

Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study protocol or product labeling; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter, vital sign measure, or 12-lead ECG assessment can represent an AE if the change is clinically relevant or if, during administration of IP, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the IP, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory results (such as hematology panel or clinical chemistry panel), vital signs, or 12-lead ECG values which were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value, vital sign, or 12-lead ECG parameter is clinically significant and represents an AE.

Appendix 3.2 Collection of Adverse Events

All AEs/SAEs and AESIs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 8.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not IP is administered.

All AEs/SAEs and AESIs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained.

Appendix 3.3 Assessment of Adverse Events

Severity Categorization

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.

All AEs and clinically significant laboratory abnormalities will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, dated November 27, 2017 (U.S. Department of Health and Human Services, 2017). For any term that is not specifically listed on the CTCAE scale, intensity will be assigned a grade of 1 through 5 using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4: Life-threatening consequences.

Grade 5: Death related to AE.

Infusion Related AE Evaluation

Infusion related AEs will be evaluated per CTCAE v5.0 for any potential systemic effects such as infusion related reactions or local infusion site events (ie, infusion site extravasation). Allergic reactions related to infusion, use injury, poisoning, and procedural complications should be reported as infusion related reaction. Do not report both. Photographs of infusions site(s) may be collected (optionally) on Day 1 (prior to start of infusion, 1-hour [±15 minutes] after start of infusion, and within 15 minutes after the end of infusion), Day 2 (24 hours post infusion [±4 hours]), Day 3 (48 hours post infusion [±4 hours]).

The catheter leakage at infusion site will be evaluated by the investigator/designee based on the following scoring system and will be reported as a mild AE if the leakage is readily observable (Score 2):

- Score 1 = Minimal leakage (ie, transient/barely observable leakage). Score 1 will be considered equivalent to Grade 1 of CTCAE v5.0 evaluation scale.
- Score 2 = Readily observable leakage (ie, continuous/inability to complete infusion at that site). Score 2 will be considered equivalent to Grade 2 of CTCAE v5.0 evaluation scale. No higher grading above Grade 2 will be applied to catheter leakage.

Relationship Categorization

A physician/investigator must make the assessment of relationship to IP for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the IP. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related." Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the IP and the occurrence of the AE, then the AE should be considered "related." The causality assessment must be documented in the source.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

Outcome Categorization

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

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

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

Appendix 3.4 Safety Reporting

Reference Safety Information

The reference for safety information for this study is the Investigator's Brochure which the sponsor has provided under separate cover to all investigators.

Reporting Procedures

1. All initial and follow-up SAE reports must be reported by the investigator to Takeda PV Operations Department and the CRO/Takeda 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 (see Appendix 3.9) unless they result in an SAE.

The investigator must complete, sign, and date the Takeda Safety Report 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 Takeda PV Operations Department.

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

A copy of the Takeda Safety Report Form must also be sent to the CRO/Takeda Medical Monitor using the details specified in the emergency contact information section of the protocol.

Appendix 3.5 Serious Adverse Event Collection Time Frame

All SAEs and AESIs (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 8.1.3, and must be reported to the Takeda PV Operations Department and the CRO/Takeda 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 Takeda PV Operations Department within 24 hours of the first becoming aware of the event.

Appendix 3.6 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms reported by the subject after signing the ICF or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

Appendix 3.7 Fatal Outcome

Any SAE that results in the subject's death (eg, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another IP action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the IP should be recorded as "dose not changed" or "not applicable" (if the subject never received IP or it is a single-dose study). The IP action of withdrawn should not be selected solely as a result of the subject's death.

Appendix 3.8 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 8.1.3.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Takeda PV Operations Department using the Takeda Pregnancy Report Form. A copy of the Takeda Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Takeda Medical Monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days and approximately 1-year post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion, or congenital abnormality are considered SAEs and must be reported using the Takeda Safety Report Form.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Takeda Safety Report Form as well as the Takeda Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

Appendix 3.9 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Appendix 3.4.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of IP when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- **Misuse** – Intentional use of IP other than as directed or indicated at any dose (Note: this includes a situation where the IP is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Intentional or unintentional intake of a dose of IP higher than the protocol-prescribed dose.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an IP. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the IP are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired IP should be considered as a reportable medication error.

Appendix 3.10 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, these do not constitute de facto deviation from the protocol. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

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

The investigator may implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the sponsor. In the event(s) of an apparent direct hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm the safety measure, in writing, within 1 calendar day of the change being implemented. The sponsor will also ensure the responsible EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

Appendix 3.11 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor is responsible for notifying the relevant regulatory authorities of related, unexpected SAEs and the site is responsible for notifying the related, unexpected SAEs to local IRB.

In addition, the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the TAK-881 program.

The investigator is responsible for notifying the local IRB/IEC 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/IEC procedures.