



Clinical Study Protocol

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Title: A Phase 1, Randomized, Open-Label, Pharmacokinetic Trial of TAK-881 and HyQvia in Healthy Adult Participants

Study Number: TAK-881-1002

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TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1, Randomized, Open-Label, Pharmacokinetic Trial of TAK-881 and HyQvia in Healthy Adult Participants

Protocol Number:	TAK-881-1002
Amendment Number:	Not Applicable
Compound Number:	TAK-881
Trial Phase:	Phase 1
Sponsor Name and Address:	Takeda Development Center Americas, Inc. 500 Kendall Street Cambridge, MA 02142 USA
Regulatory Agency Identifier Number(s):	IND: 030932
Investigational Device Manufacturer Name and Address:	Koru 24 G HIGH Flo Subcutaneous Safety Needle Sets Koru Medical Systems (on behalf of Takeda) 100 Corporate Drive Mahwah, NJ 07430 USA
Sponsor Approval Date:	The approval date is the latest of the approval dates included on the last page of this document with the electronic signatures.

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TABLE OF CONTENTS

SPONSOR SIGNATORIES:	8
INVESTIGATOR AGREEMENT	9
1.0 PROTOCOL SUMMARY	10
1.1 Protocol Synopsis	10
1.1.1 Primary and Secondary Objectives and Endpoints	10
1.1.2 Overall Design	11
1.2 Trial Schema	12
1.3 Schedule of Activities	13
2.0 INTRODUCTION	17
2.1 Purpose of Trial	17
2.2 Background	17
2.3 Summary of Benefits and Risks	19
3.0 TRIAL OBJECTIVES AND ENDPOINTS	20
3.1 Primary Objective + Associated Endpoint	20
3.2 Primary Estimand	20
3.3 Secondary Objectives + Associated Endpoints	21
4.0 TRIAL DESIGN	22
4.1 Overall Design	22
4.1.1 Dose Escalation	22
4.2 Scientific Rationale for Trial Design	22
4.2.1 Rationale for Trial Design	22
4.2.2 Rationale for Dose	22
4.2.3 Rationale for Endpoints	22
4.2.3.1 Pharmacokinetic Endpoints	22
4.2.3.2 Safety Endpoints	22
4.3 Start of Trial and End of Trial	23
4.3.1 Definition of Beginning of the Trial	23
4.3.2 Early Trial or Site Closure	23
4.3.3 Definition of End of the Trial	23
5.0 TRIAL POPULATION	24
5.1 Inclusion Criteria	24
5.2 Exclusion Criteria	24
5.3 Lifestyle Considerations	26
5.3.1 Meals and Dietary Restrictions	26
5.3.1.1 Diet and Fluid	26

5.3.2	Nicotine- and Tobacco-Containing and/or Cannabis Products	26
5.3.3	Activity	27
5.3.3.1	Physical Activity	27
5.3.3.2	Other Activities	27
5.4	Screen Failures	27
6.0	IP AND CONCOMITANT THERAPY	28
6.1	Description of IP	28
6.2	Dosing and Administration	28
6.2.1	IP Dose Modification	29
6.3	Overdose	30
6.4	Preparation, Handling, Storage, and Accountability	30
6.4.1	Preparation of IP	30
6.4.2	IP Labeling	30
6.4.3	Handling and Storage of IP	30
6.4.4	Accountability and Destruction of Sponsor-Supplied IPs	30
6.5	Randomization and Blinding	31
6.5.1	IP Blinding	31
6.5.2	Randomization	31
6.6	IP Compliance	31
6.7	Concomitant Therapy	31
6.7.1	Prohibited Concomitant Therapy	31
6.7.2	Permitted Concomitant Therapy	31
7.0	DISCONTINUATION OF IP AND PARTICIPANT WITHDRAWAL FROM TRIAL	32
7.1	Discontinuation of IP	32
7.2	Participant Withdrawal from the Trial	33
7.2.1	Trial Participant Replacement	33
7.3	Lost to Follow-up	33
7.4	Trial and Dose Stopping Rules	34
8.0	TRIAL ASSESSMENTS AND PROCEDURES	35
8.1	Screening/Baseline Assessments and Procedures	35
8.1.1	Demographics, Medical History, and Medication History	35
8.1.1.1	Demographics	35
8.1.1.2	Medical History	35
8.1.1.3	Prior and Concomitant Treatments/Medications	35
8.2	Confinement	36

8.3	Safety Assessments and Procedures	36
8.3.1	Physical Examination	36
8.3.2	Height, Weight, and BMI	36
8.3.3	Vital Signs	36
8.3.4	ECG Procedure	37
8.3.4.1	Screening and Safety ECGs	37
8.3.5	Clinical Laboratory Assessments	37
8.3.6	Additional Diagnostic Laboratory Tests	39
8.3.7	Infusion Site Reaction Assessment	40
8.4	Adverse Events and Serious Adverse Events	41
8.4.1	Definitions of AE and SAE	41
8.4.1.1	AE Definition	41
8.4.1.2	SAE Definition	42
8.4.2	Time Period and Frequency for Collecting AE and SAE Information	43
8.4.3	Identifying AEs and SAEs	43
8.4.4	Recording of AEs and SAEs	44
8.4.4.1	Recording of AEs	44
8.4.4.2	Recording of SAEs	46
8.4.5	Follow-up of AEs and SAEs	46
8.4.6	Reporting of SAEs	47
8.4.7	Regulatory Reporting Requirements for SAEs	47
8.4.8	Serious and Unexpected Adverse Reaction Reporting	47
8.4.9	Adverse Events of Special Interest	48
8.4.10	Product Complaints	48
8.4.11	Special Situation Reporting	48
8.5	Pharmacokinetics and Immunogenicity	49
8.5.1	Pharmacokinetics	49
8.5.1.1	Pharmacokinetic Sample Collection	49
8.5.1.2	Pharmacokinetic Sample Analysis	49
8.5.1.3	Pharmacokinetic Parameters	50
8.5.2	Immunogenicity	50
8.5.3	Additional Immunology Assessments	50
8.6	Blood Volume Drawn for Trial Assessments	51
9.0	STATISTICAL CONSIDERATIONS	52
9.1	Analysis Sets	52
9.2	General Approach	52

9.3	PK Analyses.....	53
9.4	Safety Analyses.....	54
9.4.1	AEs	54
9.4.2	Clinical Laboratory Evaluation	55
9.4.3	Vital Signs	55
9.4.4	ECG	55
9.4.5	Medical History	55
9.4.6	Analysis of Demographic and Other Baseline Characteristics.....	55
9.5	Immunogenicity Analysis.....	55
9.6	Interim Analysis and Criteria for Early Termination.....	55
9.7	Sample Size Determination.....	56
10.0	GENERAL CONSIDERATIONS: REGULATORY AND OPERATIONAL CONSIDERATIONS	57
10.1	Regulatory and Ethical Considerations.....	57
10.1.1	Investigator Responsibilities	57
10.1.1.1	Introduction	57
10.1.1.2	List of Investigator Responsibilities	57
10.1.1.3	Investigator Consent to Use of Personal Information	59
10.1.2	Sponsor Responsibilities	60
10.2	Informed Consent Process	60
10.2.1	Informed Consent for Use of Remaining Samples	61
10.3	Data Protection.....	61
10.3.1	Participant Confidentiality.....	61
10.3.2	Responsibilities After Termination or Suspension.....	62
10.3.3	Serious Data Breach Prevention and Reporting	62
10.4	Early Site Closure or Trial Termination	62
10.4.1	Decision Rights for Site Closure and Trial Termination.....	62
10.4.2	Criteria for Early Trial Site Closure	62
11.0	GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE.....	63
11.1	Quality Tolerance Limits	63
11.2	Data Quality Assurance	63
11.2.1	Investigator Responsibilities for Data Quality Assurance.....	63
11.2.2	Protocol Deviations	64
11.3	Source Data.....	64
11.3.1	Introduction	64

11.3.2	Investigator Expectations for Source Data	64
11.3.3	Trial Monitor Expectations for Source Data	65
11.3.4	Definition of Source Data.....	65
12.0	APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS	66
12.1	Contraception, Pregnancy Testing, and Pregnancy	66
12.1.1	Definitions Related to Childbearing Potential.....	66
12.1.1.1	Women of Childbearing Potential.....	66
12.1.1.2	Fertile Men	66
12.1.2	Contraception	66
12.1.2.1	Permitted and Unacceptable Contraception Methods	66
12.1.2.2	Duration of Contraception Use	67
12.1.3	Pregnancy Testing	68
12.1.4	Pregnancy and Postpartum Information	68
12.1.4.1	Participants Who Become Pregnant During the Trial.....	68
12.1.4.2	Male Participants Whose Partners Become Pregnant	68
12.2	Publication and Clinical Trial Registration and Disclosure Policies	69
12.2.1	Publication Policy.....	69
12.2.2	Clinical Trial Registration and Disclosure	69
12.3	Prior Protocol Amendments.....	69
13.0	APPENDIX: SAMPLE RETENTION AND USE	70
13.1	Sample Retention	70
13.2	Sample Use for Research Purposes.....	70
14.0	APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS IN MEDICAL DEVICE STUDIES: ADDITIONAL REQUIREMENTS FOR REPORTING	71
14.1	Definitions of Medical Device AE and Adverse Device Effect	71
14.2	Definitions of Medical Device SAE, Serious Adverse Device Effect, and Unanticipated Serious Adverse Device Effect.....	72
14.3	Additional Requirements for Recording and Follow-up of Device Adverse Events, SAEs, and Deficiencies.....	72
14.4	Reporting of Medical Device AEs, SAEs, SADEs, Serious Injuries, and UADEs	73
15.0	APPENDIX: RECORD RETENTION	74
15.1	Record Retention Responsibilities of the Investigator/Site	74
15.2	Record Retention Responsibilities of the Sponsor.....	74
16.0	APPENDIX: ABBREVIATIONS	75
17.0	APPENDIX: REFERENCES.....	77

LIST OF IN-TEXT TABLES

Table 1	Primary and Secondary Objectives and Associated Endpoints	10
Table 2	Primary Objective and Associated Endpoint	20
Table 3	Primary Estimand.....	20
Table 4	Secondary Objectives and Associated Endpoints	21
Table 5	Table of Investigational Products	28
Table 6	Trial Interventions Administered: Device (applicable only in the US)	29
Table 7	Safety Reporting Timeframes	41
Table 8	Primary Specimen Collections.....	49

LIST OF IN-TEXT FIGURES

Figure 1	Trial Schema	12
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SPONSOR SIGNATORIES:

Electronic signatures of the following individuals are provided on the last page of this document.

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<div>██████████, PhD ██████████ Plasma Derived Therapies Statistics</div>

The medical monitor's and sponsor's responsible medical officer's name and contact information are provided separately.

- Within 24 hours, report serious adverse events, adverse events of special interest, and pregnancies. Use the contact information provided separately.
- For other reportable safety events, refer to [Table 7](#).

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this trial in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and wellbeing of trial participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6[R2] Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 8.4 of this protocol.
- Terms outlined in the clinical trial site agreement.
- Responsibilities of the investigator (Section 10.1.1.2).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Section 10.1.1.3 of this protocol.

Electronic signature of the Investigator provided on the last page of this document.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.0 PROTOCOL SUMMARY

1.1 Protocol Synopsis

1.1.1 Primary and Secondary Objectives and Endpoints

Table 1 Primary and Secondary Objectives and Associated Endpoints

Primary Objective To characterize the pharmacokinetics (PK) of TAK-881 and HyQvia following single subcutaneous (SC) administration in healthy adult participants.	Primary Endpoint Baseline-corrected area under the concentration-time curve from Day 1 to Day 29 ($AUC_{Day1-29}$) based on serum total Immunoglobulin G (IgG) levels.
Secondary Objectives To assess baseline-uncorrected and baseline-corrected PK exposure parameters of TAK-881 and HyQvia following single SC administration in healthy adult participants.	Secondary Endpoints <p>Baseline-uncorrected PK parameters based on serum total IgG levels:</p> <ul style="list-style-type: none"> Maximum observed concentration (C_{max}) Time to C_{max} (t_{max}) $AUC_{Day1-29}$ <p>Baseline-corrected PK parameters based on serum total IgG levels:</p> <ul style="list-style-type: none"> Area under the concentration-time curve from Day 1 to infinity (AUC_{inf}) Area under the concentration-time curve from Day 1 to time of the last measurable concentration (AUC_{last}) C_{max} t_{max} Time of last measurable concentration (t_{last}) Terminal half-life ($t_{1/2z}$) Apparent clearance (CL/F) Apparent volume of distribution (V_z/F)
To assess the safety, tolerability, and immunogenicity of TAK-881 and HyQvia following single SC administration in healthy adult participants.	<p>Safety:</p> <ul style="list-style-type: none"> Occurrence of treatment-emergent adverse events (TEAEs). <p>Tolerability:</p> <ul style="list-style-type: none"> Occurrence of tolerability events during the infusion of investigational products (IPs). <p>Immunogenicity:</p> <ul style="list-style-type: none"> Occurrence of positive binding (defined as titer $\geq 1:160$) antibodies to recombinant human hyaluronidase (rHuPH20). Occurrence of neutralizing antibodies to rHuPH20.

1.1.2 Overall Design

This is a phase 1, randomized, parallel, open-label, single dose, 2-arm, PK trial in healthy adult participants.

Participants will be randomized 1:1 to receive either 1.0 g/kg TAK-881 or 1.0 g/kg HyQvia SC on Day 1 according to the randomization schedule. PK sampling for measurement of serum total IgG concentrations will be performed predose and up to Day 85 postdose.

Throughout the trial, safety will be monitored by repeated clinical and laboratory evaluations.

All participants who received at least one dose of IP (including participants who terminate the trial early) will return to the CRU on Day 85 (\pm 3 days) for the final follow-up procedures, and to determine if any AE has occurred since the last trial visit.

Number of Treatment Arms and Participants:

The trial will include 2 treatment arms.

A total of 30, healthy, adult male and female participants will be enrolled as follows:

- Arm 1: 15 participants
- Arm 2: 15 participants

Blinding:

Not applicable (no blinding).

Dose Levels and Route of Administration

- TAK-881: 1.0 g/kg SC
- HyQvia: 1.0 g/kg SC

Dose changes/Adjustment:

The dose of the IP administered to any participant should not be modified.

Duration of IP Administration and Participation:

Total duration of IP administration for each participant:

- TAK-881: Single dose on Day 1
- HyQvia: Single dose on Day 1

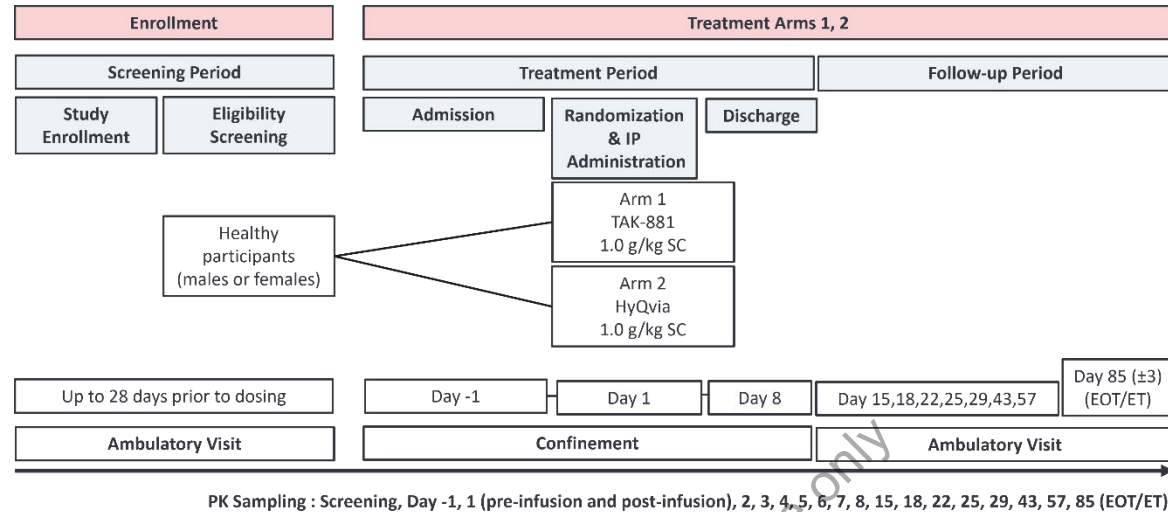
Maximum duration of participant involvement in the trial is approximately 114 days including screening period and follow-up.

Committees:

Not applicable.

1.2 Trial Schema

Figure 1 Trial Schema



EOT/ET: End-of-Trial/Early Termination, IP = investigational product, PK = pharmacokinetic, SC = subcutaneous.

1.3 Schedule of Activities

Visit	Screening		Treatment Period	Confinement Period		Follow-up Period	End of Trial/Early Termination EOT/ET
Study Day	Days -28 to -2	Day -1	Day 1	Days 2 to 7	Day 8	Days 15, 18, 22, 25, 29, 43, 57	Day 85 (± 3 days) EOT/ET
Administrative Procedures							
Informed Consent ^a	X						
Demographics ^b	X						
Ambulatory Visit at CRU ^c	X					X	X
Confinement at CRU ^c		X	X	X	X		
Inclusion/Exclusion Criteria (Eligibility)	X	X	X				
Medical History ^d	X	X					
Randomization			X				
Safety Evaluations							
Previous and Concomitant Medication Monitoring							
Physical Examination ^e	X	X					X
Height	X						
Body Weight and BMI Calculation	X	X					
Infusion Site Evaluation ^f			X	X	X	X (as clinically indicated)	
Adverse Events/Serious Adverse Events							
Drugs of Abuse/Alcohol Screen ^g	X	X				X	X
Serology (HIV, HBV, HCV) ^h	X						X

Visit	Screening		Treatment Period	Confinement Period		Follow-up Period	End of Trial/Early Termination EOT/ET
Study Day	Days -28 to -2	Day -1	Day 1	Days 2 to 7	Day 8	Days 15, 18, 22, 25, 29, 43, 57	Day 85 (± 3 days) EOT/ET
Pregnancy Test (Females Only) ⁱ	X	X					X
FSH ^j	X						
Vital Signs ^k	X	X	X	X	X	X	X
12-lead ECG ^l	X						X
Serum Chemistry, Hematology, and Urinalysis ^m	X	X			X	X (D29 only)	X
Hemolytic Panel ⁿ		X	X (as applicable)				
Coagulation Tests ^o	X	X					
rHuPH20 Immunogenicity: ADA and nAb Blood Collection		X				X (D29 only)	X
Additional immunology assessments ^p		X	X (as applicable)				
Study Drug Administration / PK							
IP Administration ^q			X				
PK blood sampling ^r	X	X	X	X	X	X	X

Abbreviations: ADA=anti-drug antibody; AE=adverse event; 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; C3=serum complement component 3; C4=serum complement component 4; CH50=50% hemolytic complement activity of serum; Ca=calcium; CBC=complete blood count; Cl=chlorine; CRU=Clinical Research Unit; CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; EOT=end of trial; ET=early termination; FSH=follicle-stimulating hormone; 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; HDL=high-density lipoprotein; Hgb=hemoglobin; HIV=human immunodeficiency virus; HR=heart rate; IgG=Immunoglobulin G; INR=international normalized ratio; IP=investigational product; K=potassium; LDH=lactate dehydrogenase; LDL=low-density lipoprotein; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; Mg=magnesium; Na=sodium; nAb=neutralizing anti-drug antibody; PI=principal investigator; PK=pharmacokinetic(s); RBC=red blood cell; RDW=red cell distribution width; rHuPH20=recombinant human hyaluronidase; RR=respiratory rate; U=units; ULN=upper limit of normal; UPCR=urine protein to creatinine ratio; WBC=white blood cells

Visit	Screening		Treatment Period	Confinement Period		Follow-up Period	End of Trial/Early Termination EOT/ET
Study Day	Days -28 to -2	Day -1	Day 1	Days 2 to 7	Day 8	Days 15, 18, 22, 25, 29, 43, 57	Day 85 (± 3 days) EOT/ET

- a Written consent must be obtained prior to performing any protocol specific procedure.
- b Age, gender, ethnicity, and race.
- c All participants will check-in on Day -1 and will be discharged after completing scheduled assessments on Day 8, followed by ambulatory visits on Day 15, Day 18, Day 22, Day 25, Day 29, Day 43, Day 57 and Day 85 (± 3 days) EOT/ET. During the confinement period, standard meals and snacks will be provided at appropriate times.
- d Medical history includes any significant or relevant diseases, surgeries, or other medical events and medication/treatment history, if applicable.
- e Physical examination: A complete physical examination will be performed at screening and EOT/ET visit, and an abbreviated physical examination may be done at the investigator's discretion to assess any new abnormalities or changes from baseline. A complete physical examination will include the following organ systems: 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. An abbreviated physical examination will include general appearance, head and neck, assessment of infusion site(s), and skin. Additional organ systems may be assessed per the investigator's judgement.
- f Infusion-related AEs will be evaluated per CTCAE v5.0 for any potential systemic effects or local infusion site events (i.e., infusion site extravasation) at 12 hours post infusion on Day 1, each day during confinement in the CRU, and as clinically indicated. Allergic reactions related to infusion should be reported as infusion related reaction. Participants 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.
- g Drug screen will include opiates (includes morphine, heroin [diacetylmorphine], codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and hydromorphone), amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, oxycodone/oxymorphone, methadone, 3,4-methylenedioxy-methamphetamine, buprenorphine/metabolite, and phencyclidine.
- h Testing will be performed by the local laboratory at screening and at EOT/ET. Tests include HCV antibody, HBsAg, HBsAb, HBcAb and HIV 1/2 antibodies. Participants who are HIV, HBsAg, or HCV antibody positive at screening will not be enrolled.
- i Pregnancy test will be done for all females. Serum pregnancy test will be obtained at screening and EOT/ET or whenever a pregnancy is suspected. If the serum pregnancy test at screening is older than 7 days, a serum pregnancy test is required on Day -1. Participants must have a negative serum pregnancy test within 7 days prior to IP administration.
- j Follicle stimulating hormone (FSH) levels may be obtained once at screening for menopausal or peri-menopausal women, or as judged by the investigator.
- k Vital signs (RR, HR, BP, and body temperature) will be measured at screening, 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 8) and as needed per investigator's judgment. Vital signs will also be measured on Day 15, Day 18, Day 22, Day 25, Day 29, Day 43, Day 57 and Day 85 (± 3 days) /EOT or ET.
- l The 12-lead ECG will be collected within at prespecified time points and as clinically indicated.

Visit	Screening		Treatment Period	Confinement Period		Follow-up Period	End of Trial/Early Termination EOT/ET
Study Day	Days -28 to -2	Day -1	Day 1	Days 2 to 7	Day 8	Days 15, 18, 22, 25, 29, 43, 57	Day 85 (± 3 days) EOT/ET

- m 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⁻, Ca²⁺, Mg²⁺, Bilirubin (total, direct, and indirect), LDH, protein (total), BUN, carbon dioxide, creatinine, γ -glutamyl transferase, uric acid, glucose, albumin, and lipid profile (triglycerides, total cholesterol, LDL, HDL). 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 $\geq 2+$ 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.
- n 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 Day -1 will serve as the baseline values. In case of absence of a Day -1 result for any reason, the 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 $2 \times$ ULN or greater will trigger analysis of the sample for LDH isoenzymes.
- o aPTT, prothrombin time, and INR: assessments will be performed at screening and Day -1 and as clinically indicated.
- p At any time during the study, participants who have a moderate or severe AE which may be a result of immune-mediated response will be asked to return to the study site to undergo additional immunology assessments (CH50, serum C3, serum C4, C1q binding assay, and circulating immune complex Raji cell assay). In addition, a repeat test for anti-rHuPH20 binding antibody titers, test (or repeat test, as applicable) for the presence of neutralizing anti-rHuPH20 antibodies along with hematology and chemistry panels will be performed.
- q Participants must be well hydrated prior to drug administration. The dose levels are 1.0 g/kg with rHuPH20 80 U/g IgG for both Treatment Arms 1 (TAK-881) and 2 (HyQvia). Participants will receive a single dose of IP with progressively increased infusion rate per the schedule presented in the site infusion manual.
- r Serum total IgG samples will be collected on Screening, Day -1, Day 1 (pre infusion), Day 1 (post infusion within 0.25 hours), Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8 (at discharge), Day 15, Day 18, Day 22, Day 25, Day 29, Day 43, Day 57, and Day 85 (± 3 days) /EOT or ET. The clinic will attempt to collect blood sampling for IgG during the same time period of the day.

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.

2.0 INTRODUCTION

2.1 Purpose of Trial

TAK-881, IGSC (Human), 20% Solution with rHuPH20 (IGSC 20% with rHuPH20) is a facilitated immune globulin subcutaneous infusion evolved from HyQvia (IGI 10% with rHuPH20). The clinical efficacy and safety of HyQvia in the indications of CIDP and PIDD are well established. The higher IG concentration of TAK-881 (as compared to HyQvia) reduces infusion volumes by 50%, which will potentially lead to decreased infusion time and an improved experience in CIDP and PIDD patients. This phase 1 trial is being conducted to assess the PK, safety, and tolerability of both TAK-881 and HyQvia in healthy adult participants with a focus on evaluating the PK of TAK-881 in comparison to HyQvia after a single SC dose administration of a representative CIDP maintenance treatment dose (1.0 g/kg).

Refer to the IB for full details about the IP.

2.2 Background

TAK-881 evolved from the currently licensed HYQVIA ([Baxalta US Inc., 2020](#)), IGI 10% (Human) with Recombinant Human Hyaluronidase, and CUVITRU, IGSC (Human), 20% Solution. Similar to HyQvia, TAK-881 is administered by sequential SC infusion of rHuPH20 first, followed by IG. The ratio of rHuPH20 to IG is the same as for HyQvia, which is 80 units rHuPH20 per gram of IG. With TAK-881, the required infusion volume is reduced by 50% at an equivalent dose level compared to HyQvia.

The IGSC, 20% component of TAK-881 is a liquid 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 hyaluronidase that depolymerizes the gel-like hyaluronan in local SC tissue where it is infused. This localized effect results in a transient increase in permeability, allowing IG to disperse and to reach the systemic circulation more readily than without rHuPH20.

Efficacy and safety data are available for the individual components of TAK-881 (IGSC 20% with rHuPH20), based on the efficacy and safety profiles of the approved products, HyQvia and CUVITRU. [REDACTED]

[REDACTED] CUVITRU and the IGI, 10% component of HyQvia share the same manufacturing process, with the exception of ultra/diafiltration and formulation at a higher concentration. IGSC, 20% maintains the same product characteristics, including antibody spectrum, molecular size distribution, and subclass distribution as IGI, 10%.

In view of the extensive pharmacological and toxicological testing conducted for HyQvia in different animal models, it was not considered necessary to repeat all nonclinical studies with TAK-881. Therefore, a bridging approach was used with regard to the nonclinical development of TAK-881, including PK and local tolerance studies, to address feasibility of administration at high infusion flow rates (5 mL/min or 300 mL/hr/site) and to evaluate the safety and local tolerability of the higher IG concentration. As TAK-881 is expected to have the same systemic safety profile as HyQvia, no additional systemic toxicity studies were conducted. Local tolerance studies were performed for TAK-881 in rabbits, mini pigs, and pigs. These studies used the SC route of administration, which is the intended clinical route for TAK-881. The studies in pigs also assessed feasible infusion flow rates of TAK-881 and evaluated the effects of in-line warming of IG to a physiological temperature on infusion pressures. While in-line warming reduced the in-line pressures during infusion, it was shown that SC infusion was feasible, with and without warming, up to an infusion flow rate of 5 mL/min or 300 mL/hr/site. TAK-881 was well tolerated in the animal studies with local effects comparable to HyQvia.

IGSC, 20% with rHuPH20 has previously been administered to a limited number of humans without the use of an in-line warming device (Study 170901). In that trial, no SAEs were reported. Clinical investigation of TAK-881 with or without warming device was initiated with a phase 1 open-label trial (TAK-881-1001) to assess the tolerability and safety of TAK-881 at various infusion rates in healthy adult participants (Nagy et al., 2023). In trial TAK-881-1001, no SAEs were reported, and the final data showed that TAK-881 could be administered safely with or without a warming device. The sponsor has therefore decided to further develop TAK-881 without in-line warming in an ongoing phase 2/3 trial (TAK-881-3001).

Relevant Data of HYQVIA/HyQvia

HYQVIA/HyQvia has been approved in both the United States and the European Union for the treatment of PIDD and CIDP. The clinical program for IGI, 10% with rHuPH20 includes 13 completed interventional clinical studies in PIDD, CIDP, and healthy volunteers, and 1 completed non-interventional registry trial in women exposed to treatment before or during pregnancy (pregnancy registry). Together, these studies demonstrate the efficacy, 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 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 (up to 600 mL/site) and utilizing maximum flow rates significantly higher than those used for IV infusions.

The rate of 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 IGIV treatment, which is in agreement with published data on IGSC treatment.

The incidence of treatment-emergent rHuPH20-reactive binding antibodies was low, and 2 cases of neutralizing antibodies have been observed in participants 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 up to 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.

Refer to the IB for full details about the IP.

2.3 Summary of Benefits and Risks

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

The risks associated with dosing TAK-881 are anticipated to be similar to those previously documented in the product labels for HyQvia and CUVITRU.

An identified risk associated with TAK-881 and HyQvia has been infusion site reactions including infusion site leaking. Infusion site reactions include swelling, redness, itching, tenderness, infusion site leaking have been reported to occur following TAK-881 administration in Phase 1 study TAK-881-1001.

Potential risks with TAK-881 and HyQvia include allergic/hypersensitivity responses, altered immune response, thromboembolic events, hemolysis/hemolytic anemia, aseptic meningitis syndrome, transmissible infectious agents, spread of localized infection, renal dysfunction/failure, and drug administration error (incorrect sequence of administration of the components of TAK-881 or HyQvia).

Hypersensitivity reactions are a known risk of products derived from human plasma. Allergic manifestations may include severe, even life-threatening reactions, though the majority are mild and reversible.

Thrombotic events are a major concern with all immunoglobulin products, but the reported rate remains low and stable over the years. Thromboembolic complications are more common in patients having risk factors such as advanced age, previous thromboembolic events, immobilization, diabetes mellitus, hypertension, or dyslipidemia.

Refer to the latest version of the TAK-881 IB and the HyQvia product label for the overall benefit/risk assessment and the most current information regarding drug metabolism, PK, efficacy, and safety of TAK-881 and HyQvia.

The inclusion and exclusion criteria, screening, and safety monitoring practices employed in this protocol (that is, 12-lead ECG, vital signs, clinical laboratory tests, AE monitoring, and physical examination) are adequate to protect the participant's safety and should detect all expected TEAEs.

3.0 TRIAL OBJECTIVES AND ENDPOINTS

3.1 Primary Objective + Associated Endpoint

Table 2 Primary Objective and Associated Endpoint

Primary Objective	Primary Endpoint
To characterize the PK of TAK-881 and HyQvia following single SC administration in healthy adult participants.	Baseline-corrected AUC _{Day1-29} based on serum total IgG levels.

3.2 Primary Estimand

Table 3 Primary Estimand

Trial objective	The primary objective of the trial is to characterize the PK of TAK-881 and HyQvia following single SC administration in healthy adult participants.
Target population	Healthy adult participants.
Analysis variable	Baseline-corrected AUC _{Day1-29} based on serum total IgG levels.
Treatment	TAK-881 or HyQvia
Intercurrent events (IEs) and strategy	IEs: Any protocol deviation that may affect the reliability of the primary endpoint following the definition of the PK per-protocol analysis set (PKPPAS). Hypothetical strategy will be utilized to address IEs. The hypothetical strategy envisions that the IE would not occur under the missing completely at random (MCAR) premise.
Population level summary	Ratio of geometric means in baseline-corrected AUC _{Day1-29} between TAK-881 and HyQvia.
Estimator	Antilog of the estimator from a two-sample t-test allowing for unequal variances by using the Welch-Satterthwaite correction of degrees of freedom and corresponding two-sided 95% CI in log-transformed variables.
Estimate	Numerical result of the estimator based on data of the PKPPAS.

3.3 Secondary Objectives + Associated Endpoints

Table 4 Secondary Objectives and Associated Endpoints

Secondary Objective	Secondary Endpoint
To assess baseline-uncorrected and baseline-corrected PK exposure parameters of TAK-881 and HyQvia following single SC administration in healthy adult participants.	<p>Baseline-uncorrected PK parameters based on serum total IgG levels:</p> <ul style="list-style-type: none"> • C_{max} • t_{max} • $AUC_{Day1-29}$ <p>Baseline-corrected PK parameters based on serum total IgG levels:</p> <ul style="list-style-type: none"> • AUC_{inf} • AUC_{last} • C_{max} • t_{max} • t_{last} • $t_{1/2z}$ • CL/F • V_z/F
To assess the safety, tolerability, and immunogenicity of TAK-881 and HyQvia following single SC administration in healthy adult participants.	<p>Safety:</p> <ul style="list-style-type: none"> • Occurrence of TEAEs. <p>Tolerability:</p> <ul style="list-style-type: none"> • Occurrence of tolerability events during the infusion of IPs. <p>Immunogenicity:</p> <ul style="list-style-type: none"> • Occurrence of positive binding (defined as titer $\geq 1:160$) antibodies to rHuPH20. • Occurrence of neutralizing antibodies to rHuPH20.

4.0 TRIAL DESIGN

4.1 Overall Design

This is a phase 1, randomized, parallel, open-label, single dose, 2-arm, PK trial in healthy adult participants.

Participants will be randomized 1:1 to receive either 1.0 g/kg TAK-881 or 1.0 g/kg HyQvia SC on Day 1 according to the randomization schedule. PK sampling for measurement of serum total IgG concentrations will be performed predose and up to Day 85 postdose.

Throughout the trial, safety will be monitored by repeated clinical and laboratory evaluations.

All participants who received at least one dose of IP (including participants who terminate the trial early) will return to the CRU on Day 85 (± 3 days) for the final follow-up procedures, and to determine if any AE has occurred since the last trial visit.

4.1.1 Dose Escalation

Not applicable.

4.2 Scientific Rationale for Trial Design

4.2.1 Rationale for Trial Design

The higher IG concentration of TAK-881 (as compared to HyQvia) reduces infusion volumes by 50%, which will potentially lead to decreased infusion time and an improved experience in CIDP and PIDD patients. This phase 1 trial is being conducted to assess the pharmacokinetics, safety, and tolerability of both TAK-881 and HyQvia in healthy adult participants with a focus on evaluating the PK of TAK-881 in comparison to HyQvia after a single SC dose administration of a representative CIDP maintenance treatment dose (1.0 g/kg).

4.2.2 Rationale for Dose

Participants will receive 1.0 g/kg TAK-881 or HyQvia subcutaneously. The most commonly used IVIG regimen for maintenance therapy for CIDP is 1 g/kg every 3 weeks as detailed in the updated EAN/PNS Guidelines (Van den Bergh et al., 2021, Van den Bergh et al., 2022). The average dose of HyQvia for maintenance therapy in CIDP was 1.0 g/kg in the ADVANCE-1 randomized clinical trial (Bril et al., 2023).

4.2.3 Rationale for Endpoints

4.2.3.1 Pharmacokinetic Endpoints

The PK endpoints are standard for this type of trial.

4.2.3.2 Safety Endpoints

The key safety endpoints are typical for phase 1 trials.

4.3 Start of Trial and End of Trial

4.3.1 Definition of Beginning of the Trial

The start date of the trial is defined as the date that the first participant signs the ICF.

4.3.2 Early Trial or Site Closure

The sponsor may suspend or terminate part of the trial, or the trial in its entirety, at any time for any reason. The sponsor reserves the right to close a trial site at its sole discretion. Sites will be closed upon trial completion.

Sites may be closed by the sponsor because of failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines; inadequate or no recruitment (evaluated after a reasonable amount of time); inclusion of the total number of participants earlier than expected; or other reasons not listed herein.

A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

Please see Section 10.4, Early Site Closure or Trial Termination, for criteria and responsibilities related to early site closure or trial termination.

4.3.3 Definition of End of the Trial

The end of trial is defined as the date that the last participant completes the last scheduled procedure. If there is an unresolved AE, end date of concomitant medication, or an assessment date that is after the end of trial, the date of trial completion will be inclusive of that resolution/assessment date.

A participant is considered to have completed the trial if the participant completed dosing, did not terminate the trial early, and has completed the last scheduled procedure (the last follow up visit) shown in the Schedule of Activities (Section 1.3).

5.0 TRIAL POPULATION

The trial population will comprise of healthy adult participants. A participant is defined as enrolled upon receipt of the first dose of TAK-881 or HyQvia. Individuals who do not meet criteria for trial eligibility must not be enrolled via protocol waivers or exemptions.

5.1 Inclusion Criteria

To be eligible to participate in this trial, an individual must meet all the following criteria:

1. Healthy, adult, male or female, 18-50 years of age, inclusive, at the screening visit.
2. Female and male participants must follow protocol-specified contraception guidance as described in Section 12.1.
3. Continuous non-smoker who has not used nicotine- and tobacco-containing products for at least 3 months prior to the first dosing based on participant self-reporting.
4. BMI ≥ 18.0 and ≤ 30.0 kg/m² and body weight < 120 kg.
5. Medically healthy with no clinically significant medical history, physical examination, clinical laboratory profiles, vital signs, or ECGs, as deemed by the investigator or designee.
6. Understands the trial procedures in the ICF, is able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent to participate in the study, and is willing and able to comply with the protocol.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this trial:

1. Any current or relevant history of medical (for example, any hematological, hepatic, respiratory, cardiovascular, renal, immunologic, or neurological) or psychiatric conditions that, in the opinion of the investigator, might compromise the safety of the participant or integrity of the trial, interfere with the participant's participation in the trial, or compromise the trial objectives, or any condition that presents undue risk from the IP or procedures.
2. History or presence of alcohol or drug abuse within the past 2 years prior to dosing.
3. History or presence of suspected intolerance or hypersensitivity to the IPs, closely related compounds, or any of the stated ingredients (for example, human IG, hyaluronidase, albumin, recombinant human hyaluronidase/rHUuPH20, or any of the excipients in accordance with the investigator brochure).
4. History or presence of hypersensitivity or severe allergic reactions (for example, urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following administration of blood or blood components.

5. History or presence of:
 - clinically significant cardiac conditions, including but not limited to, uncontrolled hypertension, myocardial infarction, unstable coronary artery disease, and clinically significant arrhythmias and conduction disorders.
 - hypercoagulable conditions (for example, Protein C, Protein S, and antithrombin III deficiency), hyperviscosity syndromes, thrombotic/thromboembolic events, or venous thrombosis.
6. Presence of severe dermatitis or anatomical abnormality that would interfere with IGSC administration or endpoint assessments.
7. Presence of significant illness, as judged by the PI, within 30 days prior to dosing. Any bacterial or viral infection, as judged by the PI within 14 days prior to dosing.
8. Female participant with a positive pregnancy test at the screening visit or at check-in or who is breastfeeding.
9. Positive urine drug or alcohol results at the screening visit or check-in.
10. Confirmed systolic blood pressure >139 mmHg or <89 mmHg, or confirmed diastolic blood pressure >89 mmHg or <49 mmHg.
11. Participants will be excluded if abnormal hematology, chemistry, and other laboratory values are $>10\%$ above the ULN or $>10\%$ below the lower limit of normal except for liver function tests and absolute neutrophils. Participants will be excluded if any of the following laboratory parameters meet the criteria below:
 - Absolute neutrophil count $\leq 1.5 \times 10^9$ cells/L.
 - ALT, AST, or ALP $\geq 1.5 \times$ ULN, or total bilirubin ≥ 1.5 mg/dL.Participants will be excluded if any other laboratory values are outside the reference range and are clinically significant per investigator's judgment.
12. Positive results for HIV, HBsAg, or HCV at the screening visit. Participants with immunity to hepatitis B from either active vaccination or from previous natural infection are eligible to participate in the trial.
13. Unable to refrain from or anticipates the use of any drugs, including prescription and non-prescription medications, herbal remedies, homeopathic preparations, or vitamin supplements beginning 14 days prior to dosing. Medication listed as part of acceptable birth control methods (refer to Section 12.1), hormone replacement therapy, and thyroid hormone replacement medication (refer to Section 6.7) will be allowed.

Note: Participants should be able and willing 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 the infusion and through 72 hours after the infusion.

14. Has tattoo(s) or scarring at or near the site of infusion or any other condition (for example, anatomical abnormality or severe dermatitis) which may interfere with SC administration or infusion site examination, in the opinion of the investigator or designee.
15. Donation of blood or significant blood loss within 60 days prior to dosing.
16. Donation of blood products (for example, plasma or platelets) within 14 days prior to dosing.
17. Participants who, at time of screening, meet the criteria below:
 - Have participated in another clinical trial involving immunoglobulin products within 12 months of screening.
 - Have taken biologic agents within 12 weeks of screening
 - Have used an IP within 30 days or 5 half-lives, whichever is longer, prior to screening.
 - Have been enrolled in a clinical trial (including vaccine studies or had been vaccinated with an approved product) that, in the investigator's opinion, may impact this trial. Participants who 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 trial until the end of the follow-up period.
 - Have any substantial changes in eating habits within 3 months, as assessed by the investigator.

5.3 Lifestyle Considerations

Excluded medications, supplements, and dietary products are summarized in Sections 5.3.2 and 6.7.

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet and Fluid

Participants should be well hydrated on Day 1 prior to IP administration. Water will be allowed ad libitum at all times.

When confined, standard meals and snacks will be provided at appropriate times, except when participants are required to fast. Additional details regarding diet and fluid intake before, during, and after IP infusion will be provided in the site infusion manual.

5.3.2 Nicotine- and Tobacco-Containing and/or Cannabis Products

Nicotine- and tobacco-containing and/or cannabis products will be prohibited from 3 months prior to dosing and until the last end of trial procedures.

5.3.3 Activity

5.3.3.1 *Physical Activity*

Trial participants will remain seated or semi-reclined for the first 4 hours post dose. Participants will be allowed to rise briefly to use the restroom under supervision. Participants will then resume normal activity.

Should AEs occur at any time, participants may be placed in an appropriate position or will be permitted to lie down on their right side.

Trial participants will be instructed to refrain from strenuous physical activity that could cause muscle aches or injury, including contact sports, at any time from screening visit before admission to the trial site and during the in-house stay at the site until completion of the trial.

5.3.3.2 *Other Activities*

Participants must follow the contraceptive requirements specified in Section 12.1, as applicable.

5.4 Screen Failures

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participant identification numbers assigned to participants who do not meet eligibility criteria should not be reused.

An individual who has been designated a screen failure may be rescreened.

The decision to rescreen a participant will be made on a case-by-case basis, following discussion between the investigator or designee and the sponsor.

Participants who are screened and qualify to enroll but are not enrolled (for example, if a cohort/group is filled) may be enrolled as a participant in a subsequent group, provided their consent and screening information is within the 28-day screening window. Qualified participants outside of the 28-day screening window will be required to reconsent and complete the screening procedures again to determine if they still qualify.

6.0 IP AND CONCOMITANT THERAPY

6.1 Description of IP

Table 5 Table of Investigational Products

	TAK-881	HyQvia
Identification:	IGSC 20% with rHuPH20	IGI 10% with rHuPH20
Dose Formulation:	Solution for SC infusion	Solution for SC infusion
Dose Strength(s):	20%	10%
Route of Administration:	SC	SC
Dosing regimen:	Single dose	Single dose
Duration	Single dose on Day 1	Single dose on Day 1

IGI: Immune Globulin Infusion

6.2 Dosing and Administration

TAK-881 and HyQvia will be administered via the SC route of administration using an SC needle set. An appropriate needle length (9 to 14 mm) to accommodate the participant's body composition variability at infusion sites will be used. Please refer to the site infusion manual for guidance if a catheter leakage occurs.

The rHuPH20 solution will be administered first and then followed by IGSC or IGI using the same needle set at the same location. The maximum daily absolute dose of TAK-881 and HyQvia is 120 g. A 24-gauge SC needle set that can infuse TAK-881 and HyQvia up to 300 mL/hour/infusion site will be used.

The rHuPH20 solution will be administered SC at an initial rate of approximately 1 to 2 mL/minute/site or 60 to 120 mL/hour/site, or as tolerated, and infusion volumes of up to a maximum of 30 mL/site. The rHuPH20 volume is not included in the total volume per infusion site.

The times of the beginning and the end of infusion will be recorded. Dosing interruptions will be recorded.

Koru 24 G HIgH Flo Subcutaneous Safety Needle Sets (Koru Needle Sets) are investigational needle sets preferred for both TAK-881 and HyQvia administration. The Koru Needle Sets infuse up to 300 mL/hour/ infusion site, thereby enabling less time to safely complete an infusion compared with 90 degree bent needle sets currently used in standard of care administration systems with HyQvia. Refer to [Table 6](#) below for additional details regarding the Koru investigational needle set to be used for all infusions.

Additional instructions for IP administration will be provided in the site infusion manual.

Table 6 Trial Interventions Administered: Device (applicable only in the US)

Intervention Name	Investigational SC needle sets
Intervention Description	The single-use only SC needle set is used to deliver TAK-881 and HyQvia to the target depth below the skin surface. One needle set (single or bifurcated) is used per infusion.
Materials	Needle material: Stainless steel Needle butterfly wings material: Polypropylene
Type	Prolonged contact, not implantable, not active
Regulatory Class	US: Class II EU: Rule 7, Class IIa
Clearance	The device is not cleared by regulatory authorities outside of the EU.
Route of Administration	SC
Use	Experimental delivery of TAK-881 and HyQvia
Investigational/Noninvestigational/Ancillary	Investigational
Sourcing	Koru Medical Systems Provided centrally by Takeda
Packaging and Labeling	Each single use device will be packaged in a sterile pouch/bag. Each sterile pouch/bag will be contained within a carton. Each pouch/bag and each carton will be labeled according to the country's regulatory requirements.
Needle Lengths	9, 12, and 14 mm needle lengths
Needle Set Configuration	Single or bifurcated
Additional Information	Device IB, IFU, Pharmacy Manual, Site Infusion Manual, and Instructional Video

EU: European Union; IB: investigator's brochure; IFU: Instructions for Use; SC=subcutaneous;
US: United States.

6.2.1 IP Dose Modification

The dose of the IP administered to any participant should not be modified. If necessary, a participant may be discontinued for the reasons described in Section 7.0.

6.3 Overdose

In this trial, an overdose is defined as a known deliberate or accidental administration of investigational drug, to a trial participant, at a dose above that which is assigned to that individual participant according to the trial protocol. It is up to the Investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the sponsor.

AEs associated with an overdose will be documented on AE CRF(s) according to Section 8.4.

SAEs of overdose should be reported according to the procedure outlined in Section 8.4.6.

In the event of drug overdose, the participant should be treated symptomatically.

6.4 Preparation, Handling, Storage, and Accountability

6.4.1 Preparation of IP

The Sponsor will supply sufficient quantities of TAK-881 and HyQvia to allow completion of this trial. The lot numbers and expiration dates (where available) of the IPs supplied will be recorded in the Clinical Study Report.

Instructions for the preparation of IPs will be provided in the pharmacy manual.

6.4.2 IP Labeling

IP containers will be affixed with a clinical label in accordance with local regulatory requirements. Please reference the pharmacy manual for details.

6.4.3 Handling and Storage of IP

IP must be stored in a secure, limited-access location under the storage conditions specified on the label and must remain in the original container until dispensed. The temperature excursion information can be found in the pharmacy manual or in the referenced compounding manual when applicable. Receipt and dispensing of IP must be recorded by authorized personnel at the trial site.

6.4.4 Accountability and Destruction of Sponsor-Supplied IPs

Records will be made of the receipt and dispensing of the IP supplied. At the conclusion of the trial, any unused IPs will be retained by Celerion, returned to the sponsor or designee, or destroyed, as per sponsor instructions. Any remaining supplies that were purchased by the Celerion will be destroyed, if appropriate. If no supplies remain, this fact will be documented in the pharmacy IP accountability records.

6.5 Randomization and Blinding

6.5.1 IP Blinding

This is an open-label trial.

6.5.2 Randomization

Each participant will be assigned a unique identification number upon the screening visit. Participants who complete the trial screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number, different from the screening number, and will receive the corresponding product, according to a randomization schedule.

Participants will be randomized in a 1:1 ratio to receive either TAK-881 or HyQvia.

6.6 IP Compliance

Before and after the SC infusion, the qualified designee will visually inspect the syringe to ensure that the participant has received the entire dose. In the case of an incomplete dosing (for example, large droplet of IP on the surface of the skin) as deemed by the investigator and/or sponsor or sponsor's designee, the participant may be withdrawn.

6.7 Concomitant Therapy

All concomitant medications, supplements, therapies, and procedures will be recorded as described in Section 8.1.1.

If deviations from the prohibited and permitted therapies detailed in Sections 6.7.1 and 6.7.2 occur, the investigator or designee, in consultation with the sponsor, will decide on a case-by-case basis whether the participant may continue participation in the trial.

6.7.1 Prohibited Concomitant Therapy

Refer to Section 5.2 for restriction on concomitant therapies prior to and during the trial.

6.7.2 Permitted Concomitant Therapy

Participants should refrain from taking any prescription and non-prescription medications, herbal remedies, homeopathic preparations, or vitamin supplements during the trial.

Birth control methods are allowed as described in Section 12.0.

Hormone replacement therapy and thyroid hormone replacement medication will be allowed if the participant has been on the same stable dose for at least 3 months prior to dosing.

Administration of other concomitant medications will be permitted for the treatment of AEs, only when deemed necessary for the safety and well-being of the participant and when agreed upon by the investigator and sponsor.

7.0 DISCONTINUATION OF IP AND PARTICIPANT WITHDRAWAL FROM TRIAL

7.1 Discontinuation of IP

Discontinuation of IP for a participant occurs when IP administration is stopped earlier than scheduled in the protocol. If IP administration is permanently discontinued, the participant should undergo all procedures scheduled for early termination as outlined in the SoA (Section 1.3). The primary reason for IP discontinuation will be recorded on the (e)CRF.

Treatment with IP may be discontinued for any of the following reasons:

- Withdrawal by participant.
- Protocol violation.

Temporary pause of the intervention if:

- The participant experiences Grade ≥ 2 AE related to the infusion as defined by NCI CTCAE v.5.0. In these cases, the infusion will be interrupted briefly, and the infusion rate will be reduced to the rate immediately below that at which no Grade 2 infusion rate-related signs and symptoms or Grade 1 or Grade 2 isolated urticaria occurred.
- The participant develops Grade 1 urticaria (urticarial lesions covering $<10\%$ BSA; topical intervention indicated) or Grade 2 urticaria (urticarial lesions covering $10\%-30\%$ BSA; oral intervention indicated) as defined by NCI CTCAE v5.0, without any other signs or symptoms from another organ system. In these cases, the participant will be observed for approximately 1 hour while vital signs are being monitored. If the urticaria resolves on its own or with 1 dose of oral antihistamine without any other intervention, the participant is stable, and does not have any additional symptoms, the infusion rate will be reduced to the rate immediately below that at which no Grade 1 or Grade 2 urticaria occurred.

Permanent discontinuation of the intervention for a participant if:

- Any Grade 3 or higher SAR graded by the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (Cox et al., 2017) or anaphylaxis defined by the NIAID and the FAAN (Sampson et al., 2006)
- Any grade of urticaria returns after the interventions related to Grade 1 or Grade 2 isolated urticaria
- Any Grade 3 or higher urticaria
- Any Grade 3 or higher AE (including infusion related reactions)
- AE that would impose an unacceptable risk to the participant's health, or due to which the participant is unwilling to continue.

7.2 Participant Withdrawal from the Trial

Participants may withdraw from the trial at any time and for any reason without prejudice to their future medical care by the physician or at the institution; alternatively, they may be withdrawn at any time at the discretion of the investigator or sponsor (for example, in the interest of participant safety). The investigator is encouraged to discuss withdrawal of a participant with the medical monitor when possible.

The investigator may discontinue a participant's trial participation at any time during the trial when the participant meets the trial termination criteria described in Section 7.1.

At the time of discontinuing from the trial, if possible, an early termination visit should be conducted, as shown in the SoA (Section 1.3). The primary criterion for termination must be recorded by the investigator.

- Difficulties in blood collection
- Positive drug or alcohol test
- Pregnancy: as described in Section 12.1.4.
- Lost to follow-up.
- Trial terminated by sponsor.
- Withdrawal by participant.

See the SoA (Section 1.3) for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Trial Participant Replacement

Not applicable (participants will not be replaced).

7.3 Lost to Follow-up

If a participant fails to return to the site for a required trial visit or for a follow-up contact, the investigator or designee must make every effort to regain contact with the participant as per site standard procedures. These contact attempts should be documented in the participant's medical record. If these attempts fail, the participant will be considered lost to follow-up.

The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

7.4 Trial and Dose Stopping Rules

The investigator and/or the sponsor may pause further dosing for safety review or discontinue the trial (after review and unanimous decision by the investigator, medical monitor, and sponsor safety physician) if any of the following stopping rules are met:

- Three or more participants with Grade 3 or higher SAR graded by the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (Cox et al., 2017) or anaphylaxis defined by NIAID/FAAN (Sampson et al., 2006).
- Three or more participants with Grade 3 treatment-emergent adverse events with the same term as rated by the NCI CTCAE v5.0.
- One or more participants experience any treatment-emergent Grade 5 AE (death), or 2 or more treatment-emergent Grade 4 AEs (life-threatening consequences and urgent intervention indicated) with the same term, as rated by the NCI CTCAE v5.0.

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8.0 TRIAL ASSESSMENTS AND PROCEDURES

Planned time points for all assessments and procedures are provided in the SoA (Section 1.3). For each procedure, participants are to be assessed by the same investigator or site personnel whenever possible. Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

For this trial, collection of blood samples for IgG levels is the critical parameter and needs to be collected as close to the exact time point as possible.

8.1 Screening/Baseline Assessments and Procedures

Written or electronic informed consent must be obtained (signed and dated) before any trial assessments and procedures can be performed, as described in Section 10.2. All screening assessments and procedures are to be performed by the investigator or a qualified designee.

8.1.1 Demographics, Medical History, and Medication History

8.1.1.1 *Demographics*

Participant demographic information will be collected before the participant receives the first dose of IP.

Demographic information to be obtained will include date of birth, sex, race, ethnicity, height, baseline weight, and history of tobacco use.

8.1.1.2 *Medical History*

Medical history, including concurrent medical conditions, will be collected and recorded in the participant's source documents and in the (e)CRF. Medical history to be obtained will include significant conditions, per the site's standard of care and appropriate clinical judgment, that resolved before the participant signed the ICF. Ongoing conditions are considered concurrent medical conditions.

8.1.1.3 *Prior and Concomitant Treatments/Medications*

Prior and concomitant treatments and medications will be collected and recorded in the participant's source document.

Prior medications/treatments are defined as those that were stopped prior to dosing.

Concomitant medications/treatments are defined as those given in addition to the IP between the dose of IP and the end of the follow-up period, inclusive, as detailed in Section 6.7.

Concomitant medications may be prescribed by a physician or obtained by the participant over the counter following approval by the investigator or designee. Concomitant medication is not provided by the sponsor.

At each trial visit, participants will be asked whether they have taken any medication or received any other IP.

The sponsor medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

8.2 Confinement

Participants will be housed on Day -1, at the time indicated by the site, until completion of trial procedures on Day 8. Participants will return for trial procedures as outlined in the SoA (Section 1.3).

A participant may be requested to remain at the site for longer at the discretion of the investigator or designee, in agreement with the sponsor.

8.3 Safety Assessments and Procedures

The SoA (Section 1.3) summarizes the safety assessments and procedures to be performed at each visit. Additional evaluations/testing may be deemed necessary by the investigator or designee and/or the sponsor for reasons related to trial participant's safety.

8.3.1 Physical Examination

A physical examination will be performed per standard of care at the times specified in the SoA (Section 1.3). Additional physical examinations may be performed at other times, if deemed necessary by the investigator or designee.

A complete physical examination will include the following organ systems: 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. An abbreviated physical examination will include general appearance, head and neck, assessment of infusion site(s), and skin. Additional organ systems may be assessed per the investigator's judgement.

8.3.2 Height, Weight, and BMI

Body height (cm) and weight (kg) will be recorded as outlined in the SoA (Section 1.3). BMI will be calculated on the basis of the measured height and weight.

8.3.3 Vital Signs

Body temperature, respiratory rate, blood pressure and pulse rate will be measured as outlined in the SoA (Section 1.3). Additional vital signs may be taken at any other times, if deemed necessary by the investigator or designee.

Blood pressure and pulse rate measurements will be performed with participants in a seated position, except when they are supine or semi-reclined because of trial procedures and/or AEs (such as nausea, dizziness) or if deemed necessary by the Investigator or designee.

Vital signs will be measured within 30 minutes before Day 1 dosing for the predose time point. Between start and end of infusion, vital signs will be performed every 30 minutes within ± 5 minutes of the scheduled time point. When scheduled post infusion, vital signs will be performed within ± 15 minutes of the scheduled time point.

8.3.4 ECG Procedure

8.3.4.1 Screening and Safety ECGs

A single 12-lead ECG will be performed as outlined in the SoA (Section 1.3). Additional ECGs may be taken at any other times if deemed necessary by the investigator or designee.

ECGs will be performed after participants have been in a supine position for at least 5 minutes at rest. All ECG tracings will be reviewed by the investigator or designee.

For abnormal and clinically significant results, the investigator will use clinical judgment regarding further monitoring and management.

8.3.5 Clinical Laboratory Assessments

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

All laboratory samples will be collected in accordance with acceptable laboratory procedures.

Hematology

The hematology assessments will include the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	Red cell distribution width
Mean corpuscular volume	Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration	

Coagulation

Coagulation will consist of the following tests:

Prothrombin time	Activated partial thromboplastin time
International normalized ratio	

Chemistry

Serum chemistry tests will be performed after at least a 12-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 12 hours before the serum chemistry sample is taken.

The chemistry assessments will include the following tests:

Albumin	Alkaline phosphatase
ALT	AST
Blood urea nitrogen	Calcium
Carbon dioxide	Chloride
Creatinine	Glucose
γ -glutamyl transferase	Sodium
Potassium	Bilirubin (total, direct and indirect)
Lactate dehydrogenase	Uric acid
Protein (total)	Magnesium
Lipid profile (triglycerides, total cholesterol, LDL, HDL)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Urinalysis

Urinalysis will consist of the following tests:

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

^a If urinalysis is positive for protein, blood, nitrite, and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed. If $\geq 2+$ protein on urine dipstick, then collect spot urine sample to calculate UPCR or collect 24 hour urine.

Hemolytic panel

Hemolytic panel will consist of the following tests:

Hemoglobin (Hgb)	Plasma-free (unbound) hemoglobin ^a
Lactate dehydrogenase (LDH)	Serum direct anti-globulin (direct Coombs) test ^b
Serum haptoglobin	Reticulocyte count
Urine hemosiderin ^a	

^a Laboratory results may have a longer turnaround time and may not be available prior to dosing.

^b Antibody elution to be performed if direct Coombs test is positive.

NOTE: The laboratory results obtained from Day -1 will serve as the baseline values. In case of absence of a Day -1 result for any reason, the 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 trial, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia. Any LDH test result of $2 \times$ ULN or greater will trigger analysis of the sample for LDH isoenzymes. It is not necessary to repeat the hemolytic panel if the drop of ≥ 1 g/dL Hgb remains constant 72 hours after the full dose of the IP or after an unscheduled visit blood draw, unless it drops further. It is recommended that the investigator uses sound medical judgement in assessing participants with an unexplained decrease in serum Hgb as other medical conditions besides hemolysis can cause this, and therefore may require additional investigations.

8.3.6 Additional Diagnostic Laboratory Tests

Additional diagnostic laboratory tests include the following:

HIV test
HBsAg/ HBsAb/ HBcAb
HCV (if antibody positive, confirm RNA negative)
Urine alcohol screen
Serum pregnancy test (for females only)
FSH (for menopausal or peri-menopausal women)
COVID-19 ^a

^a COVID-19 screen will be performed only as per the investigator or designee discretion should participant present symptoms.

The urine drug screening assessment will include the following tests:

Amphetamines	Opiates (includes morphine, heroin [diacetylmorphine], codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and hydromorphone)
Barbiturates	Oxycodone/oxymorphone
	Methadone
Benzodiazepines	Phencyclidine
Buprenorphine/metabolite	3,4-methylenedioxy-methamphetamine
Cocaine	
Cannabinoids	

8.3.7 Infusion Site Reaction Assessment

Infusion sites will be evaluated for any potential systemic effects or local infusion site events (such as infusion site extravasation, erythema, pain, or edema) at the time points outlined in the SoA (Section 1.3) and as clinically indicated. Allergic reactions related to infusion should be reported as infusion related reaction. Participants 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.

Assessment of Severity of Infusion Site-related Adverse Events:

Infusion site-related AEs, except catheter leakage, must be graded under the CTCAE term of general disorders and administration site conditions, other, specify to capture details of the infusion site-related AEs. The following CTCAE terms, but not limited to, can be considered as infusion site-related AEs: infusion site swelling, infusion site bruising, infusion site discomfort, infusion site erythema, infusion site pruritus, infusion site hematoma, infusion site hemorrhage, infusion site discoloration, infusion site induration, infusion site irritation, infusion site mass, infusion site pain etc.

Catheter leakage at an infusion site will be evaluated by the investigator/designee based on the following scoring system:

Score 1: Minimal leakage (that is, transient/barely observable leakage). Score 1 will be considered equivalent to Grade 1 of CTCAE v5.0 evaluation scale.

Score 2: Readily observable leakage (that is, 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.

Please note: Infusion-related systemic AEs (for example, infusion-related headache or chills or fever or malaise or nausea) must be graded under the specific CTCAE term in the dictionary. Infusion-related systemic AEs excluding SARs that cannot be found in the dictionary must be graded under the term of infusion-related reaction.

Assessment of SARs:

The severity of SARs will be assessed by the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (Cox et al., 2017) and Clinical Criteria for Diagnosing Anaphylaxis (Sampson et al., 2006).

8.4 Adverse Events and Serious Adverse Events

A quick reference for safety reporting is shown in [Table 7](#).

Table 7 Safety Reporting Timeframes

Safety Event	How to Report Event to Safety	Reporting Timelines to Sponsor Time Since Awareness of Event
SAEs	Complete and send paper SAE form to Safety.	<u>Within 24 hours</u>
AESIs	If event is serious complete and send paper SAE form to Safety.	<u>Within 24 hours</u>
Pregnancy	Complete and submit paper pregnancy form	<u>Within 24 hours</u>
SSR	Complete and send paper SSR form to Safety.	<u>Within 7 calendar days</u>

8.4.1 Definitions of AE and SAE

8.4.1.1 AE Definition

An AE is any untoward medical occurrence in a clinical trial participant, temporally associated with the use of the IP, whether or not the occurrence is considered related to the IP.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the IP.

An untoward finding generally may necessitate therapeutic intervention, require an invasive diagnostic procedure, or require discontinuation or a change in dose of IP or a concomitant medication. (Repeated or additional noninvasive testing [for example, laboratory or ECG retests] for verification, evaluation, or monitoring of an abnormality is not considered a therapeutic intervention.)

Events Meeting the AE Definition:

- New condition detected or diagnosed after the use of the study intervention(s), even though it may have been present before the start of the study.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency or intensity of the condition.
- Event that is of greater intensity, frequency, or duration than expected for the individual participant or an event with a reasonable possibility that it was related to the study intervention.
- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, physical examinations, vital signs measurements) that are clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease), including those that worsen from baseline (defined as the result/assessment before the first dose of study drug).

Events NOT Meeting the AE Definition:

- Situations in which an untoward medical occurrence did not occur (for example, preplanned or elective surgery).
- Presence or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Cases of overdose with any medication without manifested side effects.

Pretreatment Event Definition:

A pretreatment event is any untoward medical occurrence in a participant who has signed informed consent to participate in a trial but before administration of any trial intervention; it does not necessarily have to have a causal relationship with trial intervention.

Appendix 14.0 provides additional details and clarifications regarding AEs related to the medical device.

8.4.1.2 SAE Definition

SAEs are events that meet the AE definition described in Section 8.4.1.1 AND the criteria for seriousness below.

An SAE is defined as any untoward medical occurrence that meets 1 or more of the criteria listed below:

- Results in death.
- Is life threatening.

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

- Other situations (medically significant event):
 - Is an important medical event.
 - May require intervention to prevent one of the outcomes listed above.
 - May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
 - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
 - Is a suspected transmission of any infectious agent via an authorized medicinal product.
 - ALT/AST $\geq 3 \times$ ULN and total bilirubin $> 2 \times$ ULN or INR $> 1.5 \times$ ULN. Please also contact the medical monitor and Takeda trial clinician within 24 hours and follow the additional monitoring, evaluation, and follow-up recommendations in Section 8.4.5.

8.4.2 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from the signing of the ICF until the last follow-up visit, at the time points specified in the SoA (Section 1.3).

SAEs will be collected and reported to the sponsor medical monitor and Takeda Global Pharmacovigilance department or designee from the signing of the ICF through the last follow-up visit and recorded in the (e)CRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es).

8.4.3 Identifying AEs and SAEs

The investigator and any qualified designees are responsible for identifying events that meet the definition of an AE or SAE.

AEs will be assessed at the frequency shown in the SoA (Section 1.3) using open questions asked of the participant by the investigator or trial personnel. AEs may also be spontaneously reported at any time or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE.

8.4.4 Recording of AEs and SAEs

8.4.4.1 *Recording of AEs*

All AEs will be recorded on the appropriate page of the (e)CRF. Each reported AE should represent a single diagnosis, if the diagnosis is known. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs UNLESS the diagnosis is unknown. Worsening medical conditions, signs or symptoms present prior to initiation of IP, must be recorded as new AEs. For example, if a participant reports mild intermittent dyspepsia prior to initiation of dosing with the IP, and the dyspepsia becomes severe and more frequent after first dose of IP, a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source.

For both serious and nonserious AEs, the investigator must determine:

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the National Cancer Institute - CTCAE, version 5.0, dated 27 November 2017 ([National Cancer Institute, 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 noninvasive 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.

Relationship (that is, causality) of the event to IP administration will be determined by the investigator responding yes (related) or no (not related) to this question: Is there a reasonable possibility that the AE is associated with the IP?

The investigator must assess the relationship to both IMPs and each occurrence of each AE/SAE based on the criteria below:

Related: An AE that follows a reasonable temporal sequence from administration of the IMPs (including the course after withdrawal of the intervention), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications, and concurrent treatments, may also be responsible. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of the IMPs and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

The investigator will also consult the IB and/or product information, for marketed products, in their assessment.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

Action Taken

The investigator must make note of the action taken concerning the IP:

- Dose not changed.
- Dose increased
- Dose reduced
- Drug infusion interrupted
- Drug withdrawn.
- Infusion rate reduced.
- Not applicable: a study drug was stopped for a reason other than the particular AE (for example, the study has been terminated, the participant died, dosing with study drug was already stopped before the onset of the AE).

For any AE that was ongoing at the time of a participant's death, the study intervention action should reflect the most recent action that had been taken at the time of death (for example, drug interrupted, reduced, withdrawn). If the participant had never received the study intervention, the action taken should be recorded as "not applicable." The study intervention action of "withdrawn" should not be selected solely as a result of the participant's death.

Outcome

The investigator must make note of the outcome of any AEs that occur during the course of the trial:

- Recovered/resolved: The participant returned to first assessment status with respect to the AE.
- Recovered/resolved with sequelae: The participant recovered from an acute AE but was left with permanent/significant impairment.
- Recovering/resolving: The intensity has decreased by 1 or more stages; the diagnosis or signs/symptoms have almost disappeared; the abnormal laboratory value has improved, but has not returned to the normal range or to baseline; the participant died from a cause other than this particular AE.
- Not recovered/not resolved: There is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms, or laboratory value on the last day of the observed study period is now worse than when it started; is an irreversible congenital anomaly; the participant died from another cause.
- Fatal: The AE is considered to be the cause of death or contributed to the participant's death.
- Unknown: The course of the AE cannot be followed up due to hospital change or residence change at the end of the participant's participation in the study.

8.4.4.2 *Recording of SAEs*

All SAEs will be recorded in the (e)CRF within 24 hours of awareness.

In addition, a paper SAE form must be transmitted to Takeda Safety. A sample of the paper-based SAE form and processing directions will be provided by the sponsor. Information in the SAE report or form must be consistent with the data provided on the (e)CRF.

8.4.5 **Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts.

Regardless of causality, all AEs must be monitored until the last follow-up visit or until the participant is lost to follow-up as defined in Section 7.3.

SAEs must be monitored until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

If information not available at the time of the first SAE report becomes available at a later date, then the investigator will transmit a follow-up paper-based SAE form or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (for example, ECGs, laboratory test results, discharge summary, postmortem results) should be sent to the addressee, if requested.

8.4.6 Reporting of SAEs

Regardless of causality, SAEs must be reported by the investigator to Takeda Global Pharmacovigilance or designee within 24 hours of becoming aware of the event.

A sample of the paper-based SAE form and processing directions are provided separately. Follow-up SAE reports will follow the same procedure and time course.

8.4.7 Regulatory Reporting Requirements for SAEs

All SAEs must be recorded and reported to the sponsor or designee immediately via the procedure described in Section 8.4.4. Under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IP under clinical investigation are met. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and product labels and will notify the IRB, if appropriate, according to local requirements.

The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of the IP or that would be sufficient to consider changes in the IP's administration or in the overall conduct of the trial. The investigator also will forward a copy of all expedited reports to his or her IRB in accordance with national regulations.

8.4.8 Serious and Unexpected Adverse Reaction Reporting

The sponsor will be responsible for reporting all SUSARs to regulatory authorities, investigators, and IRBs, as applicable, in accordance with national regulations in the countries where the trial is conducted.

Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations.

8.4.9 Adverse Events of Special Interest

An AESI (serious or nonserious) is one of the scientific and medical concerns specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

The following are AESIs:

- Allergy
- Catheter leakage
- Thromboembolic events

AESIs must be recorded as AEs in the (e)CRF.

All AESIs should be reported to the sponsor within 24 hours. All serious AESIs will also be reported into the safety database as described in Section [8.4.4.2](#).

8.4.10 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Product complaints could include suspicion that an IP has been counterfeited.

Individuals who identify a potential product complaint situation should immediately report this to the sponsor using the Clinical Trial Material Complaint Form and the contact information provided therein.

Product complaints and medication errors in and of themselves are not AEs. However, AEs or SAEs resulting from a product complaint should be reported.

8.4.11 Special Situation Reporting

Abuse, misuse, medication error, overdose and other uses not foreseen in the protocol must be reported to sponsor within 7 days of awareness on a paper Special Situation Reporting form.

Definitions:

- Abuse: Persistent or sporadic, intentional excessive use of medicinal products that is accompanied by harmful physical or psychological effects.
- Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the prescribed or authorized dose, route of administration, and/or the indications(s) or within the legal status of its supply.

- Medication error: An unintentional error in the drug treatment process (prescribing, dispensing or administration, including incorrect dose or poor-quality administration) of a medicinal product while in the control of a health care provider, patient, or consumer, which leads to harm or has the potential to lead to harm.
- Overdose: An overdose is defined as a known, deliberate, or accidental administration of trial intervention to a trial participant at doses above that is assigned to that individual participant according to the trial protocol.

8.5 Pharmacokinetics and Immunogenicity

Instructions for sample collection, processing, and shipping will be provided in the Sample Handling Instructions.

Primary specimen collection parameters are provided in [Table 8](#).

Sample retention is described in [Section 13.0](#). When future use of samples is permitted, refer to [Section 13.2](#) for further details.

Table 8 Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Serum sample for IgG PK	Blood	Serum	Serum sample for PK analysis	Mandatory
Plasma sample for ADA	Blood	Plasma	Plasma sample for ADA analysis	Mandatory

ADA: antidrug antibody; IgG: Immunoglobulin G; PK: pharmacokinetic(s).

8.5.1 Pharmacokinetics

8.5.1.1 Pharmacokinetic Sample Collection

Serum PK samples will be collected at the specified time points delineated in the Schedule of Activities ([Section 1.3](#)).

8.5.1.2 Pharmacokinetic Sample Analysis

Samples from all participants will be assayed even if the participants do not complete the trial.

Samples will be analyzed for serum concentrations of total IgG using validated bioanalytical methods.

8.5.1.3 Pharmacokinetic Parameters

The following PK parameters will be calculated from serum concentrations of total IgG, unless otherwise specified:

Symbol/Term	Definition
AUC _{Day1-29}	Area under the concentration-time curve from the Day 1 to Day 29
AUC _{last}	Area under the concentration-time curve from Day 1 to time of the last measurable concentration
AUC _{inf}	Area under the concentration-time curve from Day 1 to infinity
C _{max}	Maximum observed concentration after dose administration
CL/F	Apparent clearance
t _{1/2z}	Terminal half-life
t _{last}	Time of last measurable concentration
t _{max}	Time to C _{max}
V _z /F	Apparent volume of distribution

Additional PK parameters may be calculated as appropriate. Additional details will be provided in the CPAP.

8.5.2 Immunogenicity

Samples for immunogenicity assessments will be collected at the specified time points delineated in the Schedule of Activities (Section 1.3).

All participants 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). Post dose samples with antibody titers $\geq 1:160$ will be analyzed for the presence of neutralizing-ADA using a validated assay based on neutralization of rHuPH20 activity.

8.5.3 Additional Immunology Assessments

At baseline (Day -1), samples will be collected for the following tests to be conducted: CH50, C3, C4, CIC Raji cell assay.

Participants who have (a) anti-rHuPH20 antibody titers of $\geq 1:160$ which are elevated from the participant's baseline titers, and/or (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 CRU as soon as possible to undergo additional immunology assessments. Refer to the Schedule of Activities (Section 1.3) for additional information regarding the required tests.

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

8.6 Blood Volume Drawn for Trial Assessments

Total blood volumes for each participant will not exceed 550 mL following current National Institutes of Health guidance (Policy and Communications Bulletin, Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center. M95-9 (rev.), 05 June 2009).

9.0 STATISTICAL CONSIDERATIONS

A SAP will be prepared and finalized before database lock. The SAP will provide further details regarding the definition of analysis variables and the statistical analysis methodology to address all trial objectives.

9.1 Analysis Sets

The following analysis sets are specified for this trial:

SAS: The SAS will consist of all participants who received any amount of TAK-881 or HyQvia. Analysis will be performed according to the actual treatment received.

PKFAS: The PKFAS is a subset of the SAS and will consist of all participants with an evaluable PK profile. Analysis will be performed according to the actual treatment received.

In order to be considered an evaluable PK profile, the following minimum data requirements must be met:

- Measurable IgG at baseline;
- At least 6 PK samples collected during confinement (Day 1 – Day 8);
- Day 15 or Day 18 PK sample;
- Day 22 or Day 25 PK sample;
- Day 29 PK sample

PKPPAS: The PKPPAS is a subset of the PKFAS and will consist of all participants who have no protocol violations that may affect the reliability of the total IgG PK profiles. Analysis will be performed according to the actual treatment received.

The analysis performed for PK parameters will be presented for the PKFAS and the PKPPAS. Safety, tolerability, and immunogenicity endpoints will be presented for the SAS.

9.2 General Approach

The following conventions will be applied to present the analyses results, unless otherwise specified:

- **Descriptive Statistics:**
 - For continuous data (age, height, weight, BMI, clinical laboratory data, vital signs, ECGs, etc.): n, mean, standard deviation, median, minimum, and maximum.
 - For PK: n, arithmetic mean, standard deviation, %CV, standard error of the mean, minimum, median, maximum, geometric mean, and geometric %CV.
 - For categorical data: frequency counts and percentages in each class of the categorical variable.

9.3 PK Analyses

Statistical analysis of PK data will be based on the PKFAS and PKPPAS. Additional details will be provided in the SAP and CPAP.

All PK analyses will use the actual sampling times. If actual sampling times are not available, nominal times may be used for analyses. PK parameters for TAK-881 and HyQvia will be calculated using NCA based on total IgG levels for participants with evaluable PK profiles.

Primary Endpoint:

Baseline-corrected $AUC_{Day1-29}$ will be log-transformed prior to analysis. The difference in means between TAK-881 and HyQvia and the corresponding two-sided 95% CI on the log-transformed scale will be obtained by a two-sample t-test allowing for unequal variances by using the Welch-Satterthwaite correction of degrees of freedom. Results will be back-transformed from the logarithmic scale to obtain the ratio of geometric means. The ratio of geometric means (TAK-881/HyQvia) will be presented together with a corresponding two-sided 95% CI. In addition, the geometric means and corresponding two-sided 95% CIs of baseline-corrected $AUC_{Day1-29}$ will be presented separately for TAK-881 and HyQvia.

Handling of IEs of the Primary Estimand:

IEs represent events that affect the interpretation of the analysis variable collected after the IE has occurred. The estimand framework requires strategies to define how these events are addressed in the assessment of the trial objective.

IEs are defined as protocol deviations that may affect the reliability of the primary endpoint following the definition of the PKPPAS. A primary endpoint (baseline-corrected $AUC_{Day1-29}$) collected after an IE occurred will be excluded from the analysis based on the PKPPAS.

The hypothetical strategy envisions that IEs would not occur under the MCAR premise (the probability of missing baseline-corrected $AUC_{Day1-29}$ is the same for all participants). The hypothetical strategy utilizes a complete case analysis (that is, baseline-corrected $AUC_{Day1-29}$ collected after an IE occurred will be excluded from the analysis based on the PKPPAS) which is unbiased under the MCAR premise.

Secondary Endpoints:

Secondary PK parameters (baseline-corrected [C_{max} , AUC_{inf} and AUC_{last}] and baseline-uncorrected [C_{max} and $AUC_{Day1-29}$]) will be log-transformed prior to analysis. Means and corresponding two-sided 95% CIs on the log-transformed scale for TAK-881 and HyQvia will be obtained by one-sample t-tests. Results will be back-transformed from the logarithmic scale. The geometric means and corresponding two-sided 95% CIs will be presented separately for TAK-881 and HyQvia. Baseline-corrected t_{max} , t_{last} , $t_{1/2z}$, CL/F, and V_z/F will be summarized descriptively.

9.4 Safety Analyses

All safety analyses will be based on the SAS. Dosing dates and times will be listed by participant.

TEAEs will be tabulated. The remaining quantitative safety data as well as the difference from baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

9.4.1 AEs

AEs will be coded using the most current version of MedDRA[®] available at Celerion and summarized using descriptive statistics.

TEAEs are defined as AEs that started at or after the initiation of the first administration of TAK-881 or HyQvia or any adverse event already present that worsens in either intensity or frequency following exposure to TAK-881 or HyQvia.

The severity of AEs (except SARs) will be assessed by the investigator using the NCI CTCAE, version 5.0, consisting of 5 grades:

- Grade 1: mild.
- Grade 2: moderate.
- Grade 3: severe or medically significant but not immediately life-threatening.
- Grade 4: life-threatening consequences.
- Grade 5: death related to AE.

The severity of SARs will be assessed by the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (Cox et al., 2017) and Clinical Criteria for Diagnosing Anaphylaxis (Sampson et al., 2006).

The number and percentage of participants with TEAEs and the number of TEAEs will be summarized by treatment (TAK-881 or HyQvia) using the following categories:

- Any TEAE.
- Serious TEAEs.
- TEAEs considered related to TAK-881 or HyQvia.
- Local TEAEs.
- Systemic TEAEs.
- Temporally associated TEAEs within 72 hours.
- TEAEs by maximum severity (NCI CTCAE grades 1-5).
- TEAEs leading to study discontinuation.
- TEAEs of special interest (allergy, catheter leakage, and thromboembolic events).

Tolerability:

For each treatment (TAK-881 or HyQvia), the number and percentage of participants with infusion withdrawals, interruptions, and infusion rate reductions due to TEAEs as well as the number of infusion withdrawals, interruptions, and infusion rate reductions due to TEAEs will be presented.

9.4.2 Clinical Laboratory Evaluation

Clinical laboratory results will be summarized using descriptive statistics and a shift table describing out of normal range shifts will be provided.

Individual results meeting MAVs criteria for safety clinical laboratory assessments will be listed and summarized. More details will be provided in the SAP.

9.4.3 Vital Signs

Vital signs assessments will be summarized using descriptive statistics.

Vital signs results meeting MAVs criteria for vital signs assessments will be listed and summarized. More details will be provided in the SAP.

9.4.4 ECG

ECGs will be summarized using descriptive statistics.

ECG results meeting MAVs criteria for safety ECGs will be listed and summarized. More details will be provided in the SAP.

9.4.5 Medical History

Medical history, and concurrent conditions will be coded using the MedDRA[®] and concomitant medications will be coded using the WHO drug dictionary and will be listed by participant.

9.4.6 Analysis of Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics data (including but not limited to age, sex, baseline weight, height, and BMI) will be listed and summarized using descriptive statistics. More details will be provided in the SAP.

9.5 Immunogenicity Analysis

Immunogenicity data will be listed for all participants in the safety analysis set and will be summarized using descriptive statistics. Positive binding (defined as titer $\geq 1:160$) and neutralizing antibodies to rHuPH20 will be flagged in the individual listings and summarized separately. More details will be provided in the SAP.

9.6 Interim Analysis and Criteria for Early Termination

Not applicable.

9.7 Sample Size Determination

This trial is not designed for statistical hypothesis testing.

Assuming a total variability of 25%, the planned total sample size of 24 participants in the PKPPAS (12 per treatment arm) allows estimation of the mean difference in the log-transformed baseline-corrected $AUC_{Day1-29}$ with an error margin of at most ± 0.233 for the 95% CI with a probability of 80%. For example, if the true ratio of geometric means is 1, the lower and upper 95% confidence bounds will be estimated to be within 0.79 and 1.26 ($\exp[\log(1) - 0.233]$ and $\exp[\log(1) + 0.233]$) with a probability of 80%.

The planned total sample size for this trial is at least 24 participants in the PKPPAS and is considered sufficient to achieve the trial objectives. To account for an assumed drop-out rate of 20% (including participants who have unevaluable PK profiles and participants who have protocol violations that may affect the reliability of the total IgG level time profiles), 30 participants will be randomized and treated (15 per treatment arm).

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10.0 GENERAL CONSIDERATIONS: REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines.
- ICH GCP Guidelines.
- Applicable laws and regulations (for example, US 21 CFR).

10.1.1 Investigator Responsibilities

10.1.1.1 Introduction

Each investigator will conduct the trial according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the List of Investigator Responsibilities in Section 10.1.1.2.

The trial is being funded by Takeda. Payments for the conduct of the trial that will be made to trial sites (and, if applicable, investigators and/or other trial staff) will be specified in the clinical trial site agreement(s). All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and subinvestigator before the trial starts at their trial site; in addition, any potential conflicts of interest that are not covered by this financial disclosure form should be disclosed separately to the sponsor before the start of the trial at their site.

All institutional affiliations of the investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to the sponsor before the start of the trial.

10.1.1.2 List of Investigator Responsibilities

Clinical research trials sponsored by the sponsor are participant to ICH GCP and all applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the Statement of Investigator (Form FDA 1572), which must be completed and signed before the investigator may participate in this trial.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

4. Ensure that trial-related procedures, including trial-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential participants before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
6. Secure prior approval of the trial and any changes by an appropriate IRB that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to participants. Make at least yearly reports on the progress of the trial to the IRB and issue a final report within 3 months of trial completion.
8. Ensure that requirements for informed (e)consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
9. Obtain valid informed (e)consent from each trial participant and document the date of (e)consent in the participant's medical chart. Valid informed (e)consent is the most current version approved by the IRB. Each ICF should contain a participant authorization section that describes the uses and disclosures of a participant's personal information (including personal health information) that will take place in connection with the trial. If an ICF does not include such a participant authorization, then the investigator must obtain a separate participant authorization form from each participant or the participant's LAR.
10. Prepare and maintain adequate case histories of all persons entered into the trial, including (e)CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied IPs.
13. Destroy or return all unused sponsor-supplied trial interventions to the sponsor as specified in the pharmacy manual.
14. Report adverse reactions and other reportable events to the sponsor promptly, using the reporting timeframes shown in [Table 7](#).

10.1.1.3 *Investigator Consent to Use of Personal Information*

Takeda will collect and retain personal information of the investigator, including name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (for example, the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the trial and/or other clinical trials.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other IPs used in other clinical trials that may contain the same chemical compound present in the IP.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting investigator site contact information, trial details, and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

The investigator acknowledges and consents to the use of this personal information by Takeda and other parties for the purposes described above.

10.1.2 Sponsor Responsibilities

The trial sponsor and any third party to whom aspects of the trial management or monitoring have been delegated will undertake their assigned roles for this trial in compliance with all applicable industry regulations, current ICH GCP guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the trial sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect trial data, participants' source documents, and (e)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 trial. The sponsor (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required before release of IP for shipment to the site.

10.2 Informed Consent Process

Written and electronic consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the participant's personal and personal health information for purposes of conducting the trial, including the use of electronic devices and associated technologies (if applicable). The ICF and the participant information sheet (if applicable) further explain the nature of the trial, its objectives, and potential risks and benefits and the date informed consent is given. The ICF will detail the requirements of the participant and the participant's freedom to withdraw at any time without giving a reason and without prejudice to further medical care.

The investigator is responsible for the IRB approval of the ICF and, if applicable, the participant authorization form. The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be approved by both the IRB and the sponsor before use.

The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be written in a language fully comprehensible to the prospective participant. It is the responsibility of the investigator to explain the detailed elements of the ICF, participant authorization form (if applicable), and participant information sheet (if applicable) to the participant. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. If the participant is not capable of rendering adequate written or electronic informed consent, then the participant's LAR may provide such consent for the participant in accordance with applicable laws and regulations.

The participant must be given ample opportunity to (1) inquire about details of the trial and (2) decide whether to participate in the trial. If the participant determines that the participant will take part in the trial, then the ICF and participant authorization form (if applicable) must be (e)signed and dated by the participant, or the participant's LAR, at the time of (e)consent and before the participant enters into the trial. Participants should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink in the case of written informed consent. The investigator must also (e)sign and date the ICF and participant authorization (if applicable) at the time of (e)consent and before the participant enters into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

10.2.1 Informed Consent for Use of Remaining Samples

By indicating in the ICF that they wish to participate in future research and signing, participants agree to the possible future analysis as detailed in Appendix 13.2. At any time, participants can contact the site to request that residual samples be discarded following local procedure. Any additional research on these samples unspecified by this protocol will require approval from the participants.

10.3 Data Protection

10.3.1 Participant Confidentiality

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

To comply with ICH guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (for example, US FDA, UK MHRA, Japan PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the participant's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a participant's trial participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed (e)consent process (see Section 10.2).

Copies of any participant source documents that are provided to the sponsor must have certain identifying personal information removed, for example, participant name, address, and other identifier fields not collected on the participant's (e)CRF.

10.3.2 Responsibilities After Termination or Suspension

If the trial is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies, and IRBs are notified as appropriate. The sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements.

Additionally, the discontinuation of a registered clinical trial that has been posted to a designated public website will be updated accordingly.

If the trial is prematurely terminated or suspended, the investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

10.3.3 Serious Data Breach Prevention and Reporting

If a serious data breach affecting personal data is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventive actions in response. These actions will be documented, and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of trial participants, this would be done through the investigator.

10.4 Early Site Closure or Trial Termination

10.4.1 Decision Rights for Site Closure and Trial Termination

The sponsor may suspend or terminate the trial, or part of the trial, at any time for any reason. The sponsor reserves the right to close the trial site at its sole discretion. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site-closure visit has been performed.

The investigator may, in consultation with the sponsor, initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. For further details on Trial and Dose Stopping Rules, refer to Section 7.4.

10.4.2 Criteria for Early Trial Site Closure

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- For trial termination:
 - Discontinuation of further IP development.
- For site termination:
 - Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines.
 - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
 - Total number of participants included earlier than expected.

11.0 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1 Quality Tolerance Limits

QTLs will be predefined to identify systematic issues that can affect participant safety and/or reliability of trial results. These predefined parameters will be monitored during the trial, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

11.2 Data Quality Assurance

The sponsor or designee is responsible for the data management of this trial, including quality checking of the data.

Monitoring details describing strategy, including definition of trial-critical data items and processes (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.

The sponsor assumes accountability for actions delegated to other individuals (for example, CROs).

11.2.1 Investigator Responsibilities for Data Quality Assurance

All participant data relating to the trial will be recorded on printed or (e)CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the (e)CRF.

Completion of (e)CRFs will follow Celerion standard operating procedures.

The investigator must permit trial-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents. Additionally, investigators must promptly notify Takeda of any trial-related regulatory agency inspections and will be expected to provide Takeda with a copy of the inspection report.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator as specified in Section 15.1 after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.2.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial participants. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The sponsor will assess any protocol deviation. If it is likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

The site should document all protocol deviations in the participant's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the participant, or confound interpretation of primary trial assessment.

Protocol deviations will be captured in a Part 11-compliant clinical trial management system.

11.3 Source Data

11.3.1 Introduction

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. All key data must be recorded in the participant's source documents unless otherwise noted in the protocol. It is expected that information transcribed in the (e)CRF can be traced to source documents.

11.3.2 Investigator Expectations for Source Data

The investigator (as listed on the US FDA Form 1572) is responsible for maintaining source documents. The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (for example, via audit trail).

Data entered in the (e)CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous source documents or transfer records, depending on the trial.

Source documents are filed at the investigator's site. The investigator must provide direct access to inspect facilities, including original source records relevant to this trial (regardless of media), to the sponsor's authorized representatives; respective national, local, or foreign regulatory authorities; the IRB; and auditors. Current records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (for example, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor. The (e)Consent form includes a statement granting this access to source data.

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

11.3.3 Trial Monitor Expectations for Source Data

Trial monitors will perform ongoing source data verification to confirm that data entered into the (e)CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

11.3.4 Definition of Source Data

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Electronic source data are data initially recorded in electronic form. Examples of source data include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aids or evaluation checklists, pharmacy dispensing records, audio recordings of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

12.0 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

12.1 Contraception, Pregnancy Testing, and Pregnancy

12.1.1 Definitions Related to Childbearing Potential

12.1.1.1 *Women of Childbearing Potential*

For the purpose of this trial, a person of female birth sex is considered a WOCBP, that is, fertile, after menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy.

However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

12.1.1.2 *Fertile Men*

For the purpose of this trial, a person of male birth sex is considered a fertile man after puberty unless permanently sterile by bilateral orchidectomy.

12.1.2 Contraception

12.1.2.1 *Permitted and Unacceptable Contraception Methods*

12.1.2.1.1 *Permitted Contraception Methods*

The following birth control methods are considered highly effective (can achieve a failure rate of less than 1% per year when used consistently and correctly). These methods of contraception are permitted in this trial:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
 - Oral.
 - Intravaginal.
 - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
 - Oral.
 - Injectable.
 - Implantable.
- Intrauterine device.

- IUS.
- Bilateral tubal occlusion.
- Vasectomized partner (highly effective provided that partner is the sole sexual partner of the WOCBP trial participant and the vasectomized partner has received medical assessment of the surgical success).
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of the risk associated with the IP[s]. Reliability of abstinence should be evaluated in relation to trial duration and the preferred and usual lifestyle of the trial participant.)

In addition, the following methods of contraception are also considered acceptable in this trial. These methods result in a failure rate of more than 1% per year:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.
- Combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods).

12.1.2.1.2 *Unacceptable Contraception Methods*

The following birth control methods are considered unacceptable for use in clinical trials:

- Periodic abstinence:
 - Calendar.
 - Symptothermal.
 - Postovulation.
- Withdrawal (coitus interruptus).
- Spermicides only.
- LAM.

12.1.2.2 *Duration of Contraception Use*

12.1.2.2.1 *Contraception Duration for WOCBP*

WOCBP must practice method(s) of contraception as described in Section 12.1.2.1 from the time of signing the ICF through 90 days after dose of IP. WOCBP using hormonal contraception must have been on a stable dose for at least 90 days prior to dosing and must maintain that dose throughout participation in the trial.

From signing of informed consent, throughout the duration of the trial, female participants must be advised not to donate ova during this period.

12.1.2.2.2 Contraception Duration for Fertile Men

Fertile men must practice method(s) of contraception as described in Section 12.1.2 during the entire trial treatment period and through 90 days after dose of IP.

In addition, they must be advised not to donate sperm during this period.

12.1.3 Pregnancy Testing

A serum pregnancy (choriogonadotropin beta) test will be completed for all female participants during screening; this test result must be negative for the participant to be enrolled. Additional tests will be performed at the time points outlined in the SoA (Section 1.3).

Pregnancy tests may also be repeated during the trial if requested by an IRB or if required by local regulations.

12.1.4 Pregnancy and Postpartum Information

12.1.4.1 Participants Who Become Pregnant During the Trial

12.1.4.1.1 Reporting

Pregnancy in and of itself is not an AE, unless a negative or consequential outcome occurs in the participant or child/fetus. If the negative event meets the seriousness criteria, then this is considered an SAE (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy, or pre-eclampsia) and reported per Section 8.4.6, Reporting of SAEs.

Once a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours.

All pregnancies in participants on active IP will be followed until delivery for outcomes of both the mother and child, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

12.1.4.1.2 Continued Trial Participation

Not applicable.

12.1.4.2 Male Participants Whose Partners Become Pregnant

If a female partner of a male participant becomes pregnant during the trial, to determine eligibility for follow-up, pregnancy of the female partner will be assessed on the basis of IP assignment and timing of conception in relation to the administration of the IP.

Details about all pregnancies in eligible male participants' partners will be collected from the participant's signing of the ICF and the follow-up contact. Collection of pregnancy data from a male participant's partner requires the partner's informed consent.

Once a partner pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours.

All pregnancies in eligible female partners of male participants will be followed until delivery for outcomes of both the mother and child using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

12.2 Publication and Clinical Trial Registration and Disclosure Policies

During and after the trial, only the sponsor may make trial information available to other trial investigators or to regulatory agencies, except as required by law or regulation.

12.2.1 Publication Policy

The sponsor may publish any data and information from the trial (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication venue (for example, congress, journal) will appropriately reflect contributions to the production, review, and approval of the document.

12.2.2 Clinical Trial Registration and Disclosure

Per Takeda's policy/standards and applicable laws, regulations, and guidance, Takeda will:

- Register clinical trials on ClinicalTrials.gov, or other publicly accessible websites and registries (for example, clinicaltrials.takeda.com), as applicable.
- Disclose the results of clinical trials on ClinicalTrials.gov and other publicly accessible websites (such as clinicaltrialsregister.eu), including the Takeda corporate site.

12.3 Prior Protocol Amendments

This protocol has not been amended.

13.0 APPENDIX: SAMPLE RETENTION AND USE

13.1 Sample Retention

Any residual plasma and serum samples will be stored by the sponsor or bioanalytical facility for up to 15 years determined by the sponsor following the last dosing. Tubes or containers will be identified with a barcode using an appropriate label.

13.2 Sample Use for Research Purposes

No diseases/conditions, DNA, or RNA will be the focus of these analyses. The analyses will only focus on analytes/biomarkers. Samples will not be submitted to a public database. The Sponsor and CRO(s) involved in the clinical conduct, bioanalytical analyses and PK and statistical analyses of the data will have access to the samples and/or the data that resulted from the analysis, if performed.

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14.0 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS IN MEDICAL DEVICE STUDIES: ADDITIONAL REQUIREMENTS FOR REPORTING

All of the general reporting requirements for AEs and SAEs (Section 8.4) apply to devices. This section provides additional AE and SAE definitions and reporting requirements that apply to devices.

The definitions and procedures detailed in this section are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.2 for the list of sponsor medical devices.

14.1 Definitions of Medical Device AE and Adverse Device Effect

Medical Device AE Definition
<p>A medical device AE is an event that has all of the following characteristics:</p> <ul style="list-style-type: none">• Occurs in a clinical study participant, <i>user</i>, or <i>other person</i>.• Otherwise meets the definition of an AE in Section 8.4.1.1.• Is temporally associated with <i>either</i> the use of the investigational medical device <i>or</i> comparator, or with the associated procedures. <p>Exception: Events in users or other persons only include events related to investigational medical devices.</p>

ADE Definition
<p>An ADE is defined as a medical device AE that is related to the use of an investigational medical device. This definition includes any AE resulting from:</p> <ul style="list-style-type: none">• Insufficient or inadequate instructions for use or operation.• Any malfunction of the investigational medical device.• Use error.• Intentional misuse of the investigational medical device.

14.2 Definitions of Medical Device SAE, Serious Adverse Device Effect, and Unanticipated Serious Adverse Device Effect

Medical Device SAE (Serious Injury) Definition
<p>A medical device SAE is an event that:</p> <ul style="list-style-type: none">• Occurs in a clinical study participant, <i>user</i>, or <i>other person</i>.• Is a medical device AE (Section 14.1).• Meets the SAE criteria in Section 8.4.1.2 OR leads to chronic disease (MDR 2017/745), fetal distress, or fetal death.
Medical Device SADE Definition
<p>An SADE is defined as:</p> <ul style="list-style-type: none">• An ADE (Section 14.1) that has resulted in any of the consequences characteristic of an SAE (Section 8.4.1.2).• Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
USADE Definition
<p>An USADE (also identified as an Unanticipated Adverse Device Effect [UADE] in US Regulations 21 CFR 813.3), is defined as a SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.</p>

14.3 Additional Requirements for Recording and Follow-up of Device Adverse Events, SAEs, and Deficiencies

Additional Recording Requirements for Device AEs, SAEs, and Deficiencies
<p>All requirements stated in Section 8.4 apply to medical device AEs and deficiencies.</p> <p>For device deficiencies, the investigator must also describe any corrective or remedial actions taken to prevent recurrence of the deficiency.</p> <p>A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.</p>

Assessment of Severity
<p>The investigator will make an assessment of severity for each medical device AE or deficiency reported during the study and assign it to one of the following categories/categories:</p> <ul style="list-style-type: none">• See Section 8.4.4 for standard severity scales.

Assessment of Relationship

All requirements stated in Section 8.4.4 apply to medical device AEs and deficiencies. The investigator will also consult the device IB in their assessment.

Follow-up of AE/SAE/Device AE or Deficiency
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All requirements stated in Section 8.4 apply to medical device AEs and deficiencies. The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

14.4 Reporting of Medical Device AEs, SAEs, SADEs, Serious Injuries, and UADEs

All serious injuries and UADEs must be reported to the sponsor as an SAE using the same process as described in Section 8.4.7; likewise, medical device AEs must be reported as AEs.

However, there are additional reporting obligations for medical device deficiencies that are potentially related to SAEs.

SADE Reporting to the Sponsor

Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
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The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations. The device should be sent back to the manufacturer for further evaluation/investigation.

Contacts for SAE reporting can be found in the Study Reference Manual.
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15.0 APPENDIX: RECORD RETENTION

15.1 Record Retention Responsibilities of the Investigator/Site

The investigator agrees to keep the records stipulated in this section and supporting documentation that includes (but is not limited to) the trial-specific documents, the identification log of all participating participants, source documents, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated informed (e)Consent forms (including consent to use digital tools and applications, if applicable), participant authorization forms regarding the use of personal health information (if separate from the informed (e)Consent forms), query responses/electronic copy of (e)CRFs (including the audit trail), and detailed records of IP disposition to enable evaluations or audits from regulatory authorities, the sponsor, or its designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the participant's chart to ensure long-term legibility. Furthermore, ICH E6(R2) Section 5.5.11 requires the investigator to retain essential documents specified in ICH E6(R2) (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6(R2) Section 5.5.11 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the trial site agreement between the investigator and sponsor.

Refer to the CRU site agreement for the sponsor's requirements on record retention. The investigator or designee should contact and receive written approval from the sponsor before disposing of any such documents.

15.2 Record Retention Responsibilities of the Sponsor

Data collected are stored in the trial master file for the life of the product plus 30 years unless longer retention is required by local laws.

16.0 APPENDIX: ABBREVIATIONS

PK parameter abbreviations and definitions are found in Sections 8.5.1.3. International units of measurement are not included in this list.

21 CFR	Title 21 Code of Federal Regulations
ADA	antidrug antibody
ADE	adverse device effect
ADR	adverse drug reactions
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
Bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
C3	complement component 3
C4	complement component 4
CH50	50% hemolytic complement activity of serum
CIC	circulating immune complex
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
COVID-19	coronavirus disease 2019
CPAP	clinical pharmacology analysis plan
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	Electrocardiogram
(e)CRF	(electronic) case report form
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HDL	high-density lipoprotein

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IE	intercurrent events
IEC	Institutional ethics committee
IgG	Immunoglobulin G
IGI	Immune Globulin Infusion
IGSC	Immune Globulin Subcutaneous
IP	investigational product(s)
IRB	institutional review board
IV	Intravenous
IVIG	Intravenous immunoglobulin
IUS	Intrauterine hormone-releasing system
LAR	legally authorized/acceptable representative
LDL	low-density lipoprotein
MCAR	Missing completely at random
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
NCA	non-compartmental analysis
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Disease
PIDD	primary immunodeficiency disease
PK	pharmacokinetic(s)
PKFAS	PK Full Analysis Set
PKPPAS	PK Per-Protocol Analysis Set
QTL	quality tolerance limits
rHuPH20	Recombinant Human Hyaluronidase
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	systemic allergic reaction
SC	subcutaneous(ly)
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
USADE	Unanticipated serious adverse device effect
WOCBP	woman of childbearing potential

17.0 APPENDIX: REFERENCES

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