Clinical Study Protocol

NCT Number: NCT06935266

Title: A Phase 1, Open-Label, Within-Dose-Level Randomized Trial to Assess the Tolerability, Safety, and Pharmacokinetics of Immune Globulin Subcutaneous 20% (Human) with Recombinant Human Hyaluronidase (TAK-881) with Ramp-Up and No Ramp-Up Dosing in Healthy Adult Participants

Study Number: TAK-881-1003

Document Version and Date: Final version, 20 Feb 2025

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

For non-commercial use only

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1, Open-Label, Within-Dose-Level Randomized Trial to Assess the Tolerability, Safety, and Pharmacokinetics of Immune Globulin Subcutaneous 20% (Human) with Recombinant Human Hyaluronidase (TAK-881) with Ramp-Up and No Ramp-Up Dosing in Healthy Adult Participants

Protocol Number:	TAK-881-1003
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: 027372
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.

For non-commercial use only

CONFIDENTIAL PROPERTY OF TAKEDA

This document is a confidential communication of Takeda. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from Takeda except to the extent necessary to obtain informed consent from those persons to whom the investigational product may be administered. Furthermore, the information is only meant for review and compliance by the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduct of the trial.

TABLE OF CONTENTS

SPONSOR SIGNATORIES 8
INVESTIGATOR AGREEMENT 9
1.0 PROTOCOL SUMMARY 10
1.1 Protocol Synopsis 10
1.1.1 Objectives and Endpoints 10
1.1.2 Overall Design 10
1.2 Trial Schema 11
1.3 Schedule of Activities 13
1.3.1 Ramp-Up Schedule A 13
1.3.2 Ramp-Up Schedule B 15
1.3.3 No Ramp-Up Schedule C 17
2.0 INTRODUCTION 21
2.1 Purpose of Trial 21
2.2 Background 21
2.3 Summary of Benefits and Risks 22
3.0 TRIAL OBJECTIVES AND ENDPOINTS 24
3.1 Primary Objective + Associated Endpoint 24
3.2 Secondary Objective + Associated Endpoints 24
3.3 Safety Objective + Associated Endpoint 24
3.4 Exploratory Objective + Associated Endpoints 24
4.0 TRIAL DESIGN 25
4.1 Overall Design 25
4.1.1 Dose Escalation 25
4.2 Scientific Rationale for Trial Design 26
4.2.1 Rationale for Trial Design 26
4.2.2 Rationale for Dose 26
4.2.3 Rationale for Endpoints 26
4.2.3.1 Tolerability Endpoints 26
4.2.3.2 Safety Endpoints 27
4.2.3.3 Pharmacokinetic Endpoints 27
4.3 Start of Trial and End of Trial 27
4.3.1 Definition of Beginning of the Trial 27
4.3.2 Early Trial or Site Closure 27
4.3.3 Definition of End of the Trial 27
5.0 TRIAL POPULATION 28

For non-commercial use only

5.1 Inclusion Criteria 28
5.2 Exclusion Criteria 28
5.3 Lifestyle Considerations 31
5.3.1 Meals and Dietary Restrictions 31
5.3.1.1 Diet and Fluid 31
5.3.2 Nicotine- and Tobacco-Containing and/or Cannabis Products 31
5.3.3 Activity 31
5.3.3.1 Physical Activity 31
5.3.3.2 Other Activities 32
5.4 Screen Failures 32
6.0 IP AND CONCOMITANT THERAPY 33
6.1 Description of IP 33
6.2 Dosing and Administration 33
6.2.1 IP Dose Modification 36
6.3 Overdose 36
6.4 Preparation, Handling, Storage, and Accountability 37
6.4.1 Preparation of IP 37
6.4.2 IP Labeling 37
6.4.3 Handling and Storage of IP 37
6.4.4 Accountability and Destruction of Sponsor-Supplied IPs 37
6.5 Randomization and Blinding 37
6.5.1 IP Blinding 37
6.5.2 Randomization 37
6.6 IP Compliance 38
6.7 Concomitant Therapy 38
6.7.1 Prohibited Concomitant Therapy 38
6.7.2 Permitted Concomitant Therapy 38
7.0 DISCONTINUATION OF IP AND PARTICIPANT WITHDRAWAL FROM TRIAL 39
7.1 Discontinuation of IP 39
7.2 Participant Withdrawal from the Trial 40
7.2.1 Trial Participant Replacement 40
7.3 Lost to Follow-up 40
7.4 Trial and Dose Stopping Rules 41
7.4.1 Treatment Arm Discontinuation Criteria: 41
7.4.2 Trial stopping Criteria: 41

For non-commercial use only

8.0 TRIAL ASSESSMENTS AND PROCEDURES 42
8.1 Screening/Baseline Assessments and Procedures 42
8.1.1 Demographics, Medical History, and Medication History 42
8.1.1.1 Demographic and Other Baseline Characteristics 42
8.1.1.2 Medical History 42
8.1.1.3 Prior and Concomitant Treatments/Medications 42
8.2 Confinement 43
8.3 Safety Assessments and Procedures 43
8.3.1 Physical Examination 43
8.3.2 Height, Weight, and BMI 43
8.3.3 Vital Signs 43
8.3.4 ECG Procedure 44
8.3.4.1 Screening and Safety ECGs 44
8.3.5 Clinical Laboratory Assessments 44
8.3.6 Other Diagnostic Laboratory Tests 46
8.3.7 Infusion Site Evaluation and Infusion Reaction Assessment 47
8.3.8 Suicidal Ideation and Behavior Risk Monitoring 47
8.4 Adverse Events and Serious Adverse Events 47
8.4.1 Definitions of AE and SAE 47
8.4.1.1 AE Definition 47
8.4.1.2 SAE Definition 48
8.4.2 Time Period and Frequency for Collecting AE and SAE Information 48
8.4.3 Identifying AEs and SAEs 49
8.4.4 Recording of AEs and SAEs 49
8.4.4.1 Recording of AEs 49
8.4.4.2 Recording of SAEs 52
8.4.5 Follow-up of AEs and SAEs 52
8.4.6 Reporting of SAEs 53
8.4.7 Regulatory Reporting Requirements for SAEs 53
8.4.8 Serious and Unexpected Adverse Reaction Reporting 53
8.4.9 Adverse Events of Special Interest 54
8.4.10 Product Complaints 54
8.4.11 Special Situation Reporting 54
8.5 Pharmacokinetics and Immunogenicity 55
8.5.1 Pharmacokinetics 55
8.5.1.1 Pharmacokinetic Sample Collection 55

For non-commercial use only

8.5.1.2 Pharmacokinetic Sample Analysis 55
8.5.1.3 Pharmacokinetic Parameters 56
8.5.2 Immunogenicity 56
8.5.3 Additional Immunogenicity Panel Tests 56
8.6 Blood Volume Drawn for Trial Assessments 57
9.0 STATISTICAL CONSIDERATIONS 58
9.1 Analysis Sets 58
9.2 General Approach 58
9.3 Infusion Tolerability Analyses 58
9.4 Safety Analyses 59
9.4.1 AEs 59
9.4.2 Clinical Laboratory Evaluation 60
9.4.3 Vital Signs 60
9.4.4 ECG 60
9.4.5 Medical History: 60
9.5 Immunogenicity Analysis 60
9.6 PK Analyses 60
9.7 Analysis of Demographics and Other Baseline Characteristics 61
9.8 Interim Analysis and Criteria for Early Termination 61
9.9 Sample Size Determination 61
10.0 GENERAL CONSIDERATIONS: REGULATORY AND OPERATIONAL CONSIDERATIONS 62
10.1 Regulatory and Ethical Considerations 62
10.1.1 Investigator Responsibilities 62
10.1.1.1 Introduction 62
10.1.1.2 List of Investigator Responsibilities 62
10.1.1.3 Investigator Consent to Use of Personal Information 64
10.1.2 Sponsor Responsibilities 65
10.2 Informed Consent Process 65
10.2.1 Informed Consent for Use of Remaining Samples 66
10.3 Data Protection 66
10.3.1 Participant Confidentiality 66
10.3.2 Responsibilities After Termination or Suspension 67
10.3.3 Serious Data Breach Prevention and Reporting 67
10.4 Early Site Closure or Trial Termination 67
10.4.1 Decision Rights for Site Closure and Trial Termination 67

For non-commercial use only

10.4.2 Criteria for Early Trial Site Closure 67
11.0 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE 68
11.1 Quality Tolerance Limits 68
11.2 Data Quality Assurance 68
11.2.1 Investigator Responsibilities for Data Quality Assurance 68
11.2.2 Protocol Deviations 69
11.3 Source Data 69
11.3.1 Introduction 69
11.3.2 Investigator Expectations for Source Data 69
11.3.3 Trial Monitor Expectations for Source Data 70
11.3.4 Definition of Source Data 70
12.0 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS 71
12.1 Contraception, Pregnancy Testing, and Pregnancy 71
12.1.1 Definitions Related to Childbearing Potential 71
12.1.1.1 Women of Childbearing Potential 71
12.1.1.2 Fertile Men 71
12.1.2 Contraception 71
12.1.2.1 Permitted and Unacceptable Contraception Methods 71
12.1.2.2 Duration of Contraception Use 72
12.1.3 Pregnancy Testing 73
12.1.4 Pregnancy and Postpartum Information 73
12.1.4.1 Participants Who Become Pregnant During the Trial 73
12.1.4.2 Male Participants Whose Partners Become Pregnant 74
12.2 Publication and Clinical Trial Registration and Disclosure Policies 74
12.2.1 Publication Policy 74
12.2.2 Clinical Trial Registration and Disclosure 74
12.3 Prior Protocol Amendments 74
13.0 APPENDIX: SAMPLE RETENTION AND USE 75
13.1 Sample Retention 75
13.2 Sample Use for Research Purposes 75
14.0 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS IN MEDICAL DEVICE STUDIES: ADDITIONAL REQUIREMENTS FOR REPORTING 76
14.1 Definitions of Medical Device AE and Adverse Device Effect 76
14.2 Definitions of Medical Device SAE, Serious Adverse Device Effect, and Unanticipated Serious Adverse Device Effect 77

For non-commercial use only

14.3 Additional Requirements for Recording and Follow-up of Device Adverse Events, SAEs, and Deficiencies 77
14.4 Reporting of Medical Device AEs, SAEs, SADEs, Serious Injuries, and UADEs 78
15.0 APPENDIX: RECORD RETENTION 79
15.1 Record Retention Responsibilities of the Investigator/Site 79
15.2 Record Retention Responsibilities of the Sponsor 79
16.0 APPENDIX: ABBREVIATIONS 80
17.0 APPENDIX: REFERENCES 83

LIST OF IN-TEXT TABLES

Table 1 Trial Objectives + Associated Endpoints 10
Table 2 Primary Objective + Associated Endpoint 24
Table 3 Secondary Objective + Associated Endpoints 24
Table 4 Exploratory Objective + Associated Endpoints 24
Table 5 Excluded Dietary Products 31
Table 6 TAK-881 Infusion Rates for Participants with a Body Weight of ≥40 kg 34
Table 7 TAK-881 Infusion Rates for Participants with a Body Weight of <40 kg 35
Table 8 Trial Interventions Administered: Device (applicable only in the US) 36
Table 9 Safety Reporting Timeframes 47
Table 10 Primary Specimen Collections 55
Table 11 List of Conditions/Symptoms That May be a Result of Immune-Mediated Response to Either Immunoglobulin, rHuPH20, or Other Factors 57

For non-commercial use only

LIST OF IN-TEXT FIGURES

Figure 1 Trial Schema (Ramp-Up and no Ramp-Up Schedules) 11
Figure 2 Trial Schema (Trial Design) 12

SPONSOR SIGNATORIES

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

[redacted], MD, PhD [redacted], CPED PDT Plasma-Derived Therapies, Clinical and Translational Science
[redacted], PhD [redacted], Plasma Derived Therapies Statistics, Global Portfolio Statistics

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 9.

For non-commercial use only

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[R3] 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.

For non-commercial use only

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 Objectives and Endpoints

Table 1 Trial Objectives + Associated Endpoints

Primary Objective	Primary Endpoint
To assess the tolerability of TAK-881 with and without ramp-up dosing in healthy adult participants.	• Occurrence of tolerable infusions of TAK-881. Definition: A tolerable infusion is considered to have occurred if an infusion is completed without interruption (discontinuing the infusion, or infusion rate reduction) due to any TEAE related to TAK-881.
Secondary Objectives	**Secondary Endpoints**
To assess the safety and immunogenicity of TAK-881 with and without ramp-up dosing in healthy adult participants.	• Occurrence of TEAEs. • Clinical laboratory parameters. • Vital signs. • Occurrence of positive binding (defined as titer ≥1:160) antibodies to rHuPH20. • Occurrence of neutralizing antibodies to rHuPH20.

Abbreviations: rHuPH20=Recombinant Human Hyaluronidase; TEAE=treatment-emergent adverse event

For non-commercial use only

1.1.2 Overall Design

This trial is a phase 1, open-label, within-dose-level randomized, single-center trial to assess the tolerability, safety, and pharmacokinetics (PK) of TAK-881 in healthy adult participants.

The design of the trial allows randomized evaluation of 3 different ramp-up dosing schedules (Figure 1) at target dose level (TDL) 0.6 g/kg in Cohort 1, TDL 1.0 g/kg in Cohort 2, and TDL 2.0 g/kg in Cohort 3 (Figure 2). Please see details in Section 4.1.

Number of Treatment Arms and Participants:

The trial will include 3 cohorts.

A total of 64, healthy, adult male and female participants will be enrolled and treated as follows:

- Cohort 1: 16 participants (Treatments 1 and 2)
- Cohort 2: 24 participants (Treatments 3, 4, and 5)
- Cohort 3: 24 participants (Treatments 6, 7, and 8)

Blinding:

Not applicable (no blinding).

Dose Levels and Route of Administration

TAK-881 will be administered via subcutaneous (SC) infusion at TDL of 0.6g/kg (Cohort 1) following a ramp-up or no ramp-up schedule (Schedules B and C). In Cohort 2 (TDL 1.0 g/kg) and Cohort 3 (TDL 2.0 g/kg), TAK-881 will be administered via SC infusion following a ramp-up or no ramp-up schedule (Schedules A, B, and C). The maximum daily absolute dose of TAK-881 is 120 g; some TAK-881 doses may require administration (and equal division) over multiple days.

Duration of Investigational Product (IP) Administration and Participation:

Total duration of IPs administration for each participant is 7 to 8 weeks.

Maximum duration of participant involvement in the trial is approximately 18 to 19 weeks including screening period and follow-up (EOT).

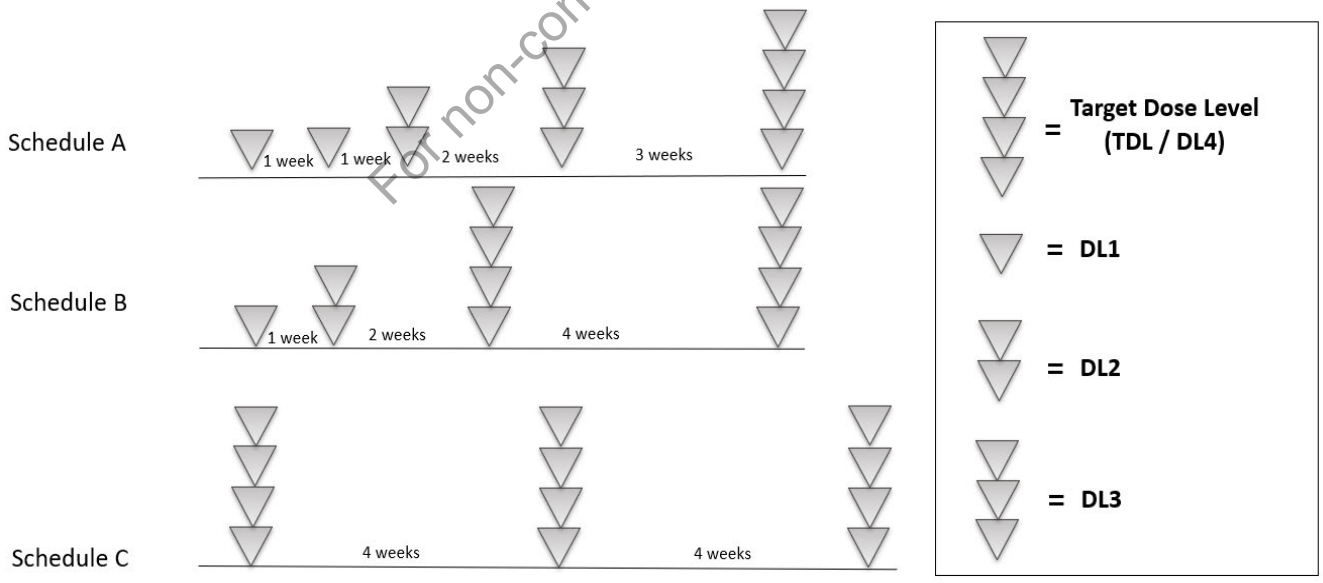
Committees:

Not applicable.

For non-commercial use only

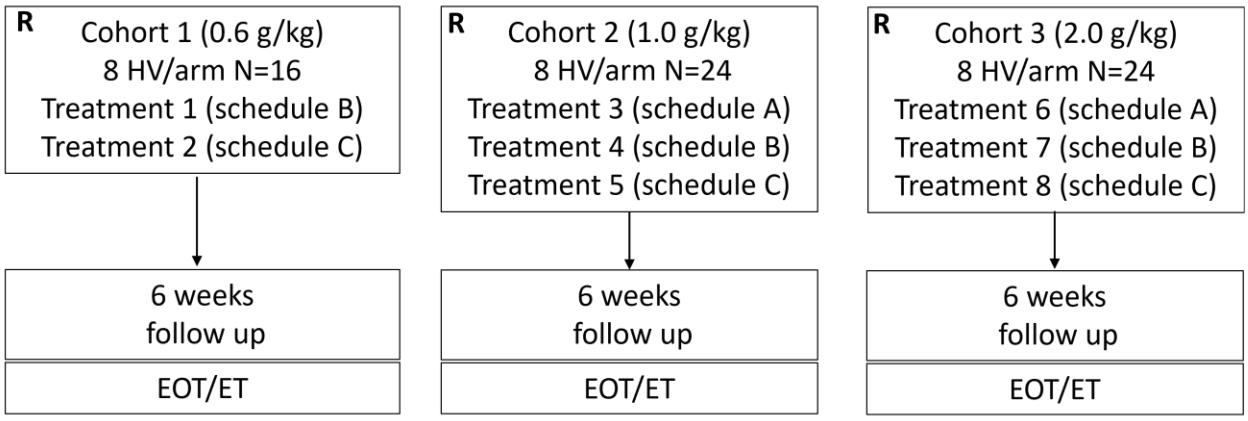
1.2 Trial Schema

Figure 1 Trial Schema (Ramp-Up and no Ramp-Up Schedules)



TDL=Target dose level; DL4=full TDL; DL1=¼ TDL; DL2=½TDL; DL3=¾TDL.

Figure 2 Trial Schema (Trial Design)



EOT/ET=end of trial/early termination; R=open-label randomization (within dose-level cohort) to 1 ramp-up schedule and 1 no-ramp-up schedule with a randomization ratio of 1:1 for Cohort 1 and open-label randomization to 2 ramp-up schedules and 1 no-ramp-up schedule with a randomization ratio of 1:1:1 for Cohorts 2 and 3.

For non-commercial use only

1.3 Schedule of Activities

1.3.1 Ramp-Up Schedule A

Trial Procedures	Scr		Trial Days																			EOT and/ or ET
Weeks and Days →			W1					W2			W3		W4	W5		W7	W8				W9	W14
	Day -28 to -2	D-1	D1	D2	D3	D4	D7	D8	D9	D14 (±2)	D15	D16	D28 (±2)	D29	D30	D49 (±3)	D50	D51	D53	D55	D57	(±1 week)
Confinement in Trial Site		X	X	X	X		X	X		X	X		X	X		X	X					
Discharge from Trial Site[1]						X			X			X			X			X				
Visits to Trial Site																			X	X	X	X
Administrative Procedures																						
Informed Consent[2]	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History[3]	X	X																				
Demographic[4]	X																					
Randomization			X																			
Safety Evaluations																						
Physical Examination[5]	X	X					X			X			X			X						X
Height	X																					
Weight	X	X					X			X			X			X						
12-Lead Safety ECG[6]	X																					X
Vital Signs (PR, BP, RR, and T)[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Hem[8], Serum Chem[8], UA[8], and Coag[9]	X	X			X (Hgb only)		X			X			X			X						X

For non-commercial use only

Trial Procedures	Scr		Trial Days																			EOT and/ or ET
Weeks and Days →			W1					W2			W3		W4	W5		W7	W8				W9	W14
	Day -28 to -2	D-1	D1	D2	D3	D4	D7	D8	D9	D14 (±2)	D15	D16	D28 (±2)	D29	D30	D49 (±3)	D50	D51	D53	D55	D57	(±1 week)
Hemolytic Panel[10]		X				X	X (As applicable)															
Serum Pregnancy Test[11] (♀ only)	X	X					X			X			X			X						X
Serum FSH (PMP ♀ only)	X																					
Urine Drug and Alcohol Screen[12]	X	X					X			X			X			X						
HIV/Hepatitis Screen (Serology and PCR)[13]	X																					X (PCR only)
AE Monitoring	X																					
Infusion Site Evaluation[14]			X	X	X	X		X	X		X	X		X	X		X	X				
Con Meds Monitoring	X																					
rHuPH20 Immunogenicity: ADA and nAb Blood Collection		X											X			X						X
Additional Immunogenicity panel[15]		X	X (As applicable)																			
IP Administration / PK																						
IP Administration[16]			DL1					DL1			DL2			DL3			DL4					
Blood PK (Predose and EOT)[17]		X	X					X			X			X			X					X
Serial Postdose Blood PK[17]																		X[17]	X[17]	X[17]	X[17]	

For non-commercial use only

1.3.2 Ramp-Up Schedule B

Trial Procedures	Scr		Trial Days																EOT and/ or ET
			W1					W2		W3	W4		W7	W8				W9	W14
Weeks and Days →	Day -28 to -2	D-1	D1	D2	D3	D4	D7	D8	D9	D21 (±2)	D22	D23	D49 (±3)	D50	D51	D53	D55	D57	(±1 week)
Confinement in Trial Site		X	X	X	X		X	X		X	X		X	X					
Discharge from Trial Site[1]						X			X			X			X				
Visit to Trial Site																X	X	X	X
Administrative Procedures																			
Informed Consent[2]	X																		
Inclusion/Exclusion Criteria	X	X																	
Medical History[3]	X	X																	
Demographic[4]	X																		
Randomization			X																
Safety Evaluations																			
Physical Examination[5]	X	X					X			X			X						X
Height	X																		
Weight	X	X					X			X			X						
12-Lead Safety ECG[6]	X																		X
Vital Signs (PR, BP, RR and T)[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Hem[8], Serum Chem[8], UA[8], and Coag[9]	X	X			X (Hgb only)		X			X			X						X
Hemolytic Panel[10]		X				X	X (As applicable)												
Serum Pregnancy Test[11] (♀only)	X	X					X			X			X						X
Serum FSH (PMP ♀ only)	X																		
Urine Drug and Alcohol Screen[12]	X	X					X			X			X						

For non-commercial use only

Trial Procedures	Scr		Trial Days																EOT and/ or ET
			W1					W2		W3	W4		W7	W8				W9	W14
Weeks and Days →	Day -28 to -2	D-1	D1	D2	D3	D4	D7	D8	D9	D21 (±2)	D22	D23	D49 (±3)	D50	D51	D53	D55	D57	(±1 week)
HIV/Hepatitis Screen (Serology and PCR)[13]	X																		X (PCR Only)
AE Monitoring	X																		
Infusion Site Evaluation[14]			X	X	X	X		X	X		X	X		X	X				
Con Meds Monitoring	X																		
rHuPH20 Immunogenicity: ADA and nAb Blood Collection		X								X			X						X
Additional immunology assessments[15]		X	X (As applicable)																
IP Administration / PK																			
IP Administration[16]			DL1					DL2			DL4			DL4					
Blood PK (Predose and EOT)[17]		X	X					X			X			X					X
Serial Postdose Blood PK[17]															X[17]	X[17]	X[17]	X[17]	

For non-commercial use only

1.3.3 No Ramp-Up Schedule C

Trial Procedures	Scr		Trial Days														EOT and/ or ET
Weeks and Days →	Day -28 to -2	D-1	W1				W2	W4	W5		W8	W9				W10	W15
			D1	D2	D3	D4	D8	D28 (±2)	D29	D30	D56 (±3)	D57	D58	D60	D62	D64	(±1 week)
Confinement in Trial Site		X	X	X	X			X	X		X	X					
Discharge from Trial Site[1]						X				X			X				
Visit to Trial Site							X							X	X	X	X
Administrative Procedures																	
Informed Consent[2]	X																
Inclusion/Exclusion Criteria	X	X															
Medical History[3]	X	X															
Demographic[4]	X																
Randomization			X														
Safety Evaluations																	
Physical Examination[5]	X	X					X	X			X						X
Height	X																
Weight	X	X						X			X						
12-Lead Safety ECG[6]	X																X
Vital Signs (PR, BP, RR and T)[7]	X		X	X	X	X	X	X	X	X	X	X	X				X
Hem[8], Serum Chem[8], UA [8], and Coag[9]	X	X			X (Hgb only)			X			X						X
Hemolytic Panel[10]		X				X	X (As applicable)										
Serum Pregnancy Test[11] (♀ only)	X	X						X			X						X

For non-commercial use only

Trial Procedures	Scr		Trial Days														EOT and/ or ET
Weeks and Days →	Day -28 to -2	D-1	W1				W2	W4	W5		W8	W9				W10	W15
			D1	D2	D3	D4	D8	D28 (±2)	D29	D30	D56 (±3)	D57	D58	D60	D62	D64	(±1 week)
Serum FSH (PMP ♀ only)	X																
Urine Drug and Alcohol Screen[12]	X	X						X			X						
HIV/Hepatitis Screen (Serology and PCR)[13]	X																X (PCR Only)
AE Monitoring	X																
Infusion Site Evaluation[14]			X	X	X	X			X	X		X	X				
Con Meds Monitoring	X																
rHuPH20 and IgG Immunogenicity: ADA and nAb Blood Collection		X						X			X						X
Additional immunology assessments[15]		X	X (As applicable)														
IP Administration / PK																	
IP Administration[16]			DL4						DL4			DL4					
Blood PK (Predose and EOT)[17]		X	X						X			X					X
Serial Postdose Blood PK[17]													X[17]	X[17]	X[17]	X[17]	

For non-commercial use only

Abbreviations: ♀=female; ADA=anti-drug antibody; AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BP=blood pressure, BUN=blood urea nitrogen; Ca=calcium; CBC=complete blood count; CH50=50% haemolytic complement; Cl=chloride; Coag=coagulation, Con Meds=Concomitant medications; CTCAE=Common Terminology Criteria for Adverse Events; D=day; DL=dose level; ECG=electrocardiogram; EOT=end of trial; ET=early termination; FSH=follicle-stimulating hormone; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; Hct=hematocrit; Hem=hematology; Hgb=hemoglobin; HIV=human immunodeficiency virus; IgG=Immunoglobulin G; INR=international normalized ratio; IP=investigational product; K=potassium; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; Mg=magnesium; Na=sodium; nAb=neutralizing anti-drug antibody; PCR=polymerase chain reaction; PK=pharmacokinetic(s); PMP=postmenopausal; PR=pulse rate; RBC=red blood cell; RDW=red cell distribution width; rHuPH20=recombinant human hyaluronidase; RR=respiratory rate; Scr=screening; T=temperature; TDL=target dose level; UA=urinalysis; UPCR=urine protein to creatinine ratio; W=week; WBC=white blood cells.

1. For each dose infusion visit, participants will check-in the day before infusion and be discharged the following day after the 24 hour post infusion evaluation and any scheduled assessments. In the case of a dose over 120g (the maximum daily absolute dose of TAK-881), additional days of confinement will be needed and participants will be discharged the following day, approximately 24 hours post the last infusion after any scheduled assessments.
2. Written consent must be obtained prior to performing any protocol specific procedure.
3. Medical history includes any significant or relevant diseases, surgeries, or other medical events and medication/treatment history, if applicable.
4. Age, sex, ethnicity, and race.
5. Physical examination: Complete physical examination will be performed at the screening visit and EOT/ET visit, and a partial physical examination may be performed at the investigator's discretion to assess any new abnormalities or changes from baseline. Complete physical examination will include general appearance, head and neck, eyes and ears, nose and throat, spine/neck/thyroid, musculoskeletal, respiratory, cardiovascular, abdomen, extremities and joints, lymph nodes, skin, and neurological. Partial physical examination will include general appearance, head and neck, assessment of infusion site(s), and skin. Other organ systems will be assessed per investigator's judgment.
6. ECGs (12-lead) will be collected at prespecified time points and as clinically indicated.
7. BP, PR, RR and temperature will be measured at each check-in, 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 end for 4 hours, at each discharge and as needed per investigator's judgment.
8. Hematology includes CBC (Hct, Hgb, RBC, RDW, MCV, MCH, MCHC, platelet count, WBC with absolute differential counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils). Serum chemistry includes ALT, AST, ALP, K^+, Na^+, Cl^-, Ca^{2+}, Mg^{2+}, bilirubin (total, direct, and indirect), carbon dioxide, LDH, protein (total), BUN, creatinine, γ-glutamyl transferase, uric acid, glucose, albumin, and lipid profile. At the screening visit, creatinine clearance will be calculated using the Cockcroft-Gault formula. Urinalysis will include color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, and leukocyte esterase. Dipstick urine test is acceptable. Microscopic analyses will be done if clinically indicated. If ≥ 2+protein on urine dipstick, then collect spot urine sample to calculate UPCR or collect 24-hour urine. Tests will be performed at prespecified time points and as clinically indicated.
9. aPTT, prothrombin time, and INR will be performed at screening, Day-1, EOT/ET and as clinically indicated.

For non-commercial use only

10. 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 hours; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible, but at the next scheduled visit, at 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 × ULN or greater will trigger analysis of the sample for LDH isoenzymes.
11. Pregnancy test will be done for all females. Serum pregnancy test will be obtained at the screening visit, scheduled time points, and whenever a pregnancy is suspected. If the serum pregnancy test at the screening visit 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).
12. Drug screen will include opiates (includes morphine, heroin [diacetylmorphine], codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and hydromorphone), amphetamines, barbiturates, benzodiazepines, cocaine, methadone, cannabinoids, oxycodone/oxymorphone, 3,4-methylenedioxy-methamphetamine, buprenorphine/metabolite, and phencyclidine.
13. PCR testing for HBV, HCV, HIV will be performed at screening and at EOT/ET. Participants who are positive for any PCR test at screening will not be enrolled. Serology test including HCV antibody, HBsAg, HBsAb, HBcAb, and HIV 1/2 antibodies will be performed at screening. Participants who are HIV, HBsAg, HBcAb, or HCV antibody positive at screening will not be enrolled.
14. Infusion sites will be evaluated for any potential local effects (such as such as infusion site extravasation, erythema, pain, oedema, and leaking). 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. Infusion related AEs will be evaluated per CTCAE v5.0 at 12 hours and, 24 hours post all infusions, and as clinically indicated. Allergic reactions related to infusion, and procedural complications should be reported as infusion related reactions.
15. At any time during the trial, participants who have a moderate or severe AE which may be a result of immune-mediated response will be asked to return to the trial 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.
16. The TDL is 0.6 g/kg (treatment arms 1, 2), or 1.0 g/kg (treatment arms 3, 4, 5), or 2.0g/kg (treatment arms 6, 7, 8), with rHuPH20 80 U/g IgG. Each DL was calculated as the following: DL1=1/4 of TDL; DL2=1/2 of TDL; DL3 =3/4 of TDL; and DL4=TDL.
17. Predose blood samples for PK will be collected within 30 minutes prior to dose; serial, post-dose blood samples for PK will be collected at 24 (±12) hours, 72 (±24) hours, 120 (±24) hours, and 168 (±24) hours post last infusion completion.

***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 IP administration.**

For non-commercial use only

2.0 INTRODUCTION

2.1 Purpose of Trial

Dose ramp-up has been considered necessary for HYQVIA/HyQvia (IGI 10% with rHuPH20) and is currently in the approved prescribing information for PIDD and CIDP patients. TAK-881 (IGSC 20% with rHuPH20) is a facilitated immune globulin SC infusion evolving from HYQVIA (IGI 10% with rHuPH20), meant to further improve experience in CIDP and PIDD patients with smaller infusion volume. Despite the current use of ramp-up dosing in an ongoing PIDD clinical trial, the tolerability and safety of TAK-881 without ramp-up has not been evaluated in clinical settings. This phase 1 trial is planned to assess the tolerability, safety, and immunogenicity profile of TAK-881 with and without ramp-up dosing in healthy adult participants and to characterize the PK of total IgG in serum after SC administration of TAK-881 in healthy adult participants.

The investigational 24-gauge SC needle set was developed and selected to allow higher infusion flow rates up to 300 mL/hour/site, with a 90°bent needle configuration in a single or bifurcated option.

Refer to the IB for full details about the IP and the investigational 24-gauge SC needle.

For non-commercial use only

2.2 Background

TAK-881 evolved from the currently licensed HYQVIA (Baxalta US Inc., 2024), 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 (U) 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 de-polymerizes the gel-like hyaluronan in local SC tissue where it is infused. This localized effect results in a transient increase in permeability, allowing 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]

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) 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, minipigs, 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/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 (Trial 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 ongoing phase 2/3 trials (TAK-881-3001, TAK-881-3002, TAK-881-3003).

For non-commercial use only

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. 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 (Baxalta US Inc., 2024)

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

Potential risks with TAK-881 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).

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 for the overall benefit/risk assessment and the most current information regarding drug metabolism, PK, efficacy, and safety of TAK-881.

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

For non-commercial use only

3.0 TRIAL OBJECTIVES AND ENDPOINTS

3.1 Primary Objective + Associated Endpoint

Table 2 Primary Objective + Associated Endpoint

Primary Objective	Primary Endpoint
To assess the tolerability of TAK-881 with and without ramp-up dosing in healthy adult participants.	• Occurrence of tolerable infusions of TAK-881. Definition: A tolerable infusion is considered to have occurred if an infusion is completed without interruption (discontinuing the infusion, or infusion rate reduction) due to any TEAE related to TAK-881.

3.2 Secondary Objective + Associated Endpoints

Table 3 Secondary Objective + Associated Endpoints

Secondary Objective	Secondary Endpoints
To assess the safety and immunogenicity of TAK-881 with and without ramp-up dosing in healthy adult participants.	• Occurrence of TEAEs. • Clinical laboratory parameters. • Vital signs. • Occurrence of positive binding (defined as titer ≥1:160) antibodies to Recombinant Human Hyaluronidase (rHuPH20). • Occurrence of neutralizing antibodies to rHuPH20.

For non-commercial use only

3.3 Safety Objective + Associated Endpoint

Safety objective is detailed as secondary objective in Section 3.2.

3.4 Exploratory Objective + Associated Endpoints

Table 4 Exploratory Objective + Associated Endpoints

Exploratory Objective	Exploratory Endpoints
To characterize the PK of total IgG in serum after SC administrations of TAK-881 in healthy adult participants	The following baseline-uncorrected and baseline-corrected PK parameters for TAK-881 based on serum total IgG level: • Maximum observed concentration after dose administration (C_{max}) at Week 8 (Schedules A and B)/ Week 9 (Schedule C). • Time to C_{max} (t_{max}) at Week 8 (Schedules A and B)/ Week 9 (Schedule C). • Observed concentration before dosing (C_{trough}).

4.0 TRIAL DESIGN

4.1 Overall Design

This trial is a phase 1, open-label, within-dose-level randomized, single-center trial to assess the tolerability, safety, and PK of TAK-881 in healthy adult participants.

A cohort of 16 participants (Cohort 1) and two cohorts of 24 participants each (Cohort 2 and Cohort 3) are planned for evaluation. Cohort 1 will evaluate either ramp-up Schedule B or no ramp-up Schedule C at a TDL of 0.6 g/kg. Cohort 2 (TDL of 1.0 g/kg) and Cohort 3 (TDL of 2.0 g/kg) will each evaluate 2 ramp-up dosing schedules (Schedules A and B) and a no ramp-up dosing schedule (Schedule C).

Dosing schedules will be as follow (refer to Figure 1):

- Schedule A:
  - DL1 (¼TDL) → 1 week interval → DL1 (¼TDL) →1 week interval → DL2 (½TDL) → 2 weeks interval → DL3 (¾TDL) → 3 weeks interval → DL4 (full TDL)
- Schedule B:
  - DL1 (¼TDL) → 1 week interval → DL2 (½TDL) → 2 weeks interval → DL4 (full TDL) → 4 weeks interval → DL4 (full TDL)
- Schedule C:
  - DL4 (full TDL) → 4 weeks interval → DL4 (full TDL) → 4 weeks interval → DL4 (full TDL)

For non-commercial use only

The initial 16 participants will be allocated to Cohort 1 (0.6 g/kg) and be randomly assigned (1:1) to Treatment 1 or 2. The following 24 participants will be allocated to Cohort 2 (1.0 g/kg) and be randomly assigned (1:1:1) to Treatment 3, 4, or 5. Another 24 participants will be allocated to Cohort 3 (2.0 g/kg) and be randomly assigned (1:1:1) to Treatment 6, 7, or 8 (refer to Figure 2).Within-cohort randomization will be conducted on Day 1. PK sampling for measurement of total IgG serum concentrations will be collected on Day -1 and prior to dosing on Day 1 and up to the follow-up/EOT visit.

Throughout the trial, safety will be monitored by repeated clinical and laboratory evaluations. Sampling for ADA will be performed on Day -1 and up to the follow-up/EOT visit.

All participants who received at least one dose of TAK-881 (including participants who terminate the trial early) will return to the CRU 6 weeks (± 1 week) after the last dose for the follow-up/EOT 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 3-step ramp-up schedule proposed in Schedule B is currently being used in the ongoing phase 3 Trial TAK-881-3001 in patients with PIDD, where it is anticipated that the 3-step ramp-up will be demonstrated as tolerable.

In this proposed trial, the 3-step Schedule B will serve as the control to assess the tolerability of no-ramp-up administration in Schedule C at the dose level higher than used for the PIDD indication.

In this proposed trial the 5-step Schedule A (the CIDP ramp-up schedule of HYQVIA) will serve as the control to assess the tolerability of the 3-step ramp-up administration in Schedule B and no-ramp-up administration in Schedule C at the dose range used in the CIDP indication.

The proposed ramp-up Schedules A and B, and no-ramp-up Schedule C are based on monthly (4-weeks) doses, which are 33% higher than the doses used for a 3-week regimen in both PIDD and CIDP indications and would be more sensitive for tolerability evaluation. The sponsor believes the outcome of the proposed 4-week regimen ramp-up evaluation can also inform tolerability of different ramp-up schedules with 3-week dose regimen.

Thus, this proposed trial will enable randomized evaluation for TAK-881 infusions following different ramp-up schedules. These schedules cover the IgG exposure levels applicable for PIDD to test no-ramp schedules and for CIDP therapy to compare 3-step ramp-up and no-ramp-up regimens with 5-step ramp-up regimens.

For non-commercial use only

4.2.2 Rationale for Dose

The target by-weight TAK-881 dose levels in the proposed trial will be 0.6 g/kg (Cohort 1), 1.0 g/kg (Cohort 2), and 2.0 g/kg (Cohort 3). The potential establishment of ramp-up schedule tolerability at the dose level of 0.6 g/kg (note that 0.3 to 0.6 g/kg is the recommended 3-week or 4-week PIDD dose in the HYQVIA labeling) or 1.0 g/kg (the maximum monthly dose for PIDD accepted in TAK-881-3001) is meant to cover the therapeutic dose range for patients with PIDD. The ramp-up schedule tolerability tested at the dose level of 1.0 g/kg and 2.0 g/kg will serve to cover the therapeutic dose levels for patients with CIDP.

4.2.3 Rationale for Endpoints

4.2.3.1 *Tolerability Endpoints*

Ramp-up dosing strategy was originally introduced by the sponsor in both HYQVIA PIDD and CIDP pivotal studies for infusion tolerability (participants drop-out) concern, given the large SC infusion volume needed for the 10% IG product. Given a 50% reduction in infusion volume compared to HYQVIA, the infusion tolerability of TAK-881 (20% IG product) is anticipated to be improved, and this can be evaluated in this proposed healthy volunteer trial.

The sponsor's goal with the tolerability endpoints is to discern if the 3-step ramp-up or 5-step ramp-up is necessary with TAK-881, or if a no ramp-up dosing schedule can be recommended for patients with PIDD, or a 3-step or no ramp-up dosing schedule can be recommended for patients with CIDP.

4.2.3.2 *Safety Endpoints*

The key safety endpoints are typical for phase 1 trials.

4.2.3.3 *Pharmacokinetic Endpoints*

The PK endpoints are standard for this type of trial.

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 signed the ICF.

For non-commercial use only

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 did not discontinue dosing for the remainder of the trial, did not terminate the trial early, and has completed the last scheduled procedure (the follow-up visit/EOT) shown in the SoA (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. Individuals who do not meet criteria for trial eligibility must not be enrolled via protocol waivers or exemptions. A correlation between BMI and infusion tolerability was not observed in previous studies with healthy volunteers (Study TAK-771-1001 and Study TAK-881-1001). Instead of enforcing BMI stratified randomization in this trial, the sponsor plans to check in on Day -1 at least 40% of the participants in the low (<25 kg/m^2) BMI range and at least of 40% of the participants in high (≥25 kg/m^2) BMI range for each cohort. This aims to achieve some representative participants enrolled across the dosing schedules within the dose-level cohorts. BMI will be calculated on the basis of the height and weight measured at the screening visit as defined in Section 8.3.2.

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. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will be assessed only at the first 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/m^2 at the screening visit.
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 at screening visit and first check-in.
6. Understands the trial procedures in the ICF, is able to voluntarily provide written, signed, and dated (personally or via a LAR) informed consent to participate in the trial, 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 or designee, 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 first dosing.

For non-commercial use only

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 investigator or designee, within 30 days prior to first dosing. Any bacterial or viral infection, as judged by the investigator or designee within 14 days prior to first dosing.
8. Female participant with a positive pregnancy test at the screening visit or at first check-in or who is breastfeeding.
9. Positive urine drug or alcohol results at the screening visit or first check-in.
10. Confirmed systolic blood pressure >139 mmHg or <89 mmHg and diastolic blood pressure >89 mmHg or <49 mmHg at screening visit and first check-in.
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 at screening visit:
    - Absolute neutrophil count $\leq 1.5 \times 10^9$ cells/L.
    - ALT, AST, or ALP ≥1.5 × ULN, or total bilirubin ≥1.5 mg/dL.
    - Calculated creatinine clearance ≤60 mL/min based on Cockcroft-Gault equation.

    Participants will be excluded if any other laboratory values are outside the reference range and are clinically significant as per investigator or designee's judgment.
12. A positive HIV, HCV, or ongoing/active HBV infection at screening visit. Positive serology results at screening visit for HIV, HBsAg, HBcAb, or HCVantibodies. Positive PCR results at screening visit for HIV, HBV, HCV. Participants with immunity to hepatitis B from either active vaccination or from previous natural infection are eligible to participate in the trial.

For non-commercial use only

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 first 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 each 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 (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 first dosing.
16. Donation of blood products (example, plasma or platelets) within 14 days prior to first dosing.
17. Participants with ≥2 of the following risk factors for thromboembolic events: use of estrogen (hormone replacement therapy or systemic contraception containing estrogen), smoking, history of myocardial infarction or current congestive heart failure, diabetes, hypertension, and/or history or presence of cancer.
18. Participant who meets the criteria below:
    - Have participated in another clinical trial involving immunoglobulin products within 12 months of the screening visit.
    - Have taken biologic agents within 12 weeks of the screening visit.
    - Have used an IP within 30 days or 5 half-lives, whichever is longer, prior to the screening visit.
    - 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 first 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 of the first dosing, as assessed by the investigator or designee.

For non-commercial use only

5.3 Lifestyle Considerations

Excluded medications, supplements, and dietary products are summarized in Table 5 and in Sections 5.3.1 and 6.7.

5.3.1 Meals and Dietary Restrictions

5.3.1.1 *Diet and Fluid*

Participants should be well hydrated prior to each IP administration. Water will be allowed ad libitum at all times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

Each meal and/or snack served at the trial site will be standardized and will be similar in caloric content and composition and will be taken at approximately the same time in each treatment.

When confined, standard meals and snacks will be provided at appropriate times, except when participants are required to fast. When confined in the trial site, participants will be required to fast from all food and drink except water between meals and snacks.

For non-commercial use only

Table 5 Excluded Dietary Products

Category	Between Screening and First Dosing (Days -28 to predose [Day 1])	After First Dosing (Day 1) to Follow-up (EOT)
Alcohol	Prohibited from 7 days prior to dosing	Prohibited from dosing until last PK sample collection.

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 first 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. Screen failure data will not be captured in the trial CRFs.

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.

For non-commercial use only

6.0 IP AND CONCOMITANT THERAPY

6.1 Description of IP

	TAK-881
Identification:	IGSC 20% with rHuPH20
Dose Formulation:	Solution for SC infusion
Dose Strength(s):	20%
Route of Administration:	SC
Dosing regimen:	Multiple dose
Duration:	Multiple doses (cohort-specific)

6.2 Dosing and Administration

TAK-881 will be administered via the SC route of administration using a SC needle set. The rHuPH20 solution will be administered first and then followed by IGSC, 20% using the same needle set at the same location.

Koru 24 G HIgH Flo Subcutaneous Safety Needle Sets (Koru Needle Sets) are an investigational needle set preferred for all TAK-881 administration. The Koru Needle Sets infuse up to 300 mL/hour/infusion site, thereby enabling less time to safely complete an infusion compared with other 90°bent needle sets currently used in standard of care administration systems with HyQvia. The user interface is the same for the investigational SC needle set as it is for the commercially available needle sets that have a 90° bent needle with appropriate needle lengths (9 mm to 14 mm) to accommodate the participant's body composition variability at infusion sites. A single or bifurcated needle set will be available in this trial.

For non-commercial use only

The maximum volume of IGSC 20% per infusion site is 300 mL. If the required IGSC 20% infusion volume is not exceeding 300 mL, a single infusion site with a single needle set will be used. If the required IGSC 20% infusion volume is more than 300 mL, a bifurcated needle set will be used to equally and simultaneously deliver the IP to 2 infusion sites.

Treatments are described in Figure 2.

	Cohort 1	Cohort 2	Cohort 3
TDL/DL4	0.6 g/kg	1.0 g/kg	2.0 g/kg
DL1 (¼TDL)	0.15 g/kg	0.25 g/kg	0.5 g/kg
DL2 (½TDL)	0.3 g/kg	0.5 g/kg	1.0 g/kg
DL3 (¾TDL)	Not applicable	0.75 g/kg	1.5 g/kg
DL4 (TDL)	0.6 g/kg	1.0 g/kg	2.0 g/kg

Dosing schedules will be as follow (refer to Figure 1):

- Schedule A: DL1 (1 week) → DL1 (1 week) → DL2 (2 weeks) → DL3 (3 weeks) →DL4.
- Schedule B: DL1 (1 week) → DL2 (2 weeks) → DL4 (4 weeks) → DL4.
- Schedule C: DL4 (4 weeks) → DL4 (4 weeks) → DL4.

OR

The following dose levels will be administered via SC infusion:

			Dosing days						
Cohort	**Dosing Schedules:**	**Treatments**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 50**	**Day 57**
1	B	1	0.15 g/kg	0.3 g/kg	N/A	0.6 g/kg	N/A	0.6 g/kg	N/A
	C	2	0.6 g/kg	N/A	N/A	N/A	0.6 g/kg	N/A	0.6 g/kg
2	A	3	0.25 g/kg	0.25 g/kg	0.5 g/kg	N/A	0.75 g/kg	1.0 g/kg	N/A
	B	4	0.25 g/kg	0.5 g/kg	N/A	1.0 g/kg	N/A	1.0 g/kg	N/A
	C	5	1.0 g/kg	N/A	N/A	N/A	1.0 g/kg	N/A	1.0 g/kg
3	A	6	0.5 g/kg	0.5 g/kg	1.0 g/kg	N/A	1.5 g/kg	2.0 g/kg	N/A
	B	7	0.5 g/kg	1.0 g/kg	N/A	2.0 g/kg	N/A	2.0 g/kg	N/A
	C	8	2.0 g/kg	N/A	N/A	N/A	2.0 g/kg	N/A	2.0 g/kg

NOTE: The maximum daily absolute dose of TAK-881 is 120 g/600 mL; some TAK-881 doses may require administration (and equal division) over multiple days. If the dose is over 120 g/600 mL and less than 240 g/1200 mL, half of the dose will be infused on the scheduled day and the other half of the dose will be infused on the following day. By-weight TAK-881 dose calculation will use body weight measured on check-in day prior to dosing.

For non-commercial use only

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

Table 6 TAK-881 Infusion Rates for Participants with a Body Weight of ≥40 kg

		First 2 infusions	Subsequent infusions
Administration		**Rate Per Infusion Site**	**Rate Per Infusion Site**
rHuPH20	To be infused first	60 mL/hour	120 mL/hour
IGSC, 20%	10 min	30 mL/hour	60 mL/hour
	10 min	60 mL/hour	120 mL/hour
	10 min	120 mL/hour	180 mL/hour
	10 min	180 mL/hour	NA
	Remainder of infusion	300 mL/hour	300 mL/hour

Table 7 TAK-881 Infusion Rates for Participants with a Body Weight of <40 kg

		First 2 infusions	Subsequent infusions
Administration		**Rate Per Infusion Site**	**Rate Per Infusion Site**
rHuPH20	To be infused first	60 ml /hour	120 mL/hour
IGSC, 20%	10 min	10 mL/hour	20 mL/hour
	10 min	20 mL/hour	40 mL/hour
	10 min	40 mL/hour	80 mL/hour
	10 min	80 mL/hour	N/A
	Remainder of infusion	160 mL/hour	160 mL/hour

If the infusion rate is reduced (infusion paused) due to any TEAE related to TAK-881, that infusion will be considered intolerable and the infusion rate will stay at the maximally tolerable infusion rate for remaining dose in that infusion (please refer to Section 7.1). The times of the beginning and the end of the SC infusion will be recorded. Dosing interruptions and reasons will be recorded.

Additional instruction for the administration of the IP will be provided in the Site Infusion Manual. Please refer to the Site Infusion Manual for infusion rate of rHuPH20 and IGSC, 20%, and guidance if a catheter leakage occurs.

For non-commercial use only

Table 8 Trial Interventions Administered: Device (applicable only in the US)

Intervention Name	Investigational SC needle sets
Intervention Description	The single-use only 24-gauge SC needle set is used to deliver TAK-881 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
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

For non-commercial use only

6.2.1 IP Dose Modification

The dose and administration of the IP(s) to any participant may 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, 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 (e)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 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.

Instruction for the preparation of IPs drugs will be provided in a separate document in the pharmacy appendices and Site Infusion 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.

For non-commercial use only

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 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 receive one treatment. In Cohort 1, participants will be randomized to 1 of 2 treatment schedules (Schedule B or C). In Cohorts 2 and 3, participants will be randomized to 1 of 3 treatment schedules (Schedule A, B, or C).

6.6 IP Compliance

Before and after the SC infusion, the qualified designee will visually inspect the syringe and pooling bag 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 or designee and/or sponsor or sponsor's designee, the participant may be withdrawn. The pump tubing will be flushed with normal saline 0.9% (injectable) to complete the intended dose of IP.

6.7 Concomitant Therapy

All concomitant medications, supplements, therapies, and procedures will be recorded as described in Section 8.1.1.3.

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, if needed, will decide on a case-by-case basis whether the participant may continue participation in the trial.

For non-commercial use only

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

Medications permitted during the trial are listed below:

Birth control methods are allowed as described in Section 12.1.

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 first dosing.

Administration of other concomitant medication, such as over-the-counter medications (for example, nonsteroidal anti-inflammatory drugs, acetaminophen [Tylenol®], vitamins) will be permitted for the treatment of AEs, only when deemed necessary and when agreed by the investigator and sponsor, except during IP administration. Premedication to IP administration is not allowed.

7.0 DISCONTINUATION OF IP AND PARTICIPANT WITHDRAWAL FROM TRIAL

7.1 Discontinuation of IP

Discontinuation of IP for a participant occurs when IP administrations are stopped earlier than scheduled in the protocol. If IPs are 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.

For non-commercial use only

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.

- Personal Reason.
- Adverse Event.
- Lost to Follow-Up.
- Non-compliance.
- Intercurrent Illness.
- Failed Drug/Alcohol Laboratory.
- Failed Check-in Laboratory.
- Sponsor Adjustment.
- Other.

For non-commercial use only

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

Participants who have discontinued or withdrawn from the trial after receiving any dose level of TAK-881 will not be replaced.

7.3 Lost to Follow-up

If a participant fails to return to the trial site for a required trial visit or for a follow-up visit 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 due to loss to follow-up will not be imputed.

7.4 Trial and Dose Stopping Rules

7.4.1 Treatment Arm Discontinuation Criteria:

Dosing within a treatment arm will be halted pending evaluation by the sponsor if 1 of the following circumstances occurs:

- 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) in 2 participants in the same treatment arm.
- Grade 3 or higher AE per NCI CTCAE version 5.0 criteria in 2 participants in the same treatment arm.
- Grade 4 or higher AE per NCI CTCAE version 5.0 criteria.
- Other findings that, at the discretion of the investigator in consultation with the sponsor's Medical Monitor and the sponsor' s Safety Physician recommendation, indicate that further dosing should be stopped.

For non-commercial use only

7.4.2 Trial stopping Criteria:

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 adverse events occurring in the same system organ class.
- 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.

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.

All procedures should be completed as close to the prescribed/scheduled time 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 *Demographic and Other Baseline Characteristics*

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, 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 trial 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.

For non-commercial use only

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

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

8.2 Confinement

Participants will be housed according to confinement and discharge plan as outlined in the SoA (Section 1.3). Participants will return for trial procedures as outlined in the SoA (Section 1.3).

A participant may be requested to remain at the trial 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.

For non-commercial use only

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: general appearance, head and neck, eyes and ears, nose and throat, spine/neck/thyroid, musculoskeletal, respiratory, cardiovascular, abdomen, extremities and joints, lymph nodes, skin, and neurological. Partial physical examinations will include general appearance, head and neck, assessment of infusion site(s), and skin. Other organ systems will be assessed per investigator's judgment.

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 height and weight measured at the screening visit.

8.3.3 Vital Signs

Measurements of 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 each 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.

For non-commercial use only

Hematology

The hematology assessments will include the following tests:

Hgb	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 being taken.

The chemistry assessments will include the following tests:

Albumin	ALP
ALT	AST
Blood urea nitrogen	Calcium
Carbon dioxide	Chloride
Creatinine[a]	Glucose
γ-glutamyl transferase	Sodium
Potassium	Bilirubin (total, direct, and indirect)
LDH	Uric acid
Protein (total)	Magnesium
Lipid profile [b]	

[a] At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

[b] Lipid profile consist of triglycerides, cholesterol, LDL, and HDL.

For non-commercial use only

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 ≥ 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:

Hgb	Plasma-free (unbound) hemoglobin [a]
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 the baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 hours; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible, but at the next scheduled visit, at 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 × 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 for Hgb remains constant 72 hours after the first full dose of the IP or after an unscheduled visit blood draw, unless it drops further. It is recommended that the investigator uses good medical judgement in assessing participants with an unexplained decrease in serum Hgb as other medical conditions beside hemolysis can cause this, and therefore may require additional investigations.

8.3.6 Other Diagnostic Laboratory Tests

Other diagnostic screening tests include the following:

HIV1/2 antibody test
HBsAg/ HBsAb/ HBcAb
HCV antibody test
PCR for HIV, HBV, HCV
Urine alcohol screen
Serum pregnancy test (for females only)
Follicle-stimulating hormone (FSH; for postmenopausal females only) [a]
COVID-19 [b]

[a] FSH levels may be done once at screening on menopausal or peri-menopausal women, or as judged by investigator

[b] 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	
Benzodiazepines	Methadone
Buprenorphine/metabolite	Oxycodone/oxymorphone
Cocaine	Phencyclidine
Cannabinoids	3,4-methylenedioxy-methamphetamine

For non-commercial use only

8.3.7 Infusion Site Evaluation and Infusion Reaction Assessment

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

8.3.8 Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

8.4 Adverse Events and Serious Adverse Events

A quick reference for safety reporting is shown in Table 9.

Table 9 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.	Within 24 hours
AESI	If event is serious complete and send paper SAE form to Safety.	Within 24 hours
Pregnancy	Complete and submit paper pregnancy form	Within 24 hours
SSR	Complete and send paper SSR form to Safety.	Within 7 calendar days

For non-commercial use only

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.)

Section 14.0 provides additional details and clarifications regarding AEs related to 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 ≥3× ULN and total bilirubin >2× ULN or INR >1.5× 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 12.2.

For non-commercial use only

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 non-commercial use only

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 NCI - 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.

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 dictionary must be graded under the term of infusion-related reaction.

For non-commercial use only

Assessment of Systemic Allergic Reactions:

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).

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.

For non-commercial use only

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 IP was stopped for a reason other than the particular AE (for example, the trial has been terminated, the participant died, dosing with IP was already stopped before the onset of the AE).

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

For non-commercial use only

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.

For non-commercial use only

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.

For non-commercial use only

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 SSR 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 a separate document.

Primary specimen collection parameters are provided in Table 10.

Sample retention is described in Section 13.0. When future use is permitted Refer to Section 13.2 for further detail on future use of samples.

For non-commercial use only

Table 10 Primary Specimen Collections

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

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 SoA (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
C_{max}	Maximum observed concentration after dose administration.
C_{trough}	Observed trough concentration before dosing.
t_{max}	Time of first occurrence of C_{max}.

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

8.5.2 Immunogenicity

Samples for rHuPH20 immunogenicity assessments will be collected at the specified time points delineated in the SoA (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). Postdose samples with antibody titers ≥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 Immunogenicity Panel Tests

At baseline (Day -1), samples will be collected for the following tests to be conducted: CH50, C3, C4, C1q binding assay, circulating immune complex Raji cell assay.

Participants who have (a) anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the participant's baseline titers, and (b) a moderate or severe AE (Grade 2 or higher as per CTCAE v5.0) which may be a result of immune-mediated response (Table 11) to either immunoglobulin, rHuPH20, or other concomitant medications, will be asked to return to the trial site as soon as possible to undergo an additional immunological assessment.

For non-commercial use only

Table 11 List of Conditions/Symptoms That May be a Result of Immune-Mediated Response to Either Immunoglobulin, rHuPH20, or Other Factors

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

For non-commercial use only

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 first participant in (randomized or dosed). The SAP will provide further details regarding the definition of analysis variables and the statistical analysis methodology to address all trial objectives. No interim analysis is planned for this trial. No statistical hypothesis testing will be performed.

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. Analysis will be performed according to the actual treatment received.

PKAS: The PKAS is a subset of the SAS and will consist of all participants who received at least one dose of TAK-881 and have at least one evaluable post-dose serum concentration for total IgG. Analysis will be performed according to the actual treatment received.

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

For non-commercial use only

9.2 General Approach

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

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

These descriptive statistics will be presented by treatment arm within each dose-level.

9.3 Infusion Tolerability Analyses

The primary endpoint is the occurrence of tolerable infusions of TAK-881. A tolerable infusion is considered to have occurred if an infusion is completed without interruption (discontinuing the infusion or infusion rate reduction) due to any TEAE related to TAK-881. An infusion is considered as intolerable if it is interrupted (discontinuation of the infusion or infusion rate reduction) due to TEAE related to TAK-881. Bifurcated infusion to 2 sites simultaneously is counted as one infusion. The dose (>120 g/600 mL daily maximum) divided over 2 days are counted as 2 infusions.

Infusion Tolerability Analyses will be based on the SAS.

The goal of these analyses is to provide a comprehensive randomized evaluation of the tolerability of different TAK-881 ramp-up dosing schedules in healthy participants. The tolerability will be evaluated for each infusion and will be summarized at both participant and infusion level.

Missing data for a participant due to lost to follow-up will not be imputed.

The primary endpoint will be summarized descriptively. The following summary statistics of the primary endpoint will be presented for each treatment arm within dose levels (cohorts), including but not limited to:

1. Number and percentage of participants who tolerated all initiated infusions and the 95% Clopper-Pearson CI (Clopper and Pearson, 1934) for the percentage.
2. Number and percentage of tolerable infusions and the 95% Clopper-Pearson CI for the percentage.
3. Average number of intolerable infusions per IG received (g/kg).

More calculation details will be provided in the SAP.

For non-commercial use only

9.4 Safety Analyses

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

9.4.1 AEs

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

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

Descriptive summaries of TEAEs (including but not limited to: TAK-881-related and non related, serious, nonserious, severity, local and systemic TEAEs, temporally associated TEAEs within 72 hours, TEAEs leading to premature discontinuation from the trial, TEAEs of special interest (allergy, catheter leakage, and thromboembolic events) and infusion-associated TEAEs will be presented by treatment (dose, schedule, combined). Note that clinically significant treatment-emergent changes in clinical laboratory measurements and vital signs will be recorded in the trial database as TEAEs.

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.

For non-commercial use only

9.4.5 Medical History:

Medical history, and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization drug dictionary and will be listed by participant.

9.5 Immunogenicity Analysis

Immunogenicity (occurrence of binding and neutralizing antibodies to rHuPH20) data will be listed for all participants in the safety analysis set and will be summarized using descriptive statistics. Positive binding (defined as titer ≥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 PK Analyses

All PK analyses will be based on the PKAS. All PK analyses will use the actual sampling times. If actual sampling times are not available, nominal times will be used for analyses. Uncorrected PK parameters for TAK-881 will be calculated using non-compartmental analysis using Phoenix WinNonlin®. Details regarding the calculation of PK parameters will be described in a separate CPAP. PK parameters to be calculated are C_{max} and t_{max} after the last dose, but additional PK parameters may be calculated at the discretion of the PK scientist.

PK parameters (both baseline corrected and uncorrected) using serum total IgG after the last dose of TAK-881 (including after Week 8 dosing for Schedules A and B and after Week 9 dosing after Schedule C), including C_{max} and t_{max} will be summarized descriptively by number of participants, mean, SD, median, V), minimum, maximum, GM, and geometric CV in each treatment arm. Serum concentration prior to TAK-881 dose (C_{trough}) will be measured prior to each dosing visit and summarized by dose and schedule. PK parameters will be calculated for all schedules and doses evaluated.

9.7 Analysis of Demographics and Other Baseline Characteristics

Continuous and categorical demographic data and other baseline characteristics will be listed and summarized using descriptive statistics. More details will be provided in the SAP

9.8 Interim Analysis and Criteria for Early Termination

Not applicable.

9.9 Sample Size Determination

This trial is not designed for statistical hypothesis testing; therefore, the sample size is not based on statistical considerations. The planned total sample size for this trial is 64 randomized and treated participants (8 participants per treatment; 8 treatments). Of the 64 participants to be randomized and treated, 48 participants are expected to complete the trial, assuming a conservative overall dropout rate of 25%.

For non-commercial use only

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 Council for International Organizations of Medical Sciences 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.

For non-commercial use only

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 9.

For non-commercial use only

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.

For non-commercial use only

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.

For non-commercial use only

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 Section 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.

For non-commercial use only

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.

For non-commercial use only

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.

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 clinical trial report.

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).

For non-commercial use only

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.

For non-commercial use only

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, European Medicines Agency, 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.

For non-commercial use only

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.

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.

For non-commercial use only

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.
- Intrauterine hormone-releasing system.

- 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).

For non-commercial use only

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.
- Lactational amenorrhea method.

Note also that female and male condoms should not be used together.

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 last dose of IP. WOCBP using hormonal contraception must have been on a stable dose for at least 90 days prior to first 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 last 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. If the serum pregnancy test at the screening visit 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 first IP administration). 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 pregnancy is suspected, requested by an IRB or if required by local regulations.

For non-commercial use only

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 visit. 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.

For non-commercial use only

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, deoxyribonucleic acid, or ribonucleic acid 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.

For non-commercial use only

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 International Organization for Standardization 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 trial. See Section 6.2 for the list of sponsor medical devices.

For non-commercial use only

14.1 Definitions of Medical Device AE and Adverse Device Effect

Medical Device AE Definition
A medical device AE is an event that has all of the following characteristics: • Occurs in a clinical trial participant, *user, or other person.* • Otherwise meets the definition of an AE in Section 8.4.1.1. • Is temporally associated with *either* the use of the investigational medical device *or* comparator, or with the associated procedures. Exception: Events in users or other persons only include events related to investigational medical devices.

ADE Definition
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: • 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
A medical device SAE is an event that: • Occurs in a clinical trial participant, *user, or other person.* • 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
An SADE is defined as: • 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.
Unanticipated SADE (USADE) Definition
An USADE (also identified as an Unanticipated Adverse Device Effect 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.

For non-commercial use only

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
All requirements stated in Section 8.4 apply to medical device AEs and deficiencies. For device deficiencies, the investigator must also describe any corrective or remedial actions taken to prevent recurrence of the deficiency. 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.

Assessment of Severity
The investigator will make an assessment of intensity for each medical device AE or deficiency reported during the trial and assign it to one of the following categories/categories: • See Section 8.4.4 for standard intensity 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
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.

For non-commercial use only

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. 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.

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(R3) Section 5.5.11 requires the investigator to retain essential documents specified in ICH E6(R3) (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(R3) 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.

For non-commercial use only

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
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BSA	Body surface area
CH50	50% hemolytic complement
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
COVID-19	Coronavirus disease 2019
CPAP	clinical pharmacology analysis plan
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	Electrocardiogram
(e)CRF	(electronic) case report form
EOT	End of Treatment
EU	European Union
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GM	geometric mean
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen

For non-commercial use only

HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IG	Immune Globulin
IgG	Immunoglobulin G
IGI	Immune Globulin Infusion
IGSC	Immune Globulin Subcutaneous
IP	investigational product(s)
IRB	institutional review board
LAR	legally authorized/acceptable representative
LDH	lactate dehydrogenase
MAV	markedly abnormal values
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Disease
NSAID	nonsteroidal anti-inflammatory drugs
OTC	0ver-the-counter
PCR	polymerase chain rection
PIDD	primary immunodeficiency disease
PK	pharmacokinetic(s)
PKAS	PK Analysis Set
QTLs	quality tolerance limits
rHuPH20	Recombinant Human Hyaluronidase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	systemic allergic reaction
SAS	safety analysis set

For non-commercial use only

SC	subcutaneous(ly)
SD	standard deviation
SoA	schedule of activities
SSR	special situation reporting
SUSAR	suspected unexpected serious adverse reactions
TDL	target dose level
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UADE	unanticipated adverse device effect
US	United States
USADE	Unanticipated serious adverse device effect
UK	United Kingdom
WOCBP	woman of childbearing potential

For non-commercial use only

17.0 APPENDIX: REFERENCES

Baxalta US Inc. 2024. HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] - Prescribing Information.Web Link: https://www.shirecontent.com/PI/PDFs/HYQVIA_USA_ENG.pdf

Clopper, C. J. & Pearson, E. S. 1934. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika,* 26, 404-413.

Cox, L. S., Sanchez-Borges, M. & Lockey, R. F. 2017. World Allergy Organization Systemic Allergic Reaction Grading System: Is a Modification Needed? *J Allergy Clin Immunol Pract,* 5, 58-62.e5.

Nagy, A., Duff, K., Bauer, A., Okonneh, F., Rondon, J. C., Yel, L. & Li, Z. 2023. A phase 1 open-label study to assess the tolerability, safety, and immunogenicity of hyaluronidase-facilitated subcutaneous immunoglobulin 20% in healthy adults. *J Clin Immunol,* 44, 28.

National Cancer Institute 2017. Common terminology criteria for adverse events (CTCAE) Version 5.0. U.S. Department Of Health And Human Services.Web Link:

Sampson, H. A., Munoz-Furlong, A., Campbell, R. L., Adkinson, N. F., Jr., Bock, S. A., Branum, A., Brown, S. G., Camargo, C. A., Jr., Cydulka, R., Galli, S. J., Gidudu, J., Gruchalla, R. S., Harlor, A. D., Jr., Hepner, D. L., Lewis, L. M., Lieberman, P. L., Metcalfe, D. D., O'Connor, R., Muraro, A., Rudman, A., Schmitt, C., Scherrer, D., Simons, F. E., Thomas, S., Wood, J. P. & Decker, W. W. 2006. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol,* 117, 391-397.

For non-commercial use only

Signature Page for TAK-881-1003 Protocol 20Feb2025
Title: TAK-881-1003 Protocol 20Feb2025

Approval Task	[redacted] Statistics 20-Feb-2025 14:40:03 GMT+0000

Approval Task	[redacted] Clinical 20-Feb-2025 19:43:40 GMT+0000

Document Number: TDN-000504714 v1.0

For non-commercial use only